Parkinsonism and Related Disorders 59 (2019) 9–20

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

A review of basal ganglia circuits and physiology: Application to deep brain stimulation

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ARTICLE INFO

Keywords:
Basal ganglia
Neuromodulation
Deep brain stimulation
Optogenetics

ABSTRACT

Introduction: Drawing on the seminal work of DeLong, Albin, and Young, we have now entered an era of basal ganglia neuromodulation. Understanding, re-evaluating, and leveraging the lessons learned from neuromodulation will be crucial to facilitate an increased and improved application of neuromodulation in human disease.
Methods: We will focus on deep brain stimulation (DBS) – the most common form of basal ganglia neuromodulation – however, similar principles can apply to other neuromodulation modalities. We start with a brief review of DBS for Parkinson's disease, essential tremor, dystonia, and Tourette syndrome. We then review hallmark studies on basal ganglia circuits and electrophysiology resulting from decades of experience in neuromodulation. The organization and content of this paper follow Dr. Okun's Lecture from the 2018 Parkinsonism and Related Disorders World Congress.
Results: Information gained from neuromodulation has led to an expansion of the basal ganglia rate model, an enhanced understanding of nuclei dynamics, an emerging focus on pathological oscillations, a revision of the tripartite division of the basal ganglia, and a redirected focus toward individualized symptom-specific stimulation. Though there have been many limitations of the basal ganglia "box model," the construct provided the necessary foundation to advance the field. We now understand that information in the basal ganglia is encoded through complex neural responses that can be reliably measured and used to infer disease states for clinical translation.
Conclusions: Our deepened understanding of basal ganglia physiology will drive new neuromodulation strategies such as adaptive DBS or cell-specific neuromodulation through the use of optogenetics.

1. Introduction

Once considered a black box, the basal ganglia are becoming increasingly well-characterized through the application of clinical and research modalities. Consisting of both input and output nuclei, the basal ganglia receive information predominately through a corticostriatal pathway (Fig. 1, see caption). The classic box-and-arrow models of the direct and indirect pathways derived by DeLong, Albin, and Young have provided a foundation for hypotheses and mechanistic explanations of basal ganglia function and dysfunction [1,2]. Stemming from this framework, the success of brain ablation studies and preliminary work applying electrical stimulation ultimately led the French neurosurgeon Alim Benabid to implant a lead within the thalamus to provide continuous delivery of electricity through a modern deep brain stimulation (DBS) system [3–5]. Basal ganglia neuromodulation is now established for the treatment of specific movement and neuropsychiatric disorders. In turn, this ongoing era of neuromodulation has expanded our understanding of basal ganglia circuitry and electrophysiology, and this has motivated improved neuromodulation techniques.

In this paper, we will review data drawn from neuromodulation studies of Parkinson's disease (PD), essential tremor (ET), dystonia, and Tourette syndrome (TS). The content will follow directly from the lecture given by Dr. Michael S. Okun at the 2018 International Association

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https://doi.org/10.1016/j.parkreldis.2019.01.009
Received 31 August 2018; Received in revised form 7 January 2019; Accepted 9 January 2019

