Response Inhibition in Parkinson's Disease: From Behavior to Neural Mechanisms

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Abstract

Objective: Parkinson's disease (PD) is classically defined by its classic motor features. While research has largely focused on dopaminergic degeneration and impaired movement initiation, accumulating evidence implicates impaired response inhibition as an important yet underrecognized component of PD pathophysiology. This review aims to examine the role of response inhibition in PD.

Methods: This review summarizes the principal behavioral paradigms for assessing response inhibition, notably the stop-signal task and Go/No-Go paradigms, and examines their neural underpinnings within the cortico-basal ganglia-thalamic network. It further explores the relationship between disrupted inhibitory control and clinical manifestations of PD, and discusses the implications for therapeutic management.

Results: Impaired inhibitory control contributes to distinct characteristic clinical features of PD, such as bradykinesia, freezing of gait, and levodopa-induced dyskinesia. Neurocircuit evidence highlights the critical role of response inhibition within the cortico-basal ganglia-thalamic network, with implications for early diagnosis, patient stratification, and treatment optimization.

Discussion: Incorporating response inhibition into both basic scientific and clinical research frameworks is warranted. A deeper mechanistic understanding of inhibitory dysfunction will be crucial for improving early diagnosis, refining patient stratification, and optimizing treatment. Moreover, establishing dynamic assessment tools that capture the heterogeneity of inhibitory deficits may further enable personalized and targeted interventions. By linking circuit-level dysfunction to clinical outcomes, this review underscores the critical role of response inhibition in PD and provides a framework for developing more precise therapeutic strategies.

Keywords: motor symptoms; neural circuits; Parkinson's disease; response inhibition

Introduction

Parkinson's disease (PD) affects approximately 1–2 individuals per 1,000 people in the general population[1]. Although the disease can occur at a younger age, fewer than 5% of PD cases begin before the age of 40. In

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most patients, symptoms typically appear between the ages of 65 and 70. After the age of 80, both the incidence and prevalence of PD increase sharply, showing an almost exponential rise with age. As the global population continues to age and life expectancy increases, the number of people affected by PD is expected to grow significantly. By 2030, the number of cases is projected to rise by more than 50%, reaching an estimated 25.2 million globally by the year 2050[2–5]. A key pathological feature of PD is the progressive loss of dopaminergic and monoaminergic neurons, particularly in the substantia nigra pars compacta. This neurodegeneration is responsible for the wide range of motor and non-motor symptoms observed in patients. Motor symptoms are often the most noticeable and include bradykinesia, stiffness, resting tremor, postural instability, and gait disturbances. Non-motor symptoms are also common and include cognitive impairment, psychiatric disorders such as depression and anxiety, sleep disturbances, autonomic dysfunction, chronic pain, and fatigue[6,7]. Motor symptoms play a central role in clinical evaluation. Hoehn and Yahr (H-Y) staging system is widely used to assess the severity of PD and categorizes patients into five stages (I–V) based on the degree of motor impairment and the distribution of symptoms. A particularly important clinical milestone is the transition from Stage II to Stage III. This change marks the beginning of more serious balance problems and gait disturbances, which can significantly affect independence and daily functioning. Although falls related to PD are not directly fatal, they are a major cause of increased morbidity and mortality due to injuries and complications[8,9]. Therefore, strategies that aim to slow disease progression and effectively manage motor symptoms are critical for improving the quality of life in PD patients. With a clinical diagnostic accuracy of 80.6% across 11 clinicopathological studies, accurately diagnosing PD remains a major challenge[10]. The diagnostic process typically begins by assessing prodromal symptoms and family history, followed by evaluating motor symptoms. A clinical diagnosis is confirmed when bradykinesia is observed along with at least one additional core motor feature, such as rigidity, resting tremor, or postural and gait impairments. Early diagnosis and personalized treatment approaches, based on specific PD subtypes and individual needs, remain essential components of comprehensive care[9,11].

Normal motor function depends on a careful balance between motor initiation and inhibition. While impaired movement initiation has long been the primary focus in PD assessment, recent studies suggest that deficits in motor inhibition also play an important role in the motor impairments seen in PD. For instance, certain forms of freezing of gait (FOG) in advanced PD may result from abnormally heightened inhibitory processes that paradoxically prevent movement[12]. The response inhibition model—now widely accepted as the main framework for understanding motor inhibition—refers to the brain's ability to suppress unwanted or inappropriate actions. Response inhibition is regulated by cortico-basal ganglia circuits, which are significantly disrupted in PD due to dopamine depletion. However, the detailed neuropathological changes underlying response inhibition deficits in PD are still not fully understood. In this review, we summarized the current findings on the relationship between the response inhibition and PD-related symptoms. Based on the evaluation of response inhibition, neural circuitry mechanisms involved in response inhibition deficits were reviewed to explore a more comprehensive understanding of early detection and treatment of PD.

