Chapter

Current Research on Deep Brain Stimulation and Cognitive Impairment in Parkinson's Disease

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Abstract

Cognitive impairment is one of the common non-motor complications in Parkinson's disease. The underlying mechanism remains elusive due to multiple reasons. As a result, treatment options for cognitive decline in Parkinson's disease are limited and not as effective as those for motor symptoms. Recent advances in neuroscience have developed new models for the pathophysiology of Parkinson's disease dementia, based on which clinical research have showed promising results. The role of multiple neurotransmitter systems in cognitive impairment have been emphasized. The change in different functional neural networks (including microscale, mesoscale, and macroscale) resulting from abnormal neurobiochemical environment partly explains the clinical picture. Accordingly, neuromodulation methods can be good candidates for symptomatic management. Several preliminary studies on deep brain stimulation have demonstrated positive results. The nucleus basalis of Meynert, a hub in the cognitive network, is chosen by most studies as the stimulation target. Deep brain stimulation for motor symptoms, on the other hand, may also cause or aggravate patients' cognitive dysfunction. Their influence on cognition is multifaceted and should be taken into account during patient selection, target design, and programming.

Keywords: parkinson's disease, cognitive impairment, dementia, deep brain stimulation

1. Introduction

Cognitive impairment in Parkinson's disease (PD) is a common non-motor symptom (NMS) frequently encountered by patients and practitioners. The cumulative prevalence of PD dementia (PDD) is about 75–90% in patients with a disease course of more than 10 years [1, 2]. It increases the mortality rate and severely impacts the quality of life in patients with PD. With the development of effective pharmacologic and non-pharmacologic interventions, motor symptoms are being better controlled than before, leaving NMSs more frustrating due to a lack of effective treatment. There are several possible reasons. First, it was not until recent years that researchers started to focus on the NMSs of PD. Although cognitive decline in PD is common, our understanding in PD with mild cognitive impairment and PDD is far from adequate. Second, compared with motor symptoms, the underlying mechanism in cognitive impairment seems to be more complicated and involves multiple neurotransmitters and neural circuits. It is not easy to define a single

biochemical system or functional hub as a treatment target from the perspective of neural network. Despite the slow progress in the development of treatment for cognitive decline, efforts have been made in this trending field.

Deep brain stimulation (DBS), a well-established treatment for PD as well as other neurological disorders, has been tested in patients with cognitive impairment. New targets such as the nucleus basalis of Meynert (NBM) were chosen based on the underlying pathophysiology of cognitive impairment in PD [3]. Recent advances in DBS have shown some promising results and will enlighten future development of more robust treatment strategies. On the other hand, traditional DBS targets and programming schemes for PD per se may cause cognitive impairment in the long run [4]. Evidence on this topic has been updated and new strategies have been proposed in target selection and programming in patients with signs of cognitive dysfunction. Here, we review the current research on DBS and the cognitive impairment in PD.

2. Mechanisms underlying the use of DBS in patients with cognitive impairment

The mechanism of PDD is multifaceted. Proposed mechanisms that contribute to cognitive decline include protein misfolding, neurotransmitter activities, synaptic dynamics, neuroinflammation, mitochondrial dysfunction, change in glial cells, genetics, epigenetics, adenosine receptor activation, and abnormal brain connectivity [5]. From the neurotransmitter point of view, evidence has shown that not only the dopaminergic system, but also non-dopaminergic activity is associated with cognitive functioning [6]. Cholinergic system is one of the most important transmitter systems involved in cognitive dysfunction in PD. Cholinesterase inhibitors are supported by robust evidence to treat PDD [7, 8]. The effectiveness of cholinesterase inhibitors further proves the essential role of cholinergic system in PDD.

The NBM is a structure of gray matter located in the substantia innominate of the basal forebrain. It harbors 90% of the cholinergic neurons and is considered as a hub in the cholinergic network [9]. The NBM has an important role in cognition including attention, arousal/sleep cycles, memory, praxis, perception, drive and spontaneity. This vast complicated array of connections results in variability in its effect from stimulation [10]. For stimulation of the NMB to be effective, identifying the appropriate targeting to activate a specific network will be essential [10]. The significance of NBM has been proposed in dementia of various etiologies, including PD (**Figure 1**).

