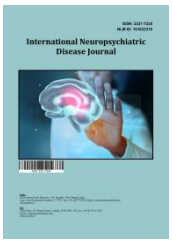

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Deep Brain Stimulation-Emerging Indications and Newer Techniques: A Current Perspective

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Deep brain stimulation (DBS) is in clinical use for more than three decades and its indications are ever expanding. Conventionally DBS is used in the treatment of Parkinson's disease (PD), tremor and dystonia, and has been approved by FDA. It has been tried in several other indications with encouraging results. Recently a DBS device has been approved for use in intractable epilepsy. DBS is giving promising results for use in obesity, trigeminal vascular cephalalgias, and Tourette syndrome and post stroke rehabilitation. Many psychiatric conditions like depression, obsessive compulsive disorder, anorexia nervosa and substance abuse can be controlled with DBS when conventional medical treatment fails to relieve the symptoms. Newer techniques in DBS like directional leads, variable frequency stimulation, newer target identifications, Newer MRI compatible devices, remote programming, newer DBS recording electrodes that can be used in finding out the pathophysiology of disease is also discussed.

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1. INTRODUCTION

Deep brain stimulation (DBS) is a neurosurgical procedure where battery operated neurostimultator are surgically implanted. Many neurological disorders are due to the electrical signals in the brain that are disorganised. The DBS electrodes are stimulated electrically to target areas in brain by pulse generator placed in the chest that can interrupt the irregular brain signals.

DBS has 3 main components

1) LEAD - thin insulated wire inserted through skull opening to be implanted in brain. It's placed in the desired target area of the brain.
2) EXTENSION: an insulated neurostimulator wire that is placed beneath the skin extending from the head, neck and shoulder connecting to the neurostimulator.
3) NEUROSTIMULATOR- stimulator that is battery operated implanted under the skin near the clavicle, or lower part of the chest or upper part of abdomen. This generates electrical stimulation that is delivered to the target areas of the brain through the DBS leads.

Deep brain stimulation (DBS) has emerged as a great modality of treatment for long term management of several neurological disorders particularly Parkinsons disease. It has been in use for more than three decades. The advanced knowledge of the neuronal networks of the brain with its relation to neurological and psychiatric disorders has led to the ever-emerging newer indications and success stories. The advancement in science and technology has further revolutionized this surgical procedure like the recent robotic targeting, directional and perceptional leads and remote programming devices.

In 1987, use of high frequency stimulation of VIM resulted in marked improvement in tremor. The same year showed many further beneficial results with stimulation of advanced GPi. The breakthrough treatment of DBS in advanced Parkinsons was reported by Benabid et al in 1991 [1].

Since then the Food and Drug administration has subsequently approved DBS for neurological disorders like tremors, early and advanced Parkinsons Disease, dystonia. The non motor effects of subthalamic nucleus DBS led to the application of DBS for varied psychiatric illness.

2. CONVENTIONAL INDICATIONS OF DBS

2.1 Parkinsons Disease

DBS has shown its striking benefits by improving the quality of life in Parkinsons. DBS have been particularly advisable for patients with suboptimal response to adequate medical therapy. Remarkable improvement has been seen in patients with advanced stages, in particular those who are highly disabled with motor and non-motor symptoms. Marked improvement have been noticed for those disabled by tremors, motor fluctuations and dyskinesia due to drugs. Researches have shown benefit for at least a time period of 5 years. DBS of STN and GPI were the target for successful results. Marked improvement was noticed for motor symptoms.

DBS for sustained tremor was first used by Irvine Cooper in 1963. It was Benabid and his colleagues who revolutionized DBS and his works invariably improved the use of neurosurgical procedures.

In 1997, DBS was first approved for the tremors in Parkinsons. By 2002, DBS was approved for all advanced symptoms' of Parkinsons. In 2016, DBS was even accepted for early cases of Parkinsons non responding to initial drug therapy.

DBS is not a cure and is not advisable for every patient with Parkinsons. Success of DBS is hugely dependent on the right patient selection. The patient selection for DBS in Parkinsons is based on the German guidelines [2].

1. Presence of motor fluctuations including levodopa-sensitive off symptoms or treatment-induced dyskinesia.
2. Tremor not responding satisfactorily with medication.
3. A levodopa-induced reduction of motor symptoms by more than 33% of the Unified Parkinson Disease Rating Scale (UPDRS), where tremor may be disregarded from the

calculation as it may be refractory to levodopa treatment while still responding well to DBS.

