Neurotherapeutics 21 (2024) e00310

Contents lists available at ScienceDirect

Neurotherapeutics

journal homepage: www.sciencedirect.com/journal/neurotherapeutics

Review

Emerging therapies for neuromodulation in Parkinson's disease

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ARTICLE INFO

Keywords:
Parkinson's disease
Neuromodulation
Deep brain stimulation
Transcranial magnetic stimulation
Electroconvulsive therapy
Transcranial direct current stimulation

ABSTRACT

Parkinson's disease is characterized by its cardinal motor symptoms: bradykinesia, rigidity, tremor, and postural instability. The underlying physiological dysfunction includes basal ganglia pathways that contribute to both motor and non-motor symptoms. These pathways can be influenced by neural network modulation through the application of electrical or magnetic fields. Neuromodulation therapy can also be used to target symptom-specific networks. Deep brain stimulation (DBS) is an example of an effective neuromodulatory approach, mainly for the treatment of motor symptoms. DBS has evolved over the last three decades through several technological advances including imaging-guided planning, brain leads with sensing capabilities, closed-loop stimulation, and segmented leads with directional steering. Less invasive forms of neuromodulation have also been introduced and these techniques can leverage disease-specific networks through the application of transcranial magnetic stimulation, transcranial direct current stimulation, and electroconvulsive therapy. Newer approaches have also emerged in the laboratory setting including temporal interference stimulation, low-frequency focused ultrasound, and magnetoelectric stimulation. We will review current and emerging neuromodulation therapies for their potential application to PD.

Introduction

Parkinson's disease (PD) is now the most rapidly growing neurological disorder and is the second most common neurodegenerative disease next to Alzheimer's disease [1]. PD is frequently identified by its characteristic combination of bradykinesia, resting tremor, rigidity, and postural instability though resting tremor may be absent in one-fifth of cases [2]. The hallmark of PD is the progressive degeneration of the dopamine-producing neurons in the substantia nigra pars compacta, and the decay of multiple motor and non-motor basal ganglia circuits [1]. The lack of dopaminergic input into the striatum as well as larger scale circuit-based degeneration contributes to abnormal basal ganglia output and to the emergence of the cardinal motor symptoms [3]. Thus, symptoms in PD occur due to the progressive degeneration of *multiple* basal ganglia-related pathways.

Many attempts have been made to create models explaining how the basal ganglia work. For example, one model has three distinct circuits running in parallel, a motor-sensory circuit, an associative circuit, and a limbic circuit [4]. The motor-sensory circuit is responsible for influencing thalamo-cortical projections, and contributing to slowing of movement [5,6]. Similarly, the associative circuit is thought to underpin memory and thinking function while the limbic circuit modules behavior.

Oral levodopa, combined with either carbidopa or benserazide, has been the cornerstone of treatment for the motor symptoms of PD since its discovery in the late 1960s. Most patients experience a consistent improvement in bradykinesia, rigidity, and tremor following the administration of levodopa [7]. The loss of dopaminergic neurons does not account for all motor features of PD. For example, tremor may only be partially responsive to levodopa. At a neurotransmitter level, cholinergic interneurons in the striatum, serotonergic neurons at the level of the raphe nucleus, and noradrenergic cells in the locus coeruleus contribute to tremor [8]. At a circuits level, patients with levodopa-resistant tremor have a higher involvement of the cerebello-thalamo-cortical pathway compared to patients with levodopa-responsive tremor [9].

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https://doi.org/10.1016/j.neurot.2023.e00310
Received 6 October 2023; Received in revised form 30 November 2023; Accepted 12 December 2023

About 50 % of patients will experience motor fluctuations after 5 years of treatment with levodopa. These symptoms manifest as wearing off, levodopa-induced dyskinesia and/or a shorter and inconsistent dose responses [10]. This is a common limiting factor in the treatment of these patients, and often limits the benefit they can get from oral medication without having bothersome dyskinesia or spending more time without adequate motor symptom control (off-time) [11].

Neuromodulation is a rapidly expanding field with the goal to target specific brain networks. As our knowledge of neural circuit function and anatomy has increased over the preceding decades, neuromodulation has been increasingly refined to transform the therapy into one that is 'symptom specific'.

Technology has been an important factor fueling the growth of neuromodulation therapies. In this review, we will discuss the current approaches used to modulate basal ganglia output using invasive and non-invasive techniques. These approaches now include deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), transcranial direct magnetic stimulation (tDCS), and electroconvulsive therapy (ECT) (see Fig. 1). Additionally, we will discuss temporal interference stimulation, low-intensity focused ultrasound, and magnetoelectric stimulation.

Deep brain stimulation (DBS)

Historical background

James Parkinson was a general practitioner in London and in his 'Essay on the Shaking Palsy' in 1817 [12] he described six patients who roughly fit the definition of PD. One of Parkinson's early patients suffered a stroke with right-sided hemiparesis and resolution of his tremor. This observation provided a clue that *intentional* lesioning within the basal ganglia could be used to treat the motor symptoms of PD. Early surgical interventions targeted the corticospinal tract to treat tremor at the cost of paresis [13]. Later, the accidental ligation of the anterior choroidal artery by Irving Cooper led to a stroke-induced lesion in the pallidum. This was an important observation for the field as it provided more evidence that specifically targeted lesions could be used as therapeutic tools. Cooper later used alcohol and radiofrequency lesioning for more specific targeting of the pallidum. The introduction of the stereotactic headframe, first in horses and then in humans in the 1960's was a critical advance as stereotactically guided lesions led to more predictable outcomes with less adverse events. One continued challenge in the field was that bilateral lesions led to speech, swallowing, and pseudobulbar side effects [14]. The neurosurgeon Alim Benabid and the neurologist Pierre Pollack later performed one of the first DBS surgeries contralateral to a previously placed thalamotomy; they observed much fewer speech and swallowing side effects as had been previously observed when using bilateral lesions. High-frequency stimulation of the thalamus suppressed tremor contralateral to the side of the DBS placement [15]. Though DBS had been used for decades, most stimulation was applied acutely or only in the operating theater. DBS was approved for use by the Food and Drug Administration (FDA) in 1997 for tremor and in 2002 for Parkinson's disease (Medtronic, Minneapolis Minn). Tremor was first targeted using the ventralis intermedius thalamic target (VIM) and Parkinson's with subthalamic nucleus (STN) or the globus pallidus pars interna (GPi) DBS. Thalamic DBS is still used in severe upper extremity tremor in the setting of PD, especially if there is a prominent postural-action component. Later, FDA approval was granted to Abbott (formerly St. Jude Medical) in 2016 and Boston Scientific in 2017 for DBS in the setting of Parkinson's disease.

Nowadays, Parkinson's disease is most common indication for DBS. It became the increasingly popular since STN-DBS proved effective at controlling motor symptoms [16], and then even more common after its FDA approval in 2002. The rise in use began to wane at 2008 but then went up again in 2009 after studies demonstrated that it was superior when treating motor symptoms in advanced PD [17].