Increasing evidence has shown that both the structural and functional networks related to NBM are compromised in PD patients with cognitive impairment. Smaller volumes in the region of NBM are associated with greater change in global cognitive functioning, higher risk of mild cognitive impairment, and more severe and rapid decline in some certain cognitive domains [11]. Increased mean diffusivity in the NBM is also predictive for the development of cognitive dysfunction [12]. Reduced density of the gray matter in the cholinergic basal forebrain correlates with impaired global cognition, attention, and visuospatial function [13]. A recent longitudinal study reported more severe cognitive impairment and significant decline in parietal and occipital metabolism in patients with NBM atrophy, further supporting that structural change in the NBM is associated with cognitive dysfunction in PD [14].

In addition to structural abnormalities, the functional network involved in the development of cognitive impairment is also remarkably disrupted. An EEG-based study showed a significantly greater reduction in alpha reactivity in Lewy body dementia than Alzheimer's disease and healthy controls. This impairment of alpha reactivity might be associated with volume loss of the NBM [15]. One study

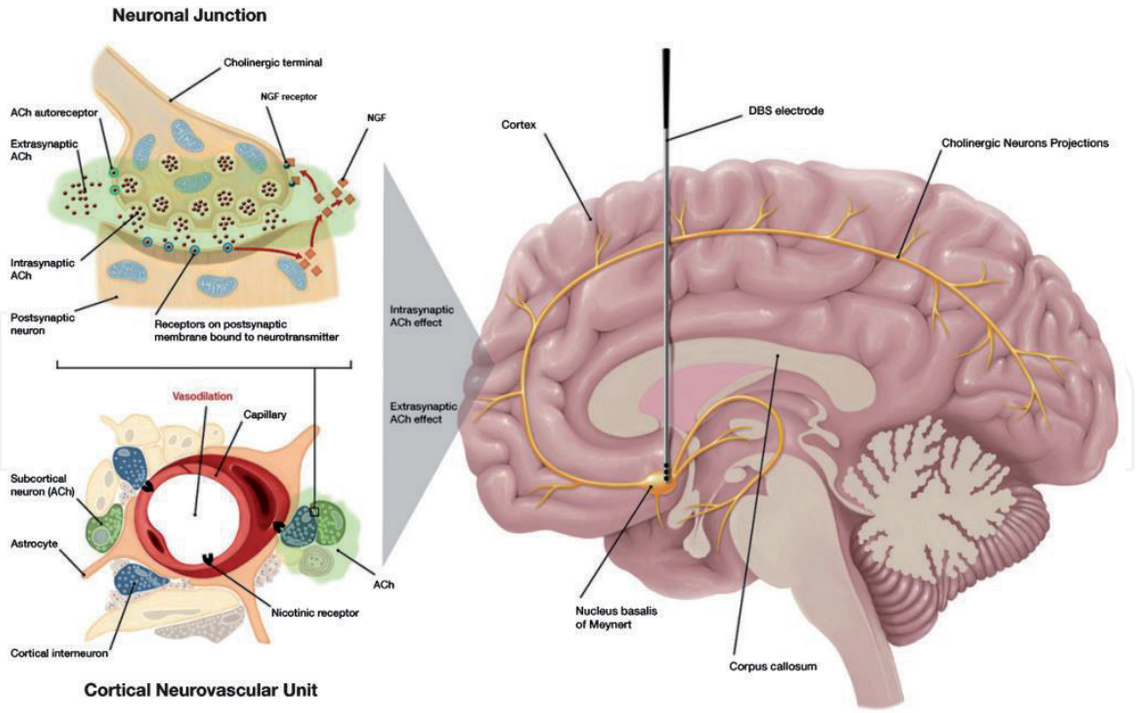

Figure 1.
"Schematic representation of the putative effect of deep brain stimulation (DBS) of the nucleus basalis of Meynert. Intra- and extra-synaptic effects of acetylcholine (ACh) are shown. Top left shows potential effect of DBS by altering cholinergic neurotransmission. Bottom left shows vasodilative effects of DBS via cholinergic activation. Right side shows NBM projection sites after DBS. NGF, nerve growth factor." ["Reprinted from the Journal of Alzheimer's Disease, volume 69 (4), Koulousakis, P, Andrade, P, Visser-Vandewalle, V, Sesia, T, The Nucleus Basalis of Meynert and Its Role in Deep Brain Stimulation for Cognitive Disorders: A Historical Perspective, Pages 905–919, 2019 with permission from IOS Press. The publication is available at IOS Press through http://dx.doi.org/10.3233/JAD-180133"].

calculated the functional connectivity via resting state functional magnetic resonance imaging (fMRI). Compared with PD without cognitive impairment, PD with mild cognitive impairment showed alterations in dynamic functional connectivity in multiple brain networks [16]. This is supported by another study with fMRI which found that the resting state functional connectivity of NBM is reduced in the right superior parietal lobe and the right postcentral gyrus in PD-MCI [17].