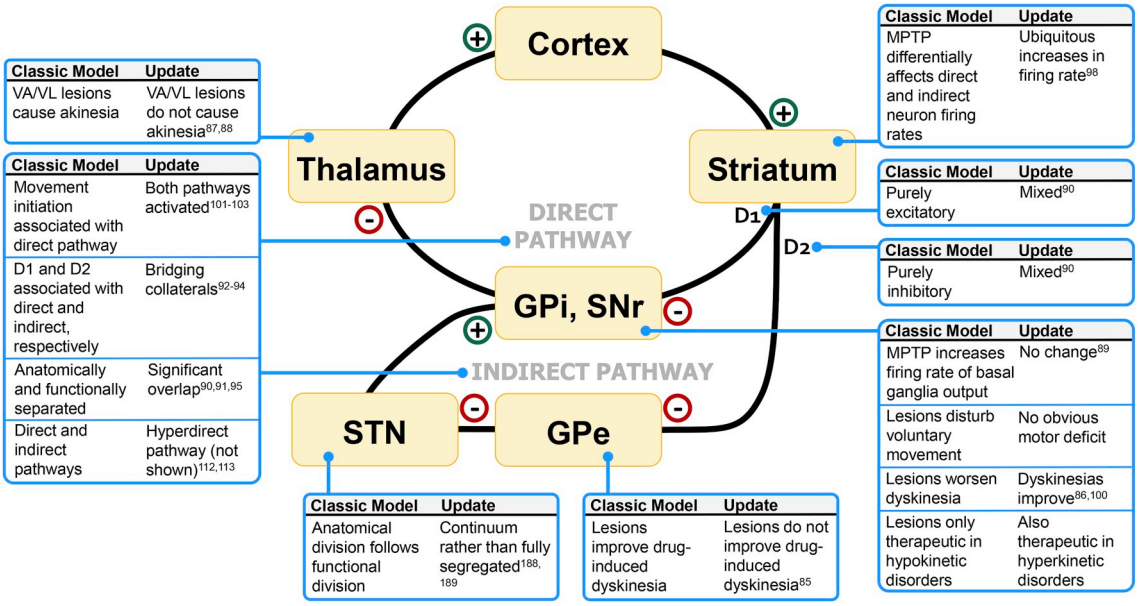

Fig. 1. Limitations of the rate model. GPi, globus pallidus internus; SNr, substantia nigra pars reticulata; GPe, globus pallidus externus; D, dopamine. Plus signs indicate glutamatergic projections and minus signs indicate GABAergic projections. Classic basal ganglia "box" models include a direct and indirect pathway. The direct and indirect pathways are classically associated with D1 and D2 receptors, respectively. The direct pathway disinhibits the thalamus via inhibition of the GPi through a direct striatal-pallidal-thalamic loop. In contrast, the indirect pathway sends inhibitory projections first to the GPe, leading to less inhibition of the STN, and subsequently more activation of the GPi. Firing rates can be measured along these pathways and are commonly used to investigate pathological under- or over-activity of these nuclei in specific diseases. Although the original rate model proved pivotal for motivating neurosurgical efforts in the treatment of basal ganglia diseases, recent observations have demonstrated its many limitations. Here, we depict a subset of examples, indicating for each what the classic model would predict and what new evidence has demonstrated.

of Parkinsonism and Related Disorders World Congress in Lyon, France. Namely, we will recount notable lessons learned about basal ganglia neuromodulation, including lesioning and stimulation, from both clinical and research perspectives. These efforts have led to an expansion of the basal ganglia rate model, an enhanced understanding of nuclei dynamics beyond simple excitation and inhibition, an emerging focus on pathological oscillations, and a revision of the tripartite division of the basal ganglia. We will also address the upcoming era of patient-specific neuromodulation.

2. Neuromodulating basal ganglia pathologies

Currently, DBS and its experimental indications remain in early stages of development. Here, we briefly review four current and growing indications of DBS, namely PD, ET, dystonia, and TS, with focused background information relating the relevant basal ganglia pathology to underlying circuitry. We will also comment briefly on the surgical targets for these indications and their potential clinical advantages.

2.1. Parkinson's disease

Though it is known that PD is underpinned by neurodegeneration of substantia nigra (SN) dopaminergic neurons and by widespread progressive brain pathology, dysfunction at the neural circuit level remains uncertain. In PD, there is decreased globus pallidus externus (GPe) activity and increased subthalamic nucleus (STN), globus pallidus internus (GPi), and SN pars reticulata (SNr) activity. Thus, PD symptoms conceptually arise from an aberrant increase of indirect pathway output via the GPe and a decrease in direct pathway activity via the GPi (Fig. 1), in which both mechanisms lead to over-inhibition of the thalamus and an under-activation of the cortex.

To date, several controlled clinical trials have demonstrated that PD-DBS applied in either the STN or GPi can improve both motor symptoms and quality of life [6–10]. Some studies even suggest an improvement in non-motor symptoms (e.g. anxiety and pain) [11,12]. However, there can be appreciable differences in responses based on target choice. Though stimulating both targets similarly impact many of the primary motor outcomes, STN-DBS may lead to higher rates of adverse cognitive outcomes [13,14]. The STN is however the target associated with more medication reduction [14], whereas the GPi may be preferable for dyskinesia control and when long-term flexibility in medication management is required [13]. Both STN- and GPi-DBS are not effective in addressing motor symptoms unresponsive to dopaminergic therapies (with the exception of tremor), including voice, cognition, gait, and balance difficulties [13].

Other brain targets have been explored in PD, including the centromedian nucleus (CM) [15,16], the zona incerta (ZI) [17], the SN [18], and the pedunculopontine nucleus (PPN) [19]. The PPN is highly underactive in the PD state due to the increased inhibitory projections from the GPi, thus gait and balance problems may subside if this inhibitory outflow is interrupted [20]. The PPN in particular may be useful for axial motor symptoms [19,21], but further studies are warranted due to inconsistent results [21–23].

2.2. Essential tremor

The pathophysiological basis of ET is emerging [24–26] and high-frequency stimulation (HFS) of the thalamus has been shown efficacious by several randomized trials [27–32]. The pathologic basis of ET has begun to emerge with post-mortem evidence supporting cerebellar degeneration [33–35] and with clinical studies demonstrating abnormal cerebellar function including tandem gait and balance problems [36,37]. One study reported brainstem Lewy bodies, especially within the locus coeruleus, where neurons synapse with Purkinje cells [33]. This reduced inhibition from Purkinje cells could result in increased disinhibition of deep cerebellar neurons, thus over-activating the cerebello-thalamo-cortical network.

Presumably to combat this over-activation, stimulation directed to the ventralis intermedius (VIM) nucleus of the thalamus (the cerebellar

recipient nucleus [27,28]) is highly effective. Other targets such as the caudal ZI (cZI) or posterior subthalamic area (PSA) have also been investigated [38–44]. Stimulation to these areas are postulated to have similar or possibly more advantageous effects on proximal tremor. Results from retrospective studies that analyzed differences in outcomes among various targets have been mixed [45,46]. Recently, one prospective, randomized trial comparing the VIM and PSA found no difference in tremor control. However, this trial demonstrated that PSA-DBS had similar clinical efficacy with lower stimulation amplitudes, potentially lessening the chance for stimulation-induced adverse effects and the rare occurrence of tolerance [47]. Overall, there is a paucity of evidence suggesting superiority of either the VIM, PSA, or cZI, and larger, prospective trials will be needed. The main issue affecting the outcome of ET-DBS has been disease progression despite neuromodulation [48], which contrasts to what is observed in PD-DBS where tremor can be suppressed long-term [49].