Behavioral paradigm of response inhibition

Response inhibition consists of two main components, reactive inhibition and proactive inhibition. Reactive inhibition, also called passive inhibition, refers to the ability to stop a movement that has already been initiated or is in progress in response to an external stop signal. A typical example is when a driver immediately presses the brake upon suddenly seeing a pedestrian crossing the road. Unlike reactive processes, proactive inhibition can be initiated by endogenous factors. Proactive inhibition involves the capacity to adjust motor strategies in anticipation of the need to stop an action, based on environmental cues. The cues often are defined according to the immediate context or retrieved from memory. Proactive inhibition maybe represent the individual prepares to suppress a planned or ongoing action if necessary. For example, when a driver notices a school zone ahead, they may slow down and respond more quickly if a child appears, showing improved stopping performance through proactive control[13,14]. A variety of behavioral paradigms are used to assess response inhibition, including the Go/No-Go

task, stop signal task, anti-saccade task, flanker task, Stroop task, Simon task, Wisconsin Card Sorting Test, Continuous Performance Test, and reversal learning task. Among these, the Go/No-Go task and the stop signal task are the most common paradigms.

Go/No-Go task

Go/No-Go task is commonly used to assess inhibitory control and typically involves the presentation of a sequence of letters. Participants are instructed to make a quick motor response when specific letters appear, referred to as Go signals, and to withhold any response when the letter "X" appears, which serves as the No-Go signal (Figure 1(a)). Performance on this task is evaluated by measuring reaction time (RT) for Go trials and the error rate, defined as the probability of pressing the response button during No-Go trials[15,16] (Figure 1(b)). However, one limitation of the Go/No-Go paradigm is that it does not clearly indicate when Go and Stop processes begin. In cases that includes short stimulus intervals or a lower proportion of No-Go trials, successful inhibition on No-Go trials may resemble the process of stopping an ongoing response, similar to that in the stop-signal task. On the other hand, in studies where the task design includes longer stimulus intervals or a higher proportion of No-Go trials, the process of successful inhibition may reflect a decision not to act, rather than stopping a response that is already underway[15]. There was no significant difference in RTs between the individuals with PD and healthy controls, but a reduction in response accuracy among PD patients, suggesting a possible speed-accuracy trade-off. PD patients responded more quickly but with decreased accuracy[17]. Moreover, RTs from the Go/No-Go task have not been effective in distinguishing between new-onset, early-treatment, and chronic stages of PD[16,18,19]. Taken