Exclusion of dementia, relevant psychiatric or somatic comorbidity, or general contraindication to undergo neurosurgery.

The target areas for DBS are decided based on the functional anatomy of the selected brain circuits and the relation with behaviour. Stimulation of ventral intermediate nucleus of thalamus is mainly for tremors of Parkinsons.

Stimulation of subthalamic nucleus or internal segment of the globus pallidus – decrease bradykinesia, rigidity, tremors and gait problems. Despite the benefits, there has been a limitation for its acceptance because of the cost, adverse effects and partial efficacy.

2.2 Tremor

DBS to the ventral intermediate nucleus of thalamus has replaced the conventional thalamotomy for drug resistant patients who suffer from disabling tremors. In fact, the very initial FDA approved indication of DBS in 1997 [3] was for essential tremor.

Researches points out to 50% of patients with essential tremors develop drug resistant tremors [4]. For this subset of patient, VIM thalamotomy which was the earlier preferred surgical treatment has been replaced by DBS because of significantly reduced side effects. The availability to perform bilateral DBS during one operative period is an added advantage.

Unilateral VIM can cause significant improvement in head and voice tremor. However, for proper control bilateral stimulation is essential. Despite the benefits certain neurological deficits, in particular related to gait and speech have been associated with DBS [5].

DBS proves a better response in distal tremors. The tremor severity is assessed by tremor rating scales like Fahn-Tolosa-Marin and the moderate to severe tremors are mainly indicated for surgery.

DBS response is seen at its best in appendicular tremors [6]. The frequency of 100-180 hz has been studied to have maximal beneficial effect [7]. Stimulation below the intercommissural line has proved to be more efficient compared to thalamic stimulus [8]. Novel researches have shown promising results with DBS in posterior subthalamic area (PSA) for proximal postural tremor, distal intentional tremor and some cerebellar outflow tremors that are otherwise hard to be well controlled by the VIM DBS [9].

2.3 Dystonia

2.3.1 Cervical dystonia

Globus pallidus Internus(GPi) & sub thalamic nucleus (STN) Deep brain stimulation has offered a promising alternative for cervical dystonia not adequately controlled with pharmacotherapy and botulinum toxin injections [10].

E Moro from Toronto reported 56.7% improvement in Toronto Western Spasmodic Torticollis Rating scale (TWSTRS) compared to baseline after mean 28 months following bilateral GPi–DBS [11].

There was also improvement noticed in TWSTRS disability score (41%), Tsui score (63%), Brain tremor score (61%). However not much improvement with quality of life was noticed in these studies. Few studies have reported following GPi DBS , subtle bradykinesia that begin in body parts which were earlier non-dystonic. However, many studies have also disproved this except for minor transient dyskinetic movements that occurred during the stimulation [10].

2.3.2 Other dystonia's

Improvement in clinical symptoms of dystonia with medical therapy is often unsatisfactory. Better outcomes have been reported following surgical approach like thalamotomy, pallidotomy and DBS.FDA approved the use of DBS for dystonia in 2003. Alterman et al. [12] reported the significant correlation between age and outcome of DBS with those younger than 21 years presented a 97% median improvement while above 21 years had only 69% improvement in Burke–Fahn–Marsden dystonia (BFMDRS – M) rating at the end of 1 year following bilateral GPi DBS.

A negative correlation between duration of symptoms and improvement of symptoms post DBS was observed [13].

Selection criteria of candidates appropriate to DBS had a great impact on the disease outcome post DBS. Review by European Task Force suggested brain imaging is necessary prior to the DBS to identify whether the dystonia is primary or secondary where the former has been reported to have higher success rates [14].

Those with fixed skeletal deformities also tend to have less favorable outcome after DBS [15].

Patients need to be screened for any psychiatric comorbidities like suicidal attempts and depression as severity of any of these symptoms could be a contraindication to DBS. However, any slight structural abnormalities in the basal ganglia are not a contraindication for DBS. The inclusion criteria for DBS are disabling motor symptoms, severe pain, impairment in activities of daily living (ADL), and symptom progression despite adequate medical treatment [16].