Procedure

The DBS system consists of an implantable pulse generator (IPG) that is attached through an extension wire that connects the 'battery' to the brain target. There is a wide variation in how the DBS implantation procedure is performed in different centers across the world and there is no 'right way' to perform the surgery. The procedure can be performed either with or without intraoperative microelectrode recording (MER) or with or without intraoperative MRI (iMRI). Some centers will do intraoperative CT scans. MRI has replaced ventriculography as a targeting technique as it has similar outcomes in electrodes placement by using a less morbid procedure [18]. Some experts use microelectrode recording (MER) applying physiology for target verification or for true brain mapping. The information gleaned from MER can be used to refine the optimal position for the DBS lead. The DBS procedure may be performed

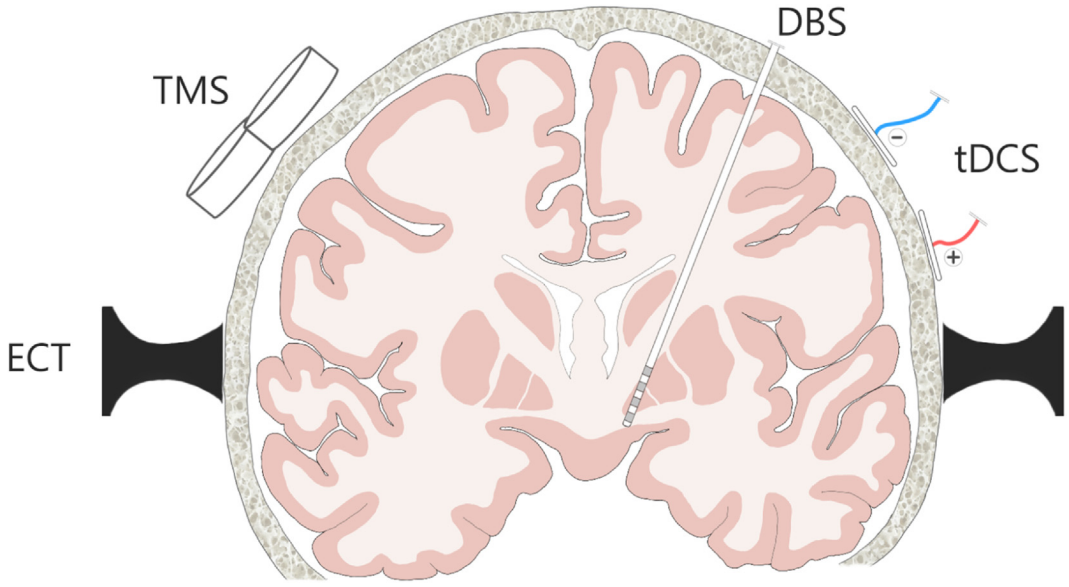

Fig. 1. Different forms of invasive and non-invasive neuromodulation for Parkinson's disease.

awake or asleep. One advantage to awake surgery is that the patient may participate in the brain mapping and testing for side effects and benefits. Experience has shown that the clinical response to electrical stimulation in the operating theater can be a critical step to optimize benefits and minimize stimulation-induced side effects [19]. Whether or not the person is awake testing the DBS lead prior to exiting the operating room is important, as if the threshold for benefit and side effects are too low, the DBS lead can be repositioned, and this could save a follow up operation. Finally, some experts will use an iMRI approach usually performed under sedation. Most of these centers applying this technique use a dedicated MRI scanner with MRI-compatible DBS implantation equipment [20].

The debate on which technique for DBS is 'best' can be misleading. The best technique is the one that your team continuously refines and documents improving outcomes. Process refinement is critical for successful DBS surgery. No amount of expert DBS programming can make up for a suboptimally placed lead. DBS teams should employ a post-operative quality assurance program to refine and improve the approach by providing feedback on imaging, programming, and clinical outcomes. Pre-operatively, a multidisciplinary evaluation should be applied including a neurologist, neurosurgeon, and neuropsychologist at a minimum. Many expert teams also employ physical therapy, occupational therapy speech/swallow therapy, nutrition, psychiatry, and social work services [21]. Following evaluation by each member of the multidisciplinary DBS team a discussion should be pursued to dialogue on choosing the appropriate brain target and approach for each symptom and each patient.

Mechanism of action

Early in the discussions of the potential mechanisms of action for DBS, experts pointed to the powerful observation that electrical stimulation of the thalamus improved tremor, similar to thalamotomy 15. Could a lesion have the same mechanism as DBS? Does a lesion affect the neural network in a similar way as DBS? Today, we do not believe that the mechanisms are exactly the same, though there may be overlapping principles.

The initial assumption for the mechanism of action for DBS was that the mechanism of DBS was 'inhibitory' [22,23]. This view proved simplistic and not completely representative. Cell bodies close to the electrical field may be inhibited; however, axons seem to be excited. Additionally, there are neurochemical, neurogenic, and neurovascular changes associated with the application of DBS. There is a larger than previously appreciated effect on glia and on brain connective tissue which may be important to trigger the release of neurochemicals such as adenosine [24]. Thus, we can conclude that there are many biological changes in the micro-scale following the application of electrical pulses, however which changes are responsible for the mechanisms of action of DBS remain unknown.

In the meso-scale, DBS can modulate the activity of the group of cells that are within its electrical field, modulating their output [25,26], modifying their ability to respond to stimuli ("informational lesion") [27], and possibly long-term plasticity changes [28]. These changes in the local electrical fields lead to widespread network changes in the macro-scale in the networks that involve the motor cortices and the basal ganglia [29,30]. The mechanisms of action of DBS are summarized in Fig. 2.

STN and GPi

The STN and GPi are the most common DBS targets that have been used to treat the motor symptoms of PD. We have drawn conclusions of the difference between these two targets based on observational studies and clinical experience, but head-to-head trials have not shown definitive differences [31]. The VIM thalamic target is still used for severe cases of tremor particularly those with a larger postural-action component. DBS improves 'off time,' on-off fluctuations, and tremor whether levodopa responsive or not [32]. Levodopa responsive features such as bradykinesia and rigidity tend to improve with DBS of the STN or GPi, whereas gait, balance, and speech usually do not. Both GPi-DBS and STN-DBS increase ON time by ~4 h [33–36] and both improve quality of life during the first 5 years post-implantation. Quality of life benefits may however diminish with disease progression [37].

A "levodopa challenge" is commonly used to estimate the acute magnitude of the effects of DBS on levodopa responsive symptoms; this is listed as evidence based in the American Academy of Neurology Guidelines [38]. Many experts use a 30 % threshold for improvement in the UPDRS part III motor scale after a levodopa challenge as a predictor of a "good candidate". Insurance companies may refuse DBS if on-off UPDRS III testing is sub-30 %, however this should be appealed, as this measure alone does not predict a good outcome for all patients [39].

Clinicians should be aware that on-off testing misses one of the most important benefits: the improvement in motor fluctuations. In particular, the role of dyskinesia in the patient's functional status is not captured by using the UPDRS part III. GPi-DBS is considered by most experts superior to STN-DBS for pure suppression of dyskinesia [31,40]. GPi-DBS directly suppresses dyskinesia, whereas STN-DBS usually but not always requires a reduction in levodopa to achieve the same outcome [41,42]. Long term, there may also be a benefit favoring GPi-DBS as there will likely be a need for more levodopa over time in many patients and GPi-DBS will facilitate management with less induction of dyskinesia when adding levodopa doses back to the regimen. Some patients with pre-existing brittle dyskinesia will experience a see-saw effect where small doses of levodopa or small adjustments in STN-DBS may result in dyskinesia [43].

There are advantages to STN-DBS. Though motor outcomes are similar between both targets, patients with STN-DBS tend to have a better response in bradykinesia. In addition, battery life is superior in STN-DBS largely because it is a smaller target and requires less current density for a therapeutic effect when compared to the GPi [44]. Many experts choose GPi-DBS if a patient has cognitive impairments or if they want more flexibility with medication in the long run [45]. Finally, GPi DBS is easier to program, and this may be relevant in areas where expertise is lacking [31,46].