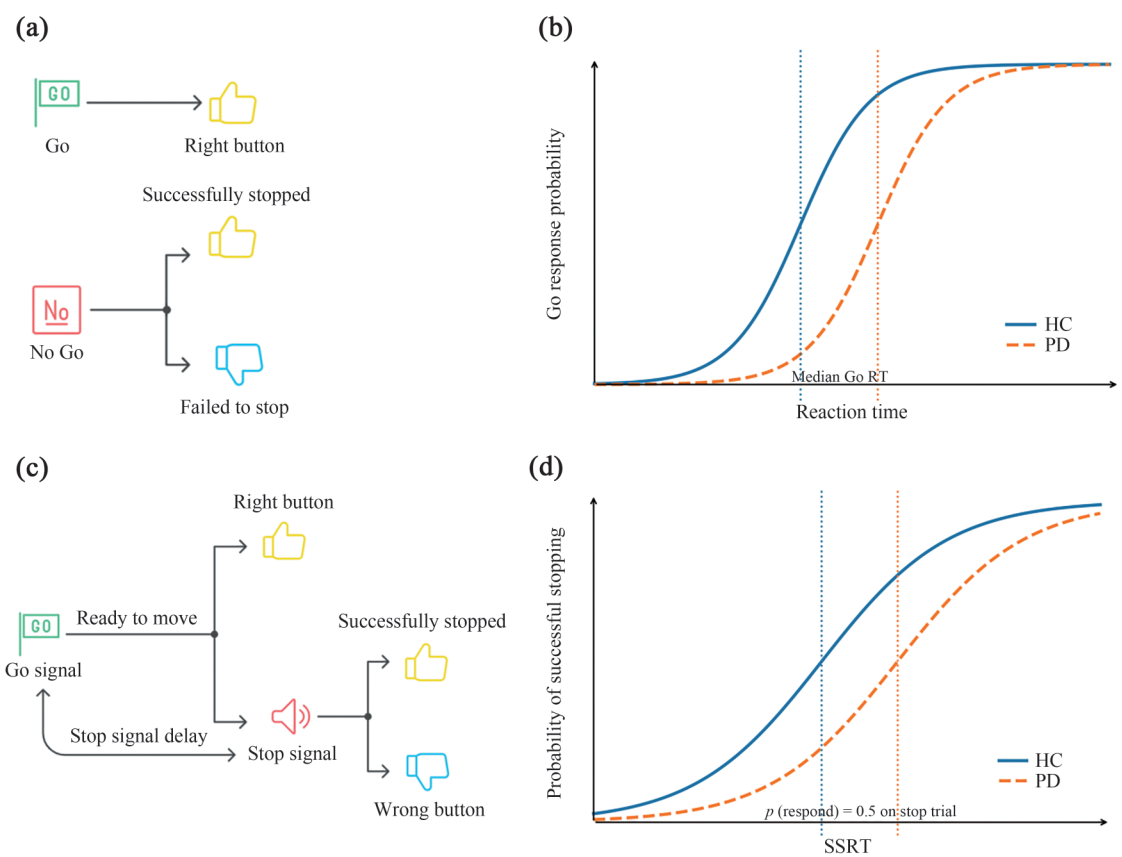


Figure 1: Behavioral performance in Go/No-Go and stop-signal tasks.

(a) Schematics of Go/No-Go task; (b) Probability of Go responses as a function of RT; (c) Schematics of stop-signal task; (d) Probability of successful stopping as a function of stop-signal RT. HC: healthy control; PD: Parkinson's disease; *p* (respond): probability of a response.

together, the Go/No-Go task may lack the necessary sensitivity for detecting inhibitory control deficits in PD and is likely unsuitable as a reliable biomarker for the disease.

Stop-signal task

The stop-signal task includes a go component and a stop component. In most trials, participants are shown a go signal and asked to respond as quickly as possible. In a smaller subset of trials, the go signal is followed by a stop signal after a randomly determined stop-signal delay (SSD). In these trials, participants must attempt to stop their response upon seeing the stop signal (Figure 1(c)). When the delay between the go and stop signals is short, participants are more likely to successfully inhibit their response. The SSD is dynamically adjusted during the task using a staircase procedure, which helps maintain a 50% success rate for inhibition. For example, the SSD might initially be set at 200 ms and increased by 50 ms after a successful stop (making stopping harder), or decreased after a failed stop, adjusting performance toward the target success rate. The main measure in the stop-signal task is the stop-signal reaction time (SSRT), calculated as mean go trial RT minus mean SSD. SSRT reflects the speed or efficiency of reactive inhibition, and a longer SSRT indicates poorer inhibitory control[20,21] (Figure 1(d)). Unlike the Go/No-Go task, the stop-signal task allows researchers to precisely control the exact time when the stopping process is triggered. The participants have already initiated their motor response before the stop signal appears. Stop-signal task reflects the process of inhibiting an already initiated action, rather than simply choosing not to act[15]. Thus, stop-signal task shows more effective for reactive inhibition studies.

To investigate proactive inhibition, researchers adapted the standard stop-signal task by providing participants with predictive cues signaling stop-signal probabilities[21]. In a subset of experiments, cues indicated that a go signal would definitely not be followed by a stop signal (certain go trials), while in others, cues signal that a Stop signal might follow the go signal (uncertain go trials). Proactive inhibition is assessed by measuring how long participants adjust their RTs during uncertain go trials. RT increases with the probability of stop-signal cues presentation, indicating participants strategically delayed their responses[22]. Further distinctions between proactive and reactive inhibition have been explored through tasks like the Continuous Movement Stop task (CMST). In the CMST, proactive inhibition is assessed in trials where participants are given advance warning of a stop cue, while reactive inhibition is measured in trials where the stop signal is unexpected[23]. Compared to the traditional stop-signal task, the CMST offers greater sensitivity in evaluating different types of inhibitory control.

Typically, the stop-signal task lasts at least 30 min and includes no fewer than 150 trials. Maintaining high levels of participant attention and task engagement across trials is a persistent methodological challenge in stop-signal paradigms. It is particularly challenging for elderly PD patients, who often experience reduced cognitive and attentional capacity. Consistency in participant performance throughout entire tasks is rarely evaluated. Future research should consider this factor in experimental design. Recently, a point-based reward system was added to the stop-signal task to enhance sustained attention[24]. Participants improve focus and task compliance through getting points for completing tasks. However, the long-term effectiveness of this method remains to be fully validated.