2.3. Dystonia

Dystonia is a hyperkinetic movement disorder characterized by involuntary sustained or sporadic movements possibly arising from decreased cortical inhibition and increased long-term potentiation of synaptic plasticity within the motor cortex [50,51]. Studies in non-human primates have suggested that dystonia arises from increased inhibition of the STN and GPi by inputs from the GPe, leading to reduced inhibition to the thalamus and increased excitation to the cortex [52]. Corroborating these results are studies reporting reduced discharge rates from the pallidum [53–56] and hyperactivity of the basal ganglia's direct pathway [57] in dystonia.

Although there are reports of STN- and thalamic-DBS for dystonia, the most common target has remained the GPi [58]; however, growing evidence suggests the STN may be equally suitable [59,60]. The sustained clinical effectiveness of DBS has been demonstrated most clearly in primary generalized and segmental dystonia [61–64], but other forms of dystonia have also been successfully treated with DBS [65–67]. Tardive dystonia specifically has a more rapid response to neuromodulation compared to other forms of dystonia where response is delayed and may evolve over weeks to months. Consequently, not all dystonia subtypes respond favorably to DBS and more research is needed to better characterize targets and applications of DBS into a largely heterogeneous population.

2.4. Tourette syndrome

Involuntary tics are thought to arise from reduced inhibition of the thalamocortical circuitry and excessive activity of frontocortical areas [68] as well as from changes in striosomes [69–71]. More specifically, research suggests that a specific set of striatal neurons may become pathologically active resulting in the inhibition of a specific set of GPi neurons. This excessive inhibition of the GPi leads to disinhibition of the thalamus and over-activation of the cortex, resulting in involuntary movement [72], similar in some respects to the mechanism reported in dystonia. Stemming from the success of ablative procedures, TS-DBS was introduced in 1999 [73,74]. There are many comorbidities in TS patients and the optimal approach and target(s) for DBS remain unknown. Since most centers lack the volume to accomplish a randomized clinical trial, a recent international registry has been created to gather cases and outcomes [75].

Brain targets for neuromodulation have included the pallidum [76–78], the nucleus accumbens, the anterior limb of the internal capsule [79,80], the STN [81], and the centromedian thalamic region [74,82–84]. For every target explored, clinical evidence has demonstrated mixed results, but overall improvements in motor and vocal tics have been reported to be approximately 30–40% [85].

3. Moving beyond the rate model

Despite empirical support for the rate model in explaining the pathophysiology of these diseases, more recent neuromodulation studies have uncovered numerous paradoxes and limitations that have motivated further investigation (Fig. 1). For instance, under the rate model, excessive and deficient thalamic output is associated with hyperkinesia and hypokinesia, respectively. It is therefore paradoxical that lesions of the GPi, leading to thalamic inhibition, could be therapeutic for PD dyskinesias [86,87] or dystonia and that thalamic ventral lateral and ventral anterior lesions actually do not cause akinesia [88,89]. Similarly, it would be expected that PD is associated with heightened activity in basal ganglia output nuclei [2], yet some 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate models have found no change in either GPi or SNr firing rates [90]. Furthermore, it is now known that there exists bi-directional and collateral connectivity within the basal ganglia, and in contrast to simplistic models, D1 and D2 receptors are not strictly associated with excitation and inhibition or even associated with the direct and indirect pathway, respectively [91–96].

Despite these observations, firing rate alone has helped explain disease pathology and subsequent lesion-induced disease improvement, where lesions act as a mean of inhibition. However, neuromodulation cannot be solely understood within the framework of the rate model, as it falls short when explaining complex patterns induced by stimulation (Fig. 2). We now know that while stimulation and lesioning may lead to similar clinical outcomes, their underlying mechanisms likely differ. One example was a MPTP primate experiment which revealed that STN-DBS increased the firing rate of the GPi [97]. Another surprising result was observed during GPe stimulation in a MPTP primate model, which unexpectedly improved bradykinesia [98]. According to the rate model,

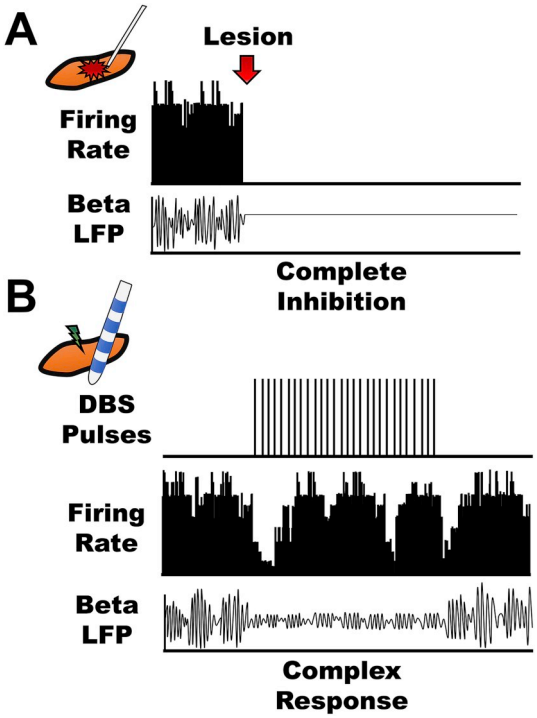

Fig. 2. Lesion versus stimulation. Once thought to be an informational lesion, we have now learned that stimulation causes complex neuronal responses within the brain, both in the stimulated and downstream nuclei. Lesions cause complete inhibition of the targeted nucleus, thus, causing a cessation of firing rate and local field potentials (LFPs) (A). In contrast, stimulation causes excitation, inhibition, or both during and after the stimulation pulses. Stimulation can also affect LFPs within target and distant areas. For example, in PD patients undergoing DBS, stimulation is known to cause a decrease in pathological beta oscillations throughout the basal ganglia (B).

