Deep Brain Stimulation for Parkinson's Disease: Recent Trends and Future Direction

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Abstract

To date, deep brain stimulation (DBS) has already been performed on more than 120,000 patients worldwide and in more than 7,000 patients in Japan. However, fundamental understanding of DBS effects on the pathological neural circuitry remains insufficient. Recent studies have specifically shown the importance of cortico-striato-thalamo-cortical (CSTC) loops, which were identified as functionally and anatomically discrete units. Three main circuits exist in the CSTC loops, namely, the motor, associative, and limbic circuits. From these theoretical backgrounds, it is determined that DBS sometimes influences not only motor functions but also the cognitive and affective functions of Parkinson's disease (PD) patients. The main targets of DBS for PD are subthalamic nucleus (STN) and globus pallidus interna (GPi). Ventralis intermedius (Vim)-DBS was found to be effective in improving tremor. However, Vim-DBS cannot sufficiently improve akinesia and rigidity. Therefore, Vim-DBS is seldom carried out for the treatment of PD. In this article, we review the present state of DBS, mainly STN-DBS and GPi-DBS, for PD. In the first part of the article, appropriate indications and practical effects established in previous studies are discussed. The findings of previous investigations on the complications caused by the surgical procedure and on the adverse events induced by DBS itself are reviewed. In the second part, we discuss target selection (GPi vs. STN) and the effect of DBS on nonmotor symptoms. In the final part, as issues that should be resolved, the suitable timing of surgery, symptoms unresponsive to DBS such as on-period axial symptoms, and the related postoperative programing of stimulation parameters, are discussed.

Key words: deep brain stimulation, Parkinson's disease, levodopa, CSTC loop

Introduction

To date, deep brain stimulation (DBS) has already been performed in more than 120,000 patients worldwide and more than 7,000 patients in Japan. These data establish the reliable efficacy and safety of DBS. In particular, DBS has become an important therapeutic strategy for Parkinson's disease (PD).

Following the first use of the stereotactic system for functional neurosurgery by Spiegel and Wycis in 1947, various ablative procedures for PD have been performed. However, these procedures became unpopular after the successful introduction of levodopa. On the other hand, in 1987 Benabid et al.[1,2] reported that the high-frequency stimulation of the ventralis intermedius (Vim) nucleus in the thalamus resulted in the complete and reversible cessation of tremors. In the same year, Siegfried et al.[3] reported the beneficial effects of the high-frequency stimulation

of the globus pallidus interna (GPi). Following these reports, the beneficial effects of the high-frequency stimulation of the subthalamic nucleus (STN) were elucidated by Benabid et al.[4] in 1993. This led to a breakthrough in the therapeutic strategy for advanced PD patients, namely DBS.

However, fundamental understanding of the effects of DBS on the pathological neural circuitry remains insufficient. Recent studies have specifically shown the importance of cortico-striato-thalamo-cortical (CSTC) loops, which were identified as functionally and anatomically discrete units.[5] The CSTC loops are composed of parallel functionally segregated neural circuits channeling information between the basal ganglia and the cortex via the thalamus.[6,7]

Three main circuits exist in the CSTC loops, namely, the motor circuit consisting of the sensorimotor and premotor cortices, the associative circuit containing the dorsolateral prefrontal cortex and lateral orbitofrontal cortex, and the limbic circuit consisting of the limbic and paralimbic cortices

and medial temporal cortex. From these theoretical backgrounds, it is determined that DBS sometimes affects not only the motor function but also the cognitive and affective functions of PD patients.

Recently, DBS has been used for treating psychiatric diseases and Alzheimer's disease. DBS was already granted a humanitarian device exemption status by the Food and Drug Administration (FDA) for treating obsessive compulsive disorder (OCD) in the United States.[7,8] Moreover, DBS has been expected as a therapeutic measure for addiction, eating disorder, post-traumatic stress disorder (PTSD), and minimally conscious state with preliminary successes shown in clinical studies.[9–13]

In this article, we review the present state of DBS for PD. In the first part of the review, we describe the appropriate indications and practical effects established in previous studies. The findings of previous studies on the surgical complications and the adverse effects of DBS are also reviewed. In the second part, we discuss the issues that should be resolved including target selection (GPi vs. STN) and the effects of DBS on nonmotor symptoms. In the concluding part, the suitable timing of surgery, symptoms unresponsive to DBS, such as on-period axial symptoms, and the related postoperative programing of stimulation parameters are discussed.

Appropriate Indications of DBS for PD

Careful patient selection is a crucial determinant of a favorable functional outcome of DBS. The main targets of DBS for PD are STN and GPi. In addition to these targets, Vim is an effective target for several types of tremor including Parkinson tremor. However, Vim-DBS cannot sufficiently improve akinesia and rigidity, which are the common symptoms of PD. Therefore, Vim-DBS is seldom carried out for the treatment of PD compared with STN-DBS and GPi-DBS.

The basic indication criteria for selecting STN as the target are similar to those for selecting GPi. The clinical features of ideal candidates for both targets have been elucidated in a number of studies. Thus far, levodopa responsiveness has been widely accepted as the best predictive factor for a good outcome of DBS. A majority of medical centers use a levodopa challenge test. In this test, a patient is evaluated as a candidate for DBS when more than 30% improvement in the Unified Parkinson Disease Rating Scale (UPDRS) motor score (part III) is noted after levodopa intake. In addition, patients with severe tremor resistant to medical treatment are also candidates and are expected to show a good outcome. Not only Vim-DBS but also GPi-DBS

and STN-DBS are effective for medically resistant Parkinson tremor.

