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Restoring The Loop: Circuit Dynamics, Pathophysiology, And The Closed-Loop Neuroengineering Future Of Parkinson's Disease

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ABSTRACT

Parkinson's disease affects more than one million Americans, manifesting primarily with hypokinetic motor symptoms including resting tremor, bradykinesia, rigidity, and postural instability. This review introduces the functional architecture of the basal ganglia circuit, focusing on its classical segregation into direct and indirect pathways with opposing roles in motor output. Cell-type-specific optogenetic methods in rodent models are examined to illustrate how direct-pathway activation can mitigate hypokinetic motor deficits in experimental settings. We further evaluate electrophysiological dynamics in non-human primate models, the neuropharmacological mechanisms and long-term limitations of L-DOPA therapy, and the network-level mechanisms of deep brain stimulation (DBS). Finally, this review synthesizes advances in adaptive neuromodulation, contrasting traditional open-loop DBS with closed-loop systems. It proposes a theoretical model for how prospective computational pipelines (like artificial intelligence) could, in principle, assist in dynamic circuit modulation.. Through a comprehensive historical synthesis of circuit discovery, electrophysiology, and neuromodulatory interventions, this work synthesizes foundational neuroscience literature to outline a theoretical pathway toward next-generation adaptive neuroprosthetics.

Keywords: Parkinson’s Disease, Neurons, Circuits, Neurodegeneration, Treatment

INTRODUCTION

In the brain, neuronal circuits of the basal ganglia (BG) are critical for motor planning and action selection. The output of the BG is high firing rate pallidal neurons that suppress unwanted movements. Pulses in this inhibition enable movements to be generated normally. This is key as we don't move all of our body parts at once. Rather, we carefully select which muscles to move and when (Lee et al., 2017). In hyperkinetic disease, patients have unwanted and uncontrolled movements due to impaired inhibitory output of the basal ganglia. In hypokinetics such as parkinsonions, patients cannot generate movement or move freely, in part because of excessive inhibitory output of the BG. A key open question is why and how the basal ganglia activity gets impaired in the first place.

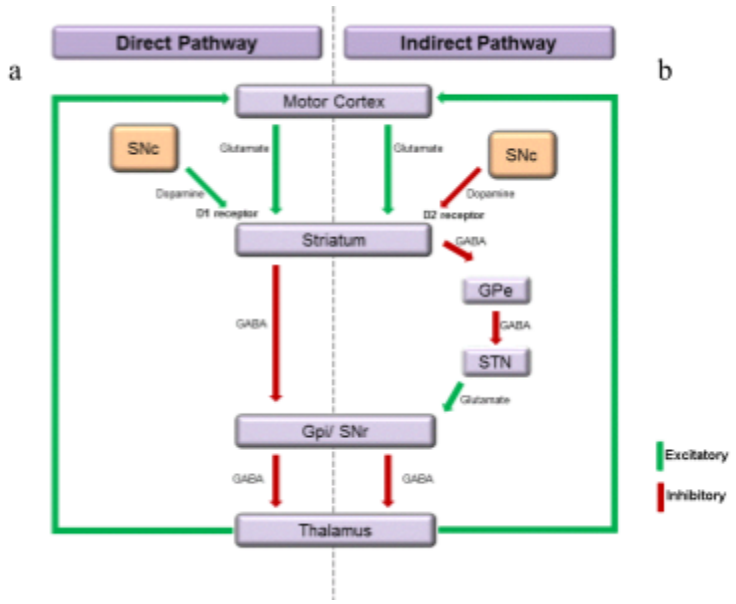

Figure 1 | Direct and Indirect BG Pathways. (a) Tracks the direct pathway after the dopaminergic modulation from the substantia nigra pars compacta (SNc) activates D1 MSNs. b. A reduction of dopaminergic input from the SNc releases the D2 MSNs from inhibition, leading to the activation of the indirect pathway. Adapted from Zhang et al. (2021) under the terms of the Creative Commons Attribution 4.0 International (CC BY 4.0) license.

In the BG, medium spiny neurons (MSNs) make up as much as 95% of the cells within the striatum and send inhibitory projections to surrounding nuclei. According to the model of BG circuit function first explained by Albin and DeLong, MSNs facilitate and suppress motor behavior via the direct and indirect pathways (Lee et al., 2017). The "direct pathway" includes medium spiny neurons of the caudate and putamen to the internal segment of the globus pallidus and substantia nigra pars reticulata, serving to release the upper motor neurons from tonic inhibition. This pathway promotes movement when dopamine binds to the MSN_{D1} (D1) neurons in the striatum, reducing activity in the BG's GABAergic output nuclei called the internal globus pallidus (GPi) (Lee et al., 2017). The reduction of the inhibitory signal leads to the disinhibition of the circuits, allowing them to execute the movements when the dopamine input is given. In contrast, the "indirect pathway" serves to moderate the disinhibitory actions of the direct pathway. When dopamine levels are lowered, MSN_{D2} (D2) neurons are released in the striatum, inhibiting the GABAergic external globus pallidus (GPe), disinhibiting GPi, and resulting in lowered movement. Refer to Figure 1 for a visual representation of this circuit. It is important to understand that the addition of dopamine to the striatum increases movement and lowering dopamine levels ultimately inhibits movement through the use of both pathways (Lee et al., 2017).

Parkinson's Disease (PD) is caused by the loss of the nigrostriatal dopaminergic neurons, leading to widespread deterioration of the substantia nigra over time. As explained earlier, the normal effects of the compacta dopaminergic input to the striatum are the excitation of the D1 neurons that project directly to the GPi and inhibition of D2 neurons that project to the GPe in the indirect pathway (Purves et al., 2001). Both of these dopaminergic effects serve to decrease the inhibitory outflow of the BG, increasing the excitability of the upper motor neurons to promote movement. When the compacta cells are destroyed in PD, the inhibitory outflow of the BG is abnormally high, and thalamic activation of the upper motor neurons in the motor cortex of the brain is less likely to occur. This leads to hypokinetic movement disorder, reflecting the failure of disinhibition normally mediated by the BG. This is why PD patients tend

to have diminished facial expressions and lack associated movements, such as hand moving while walking. Any movement is difficult to initiate and, once initiated, is mostly difficult to terminate (Purves et al., 2001).

