

Deep Brain Stimulation for Intractable Obsessive-compulsive Disorder: The International and Japanese Situation/Scenario

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Abstract

Deep brain stimulation (DBS) is used to treat symptoms by modulating the cortico-striato-thalamo-cortical (CSTC) loop in the central nervous system (CNS), and attempts to research loop circuit disorders have been globally initiated among the intractable neurological and psychiatric disorders. DBS treatment has been evaluated for all these newly found CNS loop circuit disorders. In 2011, neurosurgical treatments for psychiatric disorders were renamed from “psychosurgery” to “neurosurgery for psychiatric disorders (NPD)” by the World Society for Stereotactic and Functional Neurosurgery (WSSFN). Moreover, in 2014, “Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders” was published by the WSSFN to address the differences in correspondence of stereotactic NPD. Globally, two multicenter prospective randomized control trials regarding DBS of the subcallosal cingulate gyrus and ventral anterior internal capsule/ventral striatum for intractable depression have been terminated after futility analysis. However, DBS for intractable obsessive-compulsive disorder (OCD), unlike for intractable depression, is showing steady development. In Japan, NPDs have not been performed since 1975 following the adoption of “Resolution of total denial for psychosurgery” by the Japanese Society of Psychiatry and Neurology. Nevertheless, a trend to adopt new neuro-modulation techniques for psychiatric disorders, including DBS, are emerging. We have created a clinical research protocol for the use of DBS in intractable OCD, which has been approved by the ethical committee of Hamamatsu University School of Medicine, with the hope of commencing DBS treatment for intractable OCD patients in the near future.

Key words: deep brain stimulation, psychiatric disorders, obsessive-compulsive disorder, consensus on guideline

Introduction

When Spiegel and Wycis first invented stereotactic frames in 1944, their aim was to treat psychiatric disorders instead of involuntary movement disorder or intractable pain using these devices.¹⁾ As demonstrated by this episode, stereotactic functional neurosurgery has long been associated with psychiatric disorders. Deep brain stimulation (DBS) was first developed as an electrical stimulation therapy, similar to spinal cord stimulation, for the treatment of pain and was later applied to involuntary movement disorders in the 1980s. Experimental research on Parkinsonian disease in primates revealed the existence of the

cortico-striato-thalamo-cortical (CSTC) loop in the central nervous system (CNS) and that loop circuit dysfunction leads to Parkinson's symptoms. The benefits of subthalamic nucleus DBS (STN-DBS) were uncovered from research on such loop circuit disorders. It is noteworthy that the CSTC loops that include the limbic area or orbito-frontal 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 loops²⁾ (Fig. 1). It is already widely known that STN- or globus pallidus internus (GPi)-DBS can strongly alleviate motor symptoms in patients with Parkinson's disease by modulating these motor loops. It seems logical to hypothesize that DBS might alleviate symptoms of psychiatric disorders by modulating other CSTC loops associated with the cingulate or orbito-frontal cortex. Attempts to uncover loop circuit disorders have been globally