Previously, DBS was usually considered when medical treatment fails. In the case of medical treatment, several side effects, such as wearing-off, dopa-induced dyskinesia (DID), and hallucination, will develop approximately 10 years after the treatment initiation. DBS was often applied to resolve these symptoms related to the medical treatment. However, according to the results of a recent randomized controlled trial (RCT) study,[14] the patients who underwent DBS before their medical treatment became ineffective also showed better functional outcome than those treated only medically.

An important point on the difference in the appropriate indications for GPi-DBS and STN-DBS is associated with their efficacy for DID. In general, GPi-DBS has a direct effect on DID. In contrast, STN-DBS can attenuate DID as a result of the reduction in the dose of anti-PD drugs. Incidentally, PD patients with psychiatric symptoms may be considered as candidates for GPi-DBS.

The major contraindications for DBS are serious non-drug-induced preoperative psychiatric symptoms, cognitive dysfunction, and a high overall risk of adverse outcomes of the surgical procedure under general anesthesia for the implantation of an implantable pulse generator (IPG). Care should be taken for PD patients with hypertension and diabetes. Hypertension is a significant risk factor for intraoperative hemorrhage during the DBS electrode implantation, and diabetes is also a significant risk factor for device infection.

Effects of DBS for PD

The effects of STN-DBS can be simply expressed as the bottom-up effects and substitute effects. The bottom-up effects can improve a patient's activities of daily living (ADL) from the off-period state to the on-period state. The substitute effects of STN-DBS are the effects that take over those of anti-PD drugs in a patient with severe side effects of the drugs. Thus, we can expect that the patient can maintain his/her ADL in the on-period state and reduce his/her levodopa equivalent dose (LED) after STN-DBS surgery.

Regarding the effects of STN-DBS, five large trials,[14–18] controlled vs. best medical treatment, showed a favorable improvement of PD symptoms after STN-DBS. All these trials demonstrated the superiority of STN-DBS over the best medical treatment (Table 1). A meta-analysis of 22 studies by Kleiner-Fisman et al.[19] showed that the average improvement rate of motor score was 52%.

Table 1 Large controlled trials: deep brain stimulation vs. medical treatment

Authors	Year of publication	Target no. of pts.	Follow-up period	Improvement	Adverse events
Deuschl et al.[15]	2006	STN-DBS 78 Medical 78	6 months	DBS, better PDQ-39 (p = 0.02) UPDRS-III(p < 0.001)	Serious: DBS, worse (p < 0.04) DBS 13% Medical 4% Frequency: Medical, worse (p = 0.08) DBS 50% Medical 64%
Weaver et al.[16]	2009	STN 60 GPi 61 Medical 134	6 months	DBS, better Motor function (p < 0.001) Quality-of-life scores (p < 0.001)	DBS, worse (p < 0.001) 1 death secondary to hemorrhage
Williams et al.[17]	2010	STN-DBS 174 GPi-DBS 4 Medical 183	1 year	DBS, better PDQ-39 (p = 0.001)	Serious adverse events: DBS, worse 20 pts. in DBS (1 death) 13 pts. in medical
Okun et al.[18]	2012	STN on group 101 STN off group 35	1 year	DBS on group, better Good quality on time (p = 0.003)	DBS infection 4% and intracranial hemorrhage 3%
Schuepbach et al.[14]	2013	STN-DBS 124 Medical 127	2 years	DBS, better PDQ-39 (p = 0.0021)	Serious adverse events: DBS, worse 54.8% of DBS 44.1% of medical

GPi: globus pallidus interna, PDQ: Parkinson's Disease Questionnaire, pts.: patients, STN-DBS: subthalamic nucleus-deep brain stimulation, UPDRS: Unified Parkinson Disease Rating Scale.

Table 2 Long-term results of subthalamic nucleus-deep brain stimulation followed up for more than 8 years

Authors	Year of publication	No. of pts.	Follow-up period	Motor improvement compared with baseline	LED reduction	Significant issues
Fasano et al.[20]	2010	20	8 years	UPDRS motor score: Better than base line (p < 0.001)	60.3% reduced	Gait and postural instability Executive function
Castrioto et al.[21]	2011	18	10 years	UPDRS motor score better than baseline (p = 0.007)	Significantly reduced	Axial signs showed progressively worsen
Zibetti et al.[22]	2011	14	9 years	UPDRS motor score: 42% improved ADL score: no improvement Motor complication: 59% improved	39% reduced	Cognitive decline

ADL: activities of daily living, LED: levodopa equivalent dose, pts.: patients, UPDRS: Unified Parkinson Disease Rating Scale.

Long-term results are also available, especially those of three studies showing that the outcomes of STN-DBS in PD patients followed-up for more than 8 years are significant.[20–22] These studies demonstrate the beneficial effects of STN-DBS in the long term (Table 2). The motor and ADL scores in the off-state deteriorate after a long-term follow-up but still remain better than the baseline scores.