This paper explores how the current understanding of Parkinson's Disease and its underlying neuropathology has evolved, tracing the scientific shifts that have transformed baseline clinical paradigms into modern neurobiological models. By analyzing the landmark discoveries and changing theories surrounding basal ganglia dysfunction, this study re-examines the foundational evidence that links nigrostriatal dopaminergic loss to systemic motor control deficits. Furthermore, the progression of therapeutic strategies over time is explored, examining how historical breakthroughs in pharmacology and neuromodulation contextualize current engineering efforts toward theoretical adaptive interfaces.

REVIEW METHODOLOGY AND SCOPE

This manuscript is structured as a narrative historical and neuroengineering review designed to evaluate the translation from foundational circuit biology to adaptive neuromodulation in the clinic. Scientific papers highlighted in this review were assigned by a field expert or identified from database searches. Database searches were conducted using PubMed, Google Scholar, and Web of Science for studies published between 1980 and 2026. Search terms included combinations of: "basal ganglia direct indirect pathway," "optogenetics Parkinson's model," "L-DOPA GPi single unit recording," "closed-loop DBS Parkinson's," "population vector motor cortex," and "adaptive DBS clinical trials." Studies that were assigned by the field expert were highlighted for inclusion based on their status as foundational mechanistic discoveries (e.g., Gerfen et al., 1990; Georgopoulos et al., 1982) and pivotal translational milestones in animal models (e.g., Boraud et al., 1998; Kravitz et al., 2010; Rosin et al., 2011). Additionally, after a search engine review of research on clinical BCI/DBS benchmarks, papers were selected based on their relevance to the paper (e.g., Hochberg et al., 2006; Fleeting et al., 2026). While this paper is not an intensive systematic review with a vast amount of papers analyzed, the selected literature provides the historical and biological framework necessary to critically evaluate emerging neuroprosthetic paradigms.

THEME 1: UNDERSTANDING THE PATHOPHYSIOLOGY OF BASAL GANGLIA PATHWAYS AND EFFECTS OF L-DOPA THERAPY

Anatomical Foundations of Segregated Basal Ganglia Pathways (Gerfen et al., 1990)

Modern neurobiological understanding of BG function rests on anatomical and cell-type specific segregation of the striatal projections of the neurons. Prior to the early 1990s, the classical Albin-DeLong framework proposed that the BG influenced motor output through two opposing streams in the network, which included the direct and indirect pathways. However, the idea that there was functional segregation remained controversial. Gerfen et al. (1990) provided the empirical evidence that was critical to establishing that the dopamine receptor subtypes D_1 and D_2 are differentially expressed across different populations of the MSNs.

Using a combination of retrograde axonal tracing and in situ hybridization histochemistry, Gerfen et al. demonstrated that striatonigral projection neurons, which project directly into the internal segment of the GPi, predominantly have D_1 dopamine receptors along with the neuropeptides substance P and dynorphin. Conversely, the striatopallidal projection neurons, which project to the GPe, express D_2 dopamine receptors and co-localize with the preproenkephalin, forming the origin of the indirect pathway.

To add on, Gerfen and colleagues investigated how the dopamine loss reshapes gene expression within the segregated pathways. After the 6-hydroxydopamine (6-OHDA) lesions of the nigrostriatal pathway, they observed that the enkephalin mRNA expression in D2 neurons was increased, whereas substance P mRNA expression in D1 neurons was reduced. Treatment with agonists for D1 or D2, respectively, reversed the lesion-induced alterations in a manner that was receptor-specific. This established that adding dopamine acts differently for both pathways: it makes the direct pathway MSNs more excitable by acting in D1 type receptors, while having the opposite effects on the indirect pathway MSNs via binding at D2 receptors. This framework provided the structural blueprint for understanding how nigrostriatal degeneration precipitates PD motor deficits.

Electrophysiological Dynamics and the Rate vs Pattern Dysfunction in Primate Models (Boraud et al. 1998)

While Gerfen et al.'s anatomical mapping explains the theoretical circuitry, understanding how dopamine depletion alters real-time single-unit firing required electrophysiological investigations in primate models. According to the classical rate model, the loss of dopamine should decrease the inhibitory input to the GPe, and manifest as a mean increase in the firing rate of the GPi, which in turn would suppress movement generation and contribute to Parkinson's symptoms.

To test whether the systematic pharmacological replacement with L-DOPA could normalize the BG output signals, Boraud et al. (1998) conducted single-unit extracellular recordings in the GPe and GPi of parkinsonian monkeys. Specifically, the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), when injected into a monkey, kills dopamine neurons and causes Parkinson's, creating a model for the disease that has been useful for scientists. In this animal model, MPTP-induced nigrostriatal lesions caused a statistically significant decrease in the mean firing rate of the GPe neurons (66.8 to 51.9 Hz) and an elevation in the mean firing rate of the GPi output neurons (80.5 Hz to 106.0 Hz). This elevation of GPI firing is exactly what is thought to cause Parkinsonism by suppressing the movement generating regions downstream of the BG. Refer to Figure 2 for a comparison.

Interestingly, by applying statistical density distribution analyses, this paper revealed that the mean firing rates were just a part of the findings. Beyond the rate alterations, the MPTP treatment also induced a shift in discharge patterns, causing high-frequency bursting activity across both the GPe (71.5% to 76.4% bursting cells) and GPi (22.2% to 72.7% bursting cells).