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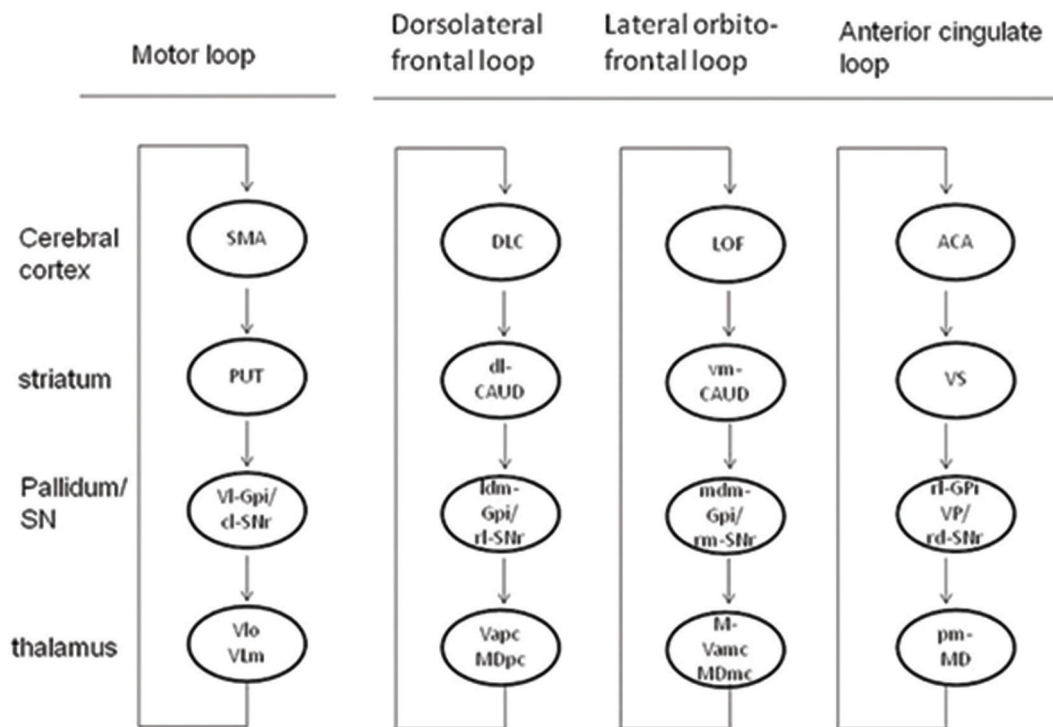


Fig. 1 Early proposal of cortico-striato-thalamo-cortical (CSTC) loops (modified from Alexander et al.²⁾ It is noteworthy that the CSTC loops that include the limbic area or orbito-frontal cortex seem to correlate with psychiatric symptoms or cognitive impairment, as well as motor related loops have been already reported in the early proposal of CSTC loops. ACA: anterior cingulate area, CAUD: caudate, DLC: dorsolateral prefrontal cortex, Gpi: globus pallidus interna, LOF: lateral orbitofrontal cortex, MDmc: medialis dorsalis pars magnocellularis, MDpc: medialis dorsalis pars parvocellularis, PUT: putamen, SMA: supplementary motor area, SNr: substantia nigra pars reticulata, VAmc: ventralis anterior pars magnocellularis, Vapc: ventralis anterior pars parvocellularis, VLm: ventralis lateralis pars medialis, VLo: ventralis lateralis pars oralis, VP: ventral pallidum, VS: ventral striatum, cl: caudolateral, dl: dorsolateral, ldm: lateral dorsomedial, m: medial, mdm: medial dorsomedial, pm: posteromedial, rd: rostrorodorsal, rl: rostrrolateral, rm: ventromedial, vl: ventrolateral.

initiated among the intractable neurological and psychiatric disorders, and DBS treatment has been evaluated for these newly discovered CNS loop circuit disorders.

Consensus on Guidelines for Stereotactic Neurosurgery for Psychiatric Disorders

Originally in the field of functional neurosurgery, stereotactic lesioning was considered as a treatment for psychiatric disorders, such as anterior cingulotomy or subcaudate tractotomy for intractable depression and obsessive-compulsive disorders (OCDs) and anterior capsulotomy for intractable OCDs. Public opinion on stereotactic lesion surgery for psychiatric disorders varies, but it has become more complicated by the addition of DBS as a new neuro-modulation technique. Opposition to brain surgery for psychiatric disorders is rather low in developing countries as reflected by lack of historical social events related

to psychosurgery in the 1960–70s. In 2011, functional neurosurgeons from 14 countries from North and South America, Europe, Asia, and Oceania participated in the WSSFN forum in Shanghai, China, and discussed the differences in stereotactic surgery for psychiatric disorders between countries. Following this discussion, it became obvious that the sense of surgical treatment of psychiatric disorders largely differs even with the developed country. In the United States, Canada, and Belgium lesioning is an established treatment, but DBS is an experimental procedure, whereas in France, lesioning is not allowed but DBS is acceptable. Outcomes from this forum, included two proposals for the WSSFN initiative. One involved the renaming of the neurosurgical treatment for psychiatric disorders as “neurosurgery for psychiatric disorders (NPD)” instead of “psychosurgery,” and the other included the formation of a global consensus on stereotactic NPD guidelines. Regarding the proposed terminology, neurosurgical treatment for psychiatric disorders