Behavioral manifestations related to PD response inhibition disorder

Response inhibition deficits in PD exhibit significant associations with motor, cognitive, and affective dysfunction. Quantitative assessment of these deficits may serve as a clinical proxy for core symptoms including bradykinesia, FOG, and impulse control disorders (ICDs). Reactive inhibition is already impaired in the early stages of PD across a range of tasks[25–28]. Proactive inhibition appears largely preserved in early PD patients, but much longer RTs during tasks requiring rapid motor decisions, such as the stop-signal task probably reflected motor bradykinesia and postural instability. Studies also reported that SSRT was significantly prolonged in PD patients compared to healthy controls during both certain go-signal and uncertain go-signal trials. Collectively, PD patients exhibited deficits in both reactive and proactive inhibitory control processes[29]. Two kinds of deficits are associated with different

PD-related symptoms. FOG emerged from excessive proactive inhibition, while levodopa-dyskinesia might result from compromised efficiency in reactive inhibition circuits[30]. In addition to motor symptoms, abnormal inhibitory control in PD also contributes to cognitive and emotional disturbances, often expressed as impulse control disorder symptoms, including pathological gambling, compulsive shopping, and other maladaptive behaviors[31]. However, reactive inhibition performance is highly heterogeneous across PD patients. Variations in disease progression are a key factor accounting for this inconsistency, as they critically modulate the severity and profile of inhibitory dysfunction.

Proactive inhibition deficits are more commonly reported in psychiatric conditions such as schizophrenia, anxiety, and depression, whereas reactive inhibition impairments are more typical of later-stage PD. Disease progression likely plays a key role in shaping inhibitory profiles in PD patients[27,29]. Most studies have focused on patients with mild-to-moderate PD, in whom proactive inhibition deficits related to cognitive-emotional dysfunction are less apparent. Future studies should aim to obtain data from advanced PD patients to provide a more complete understanding of how response inhibition deficits evolving across the full course of PD.

Neural circuits of reactive inhibition and proactive inhibition

Both reactive and proactive inhibition are primarily mediated by cortical and basal ganglia networks. Stop signals from cortico-basal ganglia loops can effectively suppress motor plans encoded in the primary motor cortex (M1). Spatial independent component analysis has demonstrated that proactive and reactive inhibition engage partially overlapping yet also distinct neural networks.

Reactive inhibition is primarily associated with the hyperdirect pathway, originating from key cortical regions including the right inferior frontal gyrus (rIFG), pre-supplementary motor area (pre-SMA), and dorsolateral prefrontal cortex (DLPFC)[32]. The right hemisphere, in particular, appears to exert stronger inhibitory control[33]. The basal ganglia, as key subcortical nuclei, receive and integrate cortical inputs and transmit them to downstream targets such as the thalamus and brainstem, regulating motor behavior. Numerous studies have demonstrated the critical role of these brain regions. Lesions to the rIFG significantly impair reactive inhibition, evidenced by prolonged stop-signal RTs and SSRTs, and increased error rates in both stop-signal and Go/No-Go tasks[34]. Functional magnetic resonance imaging and transcranial magnetic stimulation (TMS) studies confirmed the critical role of the rIFG, pre-SMA, and DLPFC in mediating reactive inhibition[33]. TMS stimulation of the pre-SMA has been shown to enhance activity in the striatum, globus pallidus, and subthalamic nucleus (STN), all of which are implicated in reactive inhibition[35,36]. Cortical input coordinates activation of the STN, which subsequently increases the output of the globus pallidus internus (GPi) and the substantia nigra pars reticulata (SNr). This heightened output strengthens the inhibitory control over the thalamus, leading to suppression of M1 activity and termination of ongoing movements via the frontal cortex → STN → GPi/SNr → thalamus → motor cortex pathway[37] (Figure 2).

Relative to reactive inhibition, proactive inhibition remains less well-defined. Prevailing theories suggested it operates primarily via indirect pathway. In modified stop-signal tasks designed to assess proactive inhibition, increased striatal activation is observed when subjects successfully withhold responses. The greater the expected probability of a stop signal, the stronger the striatal response amplitude—most notably in high-probability stop-signal trials[38]. As a downstream target of the striatum, the globus pallidus also plays a key role in motor inhibition. In animal models, globus pallidus external (GPe) neurons occupy distinct dynamic states during preparation-to-stop periods, reflecting their complex role in action inhibition[39]. When individuals anticipate the need to inhibit a response in the near future, preparatory activation of the STN is observed, indicating early engagement of the inhibitory network (anticipation of imminent response inhibition triggers pre-activation of STN, reflecting preparatory recruitment of inhibitory networks). Elevated STN activity is associated with deliberative decision-making, characterized by increased response latency and enhanced accuracy. Additionally, high-frequency stimulation induced disruption of STN function promotes impulsive actions and compromises proactive inhibitory control[24]. Stimulation