Abnormalities in brain networks other than those related to NBM have also been demonstrated. The cerebellar vermis consists of a rich population of cholinergic neurons and is involved in cognitive function. Compared with PD patients with normal cognitive function, those with cognitive impairment show a reduction in the functional connectivity between the vermis and dorsolateral prefrontal cortex, which is associated with deficits in attention, executive functioning, and global cognition [18].

The use of DBS to cause a functional blockade at specific target sites, replacing abnormal neural activity with a more tolerable pattern of activity, is considered standard therapy for several disease processes. It is currently hypothesized that the chronic high frequency electrical stimulation of the target nucleus acts as a brain pacemaker, entraining irregular neuronal firing patterns and desynchronizing pathological hypersynchronization within sensorimotor circuits. DBS is "local" therapy and affects only local circuits and brain regions within the target region [19, 20].

3. Deep brain stimulation surgery

DBS currently has FDA approval to be used in the treatment of motor symptoms for PD, essential tremor and epilepsy and FDA approval under a Humanitarian

Indications	Target
FDA-approved targets	
Parkinson's disease	Subthalamic nucleus (STN), Globus pallidus internis (GPi) Ventral intermedius nucleus (VIM) (tremor)
Essential tremor	Ventral intermedius nucleus (VIM)
Dystonia (HDE approval)	GPi
Medically resistant obsessive-compulsive disorder (OCD) (HDE approval)	Anterior limb of the internal capsule
Epilepsy	Anterior nucleus of the thalamus
Emerging/investigational targets	
Epilepsy (alternative target)	Hippocampus
Medically resistant OCD	Medial thalamus
Medically resistant depression	Nucleus accumbens
Obesity	Nucleus accumbens, Ventromedial nucleus of the hypothalamus
Anorexia nervosa	Nucleus accumbens, Ventromedial nucleus of the hypothalamus
Posture/gait in movement disorders	Pedunculopontine nucleus (PPN)
Medically refractory cluster headache	Posterior hypothalamus (PHypTh)
Medically refractory depression	Subgenual cortex (Brodmann area 25)
Dementia	Nucleus basalis of Meynert (NBM)

Table 1.
Current and emerging deep brain stimulation targets [25].

Device Exemption (HDE) application for dystonia and obsessive-compulsive disorder [21]. DBS of the subthalamic nucleus (STN) or of the internal segment of globus pallidus (GPi) has been shown to significantly improve motor symptoms in PD (such as rigidity, tremor, bradykinesia and, occasionally, disturbances of gait) [22, 23], while DBS of the ventral intermediate thalamic nucleus (Vim) has been shown to reduce tremors in PD and ET [24] (**Table 1**).

