

**Review**

# Deep Brain Stimulation

X.L. Chen Y.Y. Xiong G.L. Xu X.F. Liu

Department of Neurology, Jinling Hospital, Nanjing University School of Medicine,  
Nanjing, China**Key Words**Motor function · Essential tremor · Parkinson's disease · Primary dystonia ·  
Obsessive-compulsive disorder · Neurological diseases**Abstract**

Deep brain stimulation (DBS) has provided remarkable therapeutic benefits for people with a variety of neurological disorders. Despite the uncertainty of the precise mechanisms underlying its efficacy, DBS is clinically effective in improving motor function of essential tremor, Parkinson's disease and primary dystonia and in relieving obsessive-compulsive disorder. Recently, this surgical technique has continued to expand to other numerous neurological diseases with encouraging results. This review highlighted the current and potential future clinical applications of DBS.

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**Introduction**

The modern era of deep brain stimulation (DBS) began in 1987 with the pioneering work by Benabid et al. [1] on the treatment of Parkinson's disease (PD). The discovery that electrical stimulation of functional targets was able to mimic (in a reversible and adjustable manner) a lesion-like effect has revived the use of functional neurosurgery for movement disorders [2]. Despite the fact that the underlying therapeutic mechanisms of DBS remain mysterious and controversial [3], it has been used as an effective therapy for an increasingly expanding spectrum of neurological diseases. Up to now, DBS has largely replaced ablative procedures for the treatment of advanced essential tremor (ET), PD and primary dystonia. It is also approved for the treatment of obsessive-compulsive disorder (OCD) [4]. Scientific efforts to explore the mechanisms of action of DBS are in progress. Meanwhile, clinical

Xinfeng Liu  
Department of Neurology, Jinling Hospital  
Nanjing University School of Medicine  
305 East Zhongshan Road, Nanjing 210002 (China)  
E-Mail [xfliu2@vip.163.com](mailto:xfliu2@vip.163.com)

researchers continue excavating the potential effects of DBS in other brain disorders and defining optimal targets. Here we gave an overview of the current clinical applications and the potential future development of DBS.

### Mechanisms of DBS

The therapeutic effects of DBS involve a variety of mechanisms. Stimulation through an electrode placed within a nuclear region will affect several neuronal components including cell bodies, axons and fibers of passage, generating an inhibitory synaptic effect on the cells but a concurrent high-frequency effect on efferent axons and fibers [3, 5]. The therapy modulates pathological network activity beyond local neuronal cell bodies and axons, either monosynaptic or polysynaptic, through its electrical, chemical and other neural network influences. DBS changes the firing rate and pattern of individual neurons in the basal ganglia [6] and eliminates abnormal rhythmic oscillation between the cortex and the basal ganglia [7]. The electrical current also acts on synapses and triggers adjacent astrocytes to release a wave of calcium and to promote local release of neurotransmitters (e.g. adenosine and glutamate) from excitatory efferent neurons [8–10]. In addition, this intervention produces global increases in cerebral blood flow [11] and stimulates neurogenesis [12]. All these effects of DBS depend on a number of parameters, including amplitude and temporal characteristics of the stimulation, physiological properties of the targeted cells, geometric configuration of the electrode and the surrounding tissue, and possibly the underlying pathophysiology of different disease states [13]. The most likely mode of action so far suggests that network-wide modulatory effects of DBS mediate its clinical effects. However, it still remains unclear exactly how these influences lead to changes in the symptoms of a certain neurological disease. Therefore, the foundation of this therapy has been more or less empirical.

### Clinical Applications of Deep Brain Stimulation

DBS was approved by the US Food and Drug Administration as a treatment for ET in 1997, PD in 2002, primary dystonia in 2003 and OCD in 2009. For each of these conditions, DBS is considered when nonsurgical management has failed. DBS is also routinely used in the treatment of chronic pain and various psychiatric disorders, including epilepsy, chronic pain, depression, Tourette syndrome (TS), Huntington's disease, obesity and addictions, Alzheimer's disease (AD) and consciousness disorders.