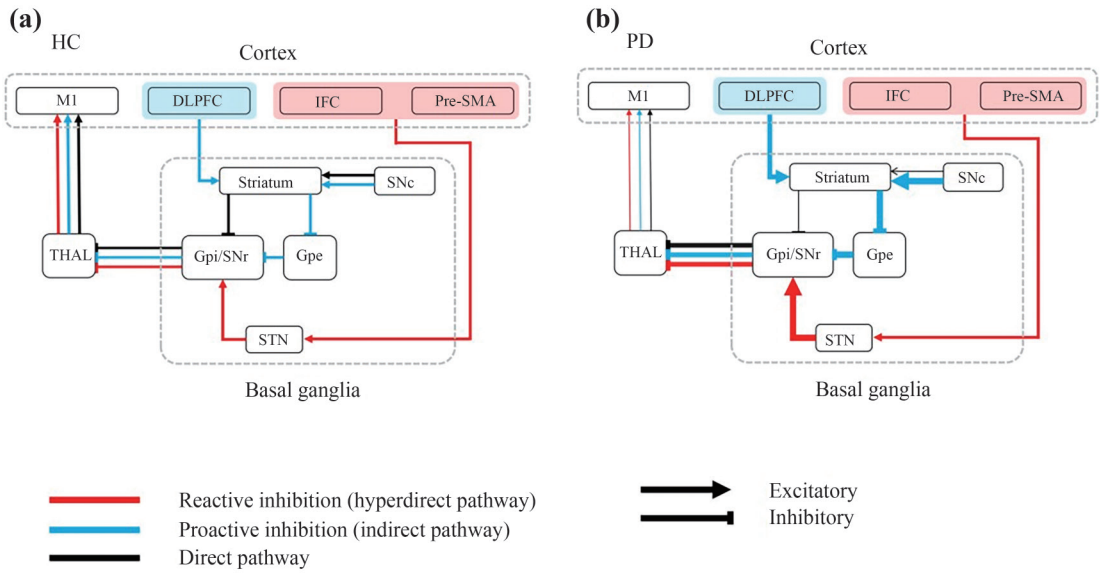


Figure 2: Schematic representation of cortico-basal ganglia pathways in different conditions.

(a) Cortico-basal ganglia circuits in healthy controls; (b) Cortico-basal ganglia circuits in PD patients. HC: healthy controls; PD: Parkinson's disease; M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; Pre-SMA: presupplementary motor area; IFC: inferior frontal cortex; THAL: thalamus; STR: striatum; Gpi/SNr = globus pallidus interna/substantia nigra pars reticulata; Gpe: globus pallidus externa; STN: subthalamic nucleus; SNc: substantia nigra pars compacta.

of the rIFG enhances functional connectivity between the frontal cortex and the basal ganglia, thereby facilitating response inhibition[40]. These findings demonstrate extensive structural and functional connectivity between cortical regions and basal ganglia supporting both reactive and proactive control (Figure 2). Aron and colleagues proposed a model of proactive inhibition involving the DLPFC-GPe-GPi-thalamus-motor cortex pathway[15]. Within this model, the frontal cortex initiates stop signals relayed to the striatum. Striatal inhibition of the GPe disinhibits the GPi, thereby enhancing its inhibitory output to the thalamus. This suppresses activity in specific motor cortical regions such as M1, resulting in the inhibition of selected motor responses. A cardinal feature of this model is its provision of a slow and selective inhibitory effect. The temporal delay is attributed to the polysynaptic nature of the indirect pathway, while selectivity stems from the striatum's role in action selection among competing motor programs. The striatum facilitates activation of motor-related nuclei and suppression of those associated with unwanted actions, enabling fine-grained control over specific movements (i.e., it orchestrates the selective facilitation of cortico-subcortical motor circuits via disinhibition while concurrently suppressing competing motor programs through enhanced inhibition, thereby ensuring precise gating of movement execution). Unlike the standard indirect pathway, the STN is excluded from this model due to its broad, non-selective inhibitory effects, which are inconsistent with the selective nature of proactive inhibition. Critically, clinical studies demonstrate that STN damage induces deficits in proactive inhibition. Patients with STN lesions exhibit reduced response delays and faster reactions to go signals, which compromises their ability to stop in time when a stop signal is presented. This provides causal evidence that the STN may also play a role in proactive inhibition[41].

Neural circuitry of inhibitory control failure in PD

In PD, dopaminergic degeneration induces the dysfunction of basal ganglia circuit through impaired modulation of the direct, indirect, and hyperdirect pathways. These disruptions lead to pathological firing patterns within nuclei critical for response inhibition. These impairments exhibit disease stage-dependent progression[42]. The progressive loss of nigrostriatal dopamine drives the dynamic clinical picture of PD. Dopamine loss overactivates the indirect pathway and suppresses direct

pathway, creating an overall imbalance in basal ganglia circuit function. As the disease advances, symptoms such as levodopa-induced dyskinesia (LID) and FOG become increasingly prominent[27,29]. These symptoms represent opposing failures of motor inhibition, LID arising from insufficient inhibition, and FOG from excessive inhibition. These opposing symptoms directly implicate dopaminergic fluctuations in bidirectional dysregulation of motor inhibition. Notably, both LID and FOG associate with functional abnormalities in the STN, prefrontal cortex, and striatum. Therefore, these symptoms provide valuable clinical models for elucidating pathological changes within the response inhibitory loop in PD.

