# Current Applications of Deep Brain Stimulation for Treatment of Neurological and Psychiatric Disorders

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**Summary.** Deep Brain Stimulation (DBS) seems to be an effective and minimally invasive surgical treatment for a variety of neurological and psychiatric disorders. In comparison to early surgical lesioning procedures, DBS has a considerably lower adverse effect rate and is usually reversible, making this procedure very attractive. Despite the clinical success of DBS, the exact therapeutic mechanism remains under active debate. Current clinical trials focus on identification of alternative targets, establishing new indications and capturing electrical biomarkers during DBS in order to improve individual stimulation parameters. In this article we provide a comprehensive review of DBS focusing on movement, psychiatric and ictal disorders, including the historical evolution of the technique, applications and outcomes with an overview of the most pertinent literature, current views on mechanisms of stimulation and description of hardware and programming techniques. Finally, we conclude with a discussion of potential future applications of neurostimulation and currently active topics of research.

**Keywords:** deep brain stimulation, Parkinson disease, tremor, dystonia, depression, Tourette syndrome, obsessive-compulsive disorder, epilepsy, treatment.

Neurologijos seminarai 2017; 21(74): 201–207

## INTRODUCTION

Deep brain stimulation (DBS) is a surgical procedure that involves unilateral or bilateral implantation of electrodes in a specific area of the brain. Electrodes are connected to wires which deliver a very fine electrical current to those regions in the brain from the generator placed inferiorly to the clavicle, under the skin. After recovery of the procedure, generators are activated and electrical parameters including pulse widths, current amplitudes and patterns of stimulation are tuned individually for each patient, hence desired clinical effect can be achieved. DBS in fact is an evolution of functional stereotactic neurosurgery techniques, initially used to produce selective lesions of specific deep brain structures. Formerly, intra-operative electrical stimulation of these targets was systematically used for the exploration and the localization of the deep cerebral nuclei and for target confirmation, but these observations led to suggestion that electrical stimulation method could not only be used for diagnostic purposes but also as a therapeutic method itself [1]. DBS is applied to a wide range of neurological and psychiatric disorders, including Parkinson's disease, essential tremor, dystonia, obsessive-compulsive disorder, treatment-resistant depression, Tourette syndrome, and epilepsy [2, 3]. The exact physiological mechanism of DBS remains unknown. Current theories include inhibition, excitation or disruption theory but to this day it is known that stimulation of certain groups of neurons in the brain stops pathological pattern of neuronal activity [4]. DBS is contraindicated for patients who have inability to operate the device or if test stimulation was unsuccessful. There is a potential for neuropsychiatric side-effects including depression, cognitive dysfunction, apathy, hallucinations or euphoria, but usually it is a consequence of poorly calibrated stimulation pattern or wrong site of implantation [5]. Additional limitations of DBS therapy that need to be considered prior to the surgery include risk for intracranial hemorrhage (in approximately 3% of all cases), electrode misplacement (in up to 2%), electrode migration (up to 1.7%) and electrode lead infection (1 to 8%) [3]. Nonetheless, principal feature of DBS attractiveness is that in case of undesired side effects it can be reversed at any time during the period of application, bringing patient back to pre-operational condition.

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## MECHANISM OF DBS

Although an effective surgical therapy for neurological and psychiatric disorders, the mechanism of action of DBS continues to be debated. The earliest hypotheses on DBS mechanisms proposed that high-frequency stimulation inhibits neurons and decreases output from the stimulated site. Inhibition of activity was initially observed in rat STN DBS and similar findings were replicated in humans and monkeys with either STN or GPI stimulation [6, 7]. It was hypothesised that the underlying inhibitory mechanism was an activation of presynaptic inhibitory afferents. Similar findings were seen with inhibitory efferents. GPI stimulation inhibited thalamic neurons in normal monkeys and patients with dystonia, and external globus pallidus stimulation inhibited STN neurons [8, 9]. Human positron emission tomography studies showed an increase in blood flow in the region of the GPI during STN DBS and an increase in cortical blood flow during thalamic DBS, both consistent with activation of output from the stimulated site [10, 11]. Similarly, a functional magnetic resonance imaging study showed an increase of blood oxygen level–dependent signal in the GPI of patients undergoing STN DBS [12]. Recent studies have shown that DBS-induced regularization of basal ganglia input into the thalamus restores the responsiveness of thalamocortical cells to the incoming sensorimotor information, resulting in improved motor function. This suggests that information processing is enhanced and DBS is associated with improved information content in the network [13]. Also, stimulation of the STN can activate nigrostriatal (increasing release of dopamine), pallidothalamic, cerebellothalamic, and pallidonigral fiber tracts, all of which could contribute to the therapeutic effects of DBS [14]. So, DBS increases output from the stimulated nucleus and activates surrounding fiber pathways resulting in a complex pattern of excitatory and inhibitory effects that modulate the entire basal ganglia-thalamocortical network. The stimulation-induced regularization of neuronal patterns prevents transmission of pathologic bursting and oscillatory activity within the network, resulting in improved processing of sensorimotor information and reduction of disease symptoms.