#### *Essential Tremor*

ET is the most common neurological movement disorder, typically recognized as involuntary rhythmic movements of the limbs, but it can also affect the head, neck, voice and other body regions. The idea of reducing tremor with DBS began to emerge in the 1960s [14], and treatment of tremor associated with ET or PD witnessed the first widespread use of DBS. The ventral intermediate nucleus of the thalamus is the most widely agreed target for treating ET with DBS [15, 16], with an average tremor control of over 80% in these patients [17–19]. Other investigators have suggested that the subthalamic region, posterior subthalamic area and caudal zona incerta nucleus may also be an effective target for ET [20–22]. The technique is, however, limited in some ET patients by relevant side effects such as dysarthria, disequilibrium and paresthesia. Bipolar configuration is proven to have fewer side effects, and stimulation at 90  $\mu$ s, 130 Hz and voltage up to 3 V tends to be effective and well tolerated [23]. Such parameters are, nevertheless, highly variable among patients to optimize tremor con-

trol. DBS for the management of midline tremor (head, voice, tongue and trunk) is less effective and generally requires bilateral stimulation for optimal results. Thalamic DBS, compared with thalamotomy, was shown to have significant functional improvement of tremor with fewer adverse effects, making it a preferential surgical choice for medically refractory ET [24, 25].

### *Parkinson's Disease*

PD affects approximately 0.3% of the general population. The cardinal features of PD are resting tremor, rigidity, bradykinesia and postural instability. In the course of the disease, about 40% of patients will develop marked motor 'on-off' fluctuations and drug-induced dyskinesias after 5 years of medical treatment [26]. Hyperactivity of the subthalamic nucleus (STN) and globus pallidus internus (GPi) is substantiated to be part of the pathophysiological mechanism of PD [27], making them the most commonly targeted sites for DBS in PD. DBS of GPi and STN to treat patients with PD was first reported by Siegfried and Lippitz [28] in 1994 and Limousin et al. [29] in 1995, respectively. Since then, DBS surgery has emerged worldwide in the treatment of PD. Long-term, high-quality evidence is available for stimulation of STN and GPi, and both provide a similar reduction of motor symptoms [30–32]. Typically, levodopa-responsive symptoms, dyskinesias, tremor and on-off fluctuations are most likely to improve with DBS, remaining stable for at least 4 years, whereas impairments in speech, balance, gait and cognition are less likely to improve and may in some cases worsen postoperatively [33–35]. Despite the controversy of its effect on cognitive functions and psychiatric side effects, STN DBS is usually favored over GPi DBS for a significantly decreased daily dose of dopaminergic medications and a better outcome of motor signs [36, 37]. Other stimulation targets, such as the pedunculopontine nucleus and the centromedian/parafascicular thalamic complex, have only short-term evidence and still require further investigation [38]. Good candidates for DBS are those who have adequate dopaminergic response while showing on-off fluctuations, dyskinesia and medication-resistant tremor with reasonable cognitive function [39]. DBS at an earlier stage of PD has also showed benefit, but was based on a small population and further verification is necessary [40]. Settings that are used for DBS are, typically, high frequency (130–185 Hz) with pulse widths of 60–120  $\mu$ s at voltages ranging from 2.0 to 5.0 V, but these are highly variable among patients, with frequent adjustment during the first few months after implantation [39, 41].

Randomized controlled clinical trials have been performed to check the effectiveness of DBS therapy. Three trials have made comparisons with medical therapy [42–44]. The primary end points were mainly the following: (1) the quality of life, as assessed by the Parkinson's Disease Questionnaire (PDQ-39; scores ranging from 0 to 100, with higher scores indicating poorer function) [45], (2) the severity of symptoms without medication, according to the Unified Parkinson's Disease Rating Scale, part III (UPDRS-III; scores ranging from 0 to 100, with higher scores indicating worse condition) [46] and (3) time spent daily in the 'on' state without dyskinesia. In a trial involving 156 patients with advanced PD and severe motor symptoms in Germany and Australia, with 6 months of follow-up, patients who underwent STN DBS gained significantly better mean scores on the PDQ-39 (31.8 vs. 40.2) and the UPDRS-III (28.3 vs. 46.0) [42]. A trial conducted in the US enrolled 255 patients with 6 months of follow-up, and patients who received DBS of STN or GPi had a mean of 4.6 h per day of 'on' time compared with 0 h per day for the best medical therapy group [43]. In another trial involving 366 patients in the UK, at 1 year the mean PDQ-39 score was 32.5 among patients undergoing STN DBS versus 38.1 among those receiving best medical therapy [44]. To compare the therapeutic efficacy of STN or GPi, two trials have been performed [31, 47], showing no significant between-group differences in the optimal DBS state at 7 and 24 months, respectively. One trial involving 20 patients with PD of short duration with mild-to-

moderate motor signs showed significantly improved life quality and motor function in the STN stimulation group compared with the medical treatment group after 18 months, indicating DBS to be a therapeutic option early in the course of PD [40].