Bradykinesia and response inhibition deficits

Under physiological conditions, D1 receptor activation facilitates motor initiation via excitation of the direct pathway, whereas D2 receptor activation suppresses the indirect pathway to attenuate excessive motor inhibition. Dopamine depletion disrupts this balance, diminishing direct pathway excitatory output while amplifying indirect pathway tone. Consequently, excessive inhibition of the thalamo-cortical pathway occurs, manifesting clinically as bradykinesia, characterized by reduced movement velocity and amplitude. Dysfunction in the cortico-basal ganglia-cerebellar network may reflect impaired motor program updating, particularly in integrating and sequencing movement. These deficits are particularly evident in sequential motor tasks, characterized by increased ordinal errors, pronounced movement dysrhythmia, and marked kinematic fragmentation during repetitive actions[43]. In response inhibition tasks, proactive inhibition mainly relies on the indirect pathway. Hyperactivity of the indirect pathway not only elevates the threshold of motor inhibition but also interferes with the prefrontal-basal ganglia circuit, impairing the flexible resolution of competing motor plans. As a result, patients exhibit delayed or failed termination when they need to stop or adjust motor plans rapidly—a deficit mechanistically linked to bradykinesia[44].

FOG and response inhibition deficits

FOG refers to the sudden inability of a patient to initiate or continue walking, typically occurring in narrow spaces or during turning[30]. It is characterized by a failure to effectively suppress inappropriate responses in high-conflict situations or during rapid decision-making, indicating significant impairments in conflict resolution[45]. Within this framework, proactive inhibition, characterized by anticipatory motor suppression during conflict preparation, is pathologically augmented in the patients with FOG. Overactivation of proactive inhibition manifests as interruptions during gait initiation or directional changes, and is associated with dysfunction in the DLPFC, anterior cingulate cortex (ACC), and basal ganglia-thalamus-brainstem circuits. The DLPFC integrates sensory inputs and guides behavior control during inhibitory tasks such as the stop-signal task. The right inferior frontal cortex (rIFC) mediates inhibitory control via its connections with the pre-SMA and motor cortex[14]. It has been proposed that the right DLPFC is particularly important in response selection[46,47]. In advanced PD patients, pathological β-band (13–30 Hz) hypersynchronization in the STN enhances functional connectivity with the DLPFC, resulting in excessive inhibition of motor planning and reduced thalamocortical transmission. This pathological synchrony contributes to a state of "motor rigidity"[48]. Additionally, the ACC has been implicated in response inhibition, particularly in monitoring conflicts arising from external stimuli rather than directly resolving them[49]. Multiple studies demonstrated ACC activation during successful stop trials, indicating its role in monitoring inhibitory performance[50]. As a key node in the proactive inhibition network, it facilitates the transition from proactive to reactive control. In PD, dopamine depletion weakens the ACC-caudate pathway, impairing anticipatory motor conflict control. As a result, the disrupted allocation of proactive inhibitory resources worsens FOG during cognitively demanding tasks like navigating narrow spaces[51].

In advanced PD patients, FOG onset arises not only from inhibitory dysfunction but also involves abnormal sensory processing, pathological β synchronization in the basal ganglia, and dopaminergic imbalance. From the perspective of abnormal sensory processing, restricted perceptual information (e.g., in dark environments) significantly increases the frequency of FOG episodes, suggesting insufficient sensory input may trigger FOG[52,53]. From the perspective of increased β-band

synchronization in the basal ganglia, abnormal oscillatory activity in the STN interferes with motor signaling and overlaps with circuits involved in both proactive and reactive inhibition[48,54]. Finally, from the perspective of dopaminergic system imbalance, overactivation of the indirect pathway suppresses both the thalamus and pedunculopontine nucleus, disrupting gait automaticity and contributing to FOG[55]. In summary, FOG results from the combined effects of multiple mechanisms.

