

Temporal Interference Stimulation in Parkinson's Disease: Targets, Parameters, and Therapeutic Mechanisms

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1. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, affecting millions worldwide and characterized by both motor and non-motor symptoms that profoundly impact quality of life [1,2]. The core motor features—bradykinesia, rigidity, resting tremor, and gait disturbances—emerge from progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta, which deprives the basal ganglia of essential dopaminergic modulation [2,3]. While dopaminergic replacement therapy remains the cornerstone of pharmacological management, its long-term efficacy is limited by motor complications, including levodopa-induced dyskinesias and wearing-off phenomena [2,4]. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus internus (GPi) has emerged as a highly effective surgical therapy for advanced PD, yet its invasive nature restricts its application to a minority of eligible patients and carries inherent surgical risks [4-6].

Remarkable progress has been made in understanding the neural mechanisms underlying PD motor symptoms. Excessive beta-band (13–35 Hz) oscillations within the cortico-basal ganglia-thalamocortical (CBTC) network have been consistently identified as a key pathophysiological hallmark, correlating with motor impairment severity and serving as a biomarker for adaptive DBS [7-10]. Abnormal beta activity manifests not only as elevated spectral power but also as altered burst dynamics—transient episodes of heightened oscillatory synchronization that interfere with information processing in motor circuits [11-13]. Complementary evidence implicates aberrant gamma oscillations, disrupted phase-amplitude coupling, and changes in aperiodic neural activity in the pathophysiology of PD motor signs [1,9,14,15].

Temporal interference stimulation (TIS) represents a transformative advancement in non-invasive neuromodulation. First described in 2017, TIS delivers two or more high-frequency electric fields (typically in the kilohertz range) with a small frequency difference through scalp electrodes [16,17]. At the intersection of these fields, the superposition generates an amplitude-modulated envelope at the difference frequency (Δf), which falls within the physiological range of neural oscillations [6,16]. This approach enables targeted modulation of deep brain structures

while minimizing stimulation of overlying cortical tissue—a capability previously achievable only through invasive DBS [6,18,19].

The potential of TIS for PD has attracted substantial research interest. Preclinical studies in rodent models have demonstrated that TIS targeting the striatum can alleviate motor deficits, confer neuroprotection, and modulate mitochondrial homeostasis [20]. Early clinical trials have reported encouraging results, including improved bradykinesia and tremor following TIS targeting the STN or GPi [21,22]. Concurrently, computational modeling studies have refined our understanding of electric field distribution, parameter optimization, and interindividual variability [23-25]. Significant knowledge gaps remain regarding optimal stimulation parameters, target selection for specific clinical phenotypes, and the mechanisms linking TIS-induced neural modulation to symptomatic improvement [6,16,26].

This review synthesizes current evidence on TIS in PD, focusing on the relationship between stimulation targets, parameter selection, and therapeutic outcomes. We first examine the neurobiological basis of basal ganglia dysfunction and abnormal oscillatory activity in PD, establishing the rationale for targeting specific deep brain structures. We then systematically review preclinical and clinical studies of TIS in PD, comparing the effects of different targets on distinct motor phenotypes. Subsequently, we analyze how stimulation parameters—including carrier frequency, envelope frequency, intensity, electrode montage, and treatment duration—influence electric field distribution, neural entrainment, and clinical efficacy. By integrating electrophysiological, neuroimaging, and behavioral evidence, we construct a mechanistic framework connecting TIS parameters to deep target engagement, network remodeling, and symptomatic improvement. Finally, we address current challenges and propose future directions for personalized, closed-loop TIS approaches in PD.

2. Neurobiological Basis of Parkinson's Disease and Rationale for Temporal Interference Stimulation

2.1 Basal Ganglia Circuit Dysfunction, Abnormal Beta Oscillations, and Motor Symptoms

The basal ganglia constitute a highly interconnected network

of subcortical nuclei that modulate cortical activity through parallel, functionally segregated loops [2,27]. The primary input structure, the striatum, receives excitatory glutamatergic projections from widespread cortical regions and dopaminergic innervation from the substantia nigra pars compacta [27,28]. Striatal medium spiny neurons (MSNs) give rise to two major output pathways: the direct pathway projecting to the GPi and substantia nigra pars reticulata, and the indirect pathway projecting to the external globus pallidus (GPe) and STN [2,27]. The STN, a key node of the indirect pathway, sends excitatory glutamatergic projections to the GPi and GPe, while the GPe provides inhibitory GABAergic feedback to the STN, forming a recurrent subthalamopallidal loop [29,30]. The GPi constitutes the primary output nucleus, projecting to the thalamus, which in turn innervates the motor cortex [2].

Dopamine depletion fundamentally disrupts this circuitry. Loss of nigrostriatal dopaminergic input alters the balance between direct and indirect pathway activity, leading to excessive inhibition of the thalamus and reduced cortical activation [2,27]. At the network level, dopamine depletion induces widespread changes in oscillatory activity, most notably a marked increase in beta-band (13–35 Hz) oscillations across the CBTC network [7,13,31]. Elevated beta power has been documented in the STN, GPi, GPe, motor cortex, and thalamus in both PD patients and animal models [10,13,31]. Longitudinal studies in non-human primates have demonstrated that beta oscillatory changes emerge early during the transition to parkinsonism and intensify with disease progression [13,31].

The relationship between beta oscillations and motor impairment is complex and multifaceted. Beta power correlates with bradykinesia and rigidity severity in many studies, although the strength of these correlations varies considerably across cohorts [10,15]. A multicenter analysis of 119 PD patients revealed that low beta power explained only a modest fraction of symptom severity variance, suggesting that beta oscillations represent one component of a broader pathophysiological landscape [15]. Beta activity in PD is not a static phenomenon but rather exhibits dynamic burst-like fluctuations. Beta bursts—transient episodes of elevated oscillatory amplitude—have been linked to motor slowing, with the cumulative history of bursting activity predicting movement velocity [12]. Longer and more frequent beta bursts are associated with greater motor impairment, and burst dynamics are modulated by dopaminergic medication [13,32]. The spatial organization of beta bursts also appears to be structured, with bursts forming spatially discrete ensembles that span multiple nodes of the CBTC network [33].