has long been referred to as “psychosurgery.” This term was coined by Egas Moniz, lobotomy pioneer, and it is often wrongly associated with lobotomy. Most of the experts agreed on the unsuitability of using a term bearing such negative denotation and proposed “NPD,” as the new term for neurosurgical treatment for psychiatric disorders. Regarding the establishment of a global consensus on stereotactic NPD guidelines, the WSSFN involved stereotactic neurosurgical societies from North and South America, Asia, Australia, as well as the World Psychiatric Association. This consensus publication (“Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders.”) is open access and Japanese translations created by several volunteers including the authors, are available for free download.³⁾ The aim of this publication was to reach an agreement on the precise guidelines for the use of stereotactic NPD in developed countries in North America and Europe, and to prevent their abuse, mainly in developing countries. The contents of this consensus relate to a variety of fields, but at first, it states that both ablative stereotactic neurosurgery and DBS remain at an investigational stage, and should be conducted under the supervision of an independent ethics committee or institutional review board associated with local or national regulatory agencies. In order for it to become an approved therapy, it was proposed that at least two blinded controlled randomized clinical trials (RCTs) from independent research groups need to be published, both indicating an acceptable risk–benefit ratio that is at least comparable to that of existing therapies. NPD needs to be performed by a multidisciplinary team that includes trained stereotactic and functional neurosurgeons, psychiatrists, neurologists, and neuropsychologists. Informed consent should be obtained from patients who have decision-making ability, as surrogate consent is strictly restricted. Research and clinical protocols should include support for long-term safety and efficacy studies of at least 5–10-year follow-up. From now on, NPDs are required to be performed in accordance with this agreed international consensus on the guidelines for stereotactic NPDs.

DBS for Depression

For the treatment of intractable depression, DBS has been targeted at several brain regions, including the ventral anterior internal capsule/ventral striatum (VC/VS),⁴⁾ the nucleus accumbens (NAc),⁵⁾ the subcallosal cingulate gyrus (area 25),⁶⁾ and the medial forebrain bundle (MFB)⁷⁾ (Figs. 2A–2D). Recently, two multicenter prospective RCTs on DBS of area 25⁶⁾

and about VC/VS⁴⁾ for intractable depression have been terminated after futility analysis. According to the study design of the trials, the former performed a 6-month and the latter a 4-month randomized comparison before conducting open-label comparisons. The reported results were difficult to interpret, as in both trials, randomized comparisons showed no statistically significant differences between the DBS and sham groups. Nevertheless, in both trials, significant depression score improvement at 24 months of open-label comparison was detected. There were some resemblances about proposed future RCT designs in a discussion from the authors of these two papers. One is that the RCT duration and timing has to be longer or later (for example, 1 year after surgery), and another is DBS targeting methods more concerned about specific fiber pathways using tractography. It was rather unexpected that the authors did not point out about heterogeneity of depression as a potential cause of RCT failure. An examination of the differences between cases where DBS was effective and ineffective in these two trials is crucial for the better understanding of the DBS effect on patients with depression.

DBS for OCD

For intractable OCDs, similar to depression, the etiological CNS loop circuit was assessed mainly by functional brain imaging of OCD patients. These observations became the theoretical backbone of DBS surgery for OCD patients. Multiple DBS targets have been reported, including the bed nucleus of the stria terminalis (BST), VC/VS, NAc, and STN (limbic and associative STN) (Figs. 3A–3C). For the identification of these targets, multicenter RCTs or high evidence level RCTs were reported, with level II for DBS of BST/VC/VS⁸⁾ and NAc,⁹⁾ and level I for DBS of STN.¹⁰⁾ A number of Meta-analyses and systematic reviews have been also reported. A meta-analysis by Kisely et al. reported a mean reduction in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of –8.93 points,¹¹⁾ while van Westen reported a mean response rate of 58.2%, and a mean reduction rate of 47.7% in a systematic review.¹²⁾ DBS for intractable OCD is approved by the Food and Drug Administration (FDA) in the US under the Humanitarian Device Exemption (HDE), and has gained a Conformité Européenne mark in Europe. These approvals have also been considered as HDE misuse by some.¹³⁾