The choice of unilateral DBS vs. bilateral DBS should be patient specific. The NIH COMPARE study [40] showed that lower baseline UPDRS score, and very asymmetric symptoms may do well with unilateral DBS in the short and long term. Severe bilateral dyskinesia and higher UPDRS score (when in the off condition) may favor a bilateral approach. Many experts stage the implantation of DBS leads over weeks to months especially if over the age of 70. Over time, the most common reason to place a second DBS lead is to address the contralateral motor symptoms or emergence of contralateral dyskinesia [47].

There are positive effects of DBS in many non-motor features of PD, however the benefits are less obvious when compared to the motor features. Sleep quality is one feature which usually improves [48]. We see some mild effects on mood, including depressive symptoms and anxiety that may improve [49]. A few patients have reported improvements in bladder function and in particular urinary frequency [50]. Cognition does not improve following DBS, and there is a common decline in verbal fluency which has been shown to be more of a lesional effect than a stimulation effect [51,52]. Post-DBS there is a similar risk of dementia compared to the general population at 6–9 years post-implantation, highlighting the importance in monitoring and managing PD features which emerge as part of disease progression [53].

Apathy and other neuropsychiatric features tend to worsen post DBS, especially with aggressive medication reduction [54,55]. Suicide and suicidal ideation should be monitored pre- and post-operatively with either STN or GPi-DBS. The importance of frequent post-operative visits to monitor neuropsychiatric symptoms is a lesson which has been learned over many years of experience with DBS for PD [56–58].

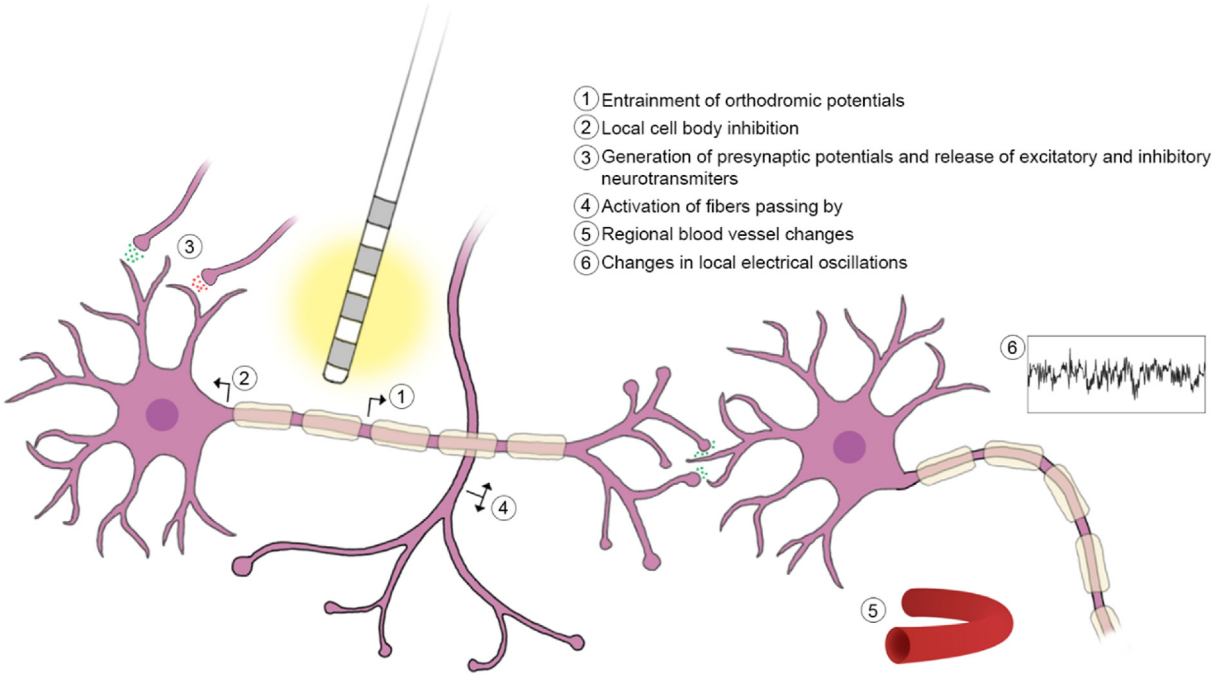

Fig. 2. Mechanism of action of deep brain stimulation. Electrophysiological mechanisms are strongly based on evidence, while other mechanisms (local neurotransmitter release and blood vessel changes) are hypothesized based on imaging studies.

VIM

If upper extremity tremor is the most disabling symptom and it is predominantly postural-action and graded at 2 or more (in a 0–4 scale) VIM DBS should be considered. Also, in cases of clear essential tremor which later develop PD, VIM-DBS should be contemplated. VIM-DBS may need to be added to STN or GPi-DBS in cases where there is a predominant postural-action component to the tremor [59–61]. This observation has led to many experts considering VIM as the initial target in these cases [61]. Other effective targets for PD tremor control may include the caudal zona incerta (cZI) [62] and the prelemniscal radiations (Raprl) [63]. There are long term follow up studies showing the effectiveness of the VIM target for PD [59].

Pedunculopontine nucleus (PPN)

The treatment of gait, balance and freezing of gait is an unmet need in PD. PPN-DBS has been studied in clinical trials PD [64].

PPN-DBS may have mild benefits on freezing of gait and mild improvements in other motor symptoms of PD, however it has largely been abandoned as the results for gait and balance have not been robust [65]. A more recent study on five patients in whom bilateral DBS targeted the most caudal region of the PPN reported an improvement in objective gait measures (velocity, the cadence, the step length, and the stride length), freezing of gait, UPDRS score, quality of life, and falls index up to 1 year after implantation suggesting the possibility that lead location or technical advances may help to rekindle interest in this brainstem target (66). Finally, the caudal region of the PPN, where most neural activity is usually recorded, revealed improvement in the timed up-and-go test [66–68].

Pitfalls

About one quarter of PD patients experience some form of side effect from DBS with speech likely the most common 69. Broadly, there are three types of side effects: surgery-related, hardware-related, and stimulation-induced.

The first group includes hemorrhage, infection, lead erosion, lead fracture, and lead migration. These are more common in older patients and especially those with other medical conditions [70]. Suicide and ideation should be monitored post-operatively [57,71,72].

Stimulation-induced side effects include tonic muscle contractions, dysarthria, or dyskinesias, sensory symptoms and vision issues [73]. Other side effects have been reported and must be separated from medication and disease progression effects (gait impairment, cognitive impairment, depression, slurring of speech, verbal fluency issues and impulsiveness are [71].

Levodopa responsiveness and tremor-dominant phenotype have been associated with better DBS outcomes [74]. A new approach called "surgicogenomics" has been proposed to identify genetic predictors of DBS however to date this has not proven clinically useful [75]. There is debate for example whether DBS should be offered to patients with a GBA1 mutation because of cognitive dysfunction in a subset [76]. In general, most groups do not exclude based on GBA status because there is a wide variation in phenotype.

Electrophysiological biomarkers

PD has been associated with the emergence of pathological synchronization between different brain regions within a distributed network. Many scientists have begun to develop techniques to identify and to modulate these Parkinson related oscillations with electrical stimulation. Local field potentials (LFP) are extracellular electrical fields generally produced by a small population of neurons recorded by a nearby DBS lead. LFPs do not reflect single-cell physiology, but rather the behavior of a group of neurons. A comparison would be a microphone recording the performance of a complete orchestra; you appreciate all the instruments at once. Single-cell recording would be the equivalent of recording each instrument or member of the orchestra independently. LFPs can be divided into different frequency bands: delta (less than 4 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–35 Hz) and gamma (more than 35 Hz). The magnitude of each of these frequency bands is measured by spectral power. LFPs can be recorded during awake DBS surgery with MER, or shortly after the lead implantation with the leads connected to

an external system. In recent years there have been neurostimulators developed capable of chronic sensing: the Medtronic Activa PC + S, and the more recent Medtronic Percept PC. These devices facilitate acute and chronic sensing of the LFP [77]. There are several other companies also working on neurostimulators capable of recording LFPs.