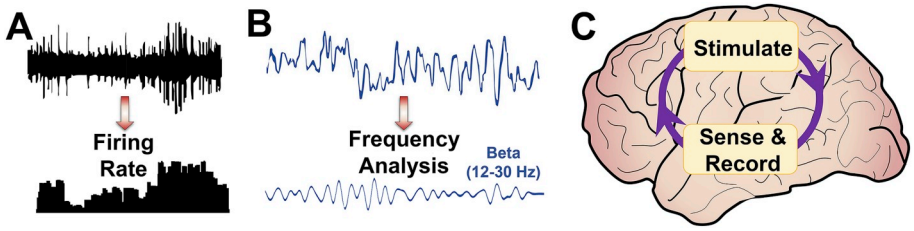

Fig. 3. From rate to rhythm. Classic models of the basal ganglia were developed under the premise that neural information is encoded through firing rate extracted from single-cell traces (A). Increasingly, firing patterns, especially local field potential oscillations (B), are being characterized with meaningful clinical translation. For instance, a pathologically elevated beta rhythm can be extracted and used for closed-loop neuromodulation to drive dynamic and personalized stimulation approaches (C). Adapted from Eisinger et al., 2018. Front. Neurosci. - https://doi.org/10.3389/fnins.2018.00385 [119] with permission.

if GPe was inhibited during HFS, PD symptoms would be worsened, which was observed in GPe lesional studies [98]. MPTP was also expected to differentially affect direct and indirect neuronal firing rates within the striatum, although, newer evidence suggests ubiquitous increases [99,100]. Similarly, the rate model does not directly explain several phenomena such as dyskinesia [86,87,101], akinesia [88,89], and movement initiation [102–104] (Fig. 1).

Overall, we now know that firing rate alone cannot account for variability in outcomes witnessed during experimental and clinical DBS. Moving beyond the rate model, researchers have begun to examine patterns of stimulation and to employ more sophisticated electrophysiological measures (Fig. 3).

4. Neural responses: excitation, inhibition, and temporal considerations

Rather than simply increasing or decreasing basal ganglia output, the therapeutic effect of neuromodulation may lie in more complex downstream or upstream effects. For example, STN-DBS was originally thought to inhibit STN output, but follow-up studies have demonstrated that HFS can drive output [97]. Still, cases have emerged that demonstrate a reduction in STN output during HFS, suggesting that the temporal sequence of modulation in firing rate could be an important consideration [105]. In fact, STN stimulation in PD primate models can elicit both excitatory and inhibitory effects on the pallidum at different time intervals following stimulation pulses [97,106].

Neural responses have also been examined in various disease models using GPi-DBS. For instance, GPi stimulation in MPTP primates caused an overall inhibition of thalamic neurons, thus increasing GPi output [107]. A separate study demonstrated a specificity of this phenomenon within high-firing rate neurons in the thalamus of a dystonia patient [108], while another study reported an increase in neuronal activity of the thalamus during the inter-stimulus interval of GPi-DBS in a patient with both dystonia and tremor [109]. Additionally, important temporal patterns, such as clustering within the inter-pulse interval, were observed in the spiking activity of neurons within the pallidum of a TS animal model [110]. It is suspected that this temporal locking phenomenon suppresses the transmission of aberrant information in the basal ganglia. GPi-DBS has been shown to induce both excitation and inhibition within the GPi and GPe [110,111], subsequently demonstrating the complex responses elicited from GPi-DBS. Complex excitation, inhibition and their related temporal sequence in the period following stimulation could be a result of bi-directional interactions between the STN and GPi and the neural pathways between the GPi and GPe [97,112].

Neuromodulation has thus taught us that both local and downstream nuclei can be differentially modulated. Beyond STN and GPi stimulation, studies have also shown mixed excitation and inhibition in the basal ganglia in response to cortical stimulation [112]. There has also been a resurgence of interest in examining upstream or retrograde effects as well, especially with regards to the hyperdirect pathway from the cortex to the STN [113–115]. Taken together, these findings have therefore added another layer of complexity to the basal ganglia network, suggesting that complex responses to stimulation likely propagate throughout the entire cortico-basal ganglia-thalamo-cortical loop.

5. Staying in rhythm: oscillations of the basal ganglia

Beyond firing rate, experimental DBS studies have taught us that applied electrical current affects brain oscillations. Unlike studies of excitation and inhibition, brain oscillations are observed at the neuronal-population level [116] and can be measured through local field potentials (LFPs) recorded from DBS electrodes. These oscillations are defined by different frequency bands, namely delta (1.5–4 Hz), theta (4–10 Hz), beta (10–30 Hz), and gamma (30–80 Hz) oscillations [116]. Although oscillatory activity can coincide with firing rates, oscillatory activity results largely from subthreshold activity and depends heavily on cell geometry [117,118]. Oscillations may reflect states of cognitive, behavioral, and motor function [119–122], and some oscillations have been identified as pathological [123]. DBS surgery has afforded the opportunity to study these brain rhythms throughout the basal ganglia, particularly in response to neuromodulation. Many studies have also reported oscillations at distant sites outside the basal ganglia, as oscillations may be important for long-range brain communication [97,119,124–127].