Similar to STN-DBS, the beneficial effects of GPi-DBS on motor symptoms have been shown by several studies. However, no randomized studies comparing the efficacy of GPi-DBS with that of the best medical treatment have been reported. GPi-DBS has always been compared with STN-DBS.[23–26] Most of the comparison studies showed that the efficacies of these procedures were similar to or that GPi-DBS is less efficacious than STN-DBS (Table 3). The rate of LED reduction is markedly different between GPi-DBS and STN-DBS. After GPi-DBS, a marked LED reduction is unexpected. The long-term effects of GPi-DBS on PD patients followed up for 3–6 years have been reported.[27,28] From these

Table 3 Comparison study related to globus pallidus interna and subthalamic nucleus

Authors	Year of publication	No. of pts.	Follow-up period	Efficacy	Safety
DBS for PD Study Group	2001	STN 96 GPi 38	6 months	STN > GPi	–
Anderson et al.[24]	2005	STN 10 GPi 10	1 year	STN > GPi	GPi > STN
Okun et al.[25]	2009	STN 22 GPi 23	7 months	STN = GPi	GPi > STN
Follett et al.[26]	2010	STN 147 GPi 152	2 years	STN = GPi	GPi > STN
St George et al.[49]	2010	STN 261 GPi 40	4 years	GPi > STN	–
Weaver et al.[50]	2012	STN 70 GPi 89	3 years	STN = GPi	STN > GPi
Odekerken et al.[51]	2013	STN 63 GPi 65	1 year	STN > GPi	STN = GPi

GPi: globus pallidus interna, PD: Parkinson's disease, pts.: patients, STN: subthalamic nucleus.

investigations, the favorable effects of GPi-DBS on tremor and dyskinesia were elucidated. However, the UPDRS scores remained higher than the baseline scores after a long-term follow-up, although speech and gait worsened and LED increased.

Surgical Complications of DBS

The surgical complications discussed here are comorbidities caused by the surgical procedure for DBS device implantation, which should be differentiated from the adverse effects of DBS, such as psychiatric symptoms and worsening of dyskinesia. We describe the adverse effects of DBS in the next chapter.

The major and serious surgical complications are intracranial hemorrhage, infection, device-related problems, and epileptic seizure. According to a recent meta-analysis of 112 papers,[29] the established hemorrhagic complication rate was 4.4% [95% confidence interval (CI): 3.8–4.9%). However, the occurrence rates of significant permanent neurological deficits due to hemorrhage were relatively low, the average of which was 1.0% (95% CI: 0.6–1.3%). On the other hand, the occurrence rate of infection in DBS patients was 4.0% (95% CI: 3.5–4.5%).[29]

The device-related problems were the specific complications of DBS, and the main problems were the migration of devices and fracture of leads. Migration occurred in 2.4% of patients (95% CI: 1.9–3.0%) and fracture occurred in 3.0% of patients (95%CI: 2.4–3.6%). Epileptic seizure was noted in 3.2% (95% CI: 2.3–4.0%) of those who underwent DBS. The actual occurrence rate of epileptic seizure was speculated to be much lower than the above-mentioned rate because

this meta-analysis did not include analytical reports that did not mention epileptic seizure.[29]

Many studies showed that a history of hypertension is a significant risk factor for intracranial hemorrhage during DBS surgery.[30–34] The relationship between age and hemorrhage is controversial. From an overall viewpoint, there is no significant increase in hemorrhage rate in elderly patients.[31,35]

The most common pathogenic bacterium causing infection after DBS is *Staphylococcus aureus,* accounting for 40–60% of all infection cases.[36,37] Sillay et al.[38] studied the risk factors for infection, namely, patient's age, experience of the surgeon, and the existence of exterior test stimulation period. They found no statistically significant difference in infection rate for these factors they examined. The duration of operation was also studied by some researchers,[39,40] but this factor showed no statistically significant relationship with infection.

Adverse Effects of DBS

The adverse effects of DBS such as cognitive decline and psychiatric symptoms are complex and a nonbiased incidence of such effects is not easy to determine, because these are also associated with the duration of PD and the reduction in the dose of anti-PD drugs. The disturbance of verbal fluency is the only significant adverse effect of DBS that almost all researchers found.

The common adverse effects that sometimes appear immediately after the surgery for DBS, especially in STN, are restlessness, hallucination, and cognitive decline. However, these symptoms frequently do

not persist for a long time and do not disturb the patient's quality-of-life (QOL).

After a long-term follow-up, dysarthria and apathy were sometimes noted. Dysarthria worsens in association with increase in stimulation intensity spreading in the corticospinal tract. Apathy seems to be related to the reduction in the dose of anti-PD drugs especially in the case of rapid reduction in the dose of levodopa. Cognitive decline is also present in the chronic state, which degrades the QOL of PD patients and is a serious problem for the families of PD patients.

Regarding cognitive function after DBS for PD, according to the results of meta-analysis by Appleby et al.,[41] severe and persistent cognitive decline seldom occurs after the intervention. However, a number of studies consistently showed the disturbance of verbal fluency after STN-DBS. A recent controlled randomized study with a 3-year follow-up has also shown that the occurrence rate of the disturbance of verbal fluency was significantly higher in patients with STN-DBS.[42] Other than the decline of phonological and semantic verbal fluency, an impaired response inhibition in conflict situation as assessed by the Stoop test[43] or go/no-go tasks[44] is regarded as another symptom suitable to disturb after DBS. According to the results of the meta-analysis of cognitive function after DBS by Parsons et al.,[45] it is rare that severe and long-term persistent cognitive decline occurs after STN-DBS and that the patient's QOL deteriorates persistently. On the other hand, it was reported that the withdrawal of levodopa therapy is related to cognitive decline.[46]

It has been considered that the effect of DBS on cognitive function is smaller in GPi than in STN. In particular, the disturbance of verbal fluency, which sometimes occurs after STN-DBS, seldom occurs after GPi-DBS. Meta-analysis by Videnovic et al.[47] revealed that the occurrence rates of cognitive decline and behavioral abnormalities were significantly lower in GPi-DBS than in STN-DBS.

In addition to cognitive decline, psychiatric symptoms should also be considered as important adverse effects of STN-DBS. However, care should be taken for patients with dementia with Lewy bodies (DLB) because this condition complicates PD and also causes cognitive decline and psychiatric symptoms.

DBS induces psychiatric symptoms such as hallucination, mood change, ICD, and dopamine dysregulation syndrome (DDS). These symptoms usually occur after STN-DBS. It does not necessarily mean that there are no symptoms at all after GPi-DBS, but they are very rare compared with those occurring after STN-DBS.