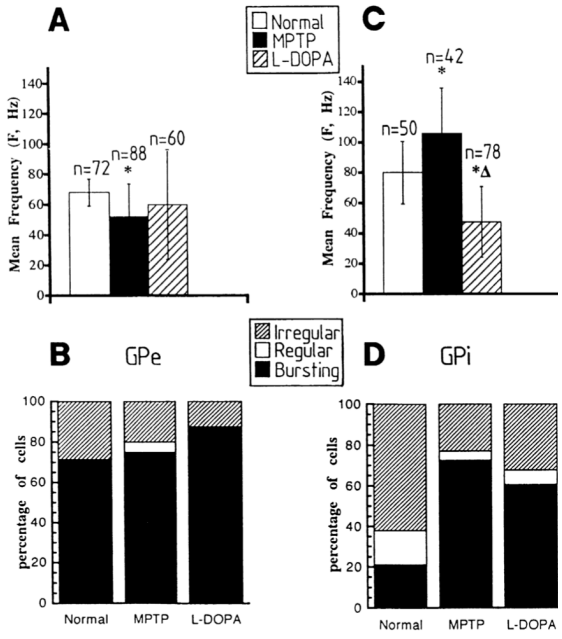

Figure 2 | Comparison of firing rate and type of cell (irregular, regular, and bursting respectively) between Normal, MPTP, and MPTP + L-Dopa subjects. Microelectrode recordings of single-firing patterns in the global pallidus following systemic L-DOPA administration in MPTP-treated non-human primates, demonstrating non-physiological suppression of pallidal output. (*p<0.05, Student's t-test). Adapted from Boraud et al. (1998), copyright © 1998 Elsevier Science B.V.

Next, the scientists examined how L-DOPA, a first-line drug treatment for PD, affected BG activity. When the PD monkeys were administered therapeutic doses of oral L-DOPA (10 mg/kg), the electrophysiological recovery was incomplete. In the GPe response, L-DOPA failed to restore GPe firing rates (60.3 Hz) or suppress the elevated proportion of bursting cells (87.5%). In addition, while L-DOPA reduced the mean firing rate of GPi neurons, it overcorrected the output, lowering the firing rates of the GPi to 47.4 Hz, which is much below the healthy level at 80.5 Hz. L-DOPA also only slightly reduced the GPi bursting patterns (60.7% remaining bursting cells vs 22.2% in healthy animals). As expected, reduced GPi firing lifted inhibition on the motor areas and restored some capacity for movement.

These findings revealed that a major limitation in systematic pharmacotherapy is that while L-DOPA can lower gross firing rates in the output nuclei, it cannot re-establish the temporal discharge patterns required for normal motor control. This shows how parkinsonian pathophysiology is not merely a quantitative disturbance in the neuronal activity levels. It is also a qualitative disruption of temporal patterning across the BG network.

Pharmacological Overshoot to Understand the Pathophysiology of Dyskinesia (Papa et al. 2001)

The observation by Boraud et al. that L-DOPA suppresses GPi discharge below physiological baseline levels raised important questions regarding the therapeutic window of dopamine replacement therapy. Fundamentally, long-term administration of levodopa in PD often leads to Levodopa-Induced Dyskinesias (LID). These are involuntary, restless, and dystonic movements that impair motor function.

To understand the exact electrophysiological profile of GPi output during dyskinetic states, Papa et al. (2001) recorded continuous single-unit activity in MPTP-treated dyskinetic monkeys through three different stages: the PD "OFF" state, the non-dyskinetic motor-improved "ON" state, and the "ON with dyskinesias" state.

This study demonstrated that the transition through these states from "OFF" to "ON" to "ON with dyskinesias" is linked to a profound shutdown of the GPi output activity. During the active dyskinetic episodes, single-unit firing rates in the GPi decrease by an average of 60-70%, with individual output neurons experiencing firing decrements as extreme as 97% relative to the parkinsonian "OFF" levels. This extreme suppression occurred when physical dyskinetic movements were expressed.

By linking severe GPi hypoactivity to involuntary hyperkinetic movements, Papa and colleagues highlighted the bi-directional vulnerability of BG motor control. They reviewed that the hyper-inhibition of thalamocortical motor targets with the excessive activation of the GPi produces the PD motor deficits, including akinesia, rigidity, and freezing. However, the overuse of L-DOPA, leading to a profound suppression of GPi activity, disinhibits thalamocortical projections, leading to chaotic involuntary motor output.

Together, the findings from Boraud et al. and Papa et al. emphasized the inherent flaw in pharmacotherapy today: rather than restoring localized, physiological patterns of endogenous dopamine release, oral L-DOPA causes continuous, non-physiological activation of dopamine receptors throughout the striatum. In these non-human primate models, this non-targeted receptor stimulation fails to normalize pathological burst firing patterns and instead suppresses tonic basal ganglia output into hypoactive states associated with L-DOPA-induced dyskinesias The next step to making these treatments longer-acting would be to target the doses of L-DOPA rather than the uncentralized oral dose.

Optogenetic Verification and Causal Circuit Control (Kravitz et al., 2010)

While the classic Albin-DeLong model established that direct and indirect pathways exert effects on motor function, this circuit-level hypothesis had not been tested in vivo. For decades after Gerfen et al.'s anatomical discoveries, the hypothesis that the direct and indirect pathways exert opposing, causal control over motor execution remained unproven. Electrical stimulation and pharmacological lesions could not selectively target D1 or D2. Kravitz et al. (2010) resolved this by using cell-type-specific optogenetics in transgenic mice to determine if the direct-pathway activation could act as a viable strategy to mitigate the motor deficits associated with PD.

The key advantage of optogenetics is the ability to manipulate the activity of specific cell types and not others. By contrast, electrical stimulation just activates all cell types in a region. To get cell-type selectivity in the BG circuit (D1 vs D2 cells of the direct and indirect pathway, respectively), the researchers utilized BAC transgenic mice expressing the Cre recombinase under either the D1 or D2 dopamine receptor to target either the direct or indirect pathway. An adeno-associated virus (AAV1) that contained a reading frame that encoded a fusion of Channelrhodopsin-2 and enhanced yellow fluorescent protein (ChR2-YFP) was injected bilaterally into the dorsomedial striatum. This restricted the light-sensitive ChR2 expression strictly to Cre-expressing direct or indirect MSNs, ensuring that only one is active when light is shone on the mouse. To selectively destroy the local dopaminergic terminals in order to induce PD motor deficits in some of the mice, they were subjected to bilateral injections of the neurotoxin 6-hydroxydopamine (6-OHDA) into the dorsomedial striatum. Together, this approach provided a mouse Parkinson's model where the D1s or D2s could be selectively activated with light.