### *Primary Dystonia*

Primary dystonia is a debilitating movement disorder with a widespread spectrum mainly in young people. It is characterized by sustained muscle contractions, causing repetitive twisting movements or abnormal postures [48]. Medical treatments of botulinum toxin, anticholinergic agents, muscle relaxants, benzodiazepines and levodopa are available, but are limited by poor efficacy and tolerability [49]. Since the early report of DBS in dystonia treatment [50], it has been increasingly proved to provide marked benefit for refractory dystonia with the generally accepted target of GPi [51, 52].

GPi DBS has been established as an effective surgical treatment alternative for primary dystonia, with a 50–80% motor benefit according to short-term [53, 54] and long-term longitudinal studies [55–58]. In a randomized controlled trial by Kupsch et al. [53], 40 patients with primary dystonia were randomly assigned to either bilateral GPi DBS or sham stimulation (in which the device was implanted but not activated) for 3 months; thereafter, all patients completed 6 months of DBS therapy and were followed annually with a 5-year follow-up period [53, 58]. Dystonia severity was assessed by the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), consisting of motor (BFMDRS-M) and disability (BFMDRS-D) subscales [59]. Treated patients improved significantly more than controls (39.3 vs. 4.9%) in the BFMDRS-M subscale; similar improvements can be noted when sham stimulation was switched to active stimulation [53]. Dystonia severity improved by 47.9% in 40 patients at 6 months, then to an overall 61.1% in 38 patients at 3 years, and to a 57.8% improvement in 32 patients who were available for follow-up at 5 years [58]. One similar controlled trial demonstrated that DBS provided sustained motor benefit after 3 years, with BFMDRS-M score improved by 51% at 1 year and still maintained at 3 years (58%); in addition, mild long-term improvements in quality of life and attention were also observed [54, 57]. Another study of 23 patients reported that BFMDRS-M scores improved by 79.6% at 1 year and by 82.5% at 2 years, and these scores were maintained for up to 8 years postoperatively [55]. A retrospective study involving 44 patients drawn from five experienced DBS centers also showed BFMDRS improvement with DBS treatment, with 74.9% at 1 year and 82.6% at 3 years [56].

Patients with primary generalized or segmental dystonia who do not achieve sufficient relief with conservative approaches are best candidates for GPi DBS therapy. Those with cervical dystonia who have failed medical management are also good DBS candidates, whereas DBS is less effective in secondary dystonia patients with the exception of tardive dystonia [48]. Younger patients with shorter duration of disease may expect a better general outcome independent of the age of onset, severity of disease, early-onset primary dystonia status and the presence of phasic or tonic involuntary movements [56, 60].

### *Obsessive-Compulsive Disorder*

OCD is a chronic psychiatric disorder manifested by obsessional ideas, compulsive behaviors and repetitive rituals, with a prevalence of 1.2–2.3% [61]. Current treatment generally uses a combination of serotonin reuptake inhibitors and cognitive behavioral intervention. However, up to 40–60% of OCD patients are resistant to these treatments [62] and 20–40% will have persistent symptoms leading to chronic functional impairment [63]. For the highly refractory OCD patients, ablative neurosurgical stereotactic treatments have been attempted, and since the first report in 1999 by Nuttin et al. [64], DBS has also been investigated.

Surgical approaches for OCD treatment provide targets of subcaudate tractotomy, cingulotomy, limbic leucotomy and anterior capsulotomy for neuroablative surgery or tractotomy [65], but the optimal target for DBS still needs to be determined for the deficiency of a clearly elucidated pathophysiological mechanism of OCD disorder [66–68]. Potential targets for OCD DBS in previous reports included the anterior limb of the internal capsule, ventral capsule/ventral striatum, nucleus accumbens (NAc), STN and inferior thalamic peduncle [69]. Generally, two major targets have been studied: the anterior limb of the internal capsule extending to adjacent ventral striatum and the STN. The internal capsule was introduced by the first DBS for the OCD series [64], and long-term outcomes have shown promising effects using the anterior limb of the internal capsule [70, 71] and ventral capsule/ventral striatum [72] as the stimulating targets. STN as a stimulating target was inspired from beneficial effects of STN DBS observed in PD patients suffering from OCD as well [73, 74]. STN DBS may lessen the severity of OCD symptoms and improve global functioning, but serious complications like suicidal ideation should be cautioned [75]. Long-term effects of STN DBS for patients with OCD are yet to be determined.

