

The Present Indication and Future of Deep Brain Stimulation

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Abstract

The use of electrical stimulation to treat pain in human disease dates back to ancient Rome or Greece. Modern deep brain stimulation (DBS) was initially applied for pain treatment in the 1960s, and was later used to treat movement disorders in the 1990s. After recognition of DBS as a therapy for central nervous system (CNS) circuit disorders, DBS use showed drastic increase in terms of adaptability to disease and the patient's population. More than 100,000 patients have received DBS therapy worldwide. The established indications for DBS are Parkinson's disease, tremor, and dystonia, whereas global indications of DBS expanded to other neuronal diseases or disorders such as neuropathic pain, epilepsy, and tinnitus. DBS is also experimentally used to manage cognitive disorders and psychiatric diseases such as major depression, obsessive-compulsive disorder (OCD), Tourette's syndrome, and eating disorders. The importance of ethics and conflicts surrounding the regulation and freedom of choice associated with the application of DBS therapy for new diseases or disorders is increasing. These debates are centered on the use of DBS to treat new diseases and disorders as well as its potential to enhance ability in normal healthy individuals. Here we present three issues that need to be addressed in the future: (1) elucidation of the mechanisms of DBS, (2) development of new DBS methods, and (3) miniaturization of the DBS system. With the use of DBS, functional neurosurgery entered into the new era that man can manage and control the brain circuit to treat intractable neuronal diseases and disorders.

Key words: deep brain stimulation, indications, future invention, ethics

History of Deep Brain Stimulation (DBS) Therapy

The history of DBS therapy tracks back to the ancient Roman or Greek era when humans realized the therapeutic effects of electrical stimulation. Ancient doctors used the torpedo fish to treat pain.¹⁾ Modern DBS was made possible by advances in surgical techniques, equipment, and scientific knowledge. These advances include the invention of the stereotactic frame and development of stereotactic surgery, invention of DBS systems, and acquisition of neuroscientific knowledge about brain nuclei, which could be targets of DBS, especially the basal ganglia. Spiegel and Wycis, who first invented stereotactic frame for human in 1947, also investigated the use of intra-operative electrical stimulation for decision making of lesioning sites in the brain.²⁾ Interestingly, modern DBS therapy was also started in the 1960s to control pain.²⁾ DBS for movement disorders began in 1987 by Benabid et al.³⁾

based on the clinical study by Hassler et al. in 1960, which reported tremor suppression by high frequency electrical stimulation during stereotactic ablation surgery.⁴⁾

On the other hand, in the 1970s, discovery of dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) enabled creation of animal models of Parkinson's disease (PD). Various discoveries of PD such as the firing properties of the involved brain regions, changes in neurotransmitters, and surgical and pharmacological therapies for PD were made possible through use of these animal models, with the primate model of PD providing the most valuable source.⁵⁾ The existence of cortico-striato-thalamo-cortical (CSTC) loop was proposed from investigations using these animal PD models in the 1970s.⁶⁾ These studies showed that malfunctioning of CSTC loops in PD by dopamine depletion causes excessive excitation of the subthalamic nucleus (STN) and globus pallidus interna (GPI). In addition, they revealed that PD symptoms could be alleviated by high frequency electrical

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stimulation of these excited neural structures. While conventional DBS targets were based on clinical experience, STN-DBS (initiated by Benabid et al.⁷⁾) was based on experimental findings in animal PD models. The development of STN-DBS was epic in terms of the history of functional neurosurgery for two reasons: first, it revealed that disorders of the CSTC loop circuit correlated with symptoms of PD, which was previously known as an intractable neurological disease; second, it revealed that DBS could re-modulate these central nervous system (CNS) circuit disorders, and control the symptoms caused by impairments to the CSTC loop. It is noteworthy that the CSTC loops that include the limbic area or orbitofrontal cortex seem to correlate with psychiatric symptoms or cognitive impairment, as well as motor-related loops have been already reported in the early proposal of CSTC loops. With these studies, DBS began to attract attention as a potential treatment method for CNS circuit disorders.