## APPLICATION OF DBS FOR PARKINSON'S DISEASE

One of the primary clinical uses of DBS is for the treatment of Parkinson's disease (PD). PD is a progressive neurodegenerative disorder characterized by tremor at rest, rigidity, bradykinesia, stooped posture, loss of postural reflexes and shuffling gait. Pathophysiology of PD could be characterised as prominent degeneration of dopaminergic neurons in substantia nigra *pars compacta* and the consequent deficiency of dopamine in brain areas that receive dopaminergic inputs from those neurons, specifically the post-commissural putamen and caudate nucleus. Loss of dopaminergic cells in substantia nigra causes failure of basal ganglia's direct pathway to successfully inhibit globus pallidus internus and this leads to over inhibition of thalamus and thalamocortical pathway [15]. Conventional treatment for Parkinson's Disease symptoms include Levodopa, COMT inhibitors, dopamine agonist and other medication, but long-term use of these pharmaceuticals leads to drug-induced motor complications. A powerful motor response to Levodopa is generally considered as essential for successful DBS outcome (except for tremor-predominant form), and stimulation may be considered when patients develop motor fluctuations and dyskinesias. Studies of DBS for PD have reported significant improvement in cardinal motor signs, including tremor, bradykinesia, and rigidity, and variable response in medication-refractory gait freezing, postural instability, and gait mechanics. Also, marked benefits in improvement of levodopa-related complications such as drug-induced dyskinesia, motor fluctuations and off-period dystonia have been demonstrated [16]. DBS for PD at this day is mainly applied to two parts of basal ganglia: subthalamic nuclei (STN) and globus pallidus internus (GPI). Electrode placement in the STN was initially favoured because of reports that it yielded greater improvement in motor scores and a greater reduction in antiparkinsonian mediations compared with placement in the GPI [17]. Additional studies have shown that GPI DBS also significantly improved the cardinal motor symptoms, drug-induced dyskinesia, and motor fluctuations [18]. Although STN remains the preferred target, GPI can be considered in patients who have speech, cognitive, and mood disturbances, as STN DBS can sometimes worsen these symptoms [19]. In study of 299 randomly assigned patients (152 pallidal and 147 subthalamic), deep-brain stimulation improved motor function in patients with Parkinson's disease who underwent either pallidal or subthalamic stimulation, with no significant difference between the two surgical targets during 24 months of follow-up [20]. DBS treatment both in long and short term is superior to the conventional treatment options in patients with advanced PD [21].

## APPLICATION OF DBS FOR TREMOR

DBS is an attractive alternative to conventional treatment for the management of tremor. Essential tremor is mainly treated with antiepileptic Primidone or beta blocker Propranolol. Both medicines improve condition in 50–70% of patients, but their use is limited because of adverse effects that include sedation, dizziness, ataxia (for Primidone) and bradychardia, bronchospasms and hypotension (for Propranolol) [22]. In comparison to pharmaceutical approach, DBS shows better results but it is not so significant to state that either method is superior to each other [23]. Surgical ablation of the ventral intermediate nucleus of the thalamus (VIN) has been used as a therapy for tremor since the 1950s [24]. Both bilateral and unilateral