In the awake and freely moving mice, bilateral optical stimulation (with a 473-nm laser, 1mW at the fiber tip) was given through surgically implanted cannulae over the dorsomedial striatum. During the behavioral trials, this light was delivered in a structured ON/OFF format using a frequency of 20 Hz to mimic MSN burst-firing. To confirm that the optical stimulation successfully drove downstream circuit dynamics, they added optrode probes that recorded real-time firing rate changes in the striatum and the GPi. They also recorded the movement velocity, freezing frequency, and the ambulatory initiations through computerized video tracking software while the mice moved in an open-field area. They established that direct and indirect pathways exert opposing and causal control over motor behavior, where activating striatal D1 facilitates movement (reducing freezing and promoting ambulation) and activating D2 suppresses movement (inducing freezing and bradykinesia). They conveyed that direct-pathway activation suppresses the firing of the GPi (promoting movement) and the indirect pathway excites the GPi, suppressing motor output.

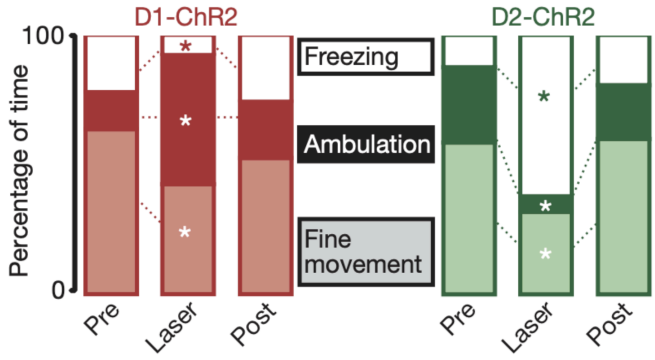

Figure 3 | Comparison of the activation of D1 vs D2 dopamine receptors in neurons of the subject using ON/OFF optogenetics. Bilateral striatal illumination in D1-ChR2 is noted in red and D2-ChR2 in green. Selective activation of the direct pathway restores movement, whereas the activation of the indirect pathway induces freezing. (*p<0.05, Student's t-test) Adapted from Kravitz et al., Nature 466, 622–626, Copyright © 2010 Springer Nature.

This prompted the understanding that the motor deficits resulting from striatal dopamine depletion are reversible via the targeted simulation of the direct-pathway circuits. Surprisingly, direct-pathway activation can entirely bypass the requirement for dopamine to restore normal motor initiation and velocity. Specifically, when the authors photoactivated D1s in parkinsonian mice, the mice were instantly able to exhibit restored, healthy locomotion. When the laser was turned off, they were instantly frozen again. The on-off control of parkinsonian symptoms was striking. Refer to Figure 3 for a comparative visual model between the motor activity before, during, and after bilateral striatal illumination in both the D1 and D2 receptors.

This direct empirical validation for the Albin-DeLong model provided by Kravitz et al. (2010) serves as a critical turning point in understanding BG pathophysiology. By demonstrating that the selective optogenetic excitation of the D1 could rescue PD motor deficits (including bradykinesia and freezing) in the 6-OHDA-lesioned mice, this study establishes a causal relationship between pathway-specific activity and motor output. This finding directly shows that PD hypokinesia is not a general system failure but rather a functional imbalance of the underactive direct pathway and the overactivity of the indirect pathway. Consequently, it suggests that bypassing the dopaminergic depletion entirely and artificially

driving the direct pathway is a viable strategy for remedying the motor deficits associated with PD. This mechanistic proof-of-concept lays the groundwork for evaluating targeted clinical therapies, such as pathway-specific deep brain stimulation, which aims to restore the precise physiological balance of the BG.

THEME 2: CURRENT DEEP BRAIN SIMULATION PROCESSES AND LIMITATIONS

Network Pathophysiology and the Limits of Open-Loop DBS (Hammond et al., 2007)

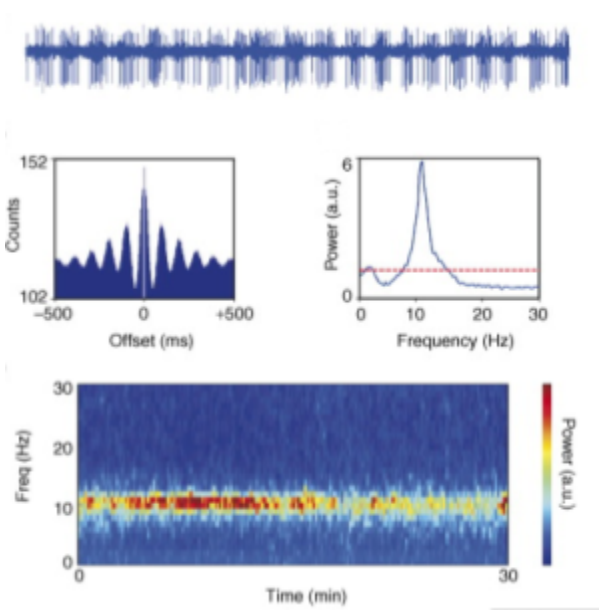

Figure 4 | Pathological synchronization in Parkinson's disease. Local field potential recordings and neural ensemble firing rates represent the pathological beta-synchronization (Adapted from Hammond et al., Brain 130(6), 1452–1473, Copyright © 2007 Oxford University Press).