Current Development of DBS

Across the world, including Japan, DBS is currently being used to treat intractable pain and movement disorders such as PD and tremor. In Japan, DBS therapy was approved for intractable pain in 1992, for PD and tremor in 2000, and for the treatment of dystonia in 2013. In Japan, the use of DBS has been strictly applied to treat intractable pain and movement disorders. However, there is one investigational DBS study where Japanese functional neurosurgeons have attempted to use this therapy for patients in a vegetative state.⁸⁾ Globally, intractable diseases in the fields of neurology and psychiatry are being re-investigated from the point-of-view of CNS circuit disorders, and DBS has been experimentally carried out for newly recognized circuit disorders i.e., cluster headaches,⁹⁾ epilepsy,¹⁰⁾ and tinnitus.¹¹⁾ DBS is also used to manage cognitive disorders like Alzheimer's disease,¹²⁾ and psychiatric diseases such as major depression,^{13,14)} obsessive-compulsive disorder (OCD),¹⁵⁾ Tourette's syndrome,^{16,17)} and eating disorders.¹⁸⁾ The use of DBS for OCD received the Communauté Européenne (CE) mark in Europe, and approval from the Food and Drug Administration with humanitarian exemption (same as that for dystonia) in the United States. The established and investigational indications for DBS are listed in Table 1. In these indications, PD, tremor, and dystonia are thought to be established indication for DBS,²⁾ whereas the other diseases or disorders are still investigational for DBS therapy. Especially about DBS for psychiatric disorders, subcommittee of World Society for Stereotactic and Functional

Table 1 Indications for deep brain stimulation

1. Movement disorders
PD
Tremor (essential, cerebellar, post-traumatic, etc.)
Dystonia (primary or secondary tardive, with ceruloplasmin disorder)
Chorea
Ballism
Others (PSP, Wilson's disease, etc.)
2. Pain
Neuropathic pain (post peripheral nerve injury, post spinal cord injury, brain stem disease, some thalamic pain)
Intractable somatic pain or mixed pain of somatic and neuropathic pain
Cluster headache
3. Epilepsy
4. Psychiatric disorders
OCD
Major depression
Tourette syndrome
Bipolar disorder
Self-injurious behaviors (Lesch-Nyhan syndrome, etc.)
Eating disorders (anorexia nervosa, excessive obesity)
5. Cognitive dysfunction (Alzheimer's disease)
6. Conscious disturbance
Vegetative state
Minimal conscious state
7. Auditory disorders
Tinnitus

In these indications PD, tremor, and dystonia are thought to be an established indication for DBS (showed in bold letter), whereas other diseases or disorders are still investigational for DBS therapy. DBS: deep brain stimulation, OCD: obsessive-compulsive disorder, PD: Parkinson's disease.

Neurosurgery (the committee for Neurosurgery for Psychiatric Disorders) published "Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders," in 2014.¹⁹⁾ These guidelines indicated that DBS for psychiatric disorders remains in an investigational stage, and that all the procedures have to be done based on the scientific protocol, by the experienced multidisciplinary team, and under ethical and regulatory oversight by the Institutional Review Board.

More than 100,000 patients have received DBS therapy worldwide, and the target population and indications of this therapy are still growing. The range of indications for DBS, similar to other neurosurgical techniques, has expanded within several decades. Additionally, there is no inaccessible area in the brain, thus no limit in terms of where the electrodes can be applied as it can be used from the peripheral nerves to the brain stem. Moreover, there seems to be no limit to the diseases DBS can treat, only if it is the CNS circuit disorders. This in turn raised ethical problems, especially regarding neuroethics,

as to the pros and cons of humane alteration of CNS circuitry.²⁰⁾ Controversy about “enhancement” (i.e., acquisition to above normal capacity) such as memory or creativity augmentation, through the use of DBS on normal subjects will become an issue in the near future. This issue is not a science fiction but a realistic problem in terms of rapid expansion in neuronal ability that could modify or alter following DBS application. Moreover, DBS can improve the situation of “disorders” instead of strictly “diseases.” Senile memory decline, for example, is one of the “disorders” that could be improved by DBS in the future. The ethics about the application of DBS should be judged based on the present social philosophy. However, the common philosophy itself could change, for example breast augmentation, which was once considered an outrageous surgery, is now accepted by most people as a choice of surgery within the scope of personal freedom. Thus, the ethics of these consequential problems should be continuously discussed and judged.