Beyond beta oscillations, other frequency bands contribute to PD pathophysiology. Gamma-band (60–90 Hz) activity, which is normally associated with movement execution, is disrupted in PD [1,14]. Phase-amplitude coupling between beta phase and gamma amplitude is pathologically enhanced, and this cross-frequency interaction correlates with bradykinesia severity [14]. The aperiodic component of the power spectrum, reflecting spiking activity and excitation-inhibition balance, also changes in PD. The aperiodic exponent and offset are altered in the STN and are modulated by dopaminergic medication [9,32,34].

Importantly, aperiodic broadband power scales with PD severity and may serve as a complementary biomarker to beta oscillations [15]. The relationship between dopamine tone and beta frequency is also notable: beta oscillation frequency shifts with dopamine levels, suggesting that frequency itself carries information about disease state [35].

The network-level consequences of these oscillatory abnormalities are profound. Excessive beta synchronization is thought to reduce the information coding capacity of basal ganglia circuits, impairing the transmission of motor commands [11,36]. During movement, beta desynchronization normally occurs to facilitate motor execution; in PD, this desynchronization is attenuated, particularly during movement preparation [37]. Gait disturbances, including freezing of gait, are associated with increased beta oscillatory activity in the STN during stepping, and gait-related frequency modulation of beta activity has been proposed as a biomarker for adaptive DBS [38,39]. These observations collectively support the hypothesis that abnormal oscillatory activity—particularly beta oscillations and their dynamic interactions with other frequency bands—constitutes a central mechanism underlying PD motor symptoms.

2.2 Key Deep Brain Targets and Their Pathological Evidence: STN, GPi, Striatum, Thalamus, and Motor Cortex

The identification of optimal neuromodulation targets for PD requires a thorough understanding of the pathological changes occurring at each node of the CBTC network. The STN has emerged as the most widely used DBS target, and its central role in PD pathophysiology is supported by extensive evidence [4,40]. In the parkinsonian state, STN neurons exhibit increased firing rates, altered firing patterns characterized by bursting activity, and enhanced oscillatory synchronization in the beta band [29,30,40]. Computational modeling studies have demonstrated that the STN-GPe loop can generate and sustain beta oscillations, with the specific dynamics depending on the intrinsic properties of STN neurons [29,30]. The STN also receives direct cortical input through the hyperdirect pathway, providing a route for cortical beta activity to entrain basal ganglia circuits [41]. Thalamic projections from the parafascicular nucleus to the STN contribute to movement initiation, and selective stimulation of this pathway can rescue motor deficits in dopamine-depleted mice [42].

The GPi, the primary output nucleus of the basal ganglia, exhibits elevated beta power in PD that correlates with bradykinesia and rigidity severity [10]. Comparative studies have shown that GPi beta power may be more readily detected and more strongly related to clinical impairment than STN beta activity, suggesting that the GPi could serve as an effective target for beta-based adaptive DBS [10]. The GPi also plays a role in non-motor symptoms; pallidal beta activity is sustained during sleep and correlates with sleep disturbance in PD patients [43]. Recent evidence indicates that cortico-pallidal beta dynamics underlie turning impairments, with excessive beta synchrony constraining movement flexibility during turning [44]. The cellular composition of the GPi, particularly parvalbumin-positive neurons, exhibits

firing rate and pattern changes that correlate with motor symptom severity [2]. The GPe, although less commonly targeted clinically, is critically involved in beta oscillation generation through its reciprocal connections with the STN [29,30]. The GPe contains distinct neuronal populations — prototypical and arky pallidal cells—with different connectivity patterns and functional roles, and dopamine-dependent changes in intrapallidal connectivity can induce oscillatory dynamics [45].

The striatum, the primary input structure of the basal ganglia, has received increasing attention as a potential TIS target. Striatal dopamine depletion leads to hyperactivity of indirect pathway MSNs and altered synaptic plasticity [28,46]. Corticostriatal glutamatergic overdrive, acting through NMDA receptors, has been implicated in the amplification and propagation of beta synchronization across the CBTC circuit [28]. The striatum also exhibits complex oscillatory dynamics involving interactions between beta, gamma, and theta rhythms, which are essential for action selection and motor program execution [27]. Computational modeling suggests that STN projections to striatal fast-spiking interneurons play a critical role in modulating striatal dynamics, and DBS may restore normal striatal rhythms by recruiting these interneurons [27]. The ventral striatum, including the nucleus accumbens, is more closely associated with reward and motivation, and its dysfunction contributes to non-motor symptoms [47,48].

The thalamus serves as the major relay between the basal ganglia and the cerebral cortex. Motor thalamic nuclei receive inhibitory input from the GPi and project to the motor cortex [2]. In PD, thalamic neurons exhibit altered firing patterns and enhanced beta oscillatory activity [31]. The thalamus is also the target for tremor-suppressing DBS, particularly the ventral intermediate nucleus, although this target is less commonly used for other PD symptoms [2]. Thalamocortical interactions are critical for the generation of sleep spindles and other physiological oscillations, and targeting the thalamus with TIS has been explored for enhancing sleep spindle activity [49].

The motor cortex represents the final common pathway for motor command generation and is intimately connected with basal ganglia circuits [2]. Cortical neurons in PD exhibit increased beta oscillatory activity and altered burst dynamics, with M1 beta burst duration correlating with movement cycle width during bradykinesia [36]. Cortical disinhibition, reflecting reduced short-interval intracortical inhibition, is an early feature of PD and may represent a prodromal biomarker [50]. The motor cortex also exhibits early decreases in mid-gamma activity that coincide with the onset of motor deficits, preceding the emergence of exaggerated beta oscillations [51]. The sensorimotor cortex, including the supplementary motor area, participates in movement preparation and execution, and its oscillatory activity is modulated by dopaminergic medication and DBS [52]. Cortical gamma oscillations, particularly in the high-gamma range, are associated with movement execution and are disrupted in PD [14,36].