DBS of VIN in study of 34 individuals showed a significant long term (up to 7 years) improvement of symptoms in >80% of patients [25]. Bilateral VIN stimulation shows slightly better outcomes, especially managing head and voice tremor [3]. However, bilateral thalamotomy is not well tolerated because of the risk of speech and swallowing deficits. Thalamic DBS has been shown to be efficacious in the treatment of essential and parkinsonian tremor, with an excellent long-term outcomes and an acceptable adverse effect profile. The main side effects of the stimulation were paresthesias, headache, dysarthria, paresis, gait disturbance, and ataxia but these adverse reactions are usually mild and effectively managed by stimulation parameter adjustment [26]. Deep brain stimulation and thalamotomy have also been used with less success in the treatment of action tremor. This type of tremor typically occurs in patients with multiple sclerosis, trauma, or stroke that leads to interruption of cerebellar outflow pathways and has a more complex pathophysiology [27]. Clinical improvement in these patients is often short lived and, in the case of multiple sclerosis, complicated by disease progression [28]. Although treatment for tremor targets the ventral intermediate nucleus, several studies have suggested that the posterior subthalamic area is a better location and that patients may be incidentally benefiting from electrode contacts located outside of the thalamus [29]. Overall, DBS for essential and parkinsonian tremor has been successful, while treatment of other causes of tremor has been more limited.

## APPLICATION OF DBS FOR DYSTONIA

DBS has also shown success in treatment of dystonia. Dystonia is a group of neurological disorders described by sustained or intermittent muscle contractions causing twisting and repetitive movements that result in abnormal, often painful postures. Dystonia can be classified according to etiology (primary or secondary), location affected (generalised or segmental) and time of onset (early or late) [30]. Patients with dystonia are thought to have malfunctioning connections between subcortical and cortical pathways resulting in a reduced activity of the globus pallidus internus of basal ganglia with already observable reduction in activity during resting state. When movement is attempted, the efferent inhibiting neurons of the GPI further reduce their activity, leading to a disinhibition of the thalamus thus causing dystonic movements [31]. Pharmaceutical treatment of dystonia with injections of botulinum toxin or anticholinergics is not always working and if drug therapy is unsatisfactory, surgical approach with favourable risk-benefit ratio is worth investigation [32]. Renewed interest in pallidotomy for PD in the early 1990s and the observation that it improved dystonic symptoms in PD led to the proposal of using pallidotomy for patients with primary generalized dystonia [33]. DBS could be applied for primary generalised and segmental dystonia, which both respond better to stimulation than secondary dystonia [34]. Unlike tremor and PD, there is typically a gradually increasing clinical response to stimulation over weeks to months of therapy. Efficacy of DBS in primary generalized and segmental dystonia has been well documented [35]. Optimal site of implantation at this day is thought to be globus pallidus internus [32, 35]. Pallidal neurostimulation study of 22 adult patients showed significant improvement in primary dystonia involving neck, trunk and limbs, but facial and speech aspects of disease were not affected [32]. The same 22 subjects were re-evaluated after 3 years and results showed sustained motor benefit of intervention [36]. Other study of 40 adult subjects, who were split into 2 groups of 20 people (one group receiving pallidal stimulation and other – sham stimulation) showed significantly better outcomes in patients receiving neurostimulation, nevertheless sham group after 3 months was assigned to neurostimulation and showed similar positive results in a 6 months follow-up [35]. Also, a beneficial effect of bilateral stimulation of the GPI has been reported in children with primary generalized dystonia, however, there has been no difference in outcomes based on DYT1 gene status but shorter disease duration has been related to better results [37, 38]. In addition, intractable cervical dystonia has also shown improvement in several smaller case series [39]. On the other hand, secondary dystonia is a set of heterogenous disorders and their response to neurostimulation is more variable. For example, tardive dyskinesias typically respond well whereas dystonias secondary to encephalitis or birth injury fare worse [40].

## APPLICATION OF DBS FOR OBSESSIVE-COMPULSIVE DISORDER (OCD)

Obsessive-compulsive disorder is characterised by intrusive thoughts or images (obsessions), which increase anxiety, and by repetitive or ritualistic actions (compulsions), which decrease anxiety. OCD is linked with neurochemical and neuroanatomical abnormalities in the brain. Structurally, basal ganglia (with increase of grey matter) and orbitofrontal/cingulate cortex (with decrease of grey matter) are thought to be defective causing cortico-striatal-thalamic-cortical pathway dysfunction [41]. Seratonin system seems to be involved as well since the selective serotonin reuptake inhibitors (SSRi) are the effective treatment for OCD [42]. Unlike movement disorders, pathophysiology of psychological disorders is more complex thus there are more potential targets for DBS. Traditional treatment of OCD involves combination of medication and psychotherapy but in severe, treatment-resistant cases, neurostimulation can provide desirable effects for the patients. Popular choices of DBS include: anterior limb of internal capsule, ventral capsule and ventral striatum, nucleus accumbens, STN and inferior thalamic peduncle with all of them showing promising results therefore it is hard to exclude superior target [43].

