IJBBE International Journal of Biophotonics & Biomedical Engineering Vol. 5, No. 1, Spring- Summer, 2025

Research Article

Computational modeling of M1-BG-Th network firing rate and beta oscillation in brain neurological diseases for treatment with electrical or optogenetic stimulation

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DOI: 10.71498/ijbbe.2025.1191596

ABSTRACT

Received: Nov. 26, 2024, Revised: Feb. 13, 2025, Accepted: Feb. 15, 2025, Available Online: Jul. 14, 2025

The development of computational models is a useful tool for studying the structure and characteristics of brain neurons. By using different modeling methods, the mechanism of neurodegenerative diseases such as Alzheimer's (AD), Epilepsy, and Parkinson's disease (PD) can be understood. Brain disease modeling studies often focus on the Cortex, Thalamus (Th), and Basal Ganglia (BG). The primary motor cortex (M1) has interconnected layers that play an important role in performing movements and treating neurological diseases of the brain. In this paper, we have considered a model of the M1-BG-Th for the neural structure of healthy and Parkinsonian brain neurons. We have investigated excessive oscillations of the beta band and changes in the firing rate of the neurons, which are dynamic characteristics of PD. We have examined characteristics of the firing rate and power spectrum of the neurons of the M1-BG-Th network model, which shows the oscillations of the beta band of neurons of the M1-BG-Th network model, and we have studied healthy and Parkinsonian states. Our aim in presenting the proposed M1-BG-Th model is to investigate optogenetic stimulation for the treatment of neurological diseases of the brain, which is a minimally invasive method and targets specifically selected brain neurons by using opsins.

KEYWORD

M1-BG-Th network model, Parkinson's Disease (PD), Optogenetic, Beta oscillation, Firing Rate (FR).

I. INTRODUCTION

The neurodegenerative disorders of the brain tissue are identified by progressive loss of the set of vulnerable selected neurons. Neurodegenerative diseases can be classified based on their primary clinical features, such as dementia, parkinsonism, or motor neuron disease. Alternatively, they can be categorized according to the anatomical distribution of

neurodegeneration, such as frontotemporal degeneration, extrapyramidal disorders, or spinocerebellar degeneration [1]. Therefore, neurodegenerative disorders can be classified based on their clinical manifestations, among which extrapyramidal movement disorders and cognitive and behavioral disorders are the most common. A small number of patients have pure syndromes, most of them are defined by common features between neurodegenerative diseases, usually by the accumulation of specific proteins and cellular anatomical vulnerability. Neurodegenerative diseases share many of the underlying processes associated with progressive neurological dysfunction and death. The important point is that disorders of the structural proteins are evident even before the onset of the clinical symptoms [1]. Today, diagnostic biomarkers are not available, except in rare cases where a genetic mutation causes the disorder.

Parkinson's disease (PD) is a common neurological disorder marked by a range of motor symptoms, involving bradykinesia, tremor, rigidity, and postural instability [2]. The degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) is a key factor in PD, leading to persistent alterations in neuronal firing rates and oscillatory activity among neurons in the Basal Ganglia (BG) [3]. One of the electrophysiological features of PD is the widespread production of synchronized beta band (13-35 Hz) oscillations (β oscillations) in BG [4]. These immoderate and synchronized oscillations affect the ability of the thalamus (Th) to transmit motor information [5]. BG dysfunction is associated with pathogenesis in PD, including changing the firing rate (FR) and excessive synchronized beta-band activity (13–30 Hz). Dopamine loss disrupts the equilibrium between the activation of direct and indirect pathways in the striatum, a critical factor in the progression of PD. These pathways establish the primary connections between the striatum and the deeper structures of the Basal Ganglia (BG). Direct pathway involves the medium spiny neurons (MSNs) in the striatum that express the dopamine D1 receptors (D1 MSNs), along with substantia nigra pars reticulata (SNr) and globus pallidus interna (GPi). In contrast, the indirect pathway consists of MSNs with the dopamine D2 receptors (D2 MSNs), globus pallidus externa (GPe), and the neurons of the subthalamic nucleus (STN).