Potential candidates are those whose symptoms are refractory to standard medical interventions. As a part of this extensive workup for movement disorder indications, the neurological examination is often videotaped on and off medications to help assess potential treatment response post-surgery and to get a clear understanding of a patient's underlying symptoms. For patients with PD, a 30% improvement on the Unified Parkinson Disease Rating Scale (UPDRS) on and off medications is recommended [26]. In addition, patients will undergo an extensive neuropsychological evaluation to rule out untreated mood disorders and to get a baseline for cognitive status. Patients will complete a screening MRI of the brain to evaluate for atrophy and any structural issues that may complicate implantation of brain leads.

Once the evaluation is completed, a multidisciplinary case conference is held to review the patient's medical history, motor testing scores, neurocognitive and psychiatric data, neuroimaging results and clinical assessment. This process provides a thorough determination of patient eligibility prior to scheduling DBS surgery.

During this meeting, the team will determine the appropriate target nucleus as well as which DBS system will be implanted. These decisions vary depending upon the therapeutic goals, patient symptoms, cognitive and behavioral issues, and surgeon's expertise [27].

To accurately implant a DBS lead into a deep brain structure, an operative plan is developed using a special high-resolution MRI scan. Targets are first identified using a 3-dimensional coordinate system, and further refined for each patient's specific neuroanatomical characteristics. A safe entry point and trajectory are determined, and the surgical plan is stored in a neuronavigation station (**Figure 2A**). Under local anesthesia, a ring is secured to the patient's skull and an additional study is obtained using a localizer box that allows the software program to guide the surgeon along the previously developed plan (**Figure 2B**).

This procedure can be done with the patient asleep or awake during the placement of the electrode(s). Traditionally, the patient is awake during microelectrode recording above and below the surgical target, which results in a physiological map that determines if the intended surgical target represents the dysfunctional area of the brain that is involved in movement (**Figure 2C** and **D**). Once the final DBS electrode is implanted, test stimulation is performed to confirm that the patient experiences therapeutic benefit without significant clinical side effects (**Figure 2E**). A final head CT is obtained to confirm that the actual lead placement is consistent with the clinical evaluation. If needed, adjustments to lead placement can be made at that time. Patients are typically discharged from the hospital 1 day after surgery.

Many patients may experience a temporary microlesion effect following surgery where their PD symptoms briefly improve. To allow sufficient time for this brief effect to subside, providers often wait approximately four weeks following lead implantation before the patient returns to the clinic to have the stimulator turned on and programmed. With lead placements targeting motor symptoms, tremor and rigidity are typically the primary focus although motor speed and gait are also

Figure 2.
A: Surgeon evaluating surgical plan on neuronavigation station. B: Localizer box has been attached to the head frame in preparation for the final preop head CT that will allow the software to guide the surgeon along the previously developed plan. C: Microelectrode recording during electrode placement. D: Motor testing during microelectrode testing. E: Intraop test stimulation after electrode placement.

assessed [28]. Adjustments in the stimulation field, amplitude, frequency, and pulse-width control the stimulation response [29]. DBS suppresses symptoms; it does not alter disease progression [20].

The patient will then return for subsequent visits to adjust the stimulator and medications, as needed. Once therapy is optimized, often within 3–6 months, patients will return to their neurologist for ongoing management [28]. It is common to conduct a 6–12-month postoperative neuropsychological evaluation to evaluate the impact of DBS surgery on cognition, psychological, emotional, and behavioral symptoms [27]. The implanted pulse generator (IPG) typically requires surgical replacement every 3–5 years, which is done on an outpatient basis under general or local anesthesia. Current rechargeable IPGs are approved for 15 years. DBS requires life-long monitoring and follow-up [30].

4. Patient selection

Proper patient selection is critical in order to maximize the post-operative benefits and minimize the surgical risks for the patient, especially for those with cognitive dysfunction. Over 30% of DBS surgical failures are attributed to inappropriate patient selection [28]. In order to justify the potential surgical risks of DBS, patients must be experiencing significant disability from their disorder, although what defines "significant disability" is subjective and needs to be individualized to each patient [20]. The current goal of DBS in PD is to intervene to maintain motor function and quality of life before disability becomes debilitating [20].