Pathological oscillations are now being delineated from normal oscillations through extensive characterization across different diseases (Fig. 4). For example, in PD patients off-medication, excessive beta rhythms and decreased gamma rhythms that correlate with disease severity have been observed in the basal ganglia and cortex [128,129] (Fig. 4a). In these patients, dopaminergic treatment subsequently decreases pathologically elevated STN-GP beta coherence [126], and can shift this synchronization to the gamma range [128]. These beta oscillations have also been characterized by their location within the STN, with more occurring near the dorsolateral region [130,131]. In the case of dystonia patients, abnormally decreased GPi beta power and increased theta power have been observed [132], as well as excessive 3–18 Hz synchronization within the GPi during pathological spasms unlike voluntary and rest conditions [133] (Fig. 4b). Pallidal peak theta activity has also been shown to significantly correlate with preoperative symptom severity in cervical dystonia subjects [134]. Conversely, studies have reported increased theta band activity at rest in dystonia patients [135]. Similarly, TS patients reportedly have increased activity within both the 2–7 Hz and 8–13 Hz band frequencies [136,137] (Fig. 4c). One study found distinct peaks in theta from both pallidal and thalamic recordings that correlated with motor tic severity, as well as significant theta and beta coherence between oscillations of the thalamus and pallidum [138]. However, several case studies have reported increased beta synchrony as well as theta and alpha frequencies within the GPi of TS patients, suggesting that more work is needed to truly characterize LFPs in TS [139,140]. Overall, various disease-specific rhythms may be a key aspect of underlying pathology in the basal ganglia, but further investigation is needed.

Apart from simple amplitude analysis, studies have also focused on

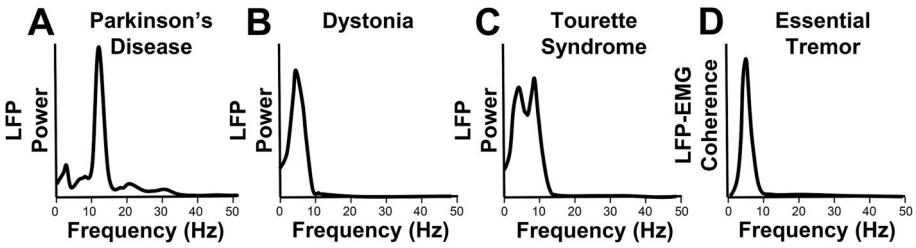

Fig. 4. Pathological oscillations. Pathological oscillations within and outside the basal ganglia can manifest in several ways. In PD, pathological oscillations are known to occur in the beta (11–30 Hz) frequency range (A) and have been recorded in several areas in the basal ganglia and even cortex. In dystonic patients, pathological oscillations mostly occur in the lower frequency range, especially theta (4–7 Hz). These oscillations have been recorded within the basal ganglia, including GPi, but also downstream in muscles during dystonic movements (B). Similarly, TS patients have increased activity in 2–7 Hz and in alpha (8–13 Hz) frequencies within the basal ganglia (C). In ET patients, oscillations within the thalamus and cortex have been coherent with peripheral tremor frequency (D). In most cases, pathological oscillations occur in low frequencies.

the length of pathological bursts within oscillations. For instance, in PD patients longer duration beta bursts are significantly higher during levodopa off conditions, whereas shorter bursts are correlated with on levodopa periods [141]. Additionally, higher amounts of shorter bursts tend to be negatively correlated with clinical impairment and conversely, higher amounts of longer bursts are positively correlated [141,142]. In TS subjects, the length of theta bursts within the pallidum and thalamus significantly correlates with pre-operative tic severity scores, especially extended theta bursts [138].

Beyond the basal ganglia, pathological oscillations can also be linked to muscular activity through coherence analyses. In PD, significant coherence was calculated during rest tremor between the primary motor cortex (M1) in a magnetoencephalography (MEG) recording and electromyography (EMG), however, M1 MEG contributed to coherence observed at double the tremor frequency [143]. Similar results were observed in coherence analyses between STN-LFP and contralateral EMG in tremor dominant PD patients during tremor epochs [144]. In dystonia, both cortico-muscular and muscular-muscular coherence demonstrates pathological synchronization in lower frequency bands (4–12 Hz) during involuntary contractions [134,145–147]. Oscillatory patterns within ET patients usually manifest as increased power at peripheral tremor frequency (4–12 Hz). Additionally, cortico-muscular and thalamo-muscular coherence at tremor frequencies in ET patients have been extensively described [148–150] (Fig. 4d). Such studies provide the basis for linking the central and peripheral nervous systems, ultimately contributing to our expanded understanding of disease pathology and our understanding of how to leverage these pathological correlates for next-generation, patient-specific neuromodulatory therapies.

6. Patient-specific neuromodulation

The diseases we modulate are heterogeneous, and thus in order to achieve the most clinically efficacious outcomes, our neuromodulation should be designed from the perspective of a precision medicine paradigm. Future neuromodulation therapies will need to focus on patient-specific approaches that are less disease-centric and more symptom-specific.