Regarding the psychiatric symptoms that appear immediately after the surgery for STN-DBS, they are highly expected to disappear completely even when severe hallucination is present. However, hallucination present before the surgery often worsens after the surgery. In such cases, preoperative identification of the cause of hallucination is important. In particular, it is important to differentiate between drug-induced hallucination and hallucination as a complication of dementia with Parkinson disease (PDD) and/or DLB. Drug-induced hallucination is expected to improve after STN-DBS because of the reduction in LED. However, a patient with hallucination as a complication of the disease itself should be excluded as a candidate for STN-DBS at the beginning of the evaluation stage for operative indication.

Depression and mania may occur after STN-DBS. Basically, we speculate that the combined effects of anti-PD drugs and STN-DBS on the limbic circuit cause such mood change. Therefore, a balance between the reduction in the dose of levodopa and the increase in STN-DBS intensity would be important. In addition to this balance, the STN part stimulated would be important. Ventromedial STN links the limbic circuit of the CSTC loops and is closely associated with emotion and mood.

The same theoretical background would be applied to impulsive compulsive disorder (ICD) and DDS. It is conceivable that ICD is one of the phenotypes of the hyperactive state of the limbic circuit of the CSTC loops. Moreover, DDS is exactly the disproportionate state of the CSTC loops. Caution is necessary when ICD and DDS occur after STN-DBS because they sometimes upset the proportionate balance of the CSTC loops. It was reported that the occurrence rate of ICD was significantly higher in the group with STN-DBS than in the medication-only group.[48]

Therefore, caution should be exercised regarding the balance between the dose of anti-PD drugs and DBS intensity in patients with psychiatric symptoms. Excessive reduction in the dose of levodopa and/or agonists with insufficient DBS intensity may induce depressive mood or apathy. In contrast, excessive accumulation of dopaminergic drugs and marked DBS of the limbic circuit of the CSTC loops would induce hyperactive-state symptoms such as mania, aggressiveness, and ICD. These strongly suggest that the balance between LED and DBS intensity is important.

Selection of Target

Selection of the best DBS target for PD is a recent topic of discussion in this field. To date, three targets have been identified for PD treatment in general: Vim, GPi, and STN. Of these targets, selection of Vim as the target for DBS does not improve any of the symptoms of PD except for tremor. Vim is,

therefore, selected for only a few patients with limited clinical conditions, namely, old age and predominant longstanding tremor.

There is no general consensus on which is the best target, GPi or STN for PD. Before the conduct of detailed RCTs, there was some impression that STN is slightly superior to GPi. However, a recent 5-year follow-up study[28] has revealed that there is no significant difference between GPi and STN in their effects on the motor symptoms. The meta-analysis of studies comparing these two targets[49] indicated the significant superiority of GPi for patients with postural instability and gait disturbance.

There are some noteworthy RCTs comparing GPi with STN.[26,50,51] The CSP468 Study Group[26] indicated no significant difference in motor improvement between these two targets, and the incidence of adverse effects, especially cognitive decline, was significantly low for GPi as the target. Another RCT[51] showed significant improvement of PD symptoms for STN as the target, and the incidence of adverse effects was almost the same for both targets.

As mentioned above, it is still difficult and probably impossible to determine which is the best target in general. Different aspects need to be considered. We should consider which is the suitable target for each patient because each target has different features. Probably, GPi is better than STN as a target in terms of improving gait, speech, postural instability, and dyskinesia. On the other hand, the prominent STN-DBS effect is reduction in LED, which leads to the improvement of the adverse events induced by anti-PD drugs, such as ICD, hallucination, and aggressiveness.

Regarding the characteristics of patients that should be considered when selecting the target, age may be important because the reduction in LED would largely benefit young patients who will cope with the disease over a long period. On the other hand, dyskinesia is sometimes the most intolerable symptom for elderly patients and it is easily affected by psychiatric adverse events induced by a change in the dose of anti-PD drugs. In addition, the battery lifetime is usually shorter for GPi-DBS because much more energy is needed to stimulate the large anatomical structure of GPi.

Effects on Nonmotor Symptoms

There are several types of nonmotor symptom induced by DBS. The symptoms we should pay attention to are autonomic symptoms, poor sleep quality, and pain.

PD patients often have autonomic symptoms such as orthostatic hypotension, constipation, neurogenic bladder, dyshidrosis, and sexual dysfunction. However, the effects of DBS on autonomic symptoms have not been studied in detail and remain obscure. Changes in blood pressure and heart rate after STN-DBS have been reported.[52] Holmberg et al.[53] conducted a prospective study and found that there was no significant difference in circulatory autonomic function between the patients with STN-DBS and those treated only with anti-PD drugs. Erola et al.[54] compared circulatory autonomic function before STN-DBS with that after 1 year of STN-DBS, and they found no statistically significant difference.

Constipation is a common autonomic symptom in PD patients. It is often recognized from the onset of the disease. The improvement of constipation after STN-DBS is often noted. However, improvement is only partial and usually patients need to take laxative drugs even after STN-DBS. The improvement of constipation appears to be related to the improvement of motor functions. Bladder dysfunction is also frequently noted in PD patients. There are some reports mentioning the direct effect of STN-DBS on bladder dysfunction. However, such an effect remains to be confirmed.

The efficacy of STN-DBS in improving sleep has been studied by sleep poligraphy. It was reported that the durations of both the slow-wave sleep and rapid eye movement (REM) sleep were extended after STN-DBS and the degree of extension was associated with the degree of improvement of motor functions.[55] A study with a two-year follow-up also showed a significant increase in total sleeping time, and this increase was associated with the improvement of bradykinesia. The reduction in LED results in a decrease in the time of sleep during the daytime and an improvement of the quality of sleep at nighttime.