DBS for PD motor symptoms is recommended when pharmacotherapy stops providing adequate symptom relief. In patients with PD, a patient's responsiveness to dopaminergic medication (i.e., levodopa) often is predictive of a patient's motor response to DBS. Signs and symptoms resistant to levodopa are often resistant to DBS [20, 28]. Ideal candidates for DBS targeting motor symptoms have dopa-responsive motor symptoms, few comorbidities, fluctuating motor symptoms and no or minimal cognitive or behavioral disorders. PD symptoms such as dysarthria, dysphagia, micrographia, severe postural instability, freezing of gait, cognitive dysfunction and dysautonomia are less responsive to DBS targeting the STN, GPi, or Vim [20, 31].

A detailed understanding of a patient's cognitive status is essential. Typically, patients with dementia or significant cognitive impairment are excluded from surgery. Patients with diminished cognitive abilities may have the following challenges: a diminished motor response post-surgery; difficulty cooperating with the awake surgical procedure; difficulty accurately describing symptoms, making adjusting the DBS settings and medications post-surgery more challenging; and, most concerning, a worsening of their cognitive status post-surgery [27, 30]. Unfortunately, there is minimal consensus regarding what level of cognitive impairment should exclude patients from this therapy, so the ultimate decision is left to the clinical judgment of the multidisciplinary team [27].

There is concern that mood disorders (depression and anxiety) can worsen following surgery. In addition, untreated mental health conditions may result in poor compliance following surgery [27]. Patients with severe, unresolved psychotic symptoms should be excluded from consideration for this procedure, at least until the psychotic episode resolves [20, 28]. Patients are often awake during the electrode lead placement, which can be quite stressful. Any neurologically compromised patient may show exacerbation of symptoms under stress. For those with cognitive deficits, severe autonomic dysfunction or severe ataxia, DBS surgery may provide an unacceptable risk of significant complications. This appears to be more concerning in patients undergoing bilateral STN DBS than GPi DBS [30, 32].

5. Surgical outcomes

In one of the most comprehensive randomized, controlled trials comparing DBS to best medical therapy, DBS was found to be more effective than best medical therapy in improving motor function and quality of life. Weaver et al. [31] found that DBS patients gained an average of 4.6 h of "on" time per day (the amount of time when patients experience relief from Parkinson's symptoms) with reductions in the amount of "on" time with dyskinesia and "off" time (the time when PD patients are not experiencing relief from their symptoms). Self-reported improvements in motor functioning showed a 29% gain. On the contrary, most patients undergoing best medical therapy did not show any improvement in motor functioning after 6 months of treatment. Understandably, these improved motor functioning scores were associated with a significant improvement in quality-of-life measurements.

Those motor and non-motor symptoms which show a strong dopaminergic response typically respond the best to DBS therapy [33]. Outcomes often depend on a variety of factors including target selection, programming settings, electrode placement, medical management and patient expectations [33]. More severe apathy, depression and axial symptoms prior to DBS surgery are predictors of negative subjective perception of outcome following surgery [33]. While desires for improvements in gait, non-motor symptoms, interpersonal relationships, and professional life often influence a patient's decision to pursue DBS surgery, these expectations are not often met post-surgically [33]. Patients may struggle with a new body image and changes in their relationships with others due to changes in caregiving needs [27]. In addition, while DBS has been shown to positively impact a patient's quality of life, several studies have shown no improvement in caregiver burden following surgery [33]. Where DBS does result in less caregiving needs, spouse caregivers may find themselves struggling to redefine their role in their relationship now that they are no longer needed in the same capacity [27].

Several studies have found slight reductions in cognitive function test results in patients who underwent DBS therapy, compared to the best medical therapy group, relating to reductions in executive functioning, verbal associative fluency, working memory and visuomotor speed [27, 31, 34]. Studies show varied results but there is suggestion that STN-DBS, more than the GPi-DBS, may result in slightly higher risk of cognitive decline after surgery [34, 35]. A meta-analysis of 41 studies looking at the effect of DBS in PD on cognition, found STN DBS correlating with slight declines in psychomotor speed, memory, attention, executive functioning and moderate declines in phonemic and semantic fluency [36]. Higher DBS pulse widths have been associated with declines in cognitive functioning in patients with ET [27]. This cognitive impact seems unresponsive to changes in DBS settings or on/off motor states suggesting it is related to lead position [33]. A variety of reasons for this response have been considered including: cortical or subcortical microtrauma following implantation of the electrode, changes in frontostriatal neuronal activation secondary to DBS, changes in neuronal activation secondary to reduced dopaminergic therapy following surgery, advancing age and lower cognitive reserve [35].