The exaggerated beta band spectral power has been a key finding that is consistent in PD. Several brain targets have revealed changes in the beta oscillatory band: GPi, STN, thalamus, and the premotor cortex [29,78].

The spectral power in the beta frequency has in several studies been associated with clinical symptoms in PD. The posterolateral GPi and the dorsolateral STN have the most publications on these correlations. Rigidity has the strongest correlation and bradykinesia has been less well correlated across studies [79]. Additionally, the beta frequency power has been shown to decrease following levodopa administration [80] and following DBS activation [81]. The lower beta range (13–20 Hz) has been correlated to motor symptoms [82], while the higher beta range (21–35 Hz) has been particularly correlated levodopa administration [83]. The beta band is the most studied biomarker for adaptive DBS (aDBS) technology; however, groups have begun to look at the gamma band particularly with correlation to dyskinesia [30].

Despite the association with bradykinesia and rigidity, the synchronization in the beta band frequency is not necessarily pathological. While we do not have electrophysiological studies of normal patients, in recordings of Tourette syndrome, epilepsy, and dystonia we observe synchronization in the beta band [84–86]. Furthermore, the bursts in the beta frequencies occurs as a part of stable to dynamic movement states, therefore it most closely reflects a lack of adaptability to new motor patterns [87].

The power in the gamma frequency in the 60–90 Hz range increases following levodopa administration [80] and this band has been associated with levodopa-induced dyskinesia [88]. Recently more attention has been drawn to higher gamma frequencies in the 250 and 350 Hz bands. Recent research has shown that following levodopa administration there is a shift in the spectral power from the 350 Hz frequency to 250 Hz, correlating with improvement in motor symptoms independent of the changes in beta frequencies [89,90].

Finally, the alpha and theta bands are referred to as the low-frequency bands. These have not been shown in PD to correlate with the motor symptoms. Interestingly these bands may possibly be associated with impulse control disorders [91,92], memory processing [93], mood disorders [94], and possibly even decision making [95]. These band-specific changes are summarized in Fig. 3.

Technological advances

The commercialization of devices capable of chronically recording LFP has expanded our understanding of brain oscillations beyond the intra-operative and immediate post-operative periods. These devices enable healthcare providers to live-stream LFP during regular follow-up consultations, passively record signals in-between visits, and actively capture the 0–100 Hz spectrum of LFP during specified events [96,97].

A series of trials on aDBS has been initiated after years of research on LFP as a biomarker to close the loop of brain stimulation (Table 1). These trials aim to determine not only the safety and effectiveness of this therapy but also to determine the optimal programming algorithms, including the adoption of machine-learning [98].

Different technologies have been developed to optimize the benefits of DBS therapy while minimizing the risk of stimulation-induced side effects. Directional leads, which facilitate horizontal steering of the electrical current have proven to widen the therapeutic window of DBS [99–102]. Some concerns have been raised about the time-consuming programming of such electrodes, once again emphasizing the need for processes guided by electrophysiology (e.g., LFP), neuroimaging, or a combination thereof [103]. Recent studies revealed that omnidirectional and directional stimulation are equally effective in the short-term [102] and most patients require a steering configuration in at least one lead to prevent or to reduce stimulation-induced side effects [104].

While featuring many new functions, the longevity of novel IPGs batteries has considerably decreased by up to 2.5 years compared to earlier models [105,106]. The battery usage challenge is linked to several factors including most prominently stimulation settings [107]. It was previously thought that bipolar configurations (i.e., cathode and anode on the same lead) may be effective in saving battery [108], but recent investigations on newer IPG models manufactured by Medtronic have challenged this view [103]; this hold true for the other manufacturers' models using constant-current devices compared to constant voltage [109,110]. Directional leads can in select cases possibly reduce battery consumption [111].

The first rechargeable IPGs were introduced more than 15 years ago. Prologued battery lifespan (ranging from 9 to 25 years) reduced the frequency of IPG replacements, with a consequent reduction of costs and with less surgery there is risk of hardware infection [111,112]. Growing evidence has revealed that these IPGs are safe and easy to recharge, even in the elderly patient population. Interestingly, patients switching from a non-rechargeable to a rechargeable device were more likely to be prone to recharging mistakes [113]. To date, the choice of rechargeable devices has depended on patients' preference, ability to manage the recharging routine and the use of the predicted life span of the non-rechargeable product [114].

Experience in early phases of PD

The 'EarlySTIM' trial was a multicenter randomized French-German study carried out to compare neurostimulation plus medical therapy and to compare it to medical therapy alone. The authors studied patients with an average disease duration of seven years who had recently reported levodopa-induced motor complications. This study confirmed the superiority of early STN-DBS for quality of life and motor improvement and it weighed the potential higher risk of serious adverse events, such as impaired wound healing (3.2 %), intracerebral abscess/edema (1.6 %), or the need for reoperation (1.6 %) [115–117].

Another prospective study enrolled 30 PD patients without any motor complications and reported that an earlier surgical approach revealed a reasonable safety profile and offered a potential longer period for overall symptom relief [117,118]. Many DBS experts worry that considering DBS after PD diagnosis and before the appearance of motor fluctuations may increase the risk of including patients with atypical parkinsonism or risk overtreating patients who may never develop the degree of disability requiring DBS [119]. This 30-patient study was small and overall and thus challenging to translate findings to clinical practice without a larger more adequately powered trial.

Thus, the precise timing for implantation of DBS remains debatable [120–122]. Select evidence supports an earlier approach to improve quality of life while minimizing the side effects which may be contributed to by pharmacological treatments. However, as DBS surgery is not a risk-free procedure, most physicians lean towards a case-by-case assessment based on an individual risk-benefit profile. Finally, clinicians should be aware that the mean age for patients enrolled in the EARLY-DBS New England Journal of Medicine trial was ~50 years. That translates in clinical practice to thinking about 'earlier DBS' in younger patients within 1–2 years of the appearance of motor fluctuations. Thus, the findings do not apply to the majority of patients with PD.

DBS in genetic forms of PD

Based on current data, approximately 15 % of PD patients have a family history of the disease, and in up to 10 % a genetic mutation can be detected [123]. Understanding how genetics may impact DBS outcomes is a novel concept referred to as 'surgicogenomics.' Surgicogenomics may in the future aid in identifying suitable DBS candidates and in setting realistic expectations. While polygenic models of PD revealed no significant differences in motor outcomes compared to idiopathic forms of PD, monogenic forms of PD have had a variable response to DBS, however in