Luyten et al. proposed that among the above-mentioned DBS targets for intractable OCD, VC/VS, and NAc could eventually be converged to BST, which is adjacent to all these regions⁸⁾ (Fig. 3B). During

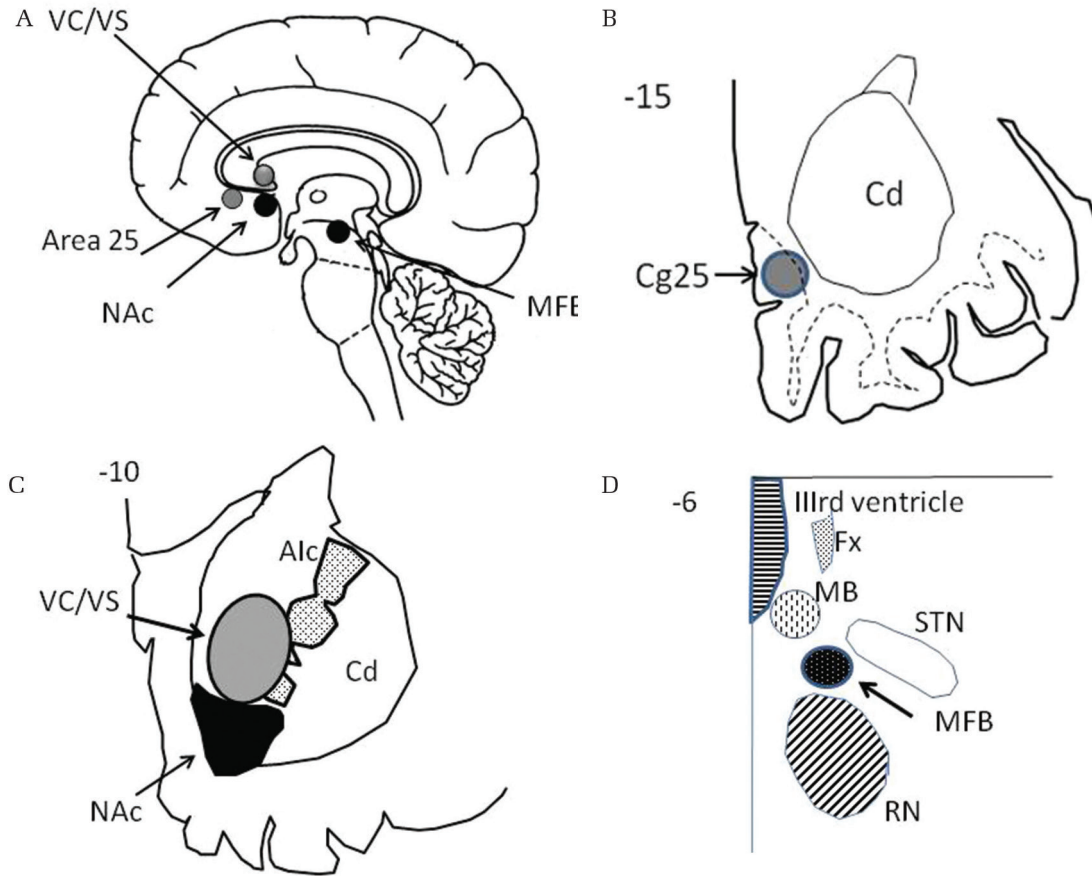


Fig. 2 Main target sites for intractable depression. All of the target sites are shown in sagittal brain section in A. VC/VS, NA, and CG 25 are shown in coronal section in B and C (modified from Mai's atlas.¹⁸⁾ MBF are shown in axial section in D (modified from Schaltenbrand and Wahren atlas.¹⁹⁾ Two targets (area 25, VC/VS) indicated by the gray circle in A, B, and C recently failed to pass through futility analysis. VC/VS: ventral anterior internal capsule/ventral striatum, NAc: nucleus accumbens, area 25: subcallosal cingulated gyrus, MFB: medial forebrain bundle.