The selection of an appropriate TIS target depends on the specific motor phenotype and the underlying

pathophysiological mechanisms. STN targeting may be most effective for bradykinesia and rigidity, given the strong association between STN beta activity and these symptoms [10,15]. GPi targeting may offer advantages for tremor and axial symptoms, based on evidence linking pallidal activity to these features [2,10]. Striatal targeting may be particularly relevant for motor learning and skill acquisition, given the role of the striatum in reinforcement learning and procedural memory [53,54]. Motor cortex targeting may be useful for modulating cortical excitability and facilitating movement initiation [55,56]. The optimal target may also depend on disease stage, with earlier-stage patients potentially benefiting more from striatal or cortical stimulation, while advanced-stage patients may require STN or GPi targeting [21,22].

3. Current Evidence of Temporal Interference Stimulation in Parkinson's Disease

3.1 Preclinical and Early Clinical Studies of TIS in Parkinson's Disease

The translational development of TIS for PD has progressed from computational modeling and rodent experiments to early human trials. Preclinical studies have provided proof-of-concept evidence that TIS can modulate deep brain structures and alleviate parkinsonian motor deficits. In a mouse model of PD induced by MPTP, striatal TIS delivered at 2 kHz and 2.02 kHz carrier frequencies with a 20 Hz offset significantly reduced motor deficits and attenuated dopaminergic neurodegeneration and α -synuclein accumulation [20]. Notably, these neuroprotective effects were associated with improvements in mitochondrial homeostasis, including mitochondrial morphology, dynamics, PINK1/Parkin-mediated mitophagy, and complex I activity. Pharmacological inhibition of mitochondrial fission with Mdivi-1 largely abolished the behavioral and neuropathological benefits of TIS, suggesting that mitochondrial quality-control pathways contribute to TIS-associated neuroprotection [20].

The striatum has also been targeted in healthy animals to establish the neural mechanisms of TIS effects. TIS applied to the primary motor cortex of mice for seven consecutive days with a 20 Hz envelope frequency improved motor performance, including rotarod and grid-walking tests [55,57]. These behavioral improvements were associated with enhanced synaptic connectivity, increased dendritic spine density, promoted neurotransmitter release, and upregulated expression of synapse-related proteins such as BDNF, PSD-95, and glutamate receptors [57]. The PI3K/AKT signaling pathway, activated by BDNF, was identified as a key mediator of TIS-induced neuroplasticity [57]. These findings demonstrate that TIS can engage neuroplastic mechanisms relevant to motor recovery, even in the absence of pathology.

In a rat model of PD induced by 6-hydroxydopamine (6-OHDA) lesions, TIS effects have been evaluated at the level of neural oscillations and motor behavior. The 6-OHDA model recapitulates key features of PD, including dopaminergic neuron loss, motor deficits, and increased beta oscillations across multiple brain regions [3]. TIS-induced modulation of neural activity in the deep brain has been

confirmed in minipigs with implanted deep brain electrodes, demonstrating intensity-dependent effects on local field potentials and entrainment of envelope oscillations below 200 Hz [58]. These large-animal studies bridge the gap between rodent experiments and human applications, confirming that TIS can reach deep brain structures in brains of human-relevant size.

Early clinical studies of TIS in PD have yielded promising but preliminary results. A pilot randomized, double-blind, sham-controlled crossover study examined the effects of a single session of transcranial TIS (tTIS) targeting the STN region in 30 patients with early-to-mid-stage PD [22]. Individualized electrode montages were designed using structural MRI. In the medication-off state, 20 minutes of 130 Hz tTIS produced significantly greater improvements in MDS-UPDRS-III scores compared to sham stimulation, with a responder rate (≥ 5 -point reduction) of 70% versus 15%. Bradykinesia and tremor showed the most consistent improvements, while rigidity and axial signs were less affected. The effects were evident immediately after stimulation and persisted for at least 60 minutes. No serious adverse events were reported, and blinding was effective, supporting the feasibility and safety of STN-targeted tTIS in PD [22].

Another pilot study evaluated tTIS targeting the right GPi in 12 patients with mild PD [21]. In the medication-on state, a single 20-minute session of tTIS significantly reduced MDS-UPDRS-III scores by 6.64 points (14.7%), with particular improvements in bradykinesia (23.5%) and tremor (15.3%). Motor symptom alleviation was more pronounced on the left side, contralateral to the stimulation target, consistent with the lateralized organization of basal ganglia motor circuits. Patients with more severe baseline symptoms experienced greater improvements, suggesting that tTIS may be most beneficial for those with greater clinical need [21].

The safety and tolerability of tTIS have been systematically evaluated in a large dataset of 119 participants undergoing 257 sessions targeting the striatum or hippocampus [59]. tTIS-evoked sensations were generally rated as mild and were equivalent between active and sham conditions, indicating robust blinding efficiency. These findings support the use of tTIS in double-blind, placebo-controlled designs for future clinical trials [59]. Additional safety assessments in healthy adults have confirmed the absence of significant neurological or neuropsychological changes following tTIS at typical parameters (2 mA, 20/70 Hz, 30 minutes) [60]. Computational modeling and phantom studies have further supported the safety of TIS in terms of thermal effects and tissue damage thresholds [61].

3.2 Target-Specific Effects of TIS: STN, Striatum, GPi, Motor Cortex, and Network Nodes

The effects of TIS vary substantially across stimulation targets, reflecting the distinct functional roles of different basal ganglia nodes and their differential involvement in specific motor symptoms.

STN-targeted TIS has been the most extensively studied in PD. The rationale for STN targeting is grounded in the

well-established role of STN beta oscillations in motor impairment and the clinical efficacy of STN DBS [4,10,40]. In the pilot crossover study described above, STN-targeted tTIS at 130 Hz produced significant improvements in bradykinesia and tremor, with effects emerging within minutes of stimulation and persisting for at least one hour [22]. Neuroimaging evidence from a separate randomized, double-blind crossover study demonstrated that STN-targeted tTIS modulates functional connectivity within the CBTC circuit [62]. Twenty-three patients with mild-to-moderate PD received 20 minutes of 130 Hz tTIS targeting the STN contralateral to the more affected side. Compared to sham stimulation, tTIS decreased functional connectivity between the targeted STN and the putamen and caudate, while increasing connectivity between the STN and the primary motor cortex. These connectivity changes are consistent with the known anatomical projections of the STN and suggest that tTIS can engage the motor circuit in a target-specific manner [62].