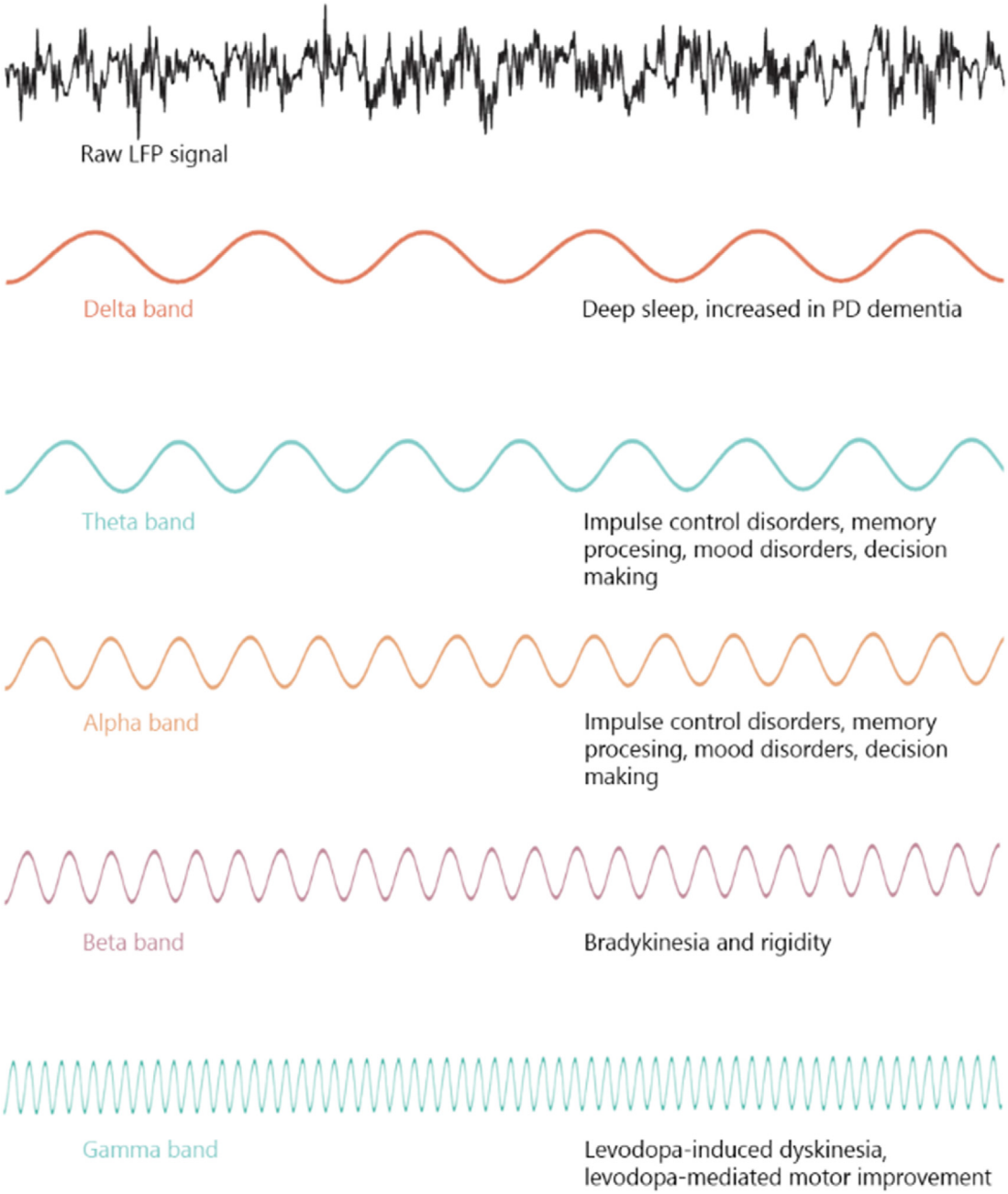

Fig. 3. Electrophysiological biomarkers in Parkinson's diseased based on local field potentials.

general most experts agree genetic forms of PD respond positively to DBS therapy [75,124].

Patients with *LRRK2* mutations have been documented to manifest an overall positive outcome following STN-DBS, although the response may in part depend somewhat on the specific mutation. Most LRRK2 patients carry the p.G2019S (c.6055G > A) mutation and have a documented positive motor outcome. In contrast, those carrying the p.T2031S (c.6091A > T) mutation may develop neuropsychiatric symptoms in the long term, while the p.R1441G (c.4321C > G) variant may be associated with less improvement and rapid symptom progression [125–128]. We should caution however that these differences do not preclude DBS for LRRK2 patients with any of these variants as sample sizes are small and there may be meaningful benefit even in more rapidly progressive cases.

Patients with *PRKN* mutations have in general revealed a favorable long-term motor outcome, although they may possibly have a greater risk of gait and balance impairment, like *PINK1* mutated patients [126,127, 129]. Again, like LRRK2 the sample sizes are so small, and it is hard to control disease progression so these slight differences in gait outcomes should be interpreted with caution.

Outcomes following DBS in *GBA* mutation carriers has been reported to be positive, although this genetic group may more frequently be prone to cognitive impairment and more severe axial motor impairment compared to non-genetic PD patients undergoing STN DBS. Very recently, it has been proposed that GPi DBS might be a safer treatment for *GBA*-mutated patients [130] though this will require more careful study to confirm. The idea that GBA patients should not be offered DBS has been rejected by most expert centers. Though GBA patients may manifest cognitive challenges there is tremendous heterogeneity among carriers and it is at present impossible to predict rapid decliners. In addition, GBA carriers can benefit from tremor, motor fluctuations and improvements in off time and thus they should be entitled to full multidisciplinary workups to determine eligibility for surgery. Early cognitive decline has

Table 1
aDBS Trials in PD.

	Title	Sites (PI)	Study Design	Primary Endpoint(s)	Other Endpoints
NCT05402163	CANadian Adaptive DBS TriAl (CAN.A.D.A)	Toronto (Fasano)	Randomized cross-over, double-blinded, 8mo prospective (open loop vs. closed loop)	UPDRS III, PDQ39, Gait, Speech Quality	UPDRS III
NL80384.018.22	AI-DBS: Applying Personalized DBS using "Neuronal Fingerprints"	AUMC (Beudel)	Observational, single-arm, 6mo prospective	UPDRS III, Diary, Wearable	UPDRS 1-II & IV
NCT04547712	ADAPT PD[a]	US, EU, CAN Multi-Center (Bronte-Stewart)	Cross-over, single-blind, 30d prospective (single vs. dual mode aDBS)	On time without troublesome dyskinesia	Safety, TEED, UPDRS I-IV, PDQ39, Speech, Patient Preference, Wearable
jRCT1042200088	Early Adapter 1[a]	Japan Multi-Center (Sekiguchi)	Observational, single-arm, prospective	Proportion of subjects with at least one acceptable aDBS mode	TEED, PDQ39, UDysRS, UPDRS III, Patient preference, Wearable
jRCT1032210376	Early Adapter 2[a]	Japan Multi-Center (Hattori)	Cross-over, single-blind, 30d prospective (cDBS vs. aDBS)	TEED	PDQ39, UDysRS, UPDRS III, Patient preference, Wearable
NCT03582891	Motor Network in PD and Dystonia: Mechanisms of Therapy	UCSF (Starr)	Randomized cross-over, double-blinded (open loop vs. closed loop)	On time without troublesome dyskinesia	UPDRS III, H&Y, Schwab & England, PDQ39, PGIC, TEED, wearable
NCT04675398	Adaptive DBS to Improve Motor and Gait Functions in PD	UCSF (Wang)	Randomized cross-over, double-blinded (open loop vs. closed loop)	Motor learning task completion, speed & accuracy	UPDRS III, NIHTB, gait and balance measures, wearable
NCT05070013	Adaptive Neurostimulation to Restore Sleep in PD	University of Nebraska, University of Colorado, University of Pennsylvania (Abosch)	Randomized cross-over, double-blinded (no stimulation vs. open loop vs. closed loop)	Sleep efficiency (ActiWatch), Subjective Sleep Quality	Duration of REM sleep
NCT03815656	Closed Loop DBS Implanted RC + S Study	Duke (Turner)	Open label (STN alone, GPi alone, STN + GPi, open loop vs. closed loop)	UPDRS I-IV On/On	UPDRS III Off/On, % good on time, PDQ39
NCT05262348	An Open-label Clinical Trial to Compare the Safety and Effectiveness of Adaptive Versus Conventional Deep Brain Stimulation (ADVENT)[a]	North America, EU Multi-Center	Initial open-label crossover phase (cDBS vs. aDBS) and a 28mo long-term follow-up phase during which patient can switch between modes.	Treatment-Emergent Adverse Events, Compare GOT when the patient receives cDBS.	Success rate measured with at least 2 h of improvement in each mode, fluctuations, UPDRS III, UDysRS, percentage of aDBS use.
NCT04681534	Safety and Efficacy of Adaptive Deep Brain Stimulation[a]	Italy, Poland Multi-Center	Randomized cross-over, double-blinded (cDBS vs. aDBS) for STN-DBS.	Safety and tolerability, TEED.	UPDRS III, UDysRS, dyskinesia using accelerometer, time ON with or without dyskinesia, time OFF, usability by patient and physician.
NCT03422757	Safety and Efficacy of Adaptive DBS Vs Conventional DBS in Patients With Parkinson's Disease[a]	Italy Multi-Center	Randomized cross-over, double-blinded (open cDBS vs. aDBS).	TEED	Adverse events, UPDRS III, UDysRS, time OFF, DBS-IS, LFP during gait, speech and sleep.
NCT04197947	Selectively Modulating Pathophysiological Biomaker to Improve Freezing of Gait in Parkinson's Disease by Adaptive Subthalamic Stimulation	Taiwan (Chen)	Observational, single-arm, prospective	UPDRS III, FoG-Q, quantitative freezing of gait.	
NCT06012461	Safety and Effectiveness of Closed-loop DBS in Parkinson's Disease: A Long-term Follow-up Study	Tsinghua University, China (Li)	Open label, single arm, 15mo prospective.	UPDRS-III, RDRS, sleep structure, PD outcomes diary.	Stimulation related adverse events, TEED, LFP changes.