6.1. How do we stimulate?

An important area of next-generation neuromodulation is closed-loop or adaptive stimulation, which is a form of neuromodulation that relies on simultaneous sensing and stimulation (Fig. 3C). Studies have tested whether pathological oscillations, recorded from either an implanted DBS lead, an electrocorticography strip, or wearable sensors, can be utilized as the control signal for closed-loop algorithms. For instance, Little and colleagues first demonstrated in 8 PD patients that the power of the STN-LFP beta band was successful at controlling not only the timing but also the amplitude of DBS [151]. Additionally, Cagnan et al. used an acceleration signal recorded from the tremulous hand to deliver stimulation at specific phases within the tremor cycle. This concept was applied to DBS therapy to decouple tremor oscillators and it was proven effective in ET but not dystonic tremor patients [152]. Adaptive DBS has even been shown to have a selective effect on pathological burst duration in LFPs by shifting the phenomenon from longer to shorter bursts, whereas conventional DBS has not been shown to change the distribution of burst duration [142]. Other forms of closed-loop DBS are currently under investigation for a variety of indications, and if perfected, these techniques could possibly be more clinically efficacious than conventional DBS [153–158]. Ultimately, identifying pathological markers of diseases will provide an input for these algorithms, however it also remains unclear what the appropriate stimulation output during each indication (i.e., disease or symptom) should be.

Stimulation parameters (frequency, amplitude, pulse width) are an important consideration for optimizing outcomes. Different diseases and basal ganglia targets require tailored stimulation settings. As such, basic and clinical investigations have shown differential effects with varying frequencies. Liu and colleagues demonstrated that increasing stimulation frequency to the GPi resulted in decreased neuronal activity within the nucleus, with HFS (> 50 Hz) completely silencing neuronal firing [159]. Depending on disease and symptoms, both low-frequency stimulation (LFS) and HFS can be favorable. Pedrosa and colleagues reported a significant reduction in ET intention tremor during HFS compared to both LFS and to no stimulation conditions [160]. Although HFS has been shown useful for ET, LFS in ET results in entrainment effects rather than tremor suppression [160–163]. Similarly in PD, STN-LFS can exacerbate specific symptoms, especially akinesia [164]. However within the PPN, LFS is considered to be more clinically efficacious than HFS [19,165]. Additionally, STN-LFS has shown preliminary success in improving cognitive control in patients with PD [166]. On the contrary, the optimal stimulation parameters in dystonia have been even more variable. In cases of STN and GPi dystonia patients, HFS was more favorable [167,168], with LFS studies reporting exacerbation rather than suppression of symptoms [169]. However, LFS has been preferable in other cohorts and may be superior in younger DYT1 subjects [170–172]. Nonetheless, individualizing stimulation parameters will require substantial time, skill, and patience, and moving forward, the success of neuromodulation approaches will likely hinge on tailoring the therapy.

Another stimulation strategy is the use of reduced pulse widths, which can limit current spread and potentially offer a larger therapeutic window. In STN-DBS patients, the therapeutic window increased two-fold when using a pulse width of 30 μsec compared to the standard setting of 60 μsec [173,174]. Additionally, shorter pulse widths required an increase in current delivered, but the total charge required for full control of rigidity decreased, suggesting that shorter pulse widths offered less risk of adverse effects and improved energy efficiency.

A more complex technique that has been explored is coordinated

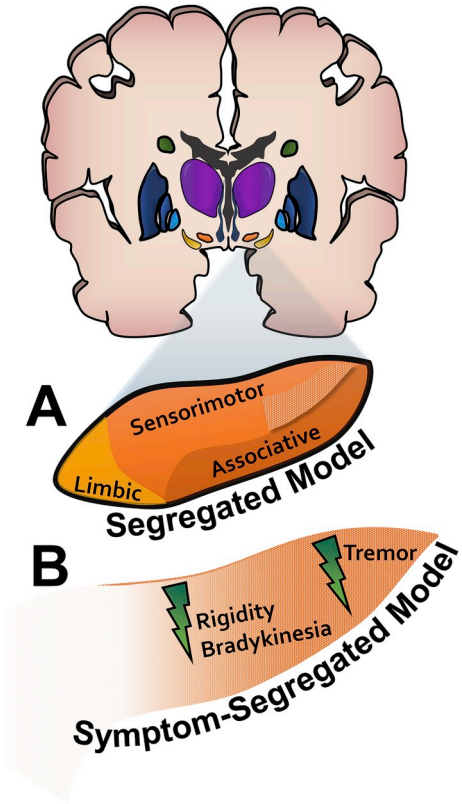

Fig. 5. Towards a symptom-segregated model. The tripartite, or segregated, model of the basal ganglia describes the anatomical separation of sensorimotor, limbic, and associative pathways. It is now recognized that the division of labor in the basal ganglia may not be so distinct and can instead be considered a continuum with overlapping boundaries. Nonetheless, there is now a shift towards a symptom-segregated model, in which specific brain targets at the millimeter or submillimeter scale are chosen to address specific predominant symptoms. Adapted from Eisinger et al., 2018. Front. Neurosci. - https://doi.org/10.3389/fnins.2018.00385 [119] with permission.

reset (CR), which involves brief, high frequency and low intensity stimulation through different contacts of the electrode to desynchronize pathological activity. Early studies with MPTP primate models demonstrated that low intensity CR-DBS had sustained after-effects on motor function, which were not elicited after CR with standard DBS intensity or classical DBS [175]. In the first human cohort, 6 STN-DBS PD patients underwent CR-DBS that resulted in cumulative after-effects on beta LFP oscillations, which were associated with an improvement in motor symptoms [176]. CR-DBS after-effects have been reported to persist up to two weeks after treatment cessation [177]. Although the results have been promising, larger clinical trials are needed.