A majority of PD patients have experienced chronic pain. A cohort study by Broetz et al.[56] showed that 74% of 101 patients had back pain. Usually, PD-related pains are classified as (1) musculoskeletal pain, (2) dystonic pain, (3) somatic pain, (4) radicular/peripheral pain, and (5) central pain. The presence of pain exacerbation during the off-period is important for differentiating PD-related pain from other types of pain.

PD-related pain is mainly associated with a chronic enhancement of muscle contraction, which is marked in musculoskeletal pain and dystonic pain. Practically, the improvement of musculoskeletal pain correlates with the improvement of rigidity, and the improvement of dystonic pain correlates with the improvement of dystonia after STN-DBS.

Pain threshold is also significantly associated with blood levodopa concentration. A decrease in

blood levodopa concentration leads to the decrease in pain threshold.[57] Therefore, patients sometimes complain of severe body discomfort after the withdrawal of levodopa. It was reported that the blood levodopa concentration in PD patients with pain is significantly lower than those in PD patients without pain and in normal subjects.[58]

In general, clinical research revealed the beneficial effects of STN-DBS on PD-related pain. Kim et al.[59] reported that 20 of the 23 patients (87%) showed improved PD-related pain after STN-DBS. In particular, dystonic pain and central pain improved markedly. However, Oshima et al.[60] reported that central pain poorly responded to STN-DBS and dystonic pain and musculoskeletal pain markedly improved after 1 year of STN-DBS.

Other Issues and Resolution

There are other issues regarding DBS for PD that need to be resolved. Postural instability and gait disturbance are the most disabling symptoms of PD. Several studies have shown that such symptoms present in the off-period are improved by STN-DBS, but those present in the on-period are not improved by this stimulation.[61–63] Meta-regression analysis by St George et al.[49] has indicated that GPi-DBS may have a better effect on gait disturbance than STN-DBS at least on the basis of their 2-year data.

Dopa-unresponsive postural instability and gait disturbance are important problems to consider from the viewpoints of selecting the appropriate stimulation target and programing of stimulation parameters. The pedunculopontine nucleus (PPN) is a new target for gait disturbance.[64] However, there is a wide variability of the results of studies of PPN as a target[65,66]; therefore, further studies are required.

To enhance the benefits of DBS, some investigators examined the timing of intervention of DBS. In particular, a recent prospective study by Schuepbach et al.[14] is worth mentioning. Previously, DBS as a therapeutic strategy for PD was considered as a last resort when medical treatment fails. Schuepbach et al.[14] have disproved such a thought on the basis of the results of their study. They randomly assigned 251 PD patients with early motor complications (mean disease duration, 7.5 years) to undergo STN-DBS plus medical therapy or medical therapy alone and compared the functional outcomes using The Parkinson's Disease Questionnaire (PDQ)-39. Their results suggest the superiority of STN-DBS plus medical therapy even at an early stage of PD. Likewise, age at surgery and PD onset age of patients would be important factors affecting the efficacy of STN-DBS for PD.[67]

Further enhancement of STN-DBS benefits would be realized by accumulating new knowledge on the programing of stimulation parameters. The motor component is known to exist in the dorsolateral part of STN. The main part for stimulation, either in the monopolar stimulation or bipolar stimulation, is consistently placed in this part. However, the stimulation site placed within the area above the STN appears to have beneficial effects on hyperkinetic symptoms such as dyskinesia and tremor.[68] On the other hand, nigral stimulation for resistant axial motor impairment, which generally shows limited response to dopaminergic medication and STN-DBS, was reported.[69] A RCT disclosed the statistically significant improvement of freezing of gait and the possible usefulness of the combined stimulation of STN and the substantia nigra pars raticulata for the PD patients with levodopa-unresponsive axial motor symptoms. In addition, Moreau et al.[70] reported a new strategy of STN-DBS against freezing of gait. Their results prompt the consideration of two-stage STN-DBS frequency optimization, with stimulation at 130 Hz and the usual voltage during the initial years and then at 60 Hz at a higher voltage in PD patients who develop severe gait disturbance.

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Conflicts of Interest Disclosure

The authors declare no conflict of interest associated with this manuscript.

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* 50: 344–346, 1987

2) Hariz MI, Blomstedt P, Zrinzo L: Deep brain stimulation between 1947 and 1987: the untold story. *Neurosurg Focus* 29: E1, 2010

3) Siegfried J, Shulman J: Deep brain stimulation. *Pacing Clin Electrophysiol* 10: 271–272, 1987

4) Benabid AL, Pollak P, Gross C, Hoffmann D, Benazzouz A, Gao DM, Laurent A, Gentil M, Perret J: Acute and long-term effects of subthalamic nucleus stimulation in Parkinson's disease. *Stereotact Funct Neurosurg* 62: 76–84, 1994

5) Rezai AR, Sharma M: Deep brain stimulation (DBS): current and emerging application. *Jpn J Neurosurg* (*Tokyo*) 23: 648–660, 2014

6) Alexander GE, DeLong MR, Strick PL: Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 9: 357–381, 1986

7) Lapidus KA, Kopell BH, Ben-Haim S, Rezai AR, Goodman WK: History of psychosurgery: a psychiatrist's perspective. *World Neurosurg* 80: S27.e1–e16, 2013

8) Kopell BH, Greenberg B, Rezai AR: Deep brain stimulation for psychiatric disorders. *J Clin Neurophysiol* 21: 51–67, 2004