Japanese neurosurgeons are quite cautious about neurosurgery for psychiatric disorders because these approaches have been a social taboo for a long time under the influence of the lobotomy since the 1970s. However, careful discussions including ethical issues in using DBS for OCD in this country are underway.

Present Direction of New Target Invention

There have been three approaches in the invention of new targets for DBS:

1. Re-adaptation of known target for ablation surgery to DBS targets for the same purpose

The ventral intermediate (Vim) thalamic nucleus or the GPi are typical targets in this category. DBS of the posterior subthalamic area for tremor treatment is also included in this category.

2. Re-adaptation of known targets of ablation surgery to DBS for completely different purposes

The centromedian-parafascicular (CM-Pf) thalamic nucleus has been used as an ablation target for intractable pain, but is used as a DBS target for vegetative states⁸⁾ and Tourette's syndrome.¹⁷⁾ Likewise, the target of Sano's hypothalamotomy for pain and psychiatric disorders²¹⁾ is used as the DBS target for cluster headaches.⁹⁾

3. Adaptation of the new targets which have been disclosed by neuroscientific studies

STN-DBS is a typical case from this category.⁷⁾ DBS of area 25 for major depression¹³⁾ is also categorized in this criteria.

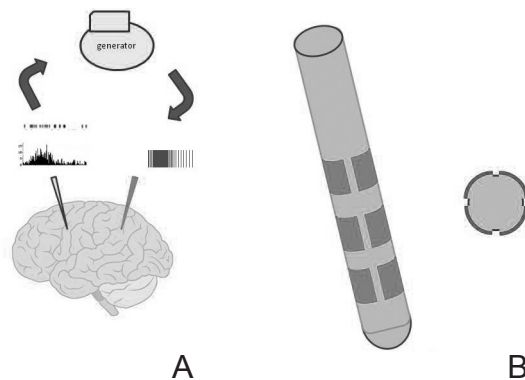


Fig. 1 Two technologies of DBS under development. **A:** Closed loop DBS system with a sensor in the apparatus, and a stimulator, which is activated only when the sensor detects abnormal brain signals. **B:** Multidirectional DBS leads where three or four electrodes surround around the lead axis. One can select not only the depth but also the direction of each current flow. DBS: deep brain stimulation.

Current and Proposed Advances in DBS Technology

Recently new implantable pulse generators (IPGs) have replaced the old IPG. Current as well as voltage mode stimulation, multiprogramming, or interleaving stimulation were made possible with these new IPGs. Rechargeable stimulators are also available in the market. A magnetic resonance imaging tolerable DBS system will also soon be available in the near future (personal communication).

The following two systems are now under development. One is a closed-loop DBS system²²⁾ (Fig. 1A), which has a sensor in the apparatus, and the stimulator is activated only when the sensor detects abnormal brain signals. Compared to current DBS systems which produce continuous stimulation, this new system not only improves the energy efficacy but also reduces the side effects produced by continuous stimulation. The second system comprises multidirectional DBS leads (Fig. 1B), unlike conventional DBS leads where the electrode is placed around the lead axis and current flows in all directions in this system, three or four electrodes surround the lead axis and the depth and direction of current flow for each electrodes can be selected. The investigational 64 channel (4 × 16) multidirectional DBS leads have been reported.²³⁾

Future Directions in DBS Therapy

We would like to propose the following three issues that should be addressed in the future:

1. Elucidation of the mechanisms of DBS therapeutic action

Table 2 Proposed mechanisms of deep brain stimulation

1. Inhibition
 - Hyperpolarization
 - Depolarization blockage
 - Neurotransmitter (glutamate) depletion
 - Release of inhibitory neurotransmitter (GABA)
2. Excitation
 - Glutamate increase
 - Dopamine release
3. Both inhibition and excitation
 - Decoupling of soma inhibition with axon excitation
 - LTP and LTD
4. Disruption of pathological oscillation
 - Produce jamming signal
 - Produce prokinetic frequencies by abolition of beta band oscillation
 - Replacement of irregular bursting with regular high frequency firing

Proposed mechanisms of deep brain stimulation (DBS) includes inhibition, excitation, simultaneous inhibition, excitation, and improvement of neural oscillations by DBS. LTD: long term depression, LTP: long-term potentiation.