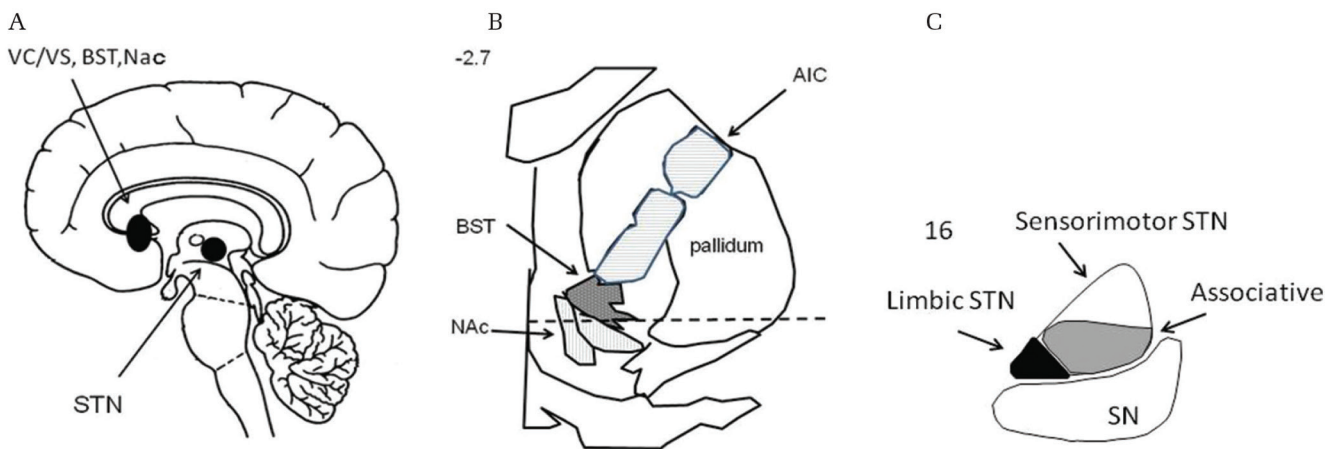


Fig. 3 Main target sites for intractable OCD. All of the target sites are shown in sagittal brain section in A. The relationship of anterior internal capsule (AIC), nucleus accumbens (NAc), and bed nucleus of the stria terminalis (BST) are shown in coronal section in B (modified from Mai's atlas.¹⁸⁾ Target sites in STN (limbic and associative STN) for OCD is shown in coronal section in C.

the last WSSFN meeting in 2017, the DBS targets for intractable OCD (VC/VS, NAc, and BST) were discussed whether they fulfill the requirement of an approved therapy, as described in “Consensus on stereotactic NPD guidelines” by WSSFN, according to which at least two independent blinded RCTs need to be published, both showing an acceptable risk–benefit ratio, comparable to that of existing therapies. The two RCTs listed at that meeting were BST-DBS ($n = 20$) reported by Luyten et al.,⁸⁾ and NAc-DBS ($n = 16$) by Denys et al.⁹⁾ Although the publication titles indicate the use of different DBS targets, the stimulation points described by Denys et al. were actually not on the NAc but on one part of the BST. The decision was postponed in the future in regard to whether DBS targets, such as VC, VS, NAc, and BST, fulfill the requirements of an approved therapy for intractable OCD. Nevertheless, DBS for intractable OCD, unlike DBS for intractable depression, seems to show steady development internationally. On the other hand, unlike to the DBS for Parkinson’s disease or essential tremor, response rates for DBS in intractable OCD have been reported as 58.2%, with the existence of some non-responders to such DBS therapies. Promising results were reported by Mantione et al. regarding cognitive and behavioral therapy, which only became effective in the patients who received DBS surgery.¹⁴⁾