Phasic hyperkinetic movements have reported to show a faster response with DBS than tonic or fixed postures [16].

3. NON-CONVENTIONAL INDICATIONS OF DBS

3.1 Tourette's Syndrome

Deep brain stimulation has emerged as a positive treatment therapy for severe Tourette's syndrome that has been refractory to conventional medication and behavioral therapy. Although patients with Tourette syndrome can improve with time with a peak display of tics in pre-adolescent period, there is a small subset in which the symptoms are likely to persist in older age and cause severe impairment of their development of social and intellectual aspects. In those with malignant tics that could be life threatening like whiplash tics causing vertebral artery dissection, deep brain stimulation can be a lifesaving treatment modality. Although TSA (Tourette syndrome association) guidelines [17] in 2006 have proposed minimum age 25 years, many experts have adjusted this minimum age limit after assessing the risk benefit ratio for DBS in TS considering the fact of children well tolerating the DBS procedure [18].

The delay in surgery could potentiate to harm their social and intellectual development in incapacitated Tourette syndrome children and possess a greater risk for physical injuries, paralysis and even death as in the case of malignant tics. Hence the recommendation includes a multidisciplinary evaluation and discussion and risk benefit assessment before considering DBS in TS.

3.2 Epilepsy

Deep brain stimulation has garnered attention for the treatment of drug refractory epilepsy; those candidates unfit for surgical treatment or have unsatisfactory results with vagal nerves stimulation. Results of the SANTE trial in 2010 laid the foundation for the efficacy and safety of DBS of the anterior nucleus of the thalamus (ANT). Long term follows up of this study had encouraging reports of 56% reduction in seizure frequency after 2 years following implantation [19].

Other target areas for DBS that have shown promising effects are caudate nucleus, STN, cerebellum, and the hippocampus.

Another long-term follow-up study, reported that 68% of the patients were good responders, while 16% of them was seizure-free [20].

In intractable mesial temporal lobe epilepsy, stimulation of the fornix and hippocampus have shown beneficial results. Finally, FDA approved for focal epilepsy in April 2018. DBS can be carried out under the following conditions:

- Age 18 years and older
- Have focal onset (also called partial seizures)
- Have medically refractory seizures defined as seizures have not been controlled with at least trials of 3 anti-seizure medications.

3.3 Meigs Syndrome

Meigs syndrome is a combination of blepharospasm and orofacial-cervical dystonia mostly affecting the adult population which begins with blepharospasm. DBS have been used in recent times for intractable dystonia. Both STN-DBS and GPI-DBS have been successfully used in Meigs syndrome in which STN-DBS has been shown to be superior in comparison to GPI DBS in certain groups of patients [21].

Some studies have reported few risks of stroke, infection and development of new neurological signs and symptoms with DBS. Hence DBS should be used only when Meigs syndrome is refractory to other treatment modalities.

3.4 Obesity

The three areas that could be associated with increased food consumption is lateral hypothalamus, the ventromedial hypothalamus, and the nucleus accumbens. The lateral hypothalamus (LH) regulates feeding behavior and appetite. In 1974, Quaade et al. reported that stereotactic electro coagulation of the lateral hypothalamus in obese patients caused a significant suppression of appetite [22].

Studies have shown that appetite regulation is through the ventromedial hypothalamus (VMH) in animals. This is regarded as the satiety center of the brain [23].

Harat et al in 2016 reported that implanted DBS electrode resulted in a reduction of obesity in 19-year-old following surgery for craniopharyngioma [24].

Thus, the targets for DBS in obesity are the hypothalamus (lateral or ventromedial) and the nucleus accumbens. The lateral and ventromedial hypothalamus have found to control the feeding by inhibition of the appetite sensation. The accumbens also plays a major role in the reward pathways and reinforcement learning.

However, studies have noticed an alteration of hormonal levels through hypothalamic pituitary axis in candidates with DBS. Thus, further comprehensive studies required before considering DBS as a treatment modality for obesity.

3.5 Headache

DBS have been now a promising treatment in controlling pain in chronic intractable cluster headache. Hypothalamic neurons have a main role in the pathophysiology of cluster headaches and hence hypothalamic implants have been used in various centers [25].

Hypothalamic stimulation has also shown to have good results in patients with SUNCT (short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing) - a disorder with close clinical and neuro-imaging similarities to the cluster headache [25].