The primary motor cortex (M1) is a layered structure, with varying morphology, function, and neuronal projections across layers. In healthy conditions, the dynamics of the M1 network are essential for performing complex movements and motor skill acquisition. The neurons that are excitatory in the primary motor cortex (M1) involve the neurons of the intratelencephalic (IT), found in layers 2 through 6, and pyramidal-tract (PT) neurons located in the layer of 5B. These neurons send projections to the striatum and the neurons of the subthalamic nucleus (STN) within the Basal Ganglia (BG), and they also receive feedback from BG and thalamus (Th) [6]. Overall, the primary motor cortex (M1) is essential for movement regulation and plays an important role in the pathophysiology of PD.

Computational network models are valuable tools for investigating pathological brain behaviors and abnormal oscillations. A classical computational model, grounded in the direct/indirect pathway theory, has been developed to explain the mechanisms underlying pathological changes in firing rates. From the perspective of computational modeling, numerous microcircuits within the Basal Ganglia (BG) network are capable of generating beta-band oscillations, which include inhibitory feedback. Among these, the STN-GPe circuit is widely recognized as a key regulator of beta oscillatory activity [7]. Physiological experiments, however, reveal more intricate synaptic connections in the BG, highlighting the complexity of its circuitry. Developing mathematical models provides an effective approach to studying the abnormal synchronized oscillations characteristic of PD [8]. Using these models alongside nonlinear dynamics methods offers insights into the pathogenic mechanisms behind these oscillations [9]. Recent studies on PD modeling have predominantly focused on the cortex, thalamus, and BG. Notably, Terman and Rubin

introduced a computational network model based on BG and thalamocortical (TC) connectivity. So et al. [10] have enhanced this model to offer more precise discharge characteristics for both Parkinsonian and healthy states. This model is frequently used to explore the mechanisms and treatments of Parkinson's disease (PD), although it does not account for the role of the intrinsic network of the striatum. Numerous biophysical studies have shown that the striatum plays a crucial role in Parkinsonian movement and that prolonged dopamine depletion results in significant changes to striatal synaptic plasticity.

Despite its importance in PD, the role of the striatum is often underestimated. Yu and Wang Meaning that most individuals with PD are not candidates for the treatment. So, there is an urgent need to develop more effective and accessible treatments for PD. In this study, we have considered the M1-BG-Th model for the neural structure of healthy and diseased (PD) brain neurons, which has BG neurons including STN, GPe, GPi, Th and M1 neurons including E23, E5A, E5P, and E5B. For the network model of the M1-BG-Th, we have examined characteristics of the firing rate of the neurons and the neurons' power spectrum (PS) indicating the oscillations of the beta band of neurons.

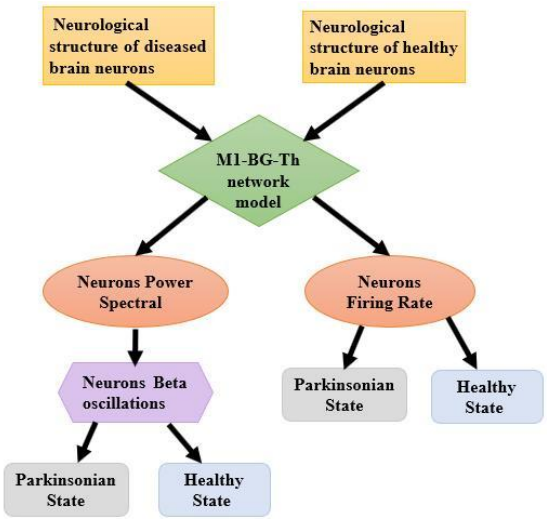


Fig. **1** The block diagram of the research method.

In each of the mentioned characteristics, we have studied healthy and Parkinsonian states. in 2019 [5], investigated the increase of the beta band oscillations in the BGTC model. Yu et al. in 2022 [4], have investigated beta activity in a computational model for GPe circuits. Wang et al. in 2023 [3], studied the dynamic mechanism of the Parkinsonian beta oscillations in the STN-GPe network. The main treatments for PD involve dopaminergic medications and deep brain stimulation (DBS). However, the effectiveness of these drugs tends to diminish over time, often accompanied by a range of side effects. In contrast, DBS is an invasive procedure that requires electrodes implanted to stimulate the deep brain regions. This option is reserved for patients who meet specific criteria,