9) Halpern CH, Wolf JA, Bale TL, Stunkard AJ, Danish SF, Grossman M, Jaggi JL, Grady MS, Baltuch GH: Deep brain stimulation in the treatment of obesity. *J Neurosurg* 109: 625–634, 2008

10) Kuhn J, Lenartz D, Huff W, Lee S, Koulousakis A, Klosterkoetter J, Sturm V: Remission of alcohol dependency following deep brain stimulation of the nucleus accumbens: valuable therapeutic implications? *J Neurol Neurosurg Psychiatr* 78: 1152–1153, 2007

11) Langevin JP, De Salles AA, Kosoyan HP, Krahl SE: Deep brain stimulation of the amygdala alleviates post-traumatic stress disorder symptoms in a rat model. *J Psychiatr Res* 44: 1241–1245, 2010

12) Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, Wherrett J, Naglie G, Hamani C, Smith GS, Lozano AM: A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. *Ann Neurol* 68: 521–534, 2010

13) Yamamoto T, Katayama Y: Deep brain stimulation therapy for the vegetative state. *Neuropsychol Rehabil* 15: 406–413, 2005

14) Schuepbach WM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, Hälbig TD, Hesekamp H, Navarro SM, Meier N, Falk D, Mehdorn M, Paschen S, Maarouf M, Barbe MT, Fink GR, Kupsch A, Gruber D, Schneider GH, Seigneuret E, Kistner A, Chaynes P, Ory-Magne F, Brefel Courbon C, Vesper J, Schnitzler A, Wojtecki L, Houeto JL, Bataille B, Maltête D, Damier P, Raoul S, Sixel-Doering F, Hellwig D, Gharabaghi A, Krüger R, Pinsker MO, Amtage F, Régis JM, Witjas T, Thobois S, Mertens P, Kloss M, Hartmann A, Oertel WH, Post B, Speelman H, Agid Y, Schade-Brittinger C, Deuschl G; EARLYSTIM Study Group: Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med* 368: 610–622, 2013

15) Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, Daniels C, Deutschländer A, Dillmann U, Eisner W, Gruber D, Hamel W, Herzog J, Hilker R, Klebe S, Kloss M, Koy J, Krause M, Kupsch A, Lorenz D, Lorenzl S, Mehdorn HM, Moringlane JR, Oertel W, Pinsker MO, Reichmann H, Reuss A, Schneider GH, Schnitzler A, Steude U, Sturm V, Timmermann L, Tronnier V, Trottenberg T, Wojtecki L, Wolf E, Poewe W, Voges J; German Parkinson Study Group, Neurostimulation Section:

A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 355: 896–908, 2006

16) Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks WJ, Rothlind J, Sagher O, Reda D, Moy CS, Pahwa R, Burchiel K, Hogarth P, Lai EC, Duda JE, Holloway K, Samii A, Horn S, Bronstein J, Stoner G, Heemskerk J, Huang GD; CSP 468 Study Group: Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 301: 63–73, 2009

17) Williams A, Gill S, Varma T, Jenkinson C, Quinn N, Mitchell R, Scott R, Ives N, Rick C, Daniels J, Patel S, Wheatley K; PD SURG Collaborative Group: 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* 9: 581–591, 2010

18) Okun MS, Gallo BV, Mandybur G, Jagid J, Foote KD, Revilla FJ, Alterman R, Jankovic J, Simpson R, Junn F, Verhagen L, Arle JE, Ford B, Goodman RR, Stewart RM, Horn S, Baltuch GH, Kopell BH, Marshall F, Peichel D, Pahwa R, Lyons KE, Tröster AI, Vitek JL, Tagliati M; SJM DBS Study Group: Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. *Lancet Neurol* 11: 140–149, 2012

19) Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R, Lang AE, Deuschl G: Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Mov Disord* 21(Suppl 14): S290–S304, 2006

20) Fasano A, Romito LM, Daniele A, Piano C, Zinno M, Bentivoglio AR, Albanese A: Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. *Brain* 133: 2664–2676, 2010

21) Castrioto A, Lozano AM, Poon YY, Lang AE, Fallis M, Moro E: Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. *Arch Neurol* 68: 1550–1556, 2011

22) Zibetti M, Merola A, Rizzi L, Ricchi V, Angrisano S, Azzaro C, Artusi CA, Arduino N, Marchisio A, Lanotte M, Rizzone M, Lopiano L: Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease. *Mov Disord* 26: 2327–2334, 2011

23) 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* 345: 956–963, 2001

24) Anderson VC, Burchiel KJ, Hogarth P, Favre J, Hammerstad JP: Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease. *Arch Neurol* 62: 554–560, 2005

25) Okun MS, Fernandez HH, Wu SS, Kirsch-Darrow L, Bowers D, Bova F, Suelter M, Jacobson CE, Wang X,

Gordon CW, Zeilman P, Romrell J, Martin P, Ward H, Rodriguez RL, Foote KD: Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. *Ann Neurol* 65: 586–595, 2009

26) Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, Marks WJ, Rothlind J, Sagher O, Moy C, Pahwa R, Burchiel K, Hogarth P, Lai EC, Duda JE, Holloway K, Samii A, Horn S, Bronstein JM, Stoner G, Starr PA, Simpson R, Baltuch G, De Salles A, Huang GD, Reda DJ; CSP 468 Study Group: Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med* 362: 2077–2091, 2010

27) Rodriguez-Oroz MC, Obeso JA, Lang AE, Houeto JL, Pollak P, Rehncrona S, Kulisevsky J, Albanese A, Volkmann J, Hariz MI, Quinn NP, Speelman JD, Guridi J, Zamarbide I, Gironell A, Molet J, Pascual-Sedano B, Pidoux B, Bonnet AM, Agid Y, Xie J, Benabid AL, Lozano AM, Saint-Cyr J, Romito L, Contarino MF, Scerrati M, Fraix V, Van Blercom N: Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. *Brain* 128: 2240–2249, 2005