3.6 Memory

There has been no treatment that is effective for memory problems in dementia so far. Despite the use of acetyl cholinesterase inhibitors there have been unsatisfactory response to this [26]. DBS in the anterior nucleus of thalamus [27] or entorhinal cortex [28] have shown to improve memory in epileptics. Promising results were obtained from phase I clinical trial in DBS fornix in 6 patients with Alzheimer's disease. The PET scan obtained improved mesial temporal lobe activity [29].

The phase II trial in advanced cases of AD observed no significant difference in the Alzheimer's Disease Assessment Scale Cognitive (ADASCog) 13 scores [30]. However, the study showed that with DBS, the disease progression was observed to be much slower in elderly patients above 65 years. The results of DBS on memory depends on the intensity of the current, the target and the treatment duration. Further studies will be required to make any firm recommendations.

3.7 Post Stroke Rehabilitation

One of the major causes of chronic disability is post stroke major impairments. Despite physical therapy, there has been disabling deficits for most patients.

In 2016, deep brain stimulation of dentate nucleus was first time tried on human for treatment of hemiparesis upper limbs. This trial continues to assess the safety profile and efficacy of dentate nucleus DBS. Earlier preclinical studies in rodents showed motor recovery when lateral nucleus stimulation was combined with physical therapy [31,32].

Furthermore, these observed an improved motor function and functional reorganization for the perilesional cortex [33].

3.8 Psychiatric Disorders

DBS is now being extensively studied for treatment of refractory psychiatric diseases and shows encouraging results. Functional imaging studies have shown role of cortico-striato-thalamocortical loops in the pathophysiology of psychiatric problems.

The two major areas with successful trials for DBS in psychiatry include depression and obsessive-compulsive disorders (OCD) [34].

3.8.1 Depression

Depression being a deadly disease globally is well tolerated with medicines. However, 20% of

the cases are resistant and is being offered with ECT and DBS. DBS of certain brain regions like ventral internal capsule or ventral striatum, nucleus accumbens showed improvement in behaviour & mood [35].

Improvement in Hamilton depression rating scale was sustained even after 4 years follow up [36]. The most accepted hypothesis being activation of inhibitory GABA ergic effect by the DBS or failure of synapsis or metabolism as a result of deep stimulation. Lozano et al reported benefit of subcallosal cingulate stimulation in resistant depression by modulating brain networks whose dysfunction leads to depression. The study concluded that DBS is well tolerated and the benefits sustained for at least 1 year [37]. Even with the cessation of stimulus, persistent benefits have been noted. This is likely because of the persistent changes in the neural network due to prolonged stimulation.

3.8.2 Obsessive compulsive disorder

Meta analysis have revealed results of 50 % improvement in the OCD score with bilateral DBS. The specific target areas of DBS for OCD include internal capsule/ventral striatum [38]. Tensor diffusion tractography guided DBS has been appearing promising medically intractable OCD as it is targeting the specific tract [39].

3.8.3 Cognitive disorders

Fornix and nucleus basalis are being studied as targets for DBS to improve dementia in Alzheimer's and Parkinson's disease. However, the studies are limited and need extensive research. Increase in the bilateral hippocampal volume have been reported with fornix DBS [40].

3.8.4 Substance abuse

Few studies have reported beneficial role of DBS in alcohol and heroin addictions. Researches are still being followed for targeting cortico striatal tract in substance abuse [41].

3.8.5 Anorexia nervosa

Stimulation of subcallosal cingulate for chronic and treatment-refractory anorexia nervosa have shown safe and rewarding in preliminary studies.

Preliminary studies with 6 patients, with stimulation of subcallosal cingulate seems to be generally safe and rewarding in chronic and treatment-refractory anorexia nervosa [42]. One year follow up data from Toronto in 16 patients of anorexia nervosa showed sustained benefit [43].

4. PROMISING INNOVATIONS

4.1 Safety in MRI Imaging

During procedures like magnetic resonance in patients with active implanted DBS, there always has been great possibility of electrode heating carrying the risk of neurological damage. The MRI machine discharges radio frequent thermal energy that is captured by the DBS electrodes leading to brain tissue damage. With the advancement, there has been development of 1.5 T and 3T MRI safe DBS electrodes. In 2016, a clinical trial to test the safety of 3T MRI compatible DBS new devices reported no side effects of MRI during the periodic follow up [44].