Abbreviations: aDBS: adaptive deep brain stimulation; cDBS: conventional continuous deep brain stimulation, DBS-IS: DBS impairment scale; FoG-Q: questionnaire of freezing of gait; GOT: good on time; H&Y: Hoehn & Yahr Scale; LFP: local field potentials; NIHTB: National Institutes of Health toolbox; PD: Parkinson's disease; PDQ-39: Parkinson's Disease Questionnaire; PGIC: Patient's Global Impression of Change; RDRS: Rush Dyskinesia Rating Scale; TEED: total electrical energy delivered; UDysRS: Unified Dyskinesia Rating Scale; UPDRS: Unified Parkinson's Disease Rating Scale.

[a] Industry-sponsored.

been described in patients with *SNCA* mutations after DBS [131,132] however similar to GBA mutations it is not clear that in an individual that surgery should be withheld based on genetic status.

As genetics have entered into the clinic, DBS centers will be confronted with decisions on surgical eligibility. Currently most experts recommend a multidisciplinary risk benefit evaluation which takes into consideration the genetic status but does not exclude anyone based on genetics alone. Shared decision making should be pursued in cases considering DBS who may be at risk group for rapid cognitive deterioration.

Indications of DBS

The Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD) was the gold standard for lesion therapies and was the model first used to assess DBS candidates [133]. Relying on the CAPSIT-PD protocol alone however is insufficient as it does not take into account important metrics such as psychosocial functioning, quality of life and expanding knowledge on phenotypes and genotypes [134]. It also does not appreciate the several decades of experience of the literature and thus CAPSIT has been replaced by multidisciplinary screening with a risk benefit analysis.

The best candidates for DBS have been traditionally described as young-onset PD patients reaching the surgical evaluation period before the age of 70 and suffering from motor fluctuations, dyskinesias and/or levodopa-resistant tremor [134,135]. Although age is not an absolute exclusion criterion, it has been linked to comorbidities such as cognitive decline and levodopa-resistant axial signs. Patients should be informed that these particular symptoms are unlikely to improve and can even worsen after DBS. The burden caused by non-motor symptoms should be considered, especially post-operative apathy and depressed mood, which may be unmasked by rapid medication reduction. Genetic testing can provide useful information on disease progression, although genetic testing should not be an absolute inclusion or exclusion criteria [136,137].

Outstanding challenges

The effect of DBS in PD on axial symptoms is variable and has been mild at best. Some axial symptoms may improve following DBS if the patient is found to improve in the best motor on dopaminergic state during the levodopa challenge test which has been recommended by the American Academy of Neurology for DBS screening. DBS does not in general help with falling or postural reflexes. Falls are a widely recognized source of morbidity, mortality, and may result in poor quality of life in PD, and are considered a major milestone in PD disease progression [138]. Several factors can act as precipitants for falls, including freezing of gait, rigid-akinetic phenotypes of PD, cognitive impairment, motor weakness, peripheral neuropathy, and impaired postural reflexes [139,140]. Patients who are falling should be approached carefully about potential DBS therapy. Falling does not exclude them, however shared decision making should address the failure of DBS on this symptom.

Postural abnormalities, including camptocormia, Pisa syndrome and anterocollis are associated with a higher risk of pain and falling in patients with PD [141]. While some patients with these symptoms may occasionally benefit from STN-DBS, a variable degree of worsening has been documented and clinicians should be cautious when advising DBS surgery for these indications [142].

Cognitive impairment remains a major limitation for potential DBS surgery, with an estimate of 23 % of patients treated with DBS having pre-surgical mild cognitive impairment [143]. While effects vary, attention and memory are frequently affected after STN-DBS in up to one-fifth of PD patients [144]. This cognitive dysfunction can be particularly challenging for patients who already have some degree of cognitive impairment from PD progression. Although DBS is generally contraindicated in patients with dementia, those with mild cognitive impairment may manifest similar outcomes to PD patients with normal or near normal cognition in the short-term [145]. This group of patients may also have significant motor symptom relief, medication reduction, and quality of life improvement [146]. Each person with PD considering DBS should have a detailed neuropsychological profile to determine risk as well as pre- and post-operative management.

Non-invasive neuromodulation

Transcranial magnetic stimulation (TMS)

TMS consists of delivering a rapidly changing magnetic field through a coil placed above the patient's scalp and is used to targeted a brain region that is located at a depth of 2–3 cm below the surface [142]. A strong magnetic pulse can result in brief activation or inhibition of a cortical region, thus resulting in widespread changes within the targeted network [147], including distal effects such as those on dopamine release in the putamen [148]. The cellular-level mechanism of action is illustrated in Fig. 4.