LID and response inhibition deficits

LID manifests as involuntary choreiform or dystonic movements, emerging with disease progression and prolonged levodopa therapy in PD, is characterized by reduced reactive inhibition[9]. Reactive inhibition refers to the ability to terminate ongoing movements in response to unexpected external signals. The involuntary movements in LID exemplify the failure of rapid inhibitory control. Emerging evidence has attempted to elucidate its underlying neural mechanisms. In rodent models, intra-striatal injection of selective D1 receptor antagonists improves reactive inhibition, whereas D2 receptor antagonists impair it[56]. However, contrasting evidence suggests that dopamine predominantly governs motor initiation rather than cessation, or that its role varies across components, with reactive inhibition being less dopamine-dependent[57]. Pulsatile levodopa delivery in PD leads to dramatic striatal dopamine fluctuations, resulting in abnormal synaptic plasticity. Chronic exposure induces sensitization of D1 receptors, hyperactivating the direct pathway while insufficiently suppressing the indirect pathway. This imbalance impairs the emergency stopping mechanism, fostering uncontrolled motor activity[58,59]. The STN, a core hub for reactive inhibition, orchestrates action arrest via the hyperdirect pathway (cortex→STN→GPi)[12]. In PD, STN exhibits pathologically elevated and hypersynchronized β-band activity, constituting both a key electrophysiological biomarker and an underlying rationale for STN-targeted deep brain stimulation (DBS)[60]. Clinical studies confirmed that the functional state of the STN has a significant impact on performance in the stop-signal task: both STN lesions and STN-DBS can substantially alter go RT and SSRT in PD patients, highlighting the central role of the STN in motor inhibition[21,33]. Complementary electrophysiology have shown that STN neurons generate rapid stop-cue responses regardless of behavioral outcomes, suggesting the STN delivers a rapid interruption signaling. Further analysis indicates that interrupting or reducing STN β activity corresponds with successful reactive inhibition, implying β desynchronization is crucial for movement termination[24]. In PD, chronic dopamine depletion exacerbates pathological β oscillations in the STN, compromising the STN's capacity for rapid response control. Meanwhile, the attenuation of low-frequency STN oscillations (θ/α bands) observed in LID, further weakens the system's ability to suppress involuntary movements[61].

Although bradykinesia, FOG, and LID all originate from dopaminergic deficiency and basal ganglia-thalamic network dysfunction, they differ markedly in triggers, underlying neural activity signatures, and long-term responses to medication. Notably, FOG and LID represent dichotomous outcomes in advanced PD: FOG is associated with excessive proactive inhibition, whereas LID stems from reactive inhibition deficiency. Despite their seemingly opposite symptoms, both conditions entail complex, bidirectional disruptions in cortico-basal ganglia circuitry. This pathophysiological imbalance highlights the nonlinear relationship between dopaminergic fluctuations and neural circuit function, revealing significant limitations in current clinical approaches for assessing and treating inhibitory dysfunction in PD. Conventional diagnostic paradigms continue to prioritize cardinal motor symptoms, such as bradykinesia, tremor, and rigidity, while underutilizing FOG and LID as potential biomarkers reflecting underlying inhibitory control deficits. Paradoxically, while levodopa remains the therapeutic cornerstone, its long-term administration frequently exacerbates circuit imbalance, complicating the achievement of sustained symptom control.

Future

Current approaches for assessing response inhibition in PD face significant limitations. For animal models, despite their critical role in elucidating PD pathogenesis, behavioral paradigms for assessing reactive inhibition remain inadequately developed. Most current animal tasks are adapted from human experimental paradigms. However, given the fundamentally distinct cognitive capacities across species, experimental paradigms designed

for humans should be carefully applied for animal studies. To enable more precise investigation of dynamic response inhibition in the context of PD pathology, future researches should integrate optogenetic or chemogenetic techniques with the development of novel, species-appropriate behavioral tasks that are both operationally tractable and neuropathologically relevant. For human studies, behavioral assessment of response inhibition in human PD populations also presents considerable challenges. Existing paradigms do not adequately capture the heterogeneity of inhibition deficits observed in PD, and lack the sensitivity to reliably distinguish between proactive and reactive inhibitory processes. Moreover, many studies fail to account for key confounding variables, including disease stage, medication status, and the presence of non-motor symptoms (e.g., mood disorders, cognitive impairment), potentially leading to the misinterpretation of results. Therefore, establishing a systematic and standardized assessment of response inhibition holds significant clinical promise. In early PD, such a tool could be potentially used as a simple, rapid, and non-invasive biomarker to aid early diagnosis. In advanced stages of PD, particularly stages IV and V on the modified H-Y scale, where disability and mortality are driven by the increased fall risk due to behavioral impairments like FOG and postural instability[8], measurements of response inhibition may serve as clinical indices. These indices could guide diagnostic and therapeutic strategies aimed at reducing adverse events while improving motor function. Looking forward, constructing a multimodal assessment framwork, integrating behavioral tasks, neuroimaging, and neurophysiological recordings, promises a more robust foundation for clinical diagnosis and personalized intervention in PD. In particular, the development of realistic virtual reality tasks that simulate complex, real-world demands on inhibitory control (e.g., driving, emergency braking, or navigating obstacles during walking) may enhance ecological validity by evaluating response inhibition in contexts that closely mirror patients' daily challenges.