4.2 Variable Frequency Stimulation

The problem of need for both the high and low frequency stimulation for movement disorders like Parkinsonism has been solved with advancement of variable frequency stimulation. This provides high frequency that helps on reducing Parkinsonism alternating with low frequency stimulation to alleviate axial disability. Clinical trials are ongoing to assess the efficacy on a long run for this variable frequency DBS [45].

4.3 Online Programming DBS

Recently remote online DBS programming system is used post operatively. Through this remote programming, clinical evaluations are done by video streaming. This introduction has greatly reduced the burden of patient visit to the specialists [46].

Oscillations from basal ganglia have a predictive value of the motor symptoms in movement disorders. Implantable local field potentials recording DBS that are currently used possess battery life of 5 years. Since the data storage capacity is limited and high-power consumption, researches are emphasized on devices that can stream data to external storage and wireless charging techniques for long term use. Presently initial clinical trial on use of rechargeable LFP sensing and data streaming DBS device G102RS in Parkinson's disease has shown promising results [47].

4.4 Pedunculopontine Nucleus Deep Brain Stimulation

Despite STN DBS showed promising results with Parkinson's disease, freezing of gait and postural instability were common symptoms not relieved with DBS and medication. Studies observed degeneration of pedunculopontine nucleus (PPN) in Parkinson's disease. Low frequency stimulation of the PPN is found to alleviate symptoms of akinesia and postural instability. Marked improvement in freezing of gait and frequent falls was observed in trials with dual STN and PPN stimulation [48].

The reciprocal connections existing between the STN and PPN have been responsible to reduce the efficacy of PPN stimulation in some studies [49].

Furthermore, gait worsening has been reported with high frequency used to stimulate the STN when applied on the PPN. Future hopes have been provided with met analysis by Wang H on PPN DBS that reported to show benefit in United Parkinson's diseases rating scores (UPDRS II) with improvement in frequent falls and gait disturbances [50].

4.5 Newer Techniques to Improve FOG in PD

Freezing of gait (FOG) is a disabling motor block leading to periodic absence or reduction of forward progression of feet despite the intention and effort to walk.

FOG is one of the common adverse effects with chronic dep brain stimulation of STN at the normally used frequency of 130 Hz. However novel studies are proving low frequency stimulation of 60 Hz can ameliorate these symptoms [51].

There have been several recent studies promising novel therapeutic approach. Multidisciplinary approach is required for the treatment. Pharmacological therapy like closed loop approach, surgical includes deep brain and spinal cord stimulation and biofeedback and cueing on demand under behavioral approach. Physiotherapy is crucial and have proved to have potential benefit in improving FOG [52].

FOG is usually resistant to medication. Currently cueing, balancing therapy, cognitive training, training in better cognition and strengthening exercise have shown some improvement in FOG. Sensory cues are based on the principle that these stimulations reach the premotor cortex and supplementary motor area which bypasses the defective basal ganglia.

Mobile smart glass technology like google glass that use visual and auditory cueing have shown to benefit FOG. Study showed that improvement of average 25 feet straight walk by 0.32 seconds and through doorway by 0.59 seconds [53].

Improvement have been seen with closed loop DBS. Stimulation is applied as a response to electrophysiological brain markers that shows specific period of activity [54].

4.6 Novel Technology in DBS Products

4.6.1 Bidirectional sensing leads

Technology have developed d directional sensing enabled DBS leads that enhances brain signals - local field potential identification. This specifically enables delivering directional stimulation while sensing itself. There are DBS neurostimulators that senses and allows personalized treatment based on objective data. Latest software combines images obtained pre and intra operative along with patient specific anatomical models that transforms the whole image to a single visual image.

4.6.2 Artificial Intelligence in DBS

Artificial intelligence focuses on creation of intelligent machines which could decipher the language and development of humans such as machine learning. This type of learning focuses on aspiring training from data and not from human programmers. There are advances made in artificial intelligence with intention to further expand the therapeutic potential of DBS. Huge training data and novel computing systems have improved artificial intelligence. These have helped to understand the various neurological disorders leading to improved treatment modality. Effective therapeutic improvement is seen in disease like Parkinsonism based on prior data. MRI compatible DBS along with artificial intelligence can help to understand better patient specific target for DBS.