Several protocols of repetitive TMS (rTMS) over different target regions have been shown to improve bradykinesia, gait [149,150], dysphagia [151], and levodopa-induced dyskinesia for up to 4 weeks after treatment [149,150]. The protocol found to be most effective in a few studies has been high frequency rTMS over the leg or hand area of the primary motor cortex (M1) or over the dorsolateral prefrontal cortex (DLPFC) [152]. Tremor does not tend to respond to rTMS of M1 cerebral

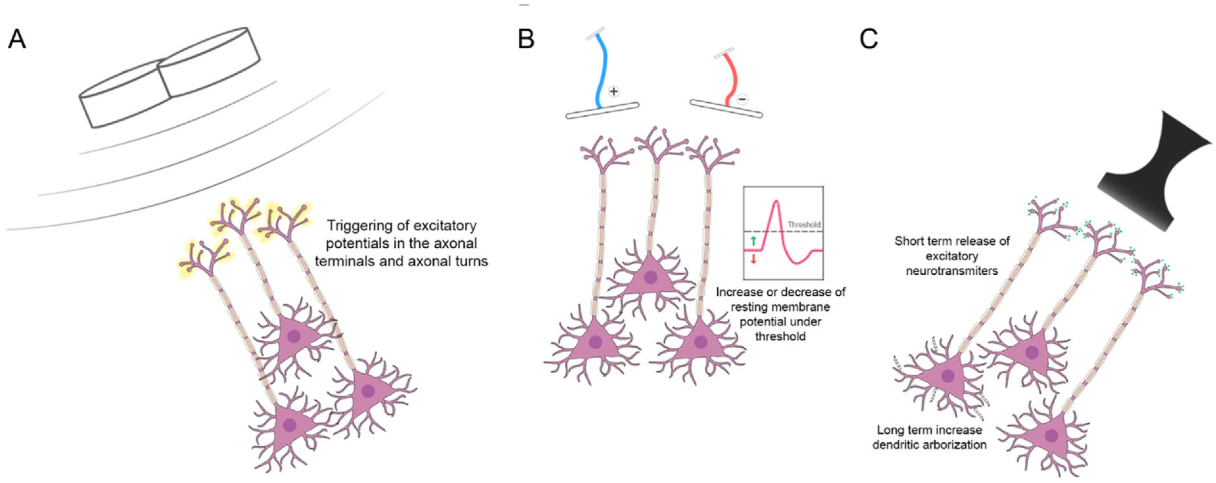

Fig. 4. Mechanism of action of transcranial magnetic stimulation (A), transcranial direct current stimulation (B), and electroconvulsive therapy (C).

cortex or cerebellum stimulation [153]. A meta-analysis of seven rTMS studies targeting M1 revealed improvement of freezing of gait and motor symptoms [154]. Another study using two sessions of high frequency rTMS over the supplementary motor area showed improvement in freezing of gait more than in M1 stimulation [155]. While these studies could be considered 'proof of concept' that modulating different nodes of the locomotive network may improve freezing, the ideal target (or targets) and the most optimal TMS paradigm are still debated. Additionally, there has been frustration among clinicians at the transient effects of TMS, which could translate in near daily treatment sessions in order to have sustained benefit.

TMS is approved for patients with drug-resistant depression regardless of other comorbidities [156]. Some studies have shown that rTMS of the left DLPFC may effective to treat PD-related depression [157–159], although a randomized trial recently reported no significant improvement [160,161].

Transcranial direct current stimulation (tDCS)

Compared to rTMS, tDCS is easier to apply and may be slightly safer [162,163]. A meta-analysis of sham-controlled tDCS studies showed that there was a significant reduction of UPDRS motor scores [164]. A randomized sham-controlled trial also revealed that eight sessions of tDCS over a period of 2.5 weeks reduced bradykinesia for up to three months after the intervention [163]. Additionally, tDCS has been shown to improve several cognitive domains, including consolidation of writing skills by targeting M1 [165], improving executive function by targeting DLPFC bilaterally [166], improving working memory [167] and improving phonemic fluency [168] by targeting the left DLPFC. It should be appreciated that these effects have only been documented to persist in acute and subacute settings.

Currently there is no recommendation to use tDCS in clinical practice and several research groups have been exploring the optimal treatment regimen and techniques to extend the benefit to longer time intervals [164,169].

Electroconvulsive therapy (ECT)

ECT consists of delivering an electrical current to the brain using scalp electrodes and it is performed under general anesthesia. Practitioners employ pharmacologic muscle paralysis, with the purpose of inducing a generalized seizure for 20–60 s. The usual ECT protocols involve 6 to 12 treatments over 2–4 weeks [170]. ECT has been used to treat psychiatric disorders since the 1950s [170] and is currently used to treat major depression [171], bipolar disorder, catatonia [172], and schizophrenia [173]. The mechanism of action is represented in Fig. 4.

A meta-analysis recently evaluated the effects of ECT on the motor symptoms in PD and a pooled analysis showed a significant improvement in motor scores after treatment, even in patients without psychiatric symptoms [174]. However, ECT has been mainly studied as a treatment for psychiatric comorbidities in PD, overall with significant improvement of depression and psychosis [174–177]. There are scattered reports of DBS patients safely treated with ECT for refractory depression and psychosis [178]. The authors of this review have anecdotally had several patients with DBS successfully undergo ECT therapy.

ECT may result in anterograde amnesia that typically resolves within 2–4 weeks [179]. There is also retrograde amnesia, with autobiographical memory gaps, that usually develops gradually over a series of treatments and then resolves gradually over the following weeks to months [170]. In PD studies no evidence of cognitive impairment after ECT has been documented [174].

We have found ECT to be the most powerful therapy for severe depression in PD with or without existing DBS implantation. ECT has a much longer lasting effect than TMS or TDCS. ECT can be life changing and can rapidly turn around severe cases of depression with associated suicidality. Because less is known about safety in the setting of DBS, a shared decision-making process should be pursued with patients and families.

Novel forms of neuromodulation

While our current neuromodulation approaches are effective in the clinics and are successfully implemented across the world, these technologies still have some shortcomings. Future technologies should improve spatial specificity, access in low-resources areas, need for long-term specialized care, and surgical or procedural risk.

Temporal interference stimulation (TIS) consists of applying converging high-frequency electrical fields (more than 1 kHz); each field having a different frequency [180]. The overlap of the two fields modulates the region of interest and does so at the difference between the two independent frequencies. In animal studies, this approach does not disrupt the tissue each field passes through to reach the intended target [181]. TIS has been widely used in mice and in-silico for modulation of specific cell populations [182]. Translation into humans has been tricky and has presented PD and other disease experts with formidable challenges. Recently TIS failed to modulate the retina cells or the occipital cortex in a pilot study of healthy human volunteers [183].

Another emerging (or *re*-emerging) technology has been high-frequency focused ultrasound to ablate brain regions and to treat tremor and potentially other symptoms associated with PD [184]. When applied at lower frequencies, focused ultrasound results in a much smaller temperature increase which can be used to modulate ion channels [185] and enzyme activity [186], as well used to induce mechanical deformation which may result in changes in electrical excitability [187, 188]. Although there are no therapeutic studies in patients with PD for this approach, there is evidence that image-guided low-frequency ultrasound may be useful to enhance drug delivery through its effects on the blood brain barrier [189].

Magnetoelectric stimulation is another technology which applies magnetoelectric nanoparticles to generate electrical fields. This technique applies a magnetic pulse to accomplish the delivery [190]. The delivery of these particles also requires stereotactic surgical implantation. A potential mechanism of action may be the activation of calcium and sodium channels though the true biology and mechanism remain unknown [191]. To date, the experiments conducted with these nanoparticles have been in ex-vivo cortical slices [192] and cell cultures [191]. It will be interesting to observe over the next several years how nanoparticle delivery systems will advance in translation and whether these techniques are prone to the same types of challenges as optogenetics and TIS.

Future directions

PD encompasses a broad spectrum of phenotypic expressions and genotypes and thus PD is not one disease. Consequently, future treatment protocols should guide healthcare providers toward more tailored therapies. This approach should emphasize the individual needs of each patient and therapies should be chosen to target specific circuits and specific symptoms. Genetics should not exclude any PD patient from neuromodulation therapy and all potential neuromodulation patients should undergo multidisciplinary evaluation and shared decision making before consideration of any intervention. This type of approach will likely facilitate an open and realistic dialogue concerning medium and long-term expectations.