After the experimental findings supported that motor behaviors could be driven by pathway-specific striatal activation (Gerfen et al., 1990; Kravitz et al., 2010), systems neuroscientists recognized that parkinsonian motor deficits were not only caused by abnormal rate changes within isolated nuclei, but by large-scale network-level dysfunction. Hammond et al. (2007) synthesized two decades of primate electrophysiology, human local field potential (LFP) recordings, and computational network models to demonstrate that Parkinson's disease is fundamentally a disease of pathological network synchronization. Under physiological conditions, BG circuits display asynchronous single-unit firing patterns with brief, transient oscillatory coupling. This dynamic allows cortical motor planning signals to pass through the BG loop. However, following severe loss of nigrostriatal dopamine neurons, the dynamic collapses. In both PD non-human primates and human patients undergoing DBS surgery, local field potentials recorded from the GPe and GPi reveal the elevated power in the beta frequency band (13-30 Hz). In addition, the GPe and GPi become pathologically phase-locked, firing in groups rather than individually. They essentially become entrained to the beta oscillation, which locks the BG-thalamic circuit in an inflexible state. Voluntary movements initiated in the cerebral cortex are unable to break through the synchronized network, manifesting as akinesia, rigidity, and freezing of gait (physical symptoms of PD). In summary, in addition to problems with BG firing rates in PD, there are also abnormalities in the temporal synchronization of firing. Refer to Figure 4 for the firing rate of the neurons in the BG, representing the beta-synchronized firing.

To disrupt the synchronization, conventional open-loop Deep Brain Stimulation (DBS) delivers continuous high-frequency electrical pulses to the GPi (around 120-130 Hz). Continuous open-loop DBS overwrites the synchronized rhythm with a continuous pulse train, unbinding the circuit to restore movement. However, Hammond et al. (2007) highlighted that open-loop DBS's main limitation is that it is static and does not adapt to the patient's needs. Since open-loop DBS runs continuously without regard for the medication status of the patient or the activity that they are performing, it delivers excessive energy during periods when the patient is already "ON" or engaged in tasks that require low energy. In addition, continuous high-frequency stimulation interferes with the normal motor encoding, inducing effects such as speech dysarthria and other physical/cognitive impairment. This continuous delivery of high-frequency pulses causes rapid battery drain, requiring frequent surgical pulse-generator replacement procedures.

Despite its static nature, conventional open-loop DBS remains a cornerstone clinical therapy as it provides long-term suppression of core motor symptoms while significantly reducing daily medicine requirements. However, since continuous stimulation runs without accounting for real-time fluctuations, which can lead to unnecessary power consumption and off-target clinical side effects, it was important to work toward finding a therapy that is able to adjust the electrical pulses to the brain.

Emergence of "Stimulation-on-Demand" Closed-Loop DBS (Rosin et al., 2011 / Santos et al., 2011)

To challenge and overcome the drawbacks of the frequently used open-loop stimulation, researchers explored the transition from continuous pulse delivery to closed-loop DBS, which is adaptive to the patient's needs, fluctuating the pulse provided through constant reevaluation of neural biomarkers. While an open-loop system runs based on an input without checking the result, a closed-loop system uses sensors to check the output and make changes in the pulse delivered to the brain.

In a landmark study, Rosin et al. (2011) tested a real-time closed-loop DBS interface in MPTP-treated PD non-human primates, which was later contextualized by the study conducted by Santos et al. (2011). Rosin et al. recorded the action potentials from the primary motor cortex in real time. When they detected a specific spike or pathological beta-phase threshold, the closed-loop controller instantly triggered a short train of electrical stimuli, which was delivered straight to the GPi. This meant that a condition had to be met to provide the electrical stimulation instead of sending pulses continuously like in open-loop DBS. In this non-human primate model, this closed-loop method demonstrated marked therapeutic efficacy in reversing parkinsonian motor deficits while delivering less than 10% of the electrical energy compared to continuous stimulation (measured via stimulation duration and total pulse count during active behavioral tasks). In addition, rather than suppressing overall firing rates, the phase-locked closed-loop pulses selectively disrupted the pathological phase coupling between cortex and BG output, returning single-unit firing patterns to a healthy, asynchronous state.

Santos et al. (2011) emphasized that Rosin et al.'s work marked a major shift where, for the first time, a neuromodulation system demonstrated that disrupting the pathological network dynamics in real time is

clinically more effective than continuous disruption. While adaptive DBS presents a promising alternative, significant barriers, such as the use of expensive equipment and time-consuming calibration, persist regarding its real-world clinical implementation. Nevertheless, these findings provided the proof-of-concept that was essential to explore closed-loop neural interfaces as the future of therapeutic neuromodulation.

THEME 3: TRANSLATIONAL BRAIN COMPUTER INTERFACES PARADIGMS AND THE FUTURE OF ADAPTIVE NEUROMODULATION

The Theoretical Infrastructure of Brain-Computer Interfaces: Population Vector Coding (Geogopoulos et al., 1982)

While closed-loop DBS demonstrated that real-time subcortical biomarkers can trigger targeted electrical delivery, constructing a truly context-aware neuroprosthetic requires decoding each patient's motor intent from the structures. Georgopoulos and colleagues established the mathematical and conceptual foundation for modern motor brain-computer interfaces (BCIs) through their discovery of population ensemble coding in the motor cortex. Before this study, single-unit electrophysiological recordings in the primary motor cortex revealed that individual neurons modulated their firing rates during limb movements in certain directions. However, questions still arose on how the nervous system specifies motor trajectories, as single-cell activity was characterized by highly variable tuning.

To resolve this gap, Geogopoulos et al. systematically recorded the single-cell discharges from the motor cortex of a primate performing simple, 2D reaching tasks towards targets arranged in a circle. Refer to Figure 5 for the findings when recording the stimulation of one of the motor cortical cells.

They discovered that individual primary motor cortex neurons have a continuous directional preference which can be modeled using a cosine tuning function. Under this model, a cell fires at its maximum rate when the movement aligns with its preferred direction (which is different for each neuron), while its discharge rate declines continuously as the movement is oriented away from its preferred direction. Since an individual neuron has a tuning curve that is broad with the cosine function, it fires at sub-maximal rates for movements adjacent to its preferred direction, meaning a single unit alone cannot uniquely specify a movement vector.