Striatal TIS represents a different therapeutic strategy, focusing on the input stage of basal ganglia processing. The striatum is critically involved in motor learning, skill acquisition, and reinforcement-based motor adaptation [53,54]. In healthy older adults, theta-burst patterned striatal tTIS increased striatal activity and associated motor network connectivity, enhancing motor performance [53]. A subsequent study demonstrated that striatal tTIS at 80 Hz, but not 20 Hz, disrupted reinforcement learning of motor skills, providing causal evidence for the role of gamma-band striatal activity in reward-based motor learning [54]. These findings suggest that striatal TIS could be used to modulate motor learning processes in PD, potentially complementing the effects of STN or GPi stimulation. However, direct evidence for striatal TIS in PD patients remains limited. The ventral striatum has been targeted with TIS in healthy adults, demonstrating modulation of reward-related brain activity and anxiety reduction [47], but the relevance of these effects to PD motor symptoms requires further investigation.

GPi-targeted TIS offers an alternative approach based on the role of the GPi as the primary output nucleus of the basal ganglia. The pilot study of GPi tTIS in PD patients demonstrated significant improvements in bradykinesia and tremor, with contralateral predominance [21]. The GPi may be particularly relevant for tremor-dominant PD, given the association between pallidal activity and tremor generation [2]. However, the current evidence base for GPi-targeted TIS is limited to a single small pilot study, and larger confirmatory trials are needed.

Motor cortex TIS has been explored primarily in healthy populations and animal models. TIS applied to the primary motor cortex of mice with a 20 Hz envelope frequency enhanced motor skill learning and neuroplasticity [55,57]. In healthy humans, TIS targeting the primary motor cortex enhanced functional connectivity between M1 and secondary motor areas, including the premotor and supplementary motor cortices [63]. A comparative study demonstrated that TIS and high-definition transcranial direct current stimulation (HD-tDCS) both enhanced sensorimotor network connectivity, but TIS produced greater improvements in network efficiency and broader effects on between-network

connections [64]. Repetitive TIS targeting the lower limb motor area improved vertical jump performance in healthy adults, suggesting that motor cortex TIS can enhance motor function relevant to daily activities [65]. In PD, cortical stimulation with TIS could potentially address cortical disinhibition and facilitate movement initiation, but direct clinical evidence is lacking [36,50].

Beyond these primary targets, TIS can modulate activity in distributed brain networks. Hippocampal TIS has been shown to enhance episodic memory in healthy humans, demonstrating the ability of TIS to engage deep structures beyond the basal ganglia [18]. Thalamic TIS has been used to enhance sleep spindle activity, with potential implications for sleep disturbances in PD [49]. The nucleus accumbens has been targeted with TIS to modulate reward circuitry and reduce anxiety [47,48]. These findings illustrate the versatility of TIS as a tool for probing and modulating diverse deep brain structures, although their specific relevance to PD requires further study.

3.3 Effects of TIS on Clinical Phenotypes: Bradykinesia, Rigidity, Tremor, and Gait Disturbances

The clinical manifestations of PD are heterogeneous, and different motor symptoms may respond differently to TIS depending on the stimulation target and parameters.

Bradykinesia, characterized by slowness of movement and reduced amplitude, is one of the most disabling PD symptoms and is strongly associated with beta oscillatory activity in the basal ganglia [10,15]. TIS targeting the STN has produced significant improvements in bradykinesia scores in early clinical trials [22]. The reduction in bradykinesia following STN tTIS is consistent with the observation that beta suppression is associated with improved motor performance [66]. Pre-movement beta desynchronization is reduced in PD and correlates with bradykinesia severity, suggesting that TIS-induced modulation of beta dynamics could facilitate movement initiation [37]. GPi-targeted tTIS also improved bradykinesia in a pilot study, with contralateral predominance [21]. The mechanisms underlying bradykinesia improvement may involve restoration of cortical gamma activity and improved information coding in motor circuits [36].

Rigidity, characterized by increased muscle tone and resistance to passive movement, is also associated with beta oscillatory activity [10]. Both STN and GPi tTIS have produced improvements in rigidity scores, although the effects were less consistent than those for bradykinesia [21,22]. The relatively modest effects on rigidity may reflect the complex pathophysiology of this symptom, which involves both central and peripheral mechanisms [67]. Rigidity is also associated with changes in spinal reflex loop oscillations, which may be less amenable to cortical or subcortical neuromodulation [67].

Tremor, particularly resting tremor, is a hallmark of PD and is associated with distinct neural mechanisms involving the cerebello-thalamo-cortical circuit [2,67]. TIS targeting the STN and GPi has produced significant improvements in tremor scores in pilot studies [21,22]. The effects of TIS on tremor may be mediated by modulation of beta oscillations in

the basal ganglia, which interact with tremor-generating circuits [67]. The ventral intermediate nucleus of the thalamus, a key node in the tremor circuit, could represent an additional TIS target for tremor-dominant PD, although clinical evidence is lacking [2].

Gait disturbances, including freezing of gait, are among the most disabling PD symptoms and are associated with abnormal oscillatory activity in the STN and other brain regions [38,39,68]. Gait-related frequency modulation of beta activity in the STN has been described, and beta oscillations increase during freezing episodes [38,39]. TIS could potentially modulate gait-related neural activity, but no clinical studies have specifically evaluated TIS effects on gait in PD. The complex multisensory and cognitive demands of gait control suggest that TIS targeting multiple network nodes, including the STN, motor cortex, and mesencephalic locomotor region, may be necessary for optimal effects [68]. The development of TIS protocols for gait disturbances represents an important avenue for future research.