### *Epilepsy*

Epilepsy is one of the most prevalent and disabling disorders characterized by recurrent unprovoked seizures, affecting 0.5–1% of the population annually [76]. Over 30% of the cases are pharmacoresistant, and they currently have relatively limited alternative treatment options such as resection [77] and vagus nerve stimulation [78]. Since the pioneering study by Cooper et al. [79] to influence epilepsy by cerebellar DBS in the early 1970s, the efficacy of DBS in the treatment of intractable epilepsy has been increasingly investigated. Up to now, DBS has been applied to several efficient targets [80] including the cerebellum, caudate nucleus, centromedian thalamus, anterior thalamus, STN and hippocampus, among which only DBS of the anterior thalamus now has class I evidence. It has favorable results from the SANTE (Stimulation of the Anterior Nucleus of Thalamus for Epilepsy) trial supporting its use and is approved by the European Union for treating epilepsy [81]. Typical settings for stimulation are 1–10 V with 90  $\mu$ s pulses in trains of 100–165 Hz, running either continuously or 1 min on and 5 min off, but which can be reprogrammed to maximize clinical affect and minimize side effects [82]. Overall, DBS therapy is quite promising for reduction in seizure in patients with partial seizures and medically refractory epilepsy.

### *Chronic Pain*

The main applications for DBS during the 70s and 80s were actually for chronic pain [83]. For over half a century, DBS has proven effective for treating a variety of neuropathic and nociceptive pain states that are not responsive to other neuromodulation techniques, including cluster headaches, chronic low back pain, failed back surgery syndrome, peripheral neuropathic pain, facial deafferentation pain and pain that is secondary to brachial plexus avulsion [84]. Benefit varies depending on the etiology, length of follow-up, definition of adequate pain relief and the site of stimulation [85]. Stimulation sites included the periventricular/periaqueductal grey matter [86], the internal capsule [87], the sensory thalamus [88] and the posterior hypothalamus [89]. The use of periventricular/periaqueductal grey matter stimulation is generally recommended for nociceptive pain and sensory thalamus DBS for deafferentation pain [90], whereas DBS of the posterior hypothalamus is an effective approach to treat refractory chronic cluster headache [91]. A meta-analysis was performed to determine the long-term efficacy of DBS in the treatment of chronic pain and found that the long-term success rate ranged from 19 to 79% with a downward tendency as the length of follow-up increases [85]. Therefore, despite evidence of efficacy [92], DBS remains off-label and investigated.



### *Depression*

Major depressive disorder as a widely distributed illness is presented with a lifetime prevalence rate of more than 12% in men and 20% in women [93]. Up to 20% are treatment-resistant depression (TRD), which has prompted the investigation of alternative treatment strategies. The initiate study of DBS in the treatment of TRD found that chronic stimulation of the subgenual cingulate white matter improved mood in 4 of 6 patients [94]. Likewise, another target located in the subcallosal cingulate gyrus has provided sustained benefit for DBS treatment of TRD with a mean reduction in the Hamilton Depression Rating Scale of 52% after 1 year [95, 96]. Kennedy et al. [97] demonstrated that DBS to the same area remained a safe and effective treatment for TRD after 3–6 years of follow-up. A single case report suggested the inferior thalamic peduncle was also an efficient target to relieve depressive symptoms [98]. In addition, the caudate nucleus [99], ventral capsule/ventral striatum area [100], NAc [101] and lateral habenula [102] have been suggested as effective DBS targets for TRD. Overall, DBS is a promising but experimental therapy for TRD and should only be administered by multidisciplinary teams.

### *Tourette Syndrome*

TS is a childhood-onset neuropsychiatric disorder with a prevalence of nearly 1% for children worldwide [103]. It is typically characterized by multiple physical (motor) and at least one phonic (vocal) tics lasting longer than 1 year. Despite a wide therapeutic spectrum, severely affected patients respond poorly to medication. Several series have reported on the effectiveness of DBS for TS treatment, and at the present time, DBS is recommended only in adult, treatment-resistant and severely affected patients [104].

The centromedial parafascicular complex of the thalamus has been the first and remains the most used target for the treatment of intractable TS by DBS [105–108]. Since then, other targets, including the GPi (the posteroventrolateral and the anteromedial part) [105, 108], the STN [109], the crosspoint of the thalamic centromedian nucleus-substantia periventricularis-nucleus ventrooralis internus [110], the NAc [111] and the anterior limb of the internal capsule [112] have been used, or a combination of different targets [113]. However, data were insufficient to determine whether one of these targets is superior to another since all targets belong to the ventral striatal-thalamo-cortical circuitries, which are thought to be dysfunctional in TS. Besides, all patients have had some degree of tic reduction with DBS in these targets.