Regression Trend toward the Ablative Procedure

The reconsideration for the use of stereotactic ablative procedures mainly emerged after the failure of two multicenter RCTs on DBS for intractable depression.¹⁵⁾ Initially, DBS was considered as a treatment option to complement the shortcomings of stereotactic ablative procedures such as coagulation. Stereotactic coagulation aimed to be therapeutic by permanently disconnecting neural structures and circuitry. Its disadvantages include symptom reappearance with nerve fiber regeneration and sometimes permanent complications might occur. Its disadvantages include symptom reappearance with nerve fiber regeneration and permanent complications. In degenerative diseases, such as Parkinson’s disease, symptom progression is frequently accompanied by CNS degeneration progression. Unlike the coagulation procedure, DBS can tune its therapeutic effect by optimizing the stimulation conditions. Moreover, stimulation-related side effects can be reversed by reducing the voltage or even stopping the stimulation. Nevertheless, they were not properly highlighted, thus, creating further DBS-related complications, such as lead break, skin erosion upon

cords or stimulator, patients’ discomfort caused by DBS devices, and increase in complication rate due to exchanging stimulators. These raised doubt on whether DBS cost-effectiveness is acceptable or not. Then, especially after the failure of two multicenter RCTs on DBS for intractable depression, the “anti-flag” against DBS was raised in countries where ablative NPD procedures have been performed. This issue is not only limited to NPD but also to stereotactic surgery for involuntary movement disorder coupled with the emergence of the focus ultrasound technique.¹⁶⁾ However, when ablative procedure is “thesis” and DBS is “antithesis,” we must essentially seek a third technique of “synthesis.” The need for this third technology is naturally high; the newly developed technology must be superior in all of the categories, such as safety, efficacy, controllability, and reversibility, to conventional techniques. Unfortunately, we still do not know in which direction this technology is aimed, but we need to keep in mind about the development of these technologies by ourselves.

Trends in Japan

When we refer to brain surgery for psychiatric disorders, lobotomy is the first topic to be discussed. This surgery has been globally abused, particularly in the United States. More than 18,000 cases of lobotomy had been performed in the United States by 1951,¹⁷⁾ also more than 1,000 cases in Japan by 1972. A global lobotomy opposition campaign, as well as student and medical intern movements in Japan occurred during the 1960–70s. In 1975, the Japanese Society of Psychiatry and Neurology adopted the “Resolution of total denial for psychosurgery.” Any kind of NPD became a social taboo for a long time since. In fact, the Japanese student movement against psychosurgery was not based on medical or scientific reasons, but on the social need to fight against University authorities at that time. Moreover, it has to be indicated that at that period, without consideration of future scientific and medical developments, the Japanese Psychiatric Society completely abandoned the possibility of surgical treatment for intractable psychiatric disorders, whose symptoms are resistant to any available drugs or other treatments. This led to Japan being secluded from worldwide advances in this area, and once led to a communication disruption between psychiatric communities and other medical, especially neurosurgical, communities. Moreover, the existence of this taboo led to the division of clinical domains into psychiatric and physical medicine and the notion that

physicians should not be involved in psychiatric medicine. However, it is scientifically impossible to clearly separate mental from somatic activities, for example, motion or sensation, with simple examples including, anxiety-linked somatic trembling, and physical pain-associated depression. Thus, it is irrational to prevent patient-related discussions between neurosurgeons and psychiatrists. Fortunately, collaborations between psychiatrists and other neurological doctors are currently resuming with the efforts of both medical communities and triggered by patients' needs.

Clinical Trial of DBS for Intractable OCD Planned in Hamamatsu University School of Medicine

Together with the psychiatrists in the Hamamatsu University, we had submitted a protocol of DBS for intractable OCD patients to the ethical committee of

Hamamatsu University School of Medicine, Japan, in March 2006. The protocols had been examined by the ethical committee of the Japanese Society of Psychiatry and Neurology and the Japanese Neurosurgical Society, and based on these reports, this issue was currently discussed by the subcommittee of the Japanese Society for Stereotactic and Functional Neurosurgery. Following the considerations of this subcommittee, we revised our submitted clinical research protocol in accordance with the WSSFN consensus on NPD guidelines and re-submitted it to the ethical committee of Hamamatsu University Hospital in 2015. This protocol was accepted by the ethical committee in November 2015.