The block diagram of the research method is shown in Fig.1.We have depicted firing rates of the STN, the GPe, the GPi, the E23, the E5A, and the E5P neurons for healthy and Parkinsonian modes, which based on the obtained results, in healthy the STN, GPe and GPi cells show an irregular discharge pattern. In the healthy state, M1 neurons fire in a random and sparse discharge pattern. In the Parkinsonian state, the GPi fires in a spiking firing pattern, GPe fires with a regular firing pattern, and an increase in STN, E23, E5A, and E5P firing rates is observed. Based on the results of the PS of the cells that show the beta oscillations, for all neurons, the healthy state has lower beta band oscillations and is at the bottom of the graph, while for the Parkinsonian state, the beta band oscillations are higher and there are significant peaks. Finally, we have calculated the average firing rate (AFR) of neurons in the M1-BG-Th network model for both healthy and Parkinsonian modes. In the Parkinsonian state, the AFR is elevated for all neurons, except for those in the GPi. This study effectively illustrates the characteristics and differences between healthy and Parkinsonian conditions using the M1-BG-Th network model.

Ⅱ. METHODS

A. *M1-BG-Th model*

This model is based on the work of Neymotin et al., developed in 2023 [11]. It describes the dynamics of the membrane potential of the Basal Ganglia (BG) and M1 neurons using the Hodgkin-Huxley (HH) framework. The model includes BG neurons such as the subthalamic nucleus (STN), globus pallidus externa (GPe), globus pallidus interna (GPi), and thalamus (Th), as well as M1 neurons like the E23 (the neurons of the intratelencephalic (IT) in the layer of 2), the E5A (the neurons of the IT in the layer of 5A), the E5B (the neurons of the IT in the layer of 5B), and the E5P (the neurons of the pyramidal tract (PT) in the layer of 5B). Additionally, the model incorporates two types of striatal neurons: The D1 medium spiny neurons (MSNs), and the D2 MSNs. Figures 2a and b depict the M1-BG-Th network model, and its connections, with excitatory Equation (1) and for E5P neurons by equation (2):

$$C_m \frac{dV}{dt} = -I_L - I_{Na} - I_K - I_M \quad (1)$$

$$C_m \frac{dV}{dt} = -I_L - I_{Na} - I_K - I_M - I_{Ca} \quad (2)$$

BG-Th model includes STN, GPe, Gpi, Th, and two types of MSN neurons D1 and D2 MSN. For D1 and D2 membrane potential dynamics, the current of the fast potassium (I_k), the current of the sodium (I_{Na}), the current of the leakage (I_L), the current of the M (I_M), and synaptic currents are considered. The membrane potential is described by equation (3) [12].

$$C_m \frac{dV_{MSN}}{dt} = -I_L - I_{Na} - I_K - I_M - I_{E5A\,/\,E5P-MSN} - I_{MSN-MSN} \quad (3)$$

Membrane dynamics of the STN, GPe, and GPi cells have been modeled using the framework presented by Terman and Rubin [13]. The equations of the specific dynamic are outlined in relations (4), (5), and (6)

$$C_m \frac{dV_{STN}}{dt} = -I_L - I_{Na} - I_K - I_T - I_{Ca} - I_{AHP} - I_{GPe-STN} - I_{ESP-STN} \quad (4)$$

$$C_m \frac{dV_{GPe}}{dt} = -I_L - I_{Na} - I_K - I_T - I_{Ca} - I_{AHP} - I_{STN-GPe} - I_{GPe-GPe} - I_{D2-GPe} \quad (5)$$

connections shown by, and inhibitory connections represented by .⊣. Based on Fig. 2b, each Th neuron inhibits one of the M1 neurons (E23, E5A, E5P, and E5B). Each E5P neuron excites three D2 MSN neurons and three STN neurons, and each E5A neuron excites three D1 MSN neurons. Each D1 MSN neuron inhibits two of its neurons and three of the GPi neurons, and each D2 MSN neuron inhibits two of its neurons and four of the GPe neurons. Each of the STN neurons excites two of the GPe neurons and two of the GPi neurons. Each of the neurons of the GPe inhibits two of its neurons, two of the neurons of the STN, and two of the neurons of the GPi. Finally, each GPi neuron sends an inhibitory input to each of the Th neurons. The membrane potential dynamics for E23, E5A, and E5B neurons are modeled by

$$C_m \frac{dV_{GPi}}{dt} = -I_L - I_{Na} - I_K - I_T - I_{Ca} - I_{AHP} - I_{STN-GPi} - I_{GPe-GPi} - I_{D1-GPi} \quad (6)$$