While GPi STN is thought to result in less worsening of impulse control disorders and psychiatric conditions, studies suggest that STN DBS may result in greater reduction in medication when targeting PD motor symptoms [27]. Caution should be taken with too rapid reduction in dopaminergic therapy as this could worsen apathy [33]. While there is evidence that candidates for DBS surgery have a higher-than-expected suicide rate after STN-DBS, correlating with an increase in post-operative depression and impulse control disorders [33], a systematic review by the Congress of Neurological Surgeons did not find an increased association with suicidal behaviors with STN v GPi targets [4]. Further supporting STN DBS

for medication reduction, a retrospective study found reduced risk of psychosis in patients with DBS for at least 8 years compared with medically managed patients with no significant risk differences with respect to dementia, institutionalization or death [37]. This study found that the rate of persistent psychosis reduced 74% in DBS treated patients compared with medically managed patients, presumably related to the reduction in dopaminergic therapy following STN-DBS.

6. Neuromodulation as a treatment for cognitive impairment in PD

As has been discussed above, abnormalities of various functional networks underlie the cognitive impairment of PD patients. Accordingly, approaches that modulate these abnormal networks could be potential treatment options. Efforts have been made exploring the safety and efficacy of neuromodulation in patients with cognitive problems in the past decade. However, robust evidence is lacking.

In 2009, a case report described an individual with Parkinson-dementia syndrome who was implanted with two electrodes in the STN and two in the NBM [38]. Stimulation of the bilateral STNs alleviated motor symptoms and stimulation of the bilateral NBMs resulted in better cognitive function. At a later report, the authors noted that the improvement in ADLs and activities of interest was due to improvement in apraxia, which only occurred with the activation of the NBM leads, not the STN leads [10].

Gratwicke et al. [3] conducted a randomized, double-blind, crossover study of 6 patients with PDD who were treated with NBM-DBS. They were appropriate DBS surgical candidates except for their diagnosis of PDD. They were still cognitively well enough to provide informed consent and meet pre-set criteria on the Mini-Mental State Examination as well as having minimal atrophy on brain MRI. All patients safely tolerated DBS surgery and low-frequency stimulation but did not show any improvement in their cognitive outcomes; yet there was an improvement noted in their neuropsychiatric scores (in particular, visual hallucinations, a parietal lobe function) on NBM-DBS. This team conducted a similar study on 6 patients with dementia with Lewy bodies (DLB) [39]. These results, combined with their previous study on PDD, showed no significant improvement in cognitive outcomes but did note possible improvement in neuropsychiatric symptoms. These studies offer further suggestions that NBM stimulation may modulate cholinergic transmission.

The DEMPARK-DBS study [40] is embarking on a sham-controlled trial of combined STN and NMB DBS for PD with dementia to evaluate the safety of bilateral STN-DBS in PDD patients and to study if NBM-DBS impacts cognitive decline. Patients with dementia are typically excluded from DBS therapy due to concerns about potential further deterioration of their cognitive status; however, many could benefit from the reduction in dopaminergic therapy that often occurs following STN-DBS implantation as this can reduce the risk of delirium or hyperdopaminergic behaviors which can exacerbate PDD symptoms. Implantation into the NBM target alone would not address motor or non-motor symptoms associated with advanced PD. This will be the first controlled study to compare STN-NBM-DBS in patients with PDD as well as to evaluate the safety of STN-DBS in patients with PDD.