The mechanisms of DBS action remain a controversial issue. For instance, it is assumed that DBS can inhibit as well as excite the nervous system via different stimulation. It is also unknown whether neuronal soma and axon can be separately stimulated.²⁴⁾ The mechanisms of DBS action proposed so far are listed in Table 2. More specifically this table lists proposed mechanisms of inhibition,²⁵⁾ excitation,²⁶⁾ simultaneous inhibition and excitation,²⁷⁾ and improved oscillation by DBS.²⁸⁾ Elucidation of the mechanisms of DBS action is a fundamental issue affecting the application of DBS therapy to a newly developed disease entity.

2. Development of different DBS methods

The search of new technology and development of different types of DBS methods should be continued. For example, development of DBS methods could be accomplished using optogenetics or neurochemical stimulation, or use of curved electrodes instead of conventional straight electrodes, etc. There are many unexplored areas which could be developed.

We would like to propose one idea for different DBS methods, which is “neuroendoscopic DBS.” It is well known that placing electrodes onto the brain surface and stimulation through these electrodes is much easier and safer than DBS. Thus, electrodes could be placed safely and easily on the surface of the ventricular wall using a neuroendoscope. There are multiple areas surrounding the ventricular wall, which are already used as targets of functional

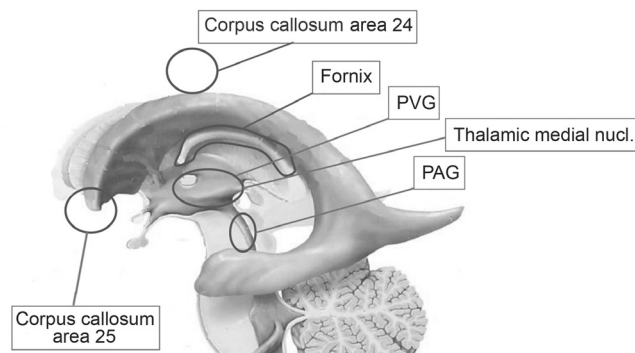


Fig. 2 Neuroendoscopic deep brain stimulation. In this method, electrodes will be placed on the ventricular wall using a neuroendoscope. There are multiple areas surrounding the ventricular wall, which are already used as the target of functional neurosurgery, or which could be used for functional stimulation.

neurosurgery, or which could be used for functional stimulation (Fig. 2). The development of this method will require the construction of new electrodes, which easily attach to the ventricular wall. Such electrodes could include clip-type electrodes, and sealing methods of these electrodes need to be developed. However it seems that the feasibility of this method is high enough if one can develop these electrodes or sealing methods.

3. Miniaturization of DBS system

A smaller stimulating generator or generator with flexible materials should be invented. A burr hole-type stimulation generator is also desirable in the future. Moreover, DBS leads that are thinner than conventional ones are required for stimulation of fine neuronal structures such as the brain stem nucleus. Furthermore, invention of a built-in electrical generator in the stimulation generator is desirable. For example, a small electrical power generator using human temperature is already in the course of development. If these small electrical power generator become available, with simultaneous development of the stimulation generator using minimized electrical power, the small size generator might not need to be recharged and the battery would not need to be replaced.

In this article, we described the current use of DBS and its future prospects. In addition, we put forward a proposal for the development of DBS in the future. With the use of DBS, functional neurosurgery entered into the new era that man can manage and control the brain circuit to treat intractable neuronal diseases and disorders. Finally, we hope DBS will continue to be used as a therapy in the future as

it will bring hope to more patients who are now suffering from neuronal diseases or disorders.

Conflicts of Interest Disclosure

All the authors declared their conflicts of interest (COI) to The Japan Neurosurgical Society (JNS) office. There are no COI with any person or organization affiliated with this work.

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