Neuromodulation addresses PD signs and symptoms applying the technology to discrete dysfunctional networks, and this facilitates a degree of personalization that cannot be achieved with other interventions. Invasive neuromodulation has proven its potential effectiveness for many technologies and remains experimental for many more. Studies will need to define its potential value in routine clinical practice and define short versus longer lasting benefits. We provide in this article an overview of many forms of neuromodulation for PD (Table 2), and we opine that the

Table 2
Comparison of different modalities of neuromodulation for Parkinson's disease.

	DBS				rTMS		tDCS		ECT	
Target structure	Gpi	STN	VIM	PPN	M1	DLPFC	M1	DLPFC	Cerebral cortex	Cerebral cortex
Symptoms that improve	Bradykinesia Tremor Rigidity Dyskinesias	Bradykinesia Tremor Rigidity Dyskinesias	Tremor	Gait speed, freezing of gait	Bradykinesia Freezing of gait	Depression	Bradykinesia	Executive function Working memory Phonemic fluency	Bradykinesia	Psychosis
Side effects of the intervention	Stimulation induced (reversible): dysarthria, tonic muscle contractions, phosphenes. Surgical: Intracerebral hemorrhage Hardware infection	Stimulation induced (reversible): paresthesia, dysarthria, tonic muscle contraction, impulsivity, personality changes. Surgical: Intracerebral hemorrhage Hardware infection	Stimulation induced (reversible): paresthesia, dysarthria, ataxia. Surgical: Intracerebral hemorrhage Hardware infection	Stimulation induced (reversible): oscillopsia, paresthesia, tonic muscle contraction. Surgical: Intracerebral hemorrhage Hardware infection	Headache, local pain, seizure.		Headache, nausea, paresthesia		Transient anterograde and retrograde amnesia.	
Stage of development	FDA approved since 2002	FDA approved since 2002	FDA approved since 1997	Ongoing clinical trials	Identifying optimal treatment paradigm. Undergoing sham-controlled studies.	FDA approved for depression in 2008.	Identifying optimal treatment paradigm. Undergoing sham-controlled studies.		Observational trials done. No ongoing trials registered.	One clinical trial done in PD patients.
Pros	Improves dyskinesia. Safer for LD-responsive gait impairment Easier to program	Longer battery life Greater dopaminergic medication reduction Greatest clinical evidence of efficacy	Safe even in older and frailer patients. Longest clinical evidence of efficacy	LD-resistant freezing of gait and imbalance are not addressed by other DBS targets	Does not require hardware. Does not require sedation.	Has been extensively studied in treatment-refractory depression. Does not require hardware. Does not require sedation.	Does not require hardware. Does not require sedation.		Does not require hardware.	Psychosis is not addressed with other forms of neuromodulation.
Cons	Need for surgical implantation	Need for surgical implantation	Only improves tremor. Need for surgical implantation	Does not improve other symptoms of PD. Experimental with variable results.	Optimal settings have yet to be determined. Repeated treatments are necessary. Relatively contraindicated in patients with DBS.				Requires generalized anesthesia, muscle paralysis, and induction of a seizure. Relatively contraindicated in patients with DBS.	

Abbreviations: DBS: deep brain stimulation; DLPFC: dorsolateral prefrontal cortex; ECT: electroconvulsive therapy; FDA: U.S Food and Drug Administration; Gpi: globus pallidus pars interna; M1: primary motor cortex; PPN: pedunculopontine nucleus; rTMS: repetitive transcranial magnetic stimulation; STN: subthalamic nucleus; tDCS: transcranial direct current stimulation; VIM: ventral intermediate nucleus of the thalamus.

Table 3
Other neuromodulation therapies.

	SCS (190,191).	tACS (192, 193).	TIS (194).	VNS (195, 196, 197).
Indications	Freezing of gait, pain.	Motor and nonmotor PD symptoms.	Unknown	Freezing of gait
Possible mechanism of action	May suppress aberrant beta-frequency corticostriatal oscillations. May facilitate spinal patter generators and dorsal roots.	Cortical activity modulation using alternating current to suppress fast cerebral oscillations.	Non-invasive deep neuronal stimulation using high-frequency external electric fields.	Activation of locus coeruleus' noradrenergic neurons.
Potential benefits	Improvement in gait measurements, reduce the risk of falling, better quality of life.	Improvement in motor outcomes, and cognition.	Unknown.	Improvement in gait, reduction of steps while turning.
Side effects of intervention	Paresthesia	Phosphenes, itching and skin redness, paresthesia.	Unknown.	Skin irritation, headache, nasopharyngitis,

Abbreviations: SCS: spinal cord stimulation; PD: Parkinson's disease; tACS: transcranial alternating current stimulation; TIs: temporal interference stimulation; VNS: vagus nerve stimulation.

field will continue to evolve as we better understand the biology and mechanisms of action of DBS therapy. Finally, many other neuromodulation approaches are presently being considered but will require much more validation and documentation of clinical benefits before proposing for routine clinical practice (Table 3).

Author contributions

AEMN: Manuscript drafting, figure drawing, manuscript editing. MBJ: Manuscript drawing, manuscript editing. MSO: Project conception, manuscript editing. AF: Project conception, manuscript editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Alfonso Fasano reports a relationship with Abbott that includes: funding grants. Alfonso Fasano reports a relationship with Boston Scientific Corp that includes: funding grants. Alfonso Fasano reports a relationship with Neuroelectrics Corp that includes: funding grants. Alfonso Fasano reports a relationship with Medtronic that includes: funding grants. Michael S. Okun reports a relationship with Parkinson's Foundation that includes: board membership. Michael S. Okun reports a relationship with National Institutes of Health that includes: funding grants. Michael S. Okun reports a relationship with The Michael J Fox Foundation that includes: funding grants. Michael S. Okun reports a relationship with Parkinson Alliance that includes: funding grants. Michael S. Okun reports a relationship with Bachmann-Strauss Dystonia and Parkinson Foundation Inc that includes: funding grants. Associate editor for New England Journal of Medicine Journal Watch Neurology and JAMA Neurology - MSO.

Disclosures

This review was partly funded by the University of Toronto and University Health Network Chair in Neuromodulation to AF.

AF received honoraria and/or research support from Abbott, Boston Scientific, Ceregate, Inbrain Neuroelectronics, Iota, and Medtronic.

Dr. Okun serves as Medical Advisor the Parkinson's Foundation, and has received research grants from NIH, Parkinson's Foundation, the Michael J. Fox Foundation, the Parkinson Alliance, Smallwood Foundation, the Bachmann-Strauss Foundation, the Tourette Syndrome Association, and the UF Foundation. Dr. Okun's research is supported by: NIH R01 NR014852, R01NS096008, UH3NS119844, U01NS119562.

Dr. Okun is PI of the NIH R25NS108939 Training Grant. Dr. Okun has received royalties for publications with Demos, Manson, Amazon, Smashwords, Books4Patients, Perseus, Robert Rose, Oxford and Cambridge (movement disorders books). Dr. Okun is an associate editor for New England Journal of Medicine Journal Watch Neurology and JAMA Neurology. Dr. Okun has participated in CME and educational activities (past 12–24 months) on movement disorders sponsored by WebMD/Medscape, RMEI Medical Education, American Academy of Neurology, Movement Disorders Society, Mediflix and by Vanderbilt University. The institution and not Dr. Okun receives grants from industry. Dr. Okun has participated as a site PI and/or co-I for several NIH, foundation, and industry sponsored trials over the years but has not received honoraria. Research projects at the University of Florida receive device and drug donations.

Acknowledgments

Both the University of Toronto and the University of Florida are supported by Center of Excellence grants from the Parkinson's Foundation. Additionally, Dr. Okun's research is supported by: NIH R01NR014852, R01NS096008, UH3NS119844 and U01NS119562 grants.

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