4. Influence of Stimulation Parameters on TIS Outcomes

4.1 Carrier Frequency, Envelope Frequency (Δf), and Their Neural Consequences

The biophysical principles underlying TIS determine how stimulation parameters influence neural responses. TIS delivers two or more high-frequency electric fields, typically in the kilohertz range, with a small frequency difference (Δf). At the target region, the superposition of these fields generates an amplitude-modulated envelope at Δf , which falls within the physiological range of neural oscillations [6,16]. The carrier frequency and envelope frequency independently influence neural responses through distinct mechanisms.

The carrier frequency determines the biophysical interaction between the electric field and neural membranes. Neuronal membranes act as low-pass filters, attenuating the response to high-frequency fields [69,70]. Early computational models suggested that TIS works through passive membrane filtering, with the envelope extracted by the membrane's frequency-dependent impedance [70]. However, subsequent analysis has challenged this view, proposing that ion-channel-mediated signal rectification is required for TIS effects [70]. The carrier frequency also influences stimulation thresholds: higher carrier frequencies require higher electric field strengths to achieve neural activation [69,71]. Experimental studies in rat hippocampal slices demonstrated that the electric field threshold for modulating gamma oscillations increased with carrier frequency, from approximately 5 V/m at 100 Hz to 60–80 V/m at 1–2 kHz [69]. In peripheral nerve preparations, stimulation thresholds were governed by the carrier frequency itself, with minimal dependence on amplitude modulation, supporting the hypothesis that suprathreshold TIS acts through kilohertz rectification rather than envelope-specific effects [72]. However, this interpretation remains debated, as other studies have demonstrated envelope-specific effects on neural activity [73].

The envelope frequency (Δf) determines the frequency of amplitude modulation and, consequently, the frequency of

neural entrainment. TIS studies in PD have predominantly used Δf values in the beta (20 Hz) or gamma (80–130 Hz) range [21,22,54]. Beta-frequency TIS (20 Hz) has been used to entrain beta oscillations in the motor cortex and striatum, with effects on motor learning and cortical excitability [55,56,74]. Gamma-frequency TIS (80 Hz) has been shown to disrupt reinforcement learning when applied to the striatum, suggesting frequency-specific effects on striatal function [54]. High-frequency TIS (130 Hz) targeting the STN has produced rapid improvements in motor symptoms, consistent with the frequency used in conventional DBS [22]. The choice of envelope frequency should be guided by the intended neural target and the physiological frequency bands relevant to the targeted symptom or function.

The relationship between carrier and envelope frequencies is critical for TIS efficacy. The carrier frequency must be high enough to avoid direct neural stimulation at the electrodes but low enough to permit effective envelope extraction at the target [16,69]. Computational modeling suggests that the optimal carrier frequency depends on the neuronal membrane time constant, with faster membranes requiring higher carrier frequencies [69]. Experimental studies in minipigs demonstrated that carrier frequencies of 1 or 2 kHz were most effective for modulating deep brain local field potentials, while higher frequencies had reduced efficacy [58]. The carrier frequency also influences the spatial distribution of the electric field, with higher frequencies producing more focal fields but requiring higher intensities [75].

4.2 Stimulation Intensity, Electrode Montage, and Electric Field Distribution

The stimulation intensity determines the magnitude of the electric field at the target and, consequently, the extent of neural modulation. TIS studies in humans have used currents ranging from 2 mA to 10 mA, with higher intensities generally producing stronger effects [18,22,76]. However, the relationship between applied current and electric field at depth is complex and depends on individual head anatomy [23,25]. Computational modeling has demonstrated that the electric field strength at deep targets is substantially lower than at the scalp, and that the required current to achieve effective deep stimulation may approach safety limits [69,77]. For example, amplitude-modulated stimulation with a 100 Hz carrier frequency required approximately 13 mA at the scalp to significantly modulate gamma oscillations, while a 1 kHz carrier required approximately 160 mA [69]. These estimates highlight the challenge of delivering sufficient current to deep targets without exceeding safety thresholds.

Electrode montage is a critical determinant of electric field distribution and targeting accuracy. Conventional TIS uses two pairs of electrodes, with each pair carrying a different carrier frequency [16]. The placement of these electrode pairs on the scalp determines the direction and magnitude of the interfering electric fields at the target. Computational optimization studies have demonstrated that electrode configuration can be optimized to maximize the electric field at the target while minimizing off-target stimulation [23,78]. Individualized optimization based on structural MRI has been shown to improve targeting accuracy compared to standard montages [23,24]. However, individualized optimization

requires specialized software and computational resources, which may limit clinical applicability [79]. Population-based optimization using group-level electric field analysis has been proposed as a compromise, achieving comparable targeting accuracy to individualized analysis while reducing the need for patient-specific MRI [79].

The number of electrode pairs can also be increased to improve focality. Multipair TIS, using more than two electrode pairs, has been shown to provide more focal stimulation than conventional two-pair TIS in computational studies [80]. Multipolar temporal interference (mTI) uses multiple carrier frequencies to create multiple overlapping amplitude-modulated envelopes, enabling independent control over the size of the stimulated region and stimulation intensity [81]. This approach has demonstrated improved focality at depth in anesthetized mice and monkeys, with the ability to evoke targeted activity in the superior colliculus of awake monkeys [81]. Phase-modulated multipair configurations, in which one electrode pair is actively phase-shifted by 180°, can create canceling fields that reduce off-target effects without compromising efficacy at the target [82].

The orientation of the electric field relative to neuronal elements is another important consideration. Neurons are polarized by electric fields in an orientation-dependent manner, with axons and dendrites responding differently to fields aligned with their long axes [83]. The direction of maximum modulation depth in TIS can be calculated using closed-form expressions, enabling the prediction of neuronal responses based on field orientation [84]. Computational modeling has demonstrated that the modulation depth along the secondary maximum orientation can be similar in strength to the maximum when interfering electric field vectors are significantly misaligned [84]. These findings have implications for TIS targeting, as the optimal electrode montage may depend on the orientation of the target neuronal population.