## APPLICATION OF DBS FOR TREATMENT- RESISTANT MAJOR DEPRESSION

Combination of genetics and environmental factors, such as childhood trauma or alcohol abuse, plays a critical role in development of depression [44]. Major depressive disorder (MMD) is a medical condition that includes abnormalities of mood and motivation, neurovegetative functions, cognition, and psychomotor activity that last longer than 2 weeks [45]. Functional magnetic resonance imaging (fMRI) studies showed that there is abnormal activity in the cingulate cortex, ventral striatum and dorsomedial orbital cortex in patients with MMD [46, 47].Traditional treatment for depression involves medication, psychotherapy and electroconvulsive therapy, but approximately 20% of depression cases are treatment-resistant [48]. In such cases, DBS could be applied as a next line treatment option. As in OCD, there are few potential targets for neurostimulation, including: subgenual cingulate (Brodmann area 25), nucleus accumbens and ventral capsule/ventral striatum with all regions responding with 50–80% of success, subgenual cingulate seeming to be superior in comparison with other targets [49–51].

## APPLICATION OF DBS FOR TOURETTE SYNDROME

Tourette syndrome (TS) is characterised by quick, nonrhythmic movements or vocalizations which patient has little or no control over, called tics. Rather than a distinct condition, TS is defined as a part of spectrum of tics disorders, being most severe of them. Etiology of TS is unknown, it seems that genetic factors play a key role while causing the disorder, although the exact type of inheritance and causative genes have not yet been identified. Additionally, both prenatal and postnatal environmental influences, such as maternal smoking/stress or certain infections, are more related to severity of TS rather than being causative factor [52]. Still pathophysiology remains uncertain, with most recent hypotheses involving dysfunction of basal ganglia-cerebellar-thalamo-cortical circuit and striatal GABAergic networks, eventually leading to excess dopaminergic input to striatum that causes undesirable disinhibition of thalamo-cortical pathways, producing tics [53, 54]. While most of cases can be controlled by medication and/or behavioral therapy, subsets of them are treatment-resistant and DBS is showing promising results for such patients. Recent meta-analysis involving 57 studies reporting total of 162 participants showed mean 52.5% improvement according to Yale Global Tics Severity Scale (YGTSS) with more than 80% participants showing >25% reduction of YGTSS score. Several potential stimulation targets exist and it is hard to exclude the ideal one. From systematic review data, both posteroventrolateral and anteromedial parts of globus pallidus internus demonstrated best average (58% and 55%, respectively) decrease in YGTSS grade, while thalamic nuclei (48%) and anterior limb of internal capsule/nucleus accumbens (44%) neurostimulation indicated slightly worse results [55]. Nevertheless, the patient numbers are too small to draw any concluding answer, yet regarding the dilemma of ideal target and optimal results may be achieved by carefully assessing each individual case.

## APPLICATION OF DBS FOR EPILEPSY

Conventional epilepsy treatment is often based on daily use of antiepileptic drugs of which there are wide variety of options available that have different targets in the brain and the choice is based on specific needs of the patients, such as age, lifestyle, other health problems and a category of epilepsy syndrome. Despite medication, epilepsy surgery, vagus nerve stimulation and ketogenic diet are also considered as a potential treatment options, but about 30% of epilepsy cases are treatment-resistant [56]. In such refractory epilepsy cases, DBS could be considered as a next step intervention. There are several potential targets for neurostimulation application, but anterior nuclei of thalamus (ANT) are most well investigated and show promising results. One prominent multicenter study involving 110 participants with medically refractory partial seizures, including secondarily generalized seizures showed an average 40.4% reduction of seizures frequency after 3 months randomized, double-blinded phase in comparison with 14.5% reduction for patients receiving sham stimulation. After blinded phase, all participants received the stimulation and after 2 years there was a mean 56% reduction in seizure frequency with 14 patients being seizure-free for at least 6 months [57]. Another study involving 15 patients with poorly controlled seizures assessed effectiveness of ANT stimulation with evaluation of progress in long-term and compared the outcome with previously described trial. Results of this study indicated an average 70.4% reduction in frequency of the seizures with a mean total amount of follow-ups being 39 months since the start of stimulation. This suggests that a short-term outcome of ANT DBS directly reflects long-term effectiveness of the treatment [58]. Anterior nuclei of thalamus are located in a key junction of Papez circuit which is believed to be involved in propogation of seizures while on the same hand anatomical position is relatively easy to reach with minimal risk of surgical complications following electrodes implantation, making it very attractive for DBS. Another potential targets for DBS application for epilepsy include cerebellum, hippocampus, subthalamic nucleus, caudate nucleus, corpus callosum and locus coeruleus, all of which showed improvement regarding epileptic seizures control but further investigation is necessary since population of studies was very small [59].