6.2. Where do we stimulate?

The discovery that the basal ganglia is organized somatotopically based on behavioral functions — motor, associative, and limbic [178–181] — catapulted an era of clinical interventions for basal ganglia diseases (Fig. 5). Support for this segregation is drawn from a vast body of evidence [97,182,183]. This tripartite model was an elegant demonstration of the possibility for precise neurosurgical targeting of specific dysfunctional pathways. It further offered explanations for specific symptoms experienced across a range of disorders. For instance, a functional map of the STN can be obtained using microelectrode recordings during DBS implantation surgeries in patients with PD. This mapping can differentially label cells associated with leg and arm movement. Specifically, the dorsolateroposterior area of the STN tends to be arm responsive, whereas the leg responsive area tends to be located more ventromedioanteriorly, supporting the further segregation of the sensorimotor region within these nuclei [184]. Somatotopic segregation has also been demonstrated using neuromodulation, such as one report describing hypomania resulting from anteromedial STN-DBS [185]. Another demonstration of the multifaceted nature of the STN and its numerous roles has been observed with neuropsychological studies of STN-DBS both in the *on* and *off* state. For example, impulsivity is a common non-motor effect of STN-DBS and is thought to stem from impaired decision-making through unintentional off-target neuromodulation [119,186]. These changes may underlie the onset of sub-clinical impulsivity or impulse control disorders observed after DBS [187]. Such observations motivate the need for further understanding of basic anatomy and physiology.

Recent studies have questioned this tripartite hypothesis and demonstrate that the parallel pathways within the basal ganglia may not be as segregated as once thought [188–190]. Some experts are now viewing these pathways as a continuum rather than entities with distinct borders [191,192]. Nevertheless, precise targeting and post-operative DBS lead localization with tractography-based imaging, combined with neuromodulation experiments, can provide vital information to guide therapy towards a symptom-segregated model (Fig. 5). Within the dorsolateral portion of the STN, which is one optimal target for STN-DBS [193], further ideal targets could be potentially identified for specific symptoms. For instance, it appears that STN connectivity with primary motor cortex predicts tremor suppression, STN connectivity with supplementary motor cortex predicts improvement in bradykinesia and rigidity, and STN connectivity to the prefrontal cortex predicts improvement in rigidity [194]. As another example, one study showed that LFS through ventral contacts worsened intention tremor, but had little influence on postural tremor [160].

Even more selectivity can be found in specific cells within these nuclei. For instance, differential cell-specific modulations within the GPe induce similar responses: excitation of parvalbumin-GPe neurons and inhibition of Lim homeobox 6-GPe neurons reversed pathological SN burst firing in dopamine-depleted mice [195] (Fig. 6), demonstrating the elegance and specificity in the structure of the basal ganglia. Such results have opened a new line of work, specifically optogenetically-inspired DBS. Conventional DBS generally has a non-specific mechanism of action, affecting both nearby and distant circuitry. Optogenetics enables the possibility for targeted neuromodulation of particular genetically-defined neurons that are engineered to express light-sensitive ion channels. Preliminary work demonstrates the clinical effectiveness of this stimulation modality as applied to animal models [195,196], but optogenetics remains largely a research tool. Through both research and clinical potential, we believe optogenetics could catapult the individualization of brain neuromodulation. In parallel, it will undoubtedly raise new and interesting challenges for the road ahead.

Despite advanced understanding of nuclei somatotopy and cell content, clinical efficacy across a range of anatomical targets and diseases is still under active investigation. Within a target, current steering has also been employed to optimize therapy [197,198]. This approach can involve new DBS lead designs [199], multiple independent current sources for the DBS contacts [200], and novel pulse shapes [201,202]. Recently, current shaping studies have focused on modulating the pulse-width waveform. This type of modulation was proven to offer selective activation of specific neuronal populations in computational models, specifically with asymmetric, charged-balanced biphasic stimulation pulses [203,204]. Clinically, a square-biphasic waveform (active rather than passive charge-balancing phase) has been investigated in recent small trials [201,202,205]. Square-biphasic pulse widths were well tolerated in dystonia and tremor, suggesting that nonconventional waveforms would be successful in ameliorating pathological symptoms while potentially reducing adverse effects. Larger and longer clinical trials are needed to validate the efficacy.