To overcome the single-cell ambiguity, the colleagues formulated the population vector hypothesis. By treating each neuron's preferred direction as a vector and weighting its magnitude by the cell's real-time firing rate minus its baseline activity, the researchers added the weighted vectors, making the population vector that pointed in the direction of the animal's actual arm movement. This discovery proved that complex motor intent is encoded at the ensemble level rather than by isolated command neurons.

However, scaling adaptive closed-loop systems to higher-level motor control remains hindered by unpredictable biomarker fluctuations, signal artifacts, and the difficulty of decoding nuanced movement intent in real time. Overcoming these control-loop l

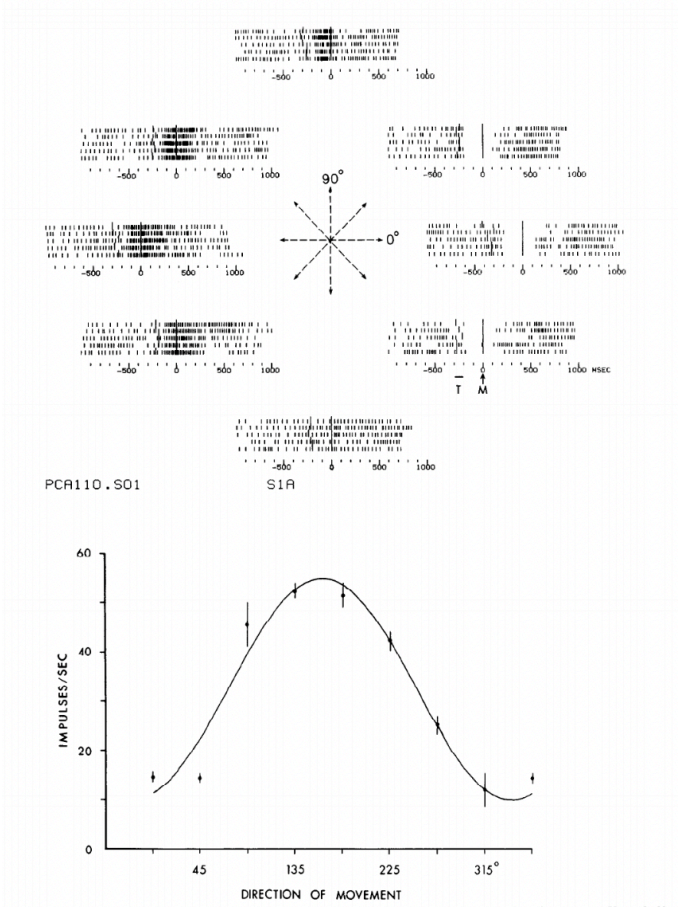

Figure 5 | Variation in the frequency of discharge of a motor cortical cell with the direction of movement. Cortical spike detection delivered to GPi. This single motor cortical cell has a preferred direction to the left, after detecting firing rate of the neuron after the subject moved in eight different directions. This helped develop the theory of directional preference for an individual neuron to understand how to make a population vector to determine the intended direction of movement. Adapted from Georgopoulos et al. (1982), copyright 1982 by the Society for Neuroscience.

imitations requires precise mathematical models capable of translating complex population-level neural activity directly into functional movement commands. Still, by demonstrating that continuous movement trajectories can be mathematically reconstructed in real time, Geogopoulos et al. established the essential conceptual infrastructure that made BCI possible. The key insight was that if enough motor cortical neurons were recorded, a population vector could be assembled to decode where the monkey was moving its arm from the neural activity alone.

Translational Logic of Cortical Motor Decoding to the Clinic (Hochberg et al., 2006)

Twenty-four years after Georgopoulos et al. established the theoretical framework of population vector coding, Hochberg and colleagues achieved a milestone by translating ensemble decoding into a human clinical application. To clinically translate the population vector framework, Hochberg et al. (2006) demonstrated that real-time cortical population vector decoding could allow a human participant with tetraplegia, resulting from a high spinal cord injury, to control a piece of hardware that had a multi-degree of freedom. Although Hochberg and colleagues evaluated a patient with a spinal cord injury rather than Parkinson's disease, this study provides a translational proof-of-concept to PD neuroprosthetics.

In the first clinical trial of the BrainGate neural interface system, Hochberg et al. investigated whether cortical neurons in a human with severe motor deprivation retained their directional tuning properties and

whether they could decode these signals to drive external prosthetic devices in real time. The participant for the study was a twenty-five year-old male who had suffered a spinal cord injury, resulting in tetraplegia.

To sync with the patient's CNS, the researchers chronically implanted a ninety-six-channel microelectrode silicon array into the hand area of the primary motor cortex. This microelectrode recorded multi-unit action potentials when the participant was instructed to imagine moving his paralyzed hand in different directions. This revealed that even after the hand had become paralyzed, the neurons still maintained directionally tuned firing modulations. By feeding these real-time firing rates into linear decoding algorithms derived from population vector dynamics, the research team enabled the participant to convert imagined motor intent into immediate physical actions.

Within days of the calibration of the neural decoder, the participant achieved real-time multidimensional control over external hardware. By imagining the hand movements, he was able to navigate a computer cursor, directed by the neural encoder, to open emails, operate TV controls, and draw simple shapes. In addition, using decoded population vectors, the participant demonstrated functional control over physical devices, operating a multi-degree-of-freedom robotic arm to grab, move, and release objects. Hochberg et al.'s findings demonstrated that human motor intentions can be extracted directly from neural ensembles in real time, highlighting BCI as a promising therapeutic strategy for severe movement disorders. More broadly, this work offers a framework for future PD-specific interventions where real-time feedback to a stimulation system could potentially be informed by real-time decoding of a patient's movement plans.