4.3 Stimulation Duration, Repeated Sessions, and Long-Term Plasticity

The duration of individual TIS sessions and the number of repeated sessions are critical parameters that influence both acute and long-term effects. Most clinical studies have used single sessions of 20 minutes, which have produced measurable improvements in motor symptoms that persist for 30–60 minutes after stimulation [21,22]. The relatively short duration of post-stimulation effects suggests that repeated sessions may be necessary for sustained clinical benefit. Preclinical studies have demonstrated that repeated TIS sessions over 7–14 days can produce cumulative effects on motor performance and neuroplasticity [20,55,57]. In the MPTP mouse model, 14 days of striatal TIS produced greater behavioral benefit than 7 days, suggesting that longer treatment durations may enhance therapeutic effects [20].

The mechanisms underlying long-term TIS effects likely involve activity-dependent plasticity. TIS-induced neural activity can trigger synaptic plasticity, including long-term potentiation and depression, depending on the stimulation frequency and pattern [16,74]. Theta-burst stimulation

protocols delivered through TIS have been shown to modulate cortical excitability in a pattern-dependent manner, with intermittent theta-burst stimulation producing potentiation and continuous theta-burst stimulation producing depression [74]. These effects are consistent with the known mechanisms of theta-burst plasticity and suggest that TIS can engage canonical plasticity mechanisms [74]. Repeated TIS sessions may also induce structural plasticity, including dendritic spine remodeling and synaptic protein expression changes [55,57]. The PI3K/AKT signaling pathway, activated by BDNF, has been identified as a key mediator of TIS-induced neuroplasticity [57].

The optimal timing and spacing of repeated TIS sessions remain to be determined. Preclinical studies have used daily sessions, but the effects of less frequent stimulation are unclear. The concept of metaplasticity—the influence of prior synaptic activity on subsequent plasticity—suggests that the timing of TIS sessions relative to behavioral training or other interventions may be critical [16]. Closed-loop approaches, in which TIS is delivered contingent on specific neural or behavioral states, may optimize the timing of stimulation to coincide with periods of heightened plasticity [16,85].

4.4 Parameter–Target–Symptom Associations and Optimization Strategies

The relationship between stimulation parameters, targeting, and clinical outcomes in TIS for PD is complex and multifactorial. Different targets may require different parameter combinations to achieve optimal effects. For example, STN-targeted TIS for bradykinesia may require beta-frequency envelope stimulation to modulate beta oscillations, while GPi-targeted TIS for tremor may benefit from higher-frequency stimulation to disrupt tremor-generating circuits [21,22]. The optimal parameters for a given target and symptom may also vary across individuals, reflecting interindividual differences in head anatomy, disease severity, and neural responsiveness [23-25].

Computational modeling has emerged as a powerful tool for parameter optimization in TIS. Finite element models of the human head can simulate electric field distribution for different electrode montages and stimulation parameters, enabling the identification of optimal configurations for specific targets [23,78,86]. Convex optimization approaches have been developed to rapidly determine optimal electrode configurations, reducing computation time from hours to minutes [86]. Machine learning approaches, including unsupervised neural networks, have been used to optimize electrode currents for high-definition TIS, achieving rapid and accurate targeting [87]. Target-specific restricted exhaustive search strategies have been proposed to reduce the computational burden of parameter optimization while maintaining reliability [88]. These computational approaches have the potential to enable personalized TIS parameter selection in clinical practice.

The development of standardized protocols for TIS parameter reporting is essential for comparing results across studies and facilitating clinical translation. Currently, there is substantial variability in stimulation parameters across studies, including carrier frequency, envelope frequency, intensity, duration,

and electrode configuration [26]. This variability complicates the interpretation of results and the identification of optimal parameters. Consensus guidelines for TIS parameter reporting, similar to those developed for other non-invasive brain stimulation techniques, would facilitate progress in this field [16,89].

5. Multimodal Evidence and Mechanisms: Constructing the TIS Action Chain

5.1 Electrophysiological Biomarkers: LFP, EEG, and Beta Burst Dynamics

Electrophysiological recordings provide direct evidence for the neural effects of TIS and enable the construction of mechanistic models linking stimulation parameters to clinical outcomes. Local field potential (LFP) recordings from deep brain structures offer the most direct assessment of TIS-induced neural modulation. In minipigs with implanted deep brain electrodes, tTIS modulated LFP activity in the STN in an intensity-dependent manner, with carrier frequencies of 1–2 kHz being most effective [58]. Envelope oscillations below 200 Hz were effectively entrained into deep-brain LFPs, demonstrating that TIS can drive neural activity at the intended frequency [58]. These findings confirm that TIS can reach deep brain structures and modulate their activity in a frequency-specific manner.

In PD patients, LFP recordings from the STN have been used to characterize beta oscillations and their dynamics. Beta bursts—transient episodes of elevated beta power—are a prominent feature of STN activity in PD and are modulated by dopaminergic medication [32,90]. The duration and amplitude of beta bursts correlate with motor impairment, and burst dynamics are altered by DBS [12,32]. TIS-induced modulation of beta bursts could potentially be assessed using LFP recordings from implanted DBS electrodes, providing a direct measure of target engagement. However, concurrent TIS and LFP recording is technically challenging due to stimulation artifacts, and few studies have achieved this combination [91]. Advances in artifact suppression techniques, including hardware-based filtering and signal processing algorithms, may enable simultaneous TIS and LFP recording in future studies [91,92].

EEG recordings offer a non-invasive alternative for assessing TIS effects on cortical activity. TIS targeting the motor cortex has been shown to modulate cortical excitability, as measured by motor-evoked potentials [56]. Alpha and gamma TIS increased MEP amplitudes compared to sham stimulation, with gamma TIS also reducing intracortical inhibition [56]. These effects are consistent with the known frequency-dependent effects of transcranial alternating current stimulation on cortical excitability [56]. However, the ability of EEG to detect TIS effects on deep brain structures is limited by the attenuation of subcortical signals at the scalp [93]. Studies using conventional tACS have demonstrated aftereffects on parieto-occipital alpha oscillations, but comparable effects have not been consistently demonstrated for tTIS [93].