Cortico-basal ganglia loop is the classical regulatory circuit for both response inhibition and motor initiation[7]. However, PD researches have historically prioritized investigating motor initiation deficits caused by dopaminergic dysfunction, and often neglected the fundamental pathogenic contribution of impaired response inhibition. This bias in focus has had direct consequences in clinical practice. For example, while levodopa replacement therapy effectively ameliorates motor initiation, it may paradoxically also induce functional anisotropy by excessively enhancing direct pathway activity, potentially exacerbating deficits of inhibitory control. Similarly, selecting DBS targets and adjusting stimulation parameters with a narrow focus on motor initiation can inadvertently increase the risk of ICDs or FOG by disrupting inhibitory circuit dynamics. To address these limitations, PD management has to reconceptualize motor control through the lens of "loop symbiosis", recognizing the co-equal necessity of balanced motor initiation and reactive inhibition (motor termination) for maintaining motor stability and behavioral integrity.

From a mechanistic standpoint, multi-channel neural recording and circuit-specific neuromodulation technologies provide promising ways to explore how initiation and termination signals are encoded separately within shared neural circuits, and how their imbalance contributes to PD pathophysiology. Deciphering these distinct neural signatures could help refine mechanistic models of the diseases. From a translational standpoint, it is necessary to establish dynamic assessment tools for response inhibition and systematically integrate them into therapeutic optimization protocols for both pharmacological (e.g., dopaminergic medication adjustments) and neuromodulation (e.g., DBS programming) strategies. Crucially, clinicians should implement dual monitoring, tracking improvements in motor initiation alongside changes in inhibitory control metrics. Achieving this bidirectional loop equilibrium may offer a promising strategy to resolve the clinical dilemma of "symptom substitution", where therapeutic gains in one domain lead to deterioration in another. Ultimately, this mechanism-guided framework could pave the way for more precise and personalized therapeutic interventions in PD.

Besides PD, deficits in response inhibition extend to numerous neuropsychiatric disorders. Poor response inhibition is closely linked to impulsivity and attentional dysregulation. Individuals with Attention-Deficit/Hyperactivity Disorder show lower neural activity in key brain regions related to response inhibition, particularly within the cortex-basal ganglia-thalamic

circuits. Structural changes in basal ganglia regions, including volumetric reductions or morphological changes in the caudate, putamen, and globus pallidus, are strongly related to these response inhibition deficits[62]. In Tourette syndrome (TS), neuroimaging studies reveal reduced gray matter volume in regions critical for inhibition, such as the orbitofrontal cortex and right inferior frontal gyrus. Notably, while TS patients often perform well on simple response inhibition tasks, their performance gets worse as tasks become more difficult. This pattern suggests the recruitment of compensatory neural mechanisms to counterbalance pathological overactivity in the cortico-striatal circuits[63]. In neurodegenerative diseases, problems with response inhibition are linked to movement dysfunction, cognitive difficulties, and poor emotional control. Huntington's disease, characterized by substantial neuronal loss within the caudate and putamen, manifests clinically as heightened impulsivity and compromised cognitive control. Similarly, behavioral variant frontotemporal dementia involves significant neuronal atrophy or loss in the frontal and anterior temporal lobes. This causes social and behavioral problems, encompassing inappropriate actions, impulsively spending, and intrusive thoughts. In acquired brain injury, particularly traumatic brain injury involving prefrontal cortex and striatal damage, consistently impair response inhibition. Furthermore patients with epillepsy react more slowly in tasks that require inhibition, and the magnitude of this delay is positively correlated with seizure frequency and severity.

In conclusion, deficits in response inhibition represent a pervasive transdiagnostic feature across a spectrum of neuropsychiatric disorders. These impairments significantly contribute to core behavioral symptomatology and are intricately linked to underlying disease pathogenesis and phenotypic expression. Therefore, elucidating the precise neural mechanisms governing response inhibition and translating this knowledge into targeted therapeutic strategies constitute central objectives for future research, essential for enhancing clinical management and patient outcomes.

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Authors' contributions

Fei Wu conceived the review and drafted the manuscript. Huijin Liu, Zhiqing Weng, and Qingqing Peng performed the literature search and collected relevant materials. Jun Jia and Ke Wang supervised the work. All authors reviewed and revised the manuscript, approved the final version, and agreed to its publication.

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Ethics approval and consent to participate

Not applicable.

Disclosure of artificial intelligence (AI) use

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were used in the preparation, analysis, or writing of this manuscript.

Competing interests

The authors declare no conflicts of interest.

Consent for publication

All the authors consent to the publication of identifiable details, which can include data within the text to be published by *Translational Neurology and Neurosurgery*.

Data availability statement

No datasets were generated or analyzed for this work.

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