DISCUSSION

Synthesis of the Basal Ganglia Paradigms (Rate, Pattern, and Network Dynamics) and Framework of the aDBS Systems

The evolutionary arc of BG neuroscience and engineering reveals progression toward more intelligent interventions. The foundational work of Gerfen et al. in 1990 mapped the segregated dopamine receptor framework of direct and indirect pathways, setting the stage for Kravitz et al. in 2010 to confirm that direct-pathway activation could reverse PD motor deficits. In parallel, electrophysiological studies by Boraud et al. in 1998 and Papa et al. in 2001 exposed the limitations of dopaminergic pharmacotherapy, showing that oral L-DOPA fails to normalize the pathologic burst dynamics and drives BG output into extreme hypoactive states associated with dyskinesias.

To bypass these pharmacological limitations, neuromodulation shifted toward DBS. Hammond et al. in 2007 demonstrated how PD is driven by the beta-band synchronization in the BG loop, providing the target for electrical intervention. After this, Rosin et al. in 2011 and Santos et al. in 2011 validated the use of closed-loop DBS, showing that real-time biomarker sensing can disrupt pathological synchronization more efficiently than the classically used continuous open-loop stimulation while also using a smaller

portion of the electrical energy. When paired with the motor decoding paradigms pioneered by Georgopollous et al. and clinically validated by Hochberg et al., the foundation was laid for bidirectional, context-aware neuroprosthetics that are capable of decoding the intent of a patient via neuronal activation while also tuning subcortical stimulation. Still, adaptive neuromodulation should not be viewed as a replacement for an inherently flawed intervention, but rather as an evolving engineering refinement intended to address the limitations of an already successful clinical standard.

Current Frontiers of aDBS Technology

The recent proceedings of the 13th Annual Deep Brain Stimulation Think Tank highlight the cutting edge of clinical neuromodulation while simultaneously exposing the major technical and biological gaps that remain in the literature (Fleeting et al., 2026). Modern clinical trials have transitioned from basic single-threshold closed-loop triggers to sophisticated sensing architectures, such as bidirectional pulse generators capable of recording subthalamic local field potentials while delivering therapeutic stimulation. Furthermore, emerging research is exploring multi-region networks, state-adaptive algorithms, and AI models to predict clinical shifts before they manifest (Fleeting et al., 2026). Specifically, current AI systems are ideal at maximizing narrowly defined objectives, such as reducing tremor (De, et al., 2023), and synthesizing large datasets, such as detecting clinical patterns related to disease progression (Rabie & Akhloufi, 2025). Refer to Figure 6 for a multilayered representation of aDBS.

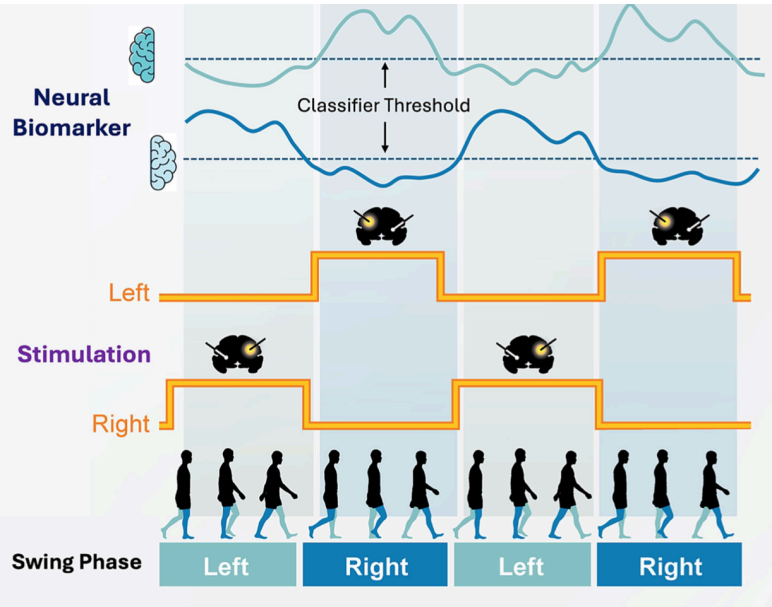

Figure 6 | Detailed Diagram of gait-phase synchronized adaptive DBS (aDBS). Using neural field potential data, Dr. Doris Wang's team identified neural biomarkers (located on top) of left and right leg swing phase (bottom panel). During contralateral leg swing, classifiers on the device were programmed to increase the stimulation amplitude (middle area). Adapted from Fleeting et al. (2026), CC BY 4.0.

Modern Gap in Research

Despite these technological advancements, a gap remains in how to combine cortical motor intent with subcortical circuit modulation. First, contemporary adaptive DBS (aDBS) systems rely on localized, subcortical local field potentials (especially the subthalamic nucleus beta-power) as a primary biomarker, a reliance critically evaluated in the proceedings of the 13th Annual Deep Brain Stimulation Think Tank detailed by Fleeting et al. (2026). However, the local beta power naturally desynchronizes during the preparation of voluntary movement in healthy brains, creating a major confounding overlap with the

suppression of pathological beta power. Current closed-loop devices frequently fail to differentiate whether a drop in beta power reflects a successful therapeutic stimulation of the patient's natural attempt to initiate a voluntary movement.

Also, a major research gap exists in the real-time integration of AI models into embedded, long-term human implants. While machine learning decoders can successfully map complex cortical population vectors (pioneered by Georgopoulos et al., 1982) or multi-frequency field potentials in laboratory settings, implementing these computationally heavy models into ultra-low-power, implantable hardware remains a major engineering hold-back. Current literature, as contextualized by Fleeting et al. (2026), lacks the long-term, multi-center human data demonstrating that AI-driven closed-loop systems can adapt to the natural dynamic shifts of PD over months and years without requiring constant manual recalibration. Whether this dual-biomarker future is ultimately accepted or rejected hinges on addressing these clinical and computational bottlenecks. Bridging these critical gaps by combining real-time cortical BCI decoding (Hochberg et al., 2006) with subcortical aDBS (Rosin et al., 2011; Santos et al., 2011) represents the essential next horizon for restoring fluid motor function in PD patients.