The analysis of beta burst dynamics provides a more sensitive biomarker for TIS effects than average beta power. Beta

bursts are characterized by their amplitude, duration, and frequency of occurrence, and these parameters are differentially modulated by dopaminergic medication and DBS [32,90]. Burst duration and spectral sharpness are specifically sensitive to oscillatory activity, while burst amplitude and spectral power are ambiguously sensitive to both oscillatory and non-oscillatory activity [9]. TIS-induced changes in beta burst dynamics could therefore provide a more specific measure of oscillatory modulation than changes in average power. Computational modeling suggests that burst termination is associated with desynchronization of the beta drive, increased theta activity, and increased phase slips [90], providing potential targets for TIS interventions.

5.2 Neuroimaging and Network-Level Evidence: fMRI, Functional Connectivity, and Structural Coupling

Neuroimaging techniques provide complementary evidence for TIS effects on brain activity and connectivity. Functional magnetic resonance imaging (fMRI) offers whole-brain coverage with good spatial resolution, enabling the assessment of TIS effects on both local activity and distributed networks.

TIS targeting the striatum has been shown to modulate striatal activity and its functional connections. In healthy older adults, theta-burst patterned striatal tTIS increased activity in the striatum and associated motor network, as measured by fMRI [53]. A subsequent study demonstrated that striatal tTIS at 80 Hz disrupted reinforcement learning of motor skills, with concurrent fMRI showing selective modulation of striatal activity [54]. These findings provide causal evidence for the role of striatal activity in reinforcement motor learning and demonstrate the ability of TIS to modulate deep brain structures in humans.

Hippocampal TIS has been validated using fMRI in healthy humans. Electric field modeling and measurements in a human cadaver verified that the locus of transcranial TI stimulation could be steerably focused in the hippocampus with minimal exposure to the overlying cortex [18]. fMRI demonstrated that TI stimulation focally modulated hippocampal activity and enhanced episodic memory accuracy [18]. These findings established the proof-of-concept for non-invasive deep brain stimulation in humans and have informed subsequent TIS studies targeting other deep structures.

TIS-induced changes in functional connectivity have been documented in several studies. STN-targeted tTIS in PD patients modulated functional connectivity within the CBTC circuit, decreasing connectivity between the STN and striatum while increasing connectivity with the motor cortex [62]. These connectivity changes are consistent with the known anatomical projections of the STN and suggest that tTIS can engage the motor circuit in a target-specific manner. TIS targeting the nucleus accumbens modulated its functional connectivity with the limbic network and caudate, with effects largely returning to baseline within 30 minutes [48]. TIS targeting the motor cortex enhanced functional connectivity between M1 and secondary motor areas, with TIS producing greater effects than tDCS [63,64]. These findings demonstrate that TIS can modulate brain network connectivity in a

target-specific and frequency-dependent manner.

The relationship between TIS-induced changes in functional connectivity and clinical outcomes has been explored in PD. In the pilot study of STN-targeted tTIS, changes in functional connectivity between the STN and motor cortex were associated with improvements in motor symptoms [62]. Personalized TIS targeting the right striatum modulated structure-function couplings in the cortico-striato-thalamo-cortical network, with acute increases in axial diffusivity in the corticospinal tract and anterior thalamic radiation [76]. A notable negative correlation between changes in functional connectivity and axial diffusivity highlighted the interplay between functional and microstructural alterations [76]. These findings suggest that TIS can induce both functional and structural plasticity in motor circuits, providing a potential mechanism for sustained clinical benefits.

5.3 Integrating Parameters, Target Engagement, Network Remodeling, and Symptomatic Improvement

The construction of a mechanistic chain linking TIS parameters to clinical outcomes requires the integration of evidence across multiple levels of analysis. The proposed action chain—"TIS parameters → deep target engagement → motor network remodeling → symptomatic improvement"—can be supported by converging evidence from computational, electrophysiological, neuroimaging, and clinical studies.

The first link, from TIS parameters to deep target engagement, is supported by computational modeling and experimental studies. Electric field simulations demonstrate that the magnitude and distribution of the electric field at deep targets depend on stimulation parameters, including carrier frequency, intensity, and electrode montage [23,25,86]. Experimental recordings in animals and humans confirm that TIS can modulate neural activity in deep brain structures, with effects dependent on stimulation parameters [58,94]. The frequency of neural entrainment is determined by the envelope frequency, providing a direct link between stimulation parameters and neural activity patterns [69,73].

The second link, from deep target engagement to network remodeling, is supported by neuroimaging studies. TIS-induced modulation of target structures has been shown to produce changes in functional connectivity across distributed brain networks [48,62,95]. The pattern of network modulation depends on the stimulation target and frequency, suggesting that different TIS protocols engage distinct neural circuits [54,64]. Structural plasticity, including changes in white matter integrity, may accompany functional changes, providing a substrate for sustained effects [76].

The third link, from network remodeling to symptomatic improvement, is supported by clinical studies in PD. TIS targeting the STN or GPi has produced improvements in motor symptoms, with effects associated with changes in functional connectivity within the motor circuit [21,22,62]. The magnitude of symptomatic improvement correlates with the degree of target engagement and network modulation, supporting a causal relationship [22,62]. However, the duration of clinical effects is limited, and the relationship between TIS-induced plasticity and long-term clinical

outcomes remains to be established.

The integration of these links into a unified framework requires consideration of individual variability. Interindividual differences in head anatomy, disease severity, and neural responsiveness influence each link in the action chain [23-25]. Personalized TIS protocols, based on individual imaging and electrophysiological data, may be necessary to optimize each link and achieve maximal clinical benefit [6,16].

6. Challenges, Knowledge Gaps, and Future Perspectives

6.1 Individualized Electric Field Modeling and Interindividual Variability

A major challenge for TIS in PD is the substantial interindividual variability in electric field distribution, which complicates the design of effective stimulation protocols. Computational modeling studies have demonstrated that the electric field strength at deep targets varies considerably across individuals for the same electrode montage and stimulation parameters [23-25]. A study of 25 subjects found that electric field strengths inside regions of interest during tTIS were highly variable at the single-subject level, emphasizing the need for individualized stimulation montages [25]. The variability arises from differences in head anatomy, including skull thickness, cerebrospinal fluid distribution, and brain morphology, which affect current flow and field distribution [23,96].