The key steps of the protocol are listed in Table 1. We chose the BST/VC as a DBS target for OCD. We included functional neurosurgeons, psychiatrists, and neurologists as researchers of this protocol. We did not include psychologists as suggested in

Table 1 Main clinical research protocol contents of "Deep brain stimulation for intractable obsessive-compulsive disorder patients" from Hamamatsu University School of Medicine, Japan

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- 1) Corresponding members of this clinical research: three neurosurgeons including two practicing neurosurgeons, three psychiatrists, and one neurologist.
 - 2) External evaluators: one psychiatrist and one functional neurosurgeon.
 - 3) Study design: randomized, double-blinded, crossover design with two 3-week phases.
 - 4) Inclusion criteria
 - 1) Patients had received a primary obsessive-compulsive disorder diagnosis, defined according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5).
 - 2) Score on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) of more than 30–40.
 - 3) A score on the global assessment functioning (GAF) scale of less than 45.
 - 4) Aged between 20 to 70 years.
 - 5) Disease duration of more than 5 years.
 - 6) Symptoms resistant to more than three anti-anxiety, anti-depressant, or psychotropic drug treatments.
 - 7) Symptoms resistant to adequate cognitive behavioral therapy (CBT).
 - 5) Exclusion criteria
 - 1) Patients with other psychiatric disorders, except tic and Tourette syndromes.
 - 2) Patients with a history of drug addiction.
 - 3) High-risk patients for surgery.
 - 4) Pregnant or lactating women.
 - 5) Patients with other conditions that researchers deemed inappropriate for this research.
 - 6) Psychiatric evaluation: Y-BOCS, GAF, Hamilton's Depression Scale (HAM-D), and Beck Depression Inventory-II (BDI-II) are measured before and 1, 3, 6, and 12 months after deep brain stimulation (DBS) surgery.
 - 7) Neuroimaging studies: patients are evaluated with MRI and positron emission tomography (PET) using fluorodeoxyglucose (FDG) before and 12 months after DBS surgery.

The primary outcome is the change in Y-BOCS score at the end of the protocol. The criteria of "improvement" are defined as more than 35% reduction in Y-BOCS score at 12 months after DBS surgery. Patients are categorized as "social life possible" when Y-BOCS is reduced to less than 20 points and in remission when Y-BOCS is reduced to less than 15 points.

the WSSFN guidelines, as in our facility psychologists are not clinically independent and work within the psychiatric department. Furthermore, we set two external evaluators, one psychiatrist and one neurosurgeon. We also limited the age of this protocol as 20–70 years old, so that we could avoid surrogate consent about informed consent. We planned the cross-over randomized on–off study at 6 months after DBS surgery, and planned to evaluate not only clinical scores, such as (1) Y-BOCS, (2) global assessment of functioning (GAF), (3) Hamilton’s depression scale (HAM-D), and (4) Beck depression inventory-II (BDI-II), but also with fludeoxyglucose-positron electron microscopy (FDG-PET). In this protocol, we set the judgment of improvement for Y-BOCS to decrease $\geq 35\%$ at 12 months after surgery, and in addition to this relative measurement, we also set the absolute judgment of “possible social life” when Y-BOCS < 20 and remission when Y-BOCS < 15. Currently, we are in the process of coordinating the resolution of various issues related to the implementation of this protocol.

Conclusions

Approximately 40 years have passed since the adoption of the resolution of total denial for psychosurgery by the Japanese Society of Psychiatry and Neurology in 1975. During 1975, Microsoft Co. was founded and the first head computed tomography (CT) scan was performed in Japan. This CT scan could only be performed for the head in only two imaging sections in four and half minutes. In this 40-year period, new imaging technologies have been developed, including helical CT, MRI, and PET, and novel neuro-modulation methods, such as DBS, have emerged. With continuous advancements in new medical concepts, the remarkable medical and scientific progress during that period is undeniable. In 2017, transcranial magnetic stimulation for intractable depression was approved in Japan, making it the first novel neuro-modulation technique to be approved since 1975. We hope that this long period of medical “seclusion” from this field in Japan will soon end in the near future.

Conflicts of Interest Disclosure

All authors have declared their conflicts of interest to the Japanese Neurosurgical Society. There are no conflicts of interest for any person or organization affiliated with this work.

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