## FUTURE APPLICATIONS OF DBS

The potentials of the DBS for therapeutic use are fascinating, but there are still many unresolved technical and ethical problems, concerning the identification of the targets for each condition, the patient selection and the evaluation of the results. Even though DBS is becoming more and more popular in clinical setting, poor understanding of physiological and therapeutic mechanism following neurostimulation remains the main limitation in further development of this technique. Fortunately, promising attempts to explain these complex processes are being made. One study showed that DBS in PD not only affects local circuit of basal ganglia but also has diffuse modulatory effect on cortical activity by influencing phase-amplitude coupling (PAC) which is thought to be a communication link between different brain regions and is responsible for the coordinated neuronal activity in different brain networks. During active stimulation of STN, PAC seemed to be reduced, similarly reducing parkinsonian motor signs, proposing that DBS of the basal ganglia improves cortical function by suppressing excessive beta phase locking of primary motor cortex neurons [60]. Interestingly, these abnormally active neurons could be used as electrical biomarkers of the disease and identification of such abnormal neuronal activity by local potential recording lead has opened the possibility for DBS devices to deliver "responsive" stimulation, in which the parameters of neurostimulation self-adjust as necessary in real-time based on recorded electrical biomarkers activity. This adaptive DBS is capable of delivering treatment that can be individualized based on patient and pathology status, thus providing more efficient therapeutic benefit with smaller amount of adverse effects and increased battery longevity. Similarly, stimulator firmware improvement may facilitate delivery of different pulses in different pulse shapes which could further improve adaptive DBS application in patient-personalized approach [61]. To continue, future DBS application should aim at the management of symptoms that are disabling and yet not treated effectively using current medical and surgical methods. Levodopa-resistant signs and symptoms such as gait and postural instability, different types of aphasia, decreased level of consciousness and cognitive or affective dysfunction are of particular importance and further advances in DBS may eliminate current limitations in treatment of these debilitating conditions. Further research is needed to expand our understanding of the physiological changes in the brain resulting from the combination of disease and electrical stimulation.

## CONCLUSION

Despite the fact that the exact underlying mechanisms of DBS remain unknown, it can be successfully applied as a long lasting and modifiable treatment for motor, psychiatric and epileptic disorders; nonetheless, the procedure also shows its efficacy for chronic pain, obesity, addictions and even recovery after traumatic brain injury [15]. Field of DBS is currently under active research and uncovering physiological mechanisms of neurostimulation might lead to wider and more reliable application of the procedure.

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## GILIOSIOS SMEGENŲ STIMULIACIJOS TAIKYMAS GYDANT NEUROLOGINIUS IR PSICHIATRINIUS SUTRIKIMUS

**Santrauka**

Gilioji smegenų stimuliacija (GSS) yra efektyvus ir plačiai naudojamas metodas gydant įvairius neurologinius ir psichiatrinius susirgimus. Lyginant su kitomis chirurginėmis procedūromis, GSS turi akivaizdžių pranašumų – daug retesnius šalutinius poveikius, yra minimaliai invazyvi, grįžtama ir nedestrukcinė operacija. Nepaisant didelio efektyvumo ir besiplečiančio naudojimo klinikinėje praktikoje, GSS mechanizmas iki šiol išlieka neaiškus. Atliekami klinikiniai GSS tyrimai daug dėmesio skiria naujų taikinių paieškai, procedūros indikacijų nustatymui ir elektrinių biomarkerių identifikacijai, kuri padėtų koreguoti stimuliacijos parametrus pagal individualią paciento būklę. Šiame straipsnyje išsamiai apžvelgiamas GSS metodas, akcentuojant jo panaudojimą motoriniams, psichiatriniams ir epilepsiniams sutrikimams gydyti, istorinę šios technikos raidą, galimą taikymą, išeitis ir potencialias ateities perspektyvas, remiantis naujausiais literatūros šaltiniais.

**Raktažodžiai:** gilioji smegenų stimuliacija, Parkinsono liga, tremoras, distonija, depresija, Tureto sindromas, obsesinis kompulsinis sutrikimas, epilepsija, gydymas.

Gauta: 2017 09 02 Priimta spaudai: 2017 09 22