Individualized electric field modeling based on structural MRI can improve targeting accuracy. Finite element models of the head, constructed from individual MRI data, enable the simulation of electric field distribution for specific electrode montages and the optimization of stimulation parameters [23,86]. However, individualized modeling requires specialized software and computational resources, which may limit clinical applicability [79]. Population-based optimization, using group-level electric field analysis to derive standardized montages, has been proposed as a compromise, achieving comparable targeting accuracy to individualized analysis while reducing the need for patient-specific MRI [79].

The integration of additional imaging modalities may further improve individualized modeling. Magnetic resonance conductivity tensor imaging can provide anisotropic conductivity information, potentially improving the accuracy of electric field simulations [97]. Diffusion tensor imaging can inform the orientation of white matter tracts, which may influence neuronal responses to electric fields [97]. The development of automated pipelines for individualized TIS modeling, such as the TI-Toolbox, may facilitate clinical translation [98].

6.2 Standardization of Stimulation Protocols and Parameter Reporting

The lack of standardized protocols for TIS delivery and parameter reporting represents a significant barrier to clinical translation. Across published studies, there is substantial

variability in carrier frequency, envelope frequency, intensity, duration, electrode montage, and treatment schedule [26]. This variability complicates the comparison of results across studies and the identification of optimal parameters. The development of consensus guidelines for TIS parameter reporting, similar to those established for other non-invasive brain stimulation techniques, would facilitate progress in this field [16,89].

Safety considerations should also be standardized. Although TIS is generally well tolerated, with mild and transient adverse effects reported across studies [59,60], the long-term safety of repeated TIS sessions remains to be established. Computational modeling of thermal effects suggests that TIS produces minimal heating at typical parameters, but the cumulative effects of repeated sessions require investigation [61]. Frequency-dependent exposure thresholds for TIS have been proposed based on comparisons with established techniques, but these require experimental validation [89].

6.3 Uncertainty Regarding Long-Term and Repeated TIS Effects

The long-term effects of repeated TIS sessions in PD remain largely unknown. Most clinical studies have used single sessions, and the duration of post-stimulation effects has been limited to 30–60 minutes [21,22]. Preclinical studies have demonstrated cumulative effects of repeated TIS sessions over 7–14 days [20,55,57], but the translation of these findings to humans is uncertain. The optimal frequency, duration, and spacing of repeated TIS sessions for PD have not been systematically investigated.

The mechanisms underlying long-term TIS effects are also incompletely understood. Activity-dependent plasticity, including long-term potentiation and depression, is likely to contribute to sustained effects [16,74]. However, the specific molecular and cellular mechanisms mediating TIS-induced plasticity in the context of PD pathology require further investigation. The potential for TIS to interact with dopaminergic medication or other treatments is also unknown, and the optimal timing of TIS relative to medication is unclear.

6.4 Phenotype-Specific Targeting and the Prospect of Closed-Loop Adaptive TIS

The heterogeneity of PD clinical phenotypes suggests that different TIS protocols may be needed for different symptom profiles. Tremor-dominant PD may benefit from targeting the cerebello-thalamo-cortical circuit, while akinetic-rigid PD may respond better to STN or GPi stimulation [2,21,22]. Gait disturbances and freezing may require targeting of the mesencephalic locomotor region and its connections [68]. The development of phenotype-specific TIS protocols requires a detailed understanding of the neural mechanisms underlying each symptom and the effects of TIS on these mechanisms.

Closed-loop adaptive TIS represents a promising future direction for PD treatment. The concept of closed-loop stimulation involves using real-time neural signals to adjust stimulation parameters, optimizing therapeutic effects while minimizing side effects [16,85]. In the context of TIS,

closed-loop approaches could use LFP or EEG recordings to detect pathological beta activity and adjust stimulation parameters accordingly. Evoked interference deep brain stimulation (eDBS) has demonstrated the feasibility of using evoked beta oscillations to predictably suppress or amplify spontaneous beta activity in the GPi of PD patients [85]. Similar approaches could be adapted for non-invasive TIS, using scalp EEG or other signals to guide stimulation.

The integration of TIS with other neuromodulation techniques may also enhance therapeutic effects. Phase-synchronized transcranial electromagnetic combined stimulation (TECS), which combines TIS with repetitive transcranial magnetic stimulation, has shown promise in enhancing motor performance in rats [99]. The development of multi-modal stimulation approaches may enable more comprehensive modulation of the CBTC network, potentially improving outcomes for patients who do not respond to single-target stimulation.

7. Conclusion

Temporal interference stimulation represents a paradigm shift in non-invasive neuromodulation, offering the potential to target deep brain structures with a precision previously achievable only through invasive DBS. The application of TIS to Parkinson's disease is supported by a growing body of evidence from computational modeling, preclinical studies, and early clinical trials. The STN, GPi, striatum, motor cortex, and other network nodes each offer distinct therapeutic opportunities, and the optimal target may depend on the specific motor phenotype and disease stage.

The relationship between stimulation parameters and clinical outcomes is complex and multifactorial. Carrier frequency, envelope frequency, intensity, electrode montage, and treatment duration all influence the electric field distribution, neural entrainment, and clinical efficacy. Computational modeling has emerged as a powerful tool for parameter optimization, enabling individualized treatment planning. However, the standardization of stimulation protocols and parameter reporting is essential for facilitating clinical translation.

Multimodal evidence from electrophysiology, neuroimaging, and clinical assessments has begun to construct a mechanistic chain linking TIS parameters to deep target engagement, network remodeling, and symptomatic improvement. Beta burst dynamics, functional connectivity, and structural plasticity provide complementary biomarkers for assessing TIS effects and guiding treatment optimization.

Several challenges remain before TIS can be widely adopted in clinical practice. Interindividual variability in electric field distribution necessitates individualized modeling approaches. The long-term effects of repeated TIS sessions require systematic investigation. The development of phenotype-specific targeting strategies and closed-loop adaptive TIS protocols represents important future directions. Despite these challenges, TIS holds promise as a non-invasive, well-tolerated, and potentially effective treatment for PD, offering new hope for patients who are not candidates for invasive DBS or who seek alternative therapeutic options.

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