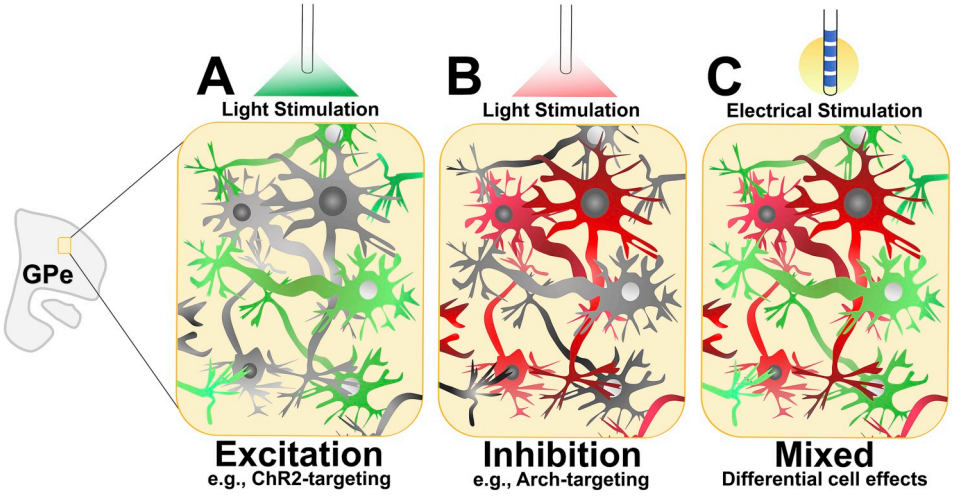

Fig. 6. Optogenetically-inspired stimulation. Cell-specific neuromodulation through optogenetics has inspired meticulous investigation of the basic mechanisms of neuromodulatory therapies. For instance, symptomatic control in PD animals can be achieved through excitation of parvalbumin-GPe neurons (A) and inhibition of Lim homeobox 6-GPe neurons (B), which can be optogenetically stimulated through ChR2 and Arch, respectively. Rather than being a non-specific stimulation modality, moving forward, new electrical stimulation approaches can aim to have specific intended differential effects at the cellular level (C).

Subsequently, the ability to reprogram the firmware on the device will offer new treatment options to patients without the need for further surgery.

7. The era ahead: clinical considerations and lessons learned

The era of basal ganglia neuromodulation is at its genesis. While much has been learned about the brain through DBS studies, we have also learned that neuromodulation systems have yet to be fully optimized. Clinically, side effects remain a limiting factor in the success of DBS due to unintended and unspecific current spread [206,207]. Neuromodulation devices have not changed much since their introduction, and the near-term future will likely harness many hardware improvements along with more tailored stimulation paradigms. One-third of PD-DBS failures today result from inappropriate patient selection and half from suboptimal placement of the DBS lead [208]. Therefore, refining brain targets and target populations within each disease model will require further improvements.

We have learned that successful neuromodulation requires a multidisciplinary approach through joint efforts across multiple clinical, research and engineering specialties partnered with industry, federal representatives, and ethicists [209]. The overarching success of neuromodulation as a treatment has spurred a list of difficult questions that remain unanswered, especially those involving the underlying mechanisms of DBS. Additionally, the optimal stimulation targets and parameters will need refinement and DBS will likely evolve to be a more symptom-based rather than disease-based therapy. At the same time, advancing accuracy for neurosurgical targeting is critical [208,210]. Stimulation-related adverse effects are common to many DBS targets and may be overcome with higher fidelity targeting procedures [211,212]. As little as 1–2 mm of targeting error can be the difference between clinical success and failure [213]. Failure can translate into revision surgery or rescue leads.

Ultimately, surgery is only the first step in a long path towards optimizing therapy. Patients require meticulous and careful postoperative DBS programming, a process that continues for many months. This is a large undertaking that requires necessary infrastructure and clinician experience. Overall, neuromodulation needs to be a patient-specific, individualized therapy tailored to the target and to the symptoms. Successful neuromodulation demands careful examination of every patient with thoughtful consideration of the clinical syndrome, surgical risk factors, and long-term prognosis.

8. Conclusion

Recent observations of basal ganglia physiology have acted as a springboard for rapid advancement of neuromodulation. Not only have we soared beyond the rate model by analyzing the complex behavior of basal ganglia circuitry, we have also characterized oscillation-level activity and are beginning to use it for tailored therapy. Initially thought of as an informational lesion, stimulation has profound impacts on basal ganglia physiology. Continuous updates of basal ganglia models will be necessary as the classical model has provided invaluable infrastructure but contains many inconsistencies. The expansion to neuropsychiatric conditions will require careful considerations of neuroethics, informed consent and regulatory oversight. The future is likely to facilitate neuromodulation spreading across a wide range of brain areas, and the many lessons learned from basal ganglia neuromodulation will undoubtedly enable these efforts.

Conflicts of interest

Robert S. Eisinger – No conflicts of interest or disclosures to submit.
Stephanie Cernera – No conflicts of interest or disclosures to submit.
Aryn Gittis, Ph.D. – No conflicts of interest or disclosures to submit.
Aysegul Gunduz, Ph.D. – No conflicts of interest or disclosures to submit.

Michael S. Okun, M.D. – Dr. Okun serves as a consultant for the National Parkinson Foundation, and has received research grants from NIH, NPF, 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 DBS research is supported by: R01 NR014852 and R01NS096008. Dr. Okun has previously received honoraria, but in the past > 60 months has received no support from industry. Dr. Okun has received royalties for publications with Demos, Manson, Amazon, Smashwords, Books4Patients, and Cambridge (movement disorders books). Dr. Okun is an associate editor for New England Journal of Medicine Journal Watch Neurology. Dr. Okun has participated in CME and educational activities on movement disorders (in the last 36) months sponsored by PeerView, Prime, QuantiaMD, WebMD, Medicus, MedNet, Henry Stewart, and by Vanderbilt University. The institution and not Dr. Okun receives grants from Medtronic, Abbvie, Allergan, and ANS/St. Jude, and the PI has no financial interest in these grants. 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.

Acknowledgements

We would like to thank Jackson Cagle for helpful comments and suggestions and Leora Lieberman for assistance with figures. We thank the Parkinson's Foundation Center of Excellence at the University of Florida, the Tourette Association of America Center of Excellence and Tyler's Hope for a Dystonia Cure. This work is supported by the NIH/NCATS Clinical and Translational Science Awards to the University of Florida UL1TR001427, KL2TR001429, and TL1TR001428.

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