This can be promising to give personalized treatment regime focusing on specific symptoms to significantly improving the quality of life much beyond only clinical capabilities. Main challenge is on the huge amount of computational case of training for adaptive stimulation.

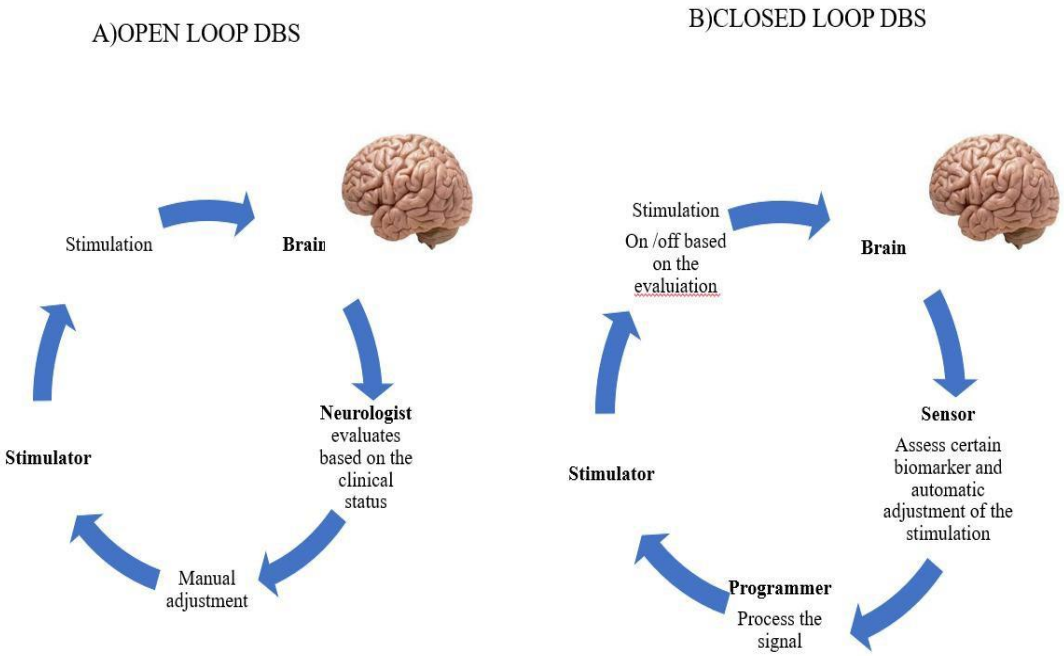

Fig. 1. Open and closed loop DBS of brain activity

4.6.3 Closed loop circuits

DBS is mainly open loop or closed loop. Open loop is the conventional method where the neurosurgeon manipulates manually based on the clinical status of the patient. This could at times over stimulate the brain during the normal phase as the adjustments are carried out in a trial-and-error manner and not on the neurophysiological activities in the brain.

Closed loop DBS makes use of feedback signal where the leads automatically sense the abnormal signals in the brain and accordingly adjust the delivered stimulus. The feedback mechanism is on the basis of various biomarkers like action potentials, local field potentials, electroencephalograms [55] Recently certain other biomarkers like electromyograms, biochemical signals have been proposed [56].

The most important challenge faced in close loop DVD is to discover biomarkers that is reliable and relatable to the patient's symptoms.

A) In Open loop DBS, the brain activity is evaluated through clinical status of the patient and accordingly stimulations to the brain are adjusted by the treating neurosurgeon B) In closed loop DBS, the programming of the electrical stimulation of the brain is done automatically by the sensor. The sensor evaluates the brain activity through biomarkers and switches OFF /ON the stimulation to brain.

5. CONCLUSION

DBS along with artificial intelligence DBS surely shows a promising therapeutic gain in movement disorder. This in particular will be beneficial to those with inadequate improvement with conventional pharmacological treatment. DBS has evolved with time and technology to a highly personalized nature of symptoms and patient specific therapeutic modalities. The emerging indications for DBS are growing rapidly. However, for favorable functional outcome there is a need for the appropriate patient selection and accurate target selection. More studies on a large scale are essential on artificial intelligence DBS and newer indications for better clinical outcome.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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