Typically, frequencies in the high gamma range (100–180 Hz) are used to target motor symptoms; however, theta stimulation (which the authors define as 5–12 Hz) has been associated with various cognitive functions [35, 41]. Hippocampal theta oscillations are involved with episodic and spatial memory encoding and retrieval [41]. STN theta oscillations have been found to be involved with executive functions such as verbal fluency, working memory, sensorimotor conflict and response inhibition [35]. In 2018, a pilot study looked at the effect of theta and gamma

stimulation on cognitive function [35]. Theta frequency stimulation was found to improve cognitive performance whereas gamma frequency stimulation worsened cognitive performance. In 2020, another study further investigated the effect of theta versus gamma frequencies on verbal fluency and executive function in PD patients [41]. Results found improvements in episodic category verbal fluency during theta versus gamma frequency STN stimulation, confirming the role of theta oscillations in hippocampal-dependent memory processes [41]. Since theta frequencies do not improve motor functions, the authors propose further investigation into the possibility of interleaving theta and gamma stimulation to address both the motor and cognitive symptoms of PD.

7. The future of DBS technology

As we have discussed, the benefits of DBS are often limited by side effects and rapid battery drain. Recent and future DBS technologies are focusing on reducing side effects, maximizing benefit, and prolonging battery life. The presence of multiple DBS manufacturers has resulted in a rapid advancement in this technology due to global competition. Newer technologies include segmented leads, directional stimulation, increased battery longevity, increased programming flexibility, remote programming, expanded MRi compatibility and neural recording capabilities [42].

Previously, the FDA approved implanted leads were omnidirectional, putting stimulation out in all directions, in a sphere-like shape. The challenge with these omnidirectional leads is that in creating a stimulation field strong enough to address the symptoms of concern, non-desired side effects often occurred as a result of stimulating adjacent structures. "Field shaping," where programmers can focus the stimulation on desired targets and move away from targets of concern has been a recent focus. Recently, several "directional" leads have received FDA approval. These directional leads allow the programmers to steer the stimulation away from structures that may be contributing to side effects and towards structures of clinical interest. DBS systems that offer multiple independent current control, where each individual lead contact has its own current source, provide additional precision in programming, compared with single-source current source systems, where all electrodes share a single current source [42, 43].

Conventional DBS (cDBS) technology uses an open-loop platform that, oftentimes, makes balancing stimulation to maximize benefits but minimize side effects challenging. In addition, limited battery capacity makes cDBS cumbersome due to the need for numerous battery replacement surgeries over an individual's lifespan. As noted earlier, cDBS settings result in a in a continuous stimulation field. These settings are created by the clinician and adjustments are made as needed based on a patient's response at a future clinical visit. This continuous stimulation does not match the fluctuating clinical state of the patient, often making patients more prone to side effects and using more energy than may be required [43].

Newer technologies are exploring a closed-loop or adaptive DBS (aDBS) system that can make real-time adjustments in stimulation based on continuous feedback. The ability to adjust stimulation parameters to better match the fluctuating state of the patient may result in fewer side effects and less energy drain on the implanted battery. By recording local field potentials (LFPs), new DBS IPGs provide an opportunity to correlate clinical symptoms with this input signal. Studies are underway to help standardize interpretation of these signals. The ultimate goal is to create a standardized interpretation of these signals and to optimize artificial intelligence-based programming, reducing the time burden on clinicians fr0m the current "trial and error" approach and improving differentiation of stimulation needs for various PD phenotypes [42, 43].

8. Conclusion

While there is growing evidence that neuromodulation of the cholinergic network may have a role in addressing neuropsychiatric symptoms in patients with PD, exacerbation of cognitive impairment, in particular a reduction in verbal fluency, following DBS is a concern. Lower pulse widths and the use of theta frequency stimulation appear to dampen the impact of DBS on cognitive performance. Newer and emerging technologies including closed-loop adaptive DBS, multiple-source stimulation, and directional current steering may help reduce negative outcomes and improve DBS efficacy although there is still limited data on the impacts of these on cognition [33].

Conflict of interest

Kia Shahlaie – Consultant for Abbott.
Laura Sperry – Consultant for Abbott, DBS Advisory Panel for Medtronic.

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