28) Moro E, Lozano AM, Pollak P, Agid Y, Rehncrona S, Volkmann J, Kulisevsky J, Obeso JA, Albanese A, Hariz MI, Quinn NP, Speelman JD, Benabid AL, Fraix V, Mendes A, Welter ML, Houeto JL, Cornu P, Dormont D, Tornqvist AL, Ekberg R, Schnitzler A, Timmermann L, Wojtecki L, Gironell A, Rodriguez-Oroz MC, Guridi J, Bentivoglio AR, Contarino MF, Romito L, Scerrati M, Janssens M, Lang AE: Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. *Mov Disord* 25: 578–586, 2010

29) Fukaya C, Yamamoto T: [Systematic review of complications for proper informed consent(13)stereotactic and functional neurosurgery]. *No Shinkei Geka* 42: 751–768, 2014

30) Ben-Haim S, Asaad WF, Gale JT, Eskandar EN: Risk factors for hemorrhage during microelectrode-guided deep brain stimulation and the introduction of an improved microelectrode design. *Neurosurgery* 64: 754–762; discussion 762–763, 2009

31) Elias WJ, Sansur CA, Frysinger RC: Sulcal and ventricular trajectories in stereotactic surgery. *J Neurosurg* 110: 201–207, 2009

32) Gorgulho A, De Salles AA, Frighetto L, Behnke E: Incidence of hemorrhage associated with electrophysiological studies performed using macroelectrodes and microelectrodes in functional neurosurgery. *J Neurosurg* 102: 888–896, 2005

33) Sansur CA, Frysinger RC, Pouratian N, Fu KM, Bittl M, Oskouian RJ, Laws ER, Elias WJ: Incidence of symptomatic hemorrhage after stereotactic electrode placement. *J Neurosurg* 107: 998–1003, 2007

34) Xiaowu H, Xiufeng J, Xiaoping Z, Bin H, Laixing W, Yiqun C, Jinchuan L, Aiguo J, Jianmin L: Risks of intracranial hemorrhage in patients with Parkinson's disease receiving deep brain stimulation and ablation. *Parkinsonism Relat Disord* 16: 96–100, 2010

35) Binder DK, Rau GM, Starr PA: Risk factors for hemorrhage during microelectrode-guided deep brain stimulator implantation for movement disorders. *Neurosurgery* 56: 722–732; discussion 722–732, 2005

36) Beric A, Kelly PJ, Rezai A, Sterio D, Mogilner A, Zonenshayn M, Kopell B: Complications of deep brain stimulation surgery. *Stereotact Funct Neurosurg* 77: 73–78, 2001

37) Chan DT, Zhu XL, Yeung JH, Mok VC, Wong E, Lau C, Wong R, Lau C, Poon WS: Complications of deep brain stimulation: a collective review. *Asian J Surg* 32: 258–263, 2009

38) Sillay KA, Larson PS, Starr PA: Deep brain stimulator hardware-related infections: incidence and management in a large series. *Neurosurgery* 62: 360–366; discussion 366–367, 2008

39) Lyons KE, Wilkinson SB, Overman J, Pahwa R: Surgical and hardware complications of subthalamic stimulation: a series of 160 procedures. *Neurology* 63: 612–616, 2004

40) Seijo FJ, Alvarez-Vega MA, Gutierrez JC, Fdez-Glez F, Lozano B: Complications in subthalamic nucleus stimulation surgery for treatment of Parkinson's disease. Review of 272 procedures. *Acta Neurochir* (*Wien*) 149: 867–875; discussion 876, 2007

41) Appleby BS, Duggan PS, Regenberg A, Rabins PV: Psychiatric and neuropsychiatric adverse events associated with deep brain stimulation: A meta-analysis of ten years' experience. *Mov Disord* 22: 1722–1728, 2007

42) Zangaglia R, Pacchetti C, Pasotti C, Mancini F, Servello D, Sinforiani E, Cristina S, Sassi M, Nappi G: Deep brain stimulation and cognitive functions in Parkinson's disease: A three-year controlled study. *Mov Disord* 24: 1621–1628, 2009

43) Witt K, Pulkowski U, Herzog J, Lorenz D, Hamel W, Deuschl G, Krack P: Deep brain stimulation of the subthalamic nucleus improves cognitive flexibility but impairs response inhibition in Parkinson disease. *Arch Neurol* 61: 697–700, 2004

44) Hershey T, Revilla FJ, Wernle A, Gibson PS, Dowling JL, Perlmutter JS: Stimulation of STN impairs aspects of cognitive control in PD. *Neurology* 62: 1110–1114, 2004

45) Parsons TD, Rogers SA, Braaten AJ, Woods SP, Tröster AI: Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. *Lancet Neurol* 5: 578–588, 2006

46) Gotham AM, Brown RG, Marsden CD: 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. *Brain* 111 (Pt 2): 299–321, 1988

47) Videnovic A, Metman LV: Deep brain stimulation for Parkinson's disease: prevalence of adverse events and need for standardized reporting. *Mov Disord* 23: 343–349, 2008