LIMITATIONS

While this literature review connects foundational mouse optogenetics, primate electrophysiology, DBS, and BCI paradigms, several translational and methodological limitations must be acknowledged before these approaches can be applied clinically.

Methodological Scope and Selection Bias

As a narrative review, the literature selection primarily focuses on landmark mechanistic studies.. While this structural choice highlights foundational breakthroughs in animals, it's clear that not all approaches that are feasible in lab animals can be swiftly repurposed for human patients. The use of a curated selection of animal studies, electrophysiological papers, and a constrained set of human clinical trials means that synthesized conclusions reflect proof-of-concept benchmarks rather than comprehensive, population-wide empirical data for current and future treatments.

Translational Gaps Between Preclinical Models and Human Pathology

An important disconnect exists between preclinical cell-type targeting and clinical electrical neuromodulation. For example, the direct pathway rescue demonstrated by Kravitz et al. (2010) relied on cell-type-specific optogenetic stimulation of D1-expressing striatal neurons in dopamine-depleted mice that were genetically engineered to express Cre in D1 or D2 MSNs. Since we do not genetically engineer humans to generalize a clinical therapeutic measure, these studies may not be able to be reproduced clinically and rather serve as proof-of-concept studies to demonstrate the reasons why future interventions in humans must address the lack of cell-type specificity.

In addition, clinical open-loop DBS non-specifically depolarizes surrounding axon fibers, local somas,

and glial networks without cell-type selectivity (Hammond et al., 2007). This distinction represents a key limitation because preclinical optogenetic rescues rely on precise genetic targeting of specific neuron populations (Kravitz et al., 2010), whereas clinical deep brain stimulation broadly affects all surrounding cell types and pathways indiscriminately, making direct therapeutic translation difficult. In addition, toxicological animal models, such as 6-OHDA rodent models or MPTP non-human primate models (Boraud et al., 1998), include selective nigrostriatal lesioning. These preparations fail to fully mirror the progressive, complex neurodegenerative pathology of human Parkinson's disease, reflecting the studies' establishment as preclinical measures to understand the effects of Parkinson's disease on the brain (Meredith et al., 2008).

Limited Evidence for Clinical Benefits of Proposed Frameworks

Although closed-loop or adaptive DBS in animal models demonstrates theoretical advantages, large-scale clinical trials verifying its multi-year efficacy, stability, and efficiency across diverse patient populations remain limited (Fleeting et al., 2026). The proposed AI-driven bidirectional neuroprosthetic pipeline represents a theoretical framework synthesized from converging cross-disciplinary data. There is no direct clinical validation for an integrated system that autonomously decodes motor cortical population vectors, models subcortical circuit dynamics, and delivers adaptive stimulation in real time. Translating this conceptual framework into clinical therapy requires overcoming significant hurdles in long-term signal stability, real-time edge processing, and prospective human trials. Yet given the possible therapeutic advantages, these changes in therapeutic approach to Parkinson's and other neurological disorders are inevitable given advances in brain-computer interface hardware and AI systems.

CONCLUSION

The Future of Adaptive Deep Brain Stimulation and Intersection with Brain-Computer Interfaces

The clinical management of PD has evolved from crude, systemic neuropharmacology to increasingly targeted, real-time neuromodulation of specific circuit elements. The classical Albin-DeLong framework laid the foundation by defining the direct (D1) and indirect (D2) BG pathways, a dual-stream architecture that was later verified through optogenetic circuit manipulation (Kravitz et al., 2010). Early electrophysiological investigations into dopaminergic replacement therapy revealed why oral L-DOPA remains an incomplete solution without the ability to normalize the pathological burst dynamics in BG output structures and with the frequent suppression of GPi activity to extreme levels in high doses that manifest as dyskinesias (Papa et al. 2001). These findings demonstrated that restoring motor function requires preserving precise spatial and temporal network signaling patterns (e.g. burstiness and synchrony) rather than altering firing rates throughout the circuit.

Recognizing that PD is fundamentally a disorder of pathologic beta-band hyper-synchronization, DBS emerged as a powerful tool to unbind the BG loops (Hammond et al., 2007). While traditional open-loop stimulation was effective and remains the first-line approach in clinical therapy, its continuous delivery mechanism introduces off-target side effects and ignores real-time shifts in patient state. The

implementation of closed-loop adaptive stimulation in non-human primates established that disrupting pathological synchronization exclusively when triggered by neural biomarkers can, in principle, yield superior clinical outcomes with less electrical energy (Rosin et al., 2011). However, the impact of this study has not yet reached the clinic, and the human side effects are not well explored.

While open-loop DBS is a powerful and widespread therapeutic measure used in PD patients, there are many side effects, including dysarthria, hypophonia, worsening balance, increased gait freezing, declines in verbal fluency, unintended muscle contractions or tingling from capsular current spread, and neuropsychiatric shifts (Hariz & Blomstedt, 2022). These side effects could be mitigated by future efforts in exploring the implementation of artificial intelligence models in adaptive DBS as a neuroprosthetic for PD patients, which can be controlled more fluidly and adjusted in real time to account for side effects. Nevertheless, there is a trade-off: on the plus side, adaptive DBS could reduce the side effects of open-loop DBS, but adjusting stimulation paradigms in a real human patient could be viewed as risky and may carry additional concerns such as a more expensive neuroprosthetic, inevitable errors in adjustment, worse motor control, etc.

To overcome the fundamental limitations of contemporary neuromodulation, specifically the inability of single-site subcortical sensors to differentiate intentional movement preparation from disease pathology, this literature review proposes a novel, AI-driven bidirectional neuroprosthetic. By synthesizing real-time population vector decoding with adaptive subcortical stimulation, this proposed model offers a clear path forward. Implementing context-aware decoding models into implantable hardware promises to eliminate electrical interference during intended movement while dynamically suppressing pathological dynamics at rest, ultimately delivering seamless, natural motor restoration for individuals living with Parkinson's disease.

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