### *Huntington's Disease*

Huntington's disease is an autosomal dominant disease which produces debilitating motor abnormalities that are poorly responsive to medical therapy. Moro et al. [114] reported the first case study showing that bilateral GPi DBS has the potential to improve chorea without aggravating bradykinesia. Other case reports further investigated the long-term effects and showed a sustained alleviation of Huntington's disease-associated choreoathetosis [115, 116], while it may cause deterioration in motor function and cognition [117]. With these few clinical reports, the precise selection criteria and optimal stimulation parameters remain to be further defined.

### *Obesity and Addictions*

Obesity is a growing health problem worldwide and DBS has been used in obese patients [118]. The primary DBS attempted to modulate the homeostatic mechanisms of weight control (the satiety center of the ventromedial hypothalamus and the feeding center of the lateral hypothalamus) but gained limited success [119, 120]. Other authors have proposed regions of the brain's reward circuitry, such as the NAc, as promising alternatives for DBS in

obesity control [121]. Specifically, low-frequency stimulation (50 Hz) led to initial weight loss but was followed by regaining of the weight [122]. One analysis has suggested that DBS must achieve a success rate of 83% to be equivalent to bariatric surgery [123]. Interestingly, obesity was also observed as a complication in PD patients after they underwent STN DBS [124]. Besides obesity, smoking, alcoholism and other drug addictions have been reported to improve after NAc DBS [125–127].

#### *Alzheimer's Disease*

AD is an increasingly prevalent degenerative disorder causing a range of progressive neuropsychiatric symptoms and cognitive deficits [128]. Due to the limited effectiveness of current treatment, novel therapeutic approaches are needed. Hamani et al. [122] observed memory enhancement in a patient who underwent fornix/hypothalamus DBS for obesity. This gives impetus to a phase I trial of DBS in 6 patients with mild AD, which found possible improvements or slowing in the rate of cognitive decline at 6 and 12 months after DBS; in addition, increased glucose metabolism was observed in the temporal and parietal cortical areas both at the 1-month and 1-year follow-up [129]. Another open-label trial involving 5 mild AD patients also found persistent cortical metabolic increases after 1 year of DBS that were associated with better clinical outcomes, providing evidence that DBS resulted in changes to neural circuitry and enhanced functional connectivity; these results were more effective than pharmacotherapy in AD [130]. Given the destructive nature of AD and cognitive improvements of DBS therapy, future studies investigating the appliance of DBS to treat AD are warranted.

#### *Consciousness Disorders*

Severe traumatic brain injury is a leading cause of persistent vegetative state or minimally conscious state as a result of widespread deafferentation and compression injuries to the thalamus and midbrain [131]. Consideration of thalamic DBS to treat patients with severe disorders of consciousness has a long history and has been proved to improve cognitive functioning and behavioral responsiveness in recent studies [132, 133]. DBS for consciousness disorders can be appreciated as a potential option for future clinical research, albeit its off-label status [134].

### **Adverse Effects**

Adverse effects of DBS consist of a wide variety of accurate or chronic neurological and neuropsychological complications such as those related to surgery, hardware and stimulation. The major surgery-related risk is intracranial hemorrhage. A recent extensive review suggests that the overall incidence of hemorrhage was 5.0%, with symptomatic hemorrhage occurring in 2.1% of patients and hemorrhage resulting in permanent neurological deficit or death in 1.1% [135]. Postoperative seizures have also been reported and generally occur within 48 h of surgery [136], with an estimated incidence of 2.4% [137]. The most common hardware complications include infections, electrode migrations or misplacements, wire fractures, skin erosion and device malfunction [138], and the rate varies greatly between different centers, ranging from 4.3 to 17.8% [139–143]. Infections are the most reported hardware complications [144], which often require device removal and a period of antibiotic treatment before consideration for device replacement [145]. Surgery- and hardware-related complications could generally be reduced with increased surgical experience and the introduction of new surgical equipment and technology. Stimulation-related adverse effects include muscle contractions, dysarthria, ocular deviations, tremor, dyskinesia, headache,

pain and paresthesias, which are very useful during intraoperative target exploration and can often be ameliorated by adjustment of stimulation settings or discontinuation of therapy [146]. Verbal fluency is the most common cognitive adverse effect of STN DBS, owing to the effect of surgical electrode implantation rather than stimulation-induced interference [39]. Chronic changes like mania, depression, apathy, panic, impulsivity, anxiety, hallucinations, and even suicidal ideation, are probably multifactored by medication changes, neuronal plasticity following DBS, adaptation difficulties and dramatic sociofamilial modification induced by the motor effects of DBS; they should be screened and managed by a multidisciplinary approach [147].

In general, DBS is a relatively safe approach associated with an encouragingly low rate of adverse effects, which is an effective therapeutic option to assist in a multitude of otherwise treatment-resistant neurological diseases.

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