48) Hälbig TD, Tse W, Frisina PG, Baker BR, Hollander E, Shapiro H, Tagliati M, Koller WC, Olanow CW: Subthalamic deep brain stimulation and impulse

control in Parkinson's disease. *Eur J Neurol* 16: 493–497, 2009

49) 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* 75: 1292–1299, 2010

50) Weaver FM, Follett KA, Stern M, Luo P, Harris CL, Hur K, Marks WJ, Rothlind J, Sagher O, Moy C, Pahwa R, Burchiel K, Hogarth P, Lai EC, Duda JE, Holloway K, Samii A, Horn S, Bronstein JM, Stoner G, Starr PA, Simpson R, Baltuch G, De Salles A, Huang GD, Reda DJ; CSP 468 Study Group: Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. *Neurology* 79: 55–65, 2012

51) Odekerken VJ, van Laar T, Staal MJ, Mosch A, Hoffmann CF, Nijssen PC, Beute GN, van Vugt JP, Lenders MW, Contarino MF, Mink MS, Bour LJ, van den Munckhof P, Schmand BA, de Haan RJ, Schuurman PR, de Bie RM: Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. *Lancet Neurol* 12: 37–44, 2013

52) Kaufmann H, Bhattacharya KF, Voustianiouk A, Gracies JM: Stimulation of the subthalamic nucleus increases heart rate in patients with Parkinson disease. *Neurology* 59: 1657–1658, 2002

53) Holmberg B, Corneliusson O, Elam M: Bilateral stimulation of nucleus subthalamicus in advanced Parkinson's disease: no effects on, and of, autonomic dysfunction. *Mov Disord* 20: 976–981, 2005

54) Erola T, Haapaniemi T, Heikkinen E, Huikuri H, Myllyä V: Subthalamic nucleus deep brain stimulation does not alter long-term heart rate variability in Parkinson's disease. *Clin Auton Res* 16: 286–288, 2006

55) Monaca C, Ozsancak C, Jacquesson JM, Poirot I, Blond S, Destee A, Guieu JD, Derambure P: Effects of bilateral subthalamic stimulation on sleep in Parkinson's disease. *J Neurol* 251: 214–218, 2004

56) Broetz D, Eichner M, Gasser T, Weller M, Steinbach JP: Radicular and nonradicular back pain in Parkinson's disease: a controlled study. *Mov Disord* 22: 853–856, 2007

57) Brefel-Courbon C, Payoux P, Thalamas C, Ory F, Quelven I, Chollet F, Montastruc JL, Rascol O: Effect of levodopa on pain threshold in Parkinson's disease: a clinical and positron emission tomography study. *Mov Disord* 20: 1557–1563, 2005

58) Djaldetti R, Shifrin A, Rogowski Z, Sprecher E, Melamed E, Yarnitsky D: Quantitative measurement of pain sensation in patients with Parkinson disease. *Neurology* 62: 2171–2175, 2004

59) Kim HJ, Paek SH, Kim JY, Lee JY, Lim YH, Kim MR, Kim DG, Jeon BS: Chronic subthalamic deep brain stimulation improves pain in Parkinson disease. *J Neurol* 255: 1889–1894, 2008

60) Oshima H, Katayama Y, Morishita T, Sumi K, Otaka T, Kobayashi K, Suzuki Y, Fukaya C, Yamamoto T: Subthalamic nucleus stimulation for attenuation of

pain related to Parkinson disease. *J Neurosurg* 116: 99–106, 2012

61) Stolze H, Klebe S, Poepping M, Lorenz D, Herzog J, Hamel W, Schrader B, Raethjen J, Wenzelburger R, Mehdorn HM, Deuschl G, Krack P: Effects of bilateral subthalamic nucleus stimulation on parkinsonian gait. *Neurology* 57: 144–146, 2001

62) Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, Koudsie A, Limousin PD, Benazzouz A, LeBas JF, Benabid AL, Pollak P: Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 349: 1925–1934, 2003

63) Maurer C, Mergner T, Xie J, Faist M, Pollak P, Lücking CH: Effect of chronic bilateral subthalamic nucleus (STN) stimulation on postural control in Parkinson's disease. *Brain* 126: 1146–1163, 2003

64) Mazzone P, Lozano A, Stanzione P, Galati S, Scarnati E, Peppe A, Stefani A: Implantation of human pedunculopontine nucleus: a safe and clinically relevant target in Parkinson's disease. *Neuroreport* 16: 1877–1881, 2005

65) Stefani A, Lozano AM, Peppe A, Stanzione P, Galati S, Tropepi D, Pierantozzi M, Brusa L, Scarnati E, Mazzone P: Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. *Brain* 130: 1596–1607, 2007

66) Moreau C, Defebvre L, Devos D, Marchetti F, Destée A, Stefani A, Peppe A: STN versus PPN-DBS for alleviating freezing of gait: toward a frequency modulation approach? *Mov Disord* 24: 2164–2166, 2009

67) Otaka T, Oshima H, Katayama Y, Kano T, Kobayashi K, Suzuki Y, Fukaya C, Yamamoto T: Impact of subthalamic nucleus stimulation on young-onset Parkinson's disease. *Neuromodulation* 13: 10–16, 2010

68) Katayama Y, Oshima H, Kano T, Kobayashi K, Fukaya C, Yamamoto T: Direct effect of subthalamic nucleus stimulation on levodopa-induced peak-dose dyskinesia in patients with Parkinson's disease. *Stereotact Funct Neurosurg* 84: 176–179, 2006

69) Weiss D, Walach M, Meisner C, Fritz M, Scholten M, Breit S, Plewnia C, Bender B, Gharabaghi A, Wächter T, Krüger R: Nigral stimulation for resistant axial motor impairment in Parkinson's disease? A randomized controlled trial. *Brain* 136: 2098–2108, 2013

70) Moreau C, Defebvre L, Destée A, Bleuse S, Clement F, Blatt JL, Krystkowiak P, Devos D: STN-DBS frequency effects on freezing of gait in advanced Parkinson disease. *Neurology* 71: 80–84, 2008

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