For Th neurons, membrane potentials are expressed by equation (7):

$$C_m \frac{dV_{Th}}{dt} = -I_L - I_{Na} - I_K - I_T - I_{CPi-Th} \quad (7)$$

B. *Different states of M1-BG-Th model healthy and PD states*

Neurological brain diseases lead to an imbalance between the activity of neurons in the direct and indirect paths. Disturbance and change in the mechanism of neurons in the direct and indirect paths lead to abnormal function in the network model of the M1-BG-Th due to the creation of pathological activities of neurological brain diseases. One of the characteristics of pathological activities is the change in the firing rate of the M1-BG-Th model neurons. The firing rate of neurons, which indicates how neurons work, will be different in healthy and PD states. In this way, M1-BGTh model neurons in a healthy state can show an irregular and random firing pattern, while in a PD state, their firing can be regular, increasing, or decreasing [2, 3].

C. *Evaluation of the M1-BG-Th network model function*

In this section, to evaluate the performance of the M1-BG-Th network model, we have calculated the AFR of the neuron population and beta oscillations by calculating the PS of the neurons. AFR is defined as the average firing rate of all the neurons within a population. We have calculated AFR in the form of equation (8) [14] and used it for the network model of the M1-BG-Th neurons, which is a suitable concept for statistical explanation and measurement of nerve spike activity.

$$AFR(t) = \frac{1}{\Delta t} \frac{n_{act}(t;t+\Delta t)}{N} \quad (8)$$

Where N is the population size of the $n_{act}(t; t + \Delta t)$is number of the spikes occurring between t nd $+\Delta t$, and ΔtIs a small-time interval. A high level of AFR indicates a faster firing rate and neural excitation, and a low level of AFR indicates a slower firing rate and inhibition of neural activity. The power spectrum of a train of spikes is a key measure for investigating neural variability, and its calculation is a key challenge for investigating neural firing variability. In practice, the power spectrum is calculated from an averaging process [15]. The power spectrum of neurons reveals key characteristics of their activity. Neurons exhibit various peaks in their responses, with the shape and location of these peaks being influenced by factors like the applied stimuli and the intrinsic biophysical properties, like the input current density and the channel noise. Estimating the power spectrum of neuronal activity is a useful approach for analyzing neural outputs, commonly applied in neurophysiological recordings like the multiunit activity (MUA), the single spike trains, and potentials of the cell membrane. It is also utilized in the outputs of

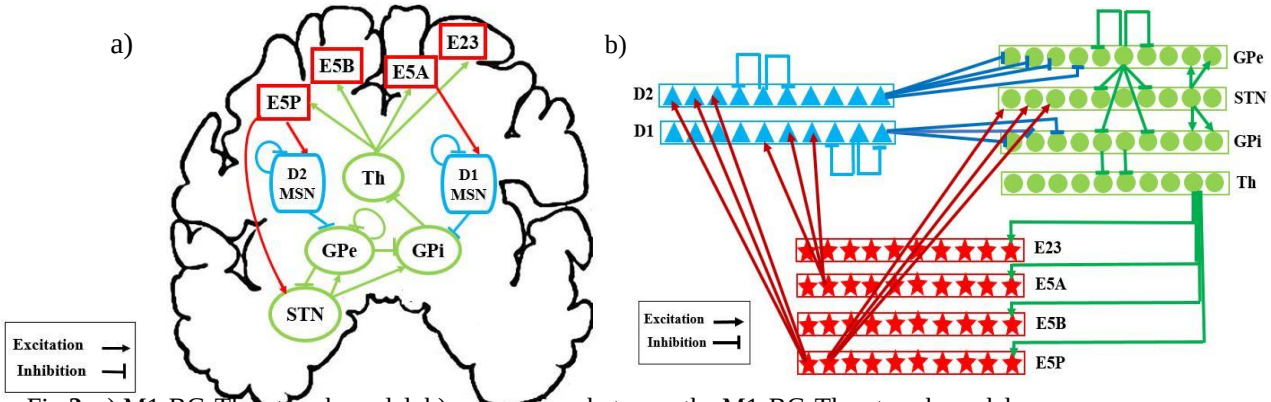


Fig.**2** a) M1-BG-Th network model. b) connections between the M1-BG-Th network model neurons.

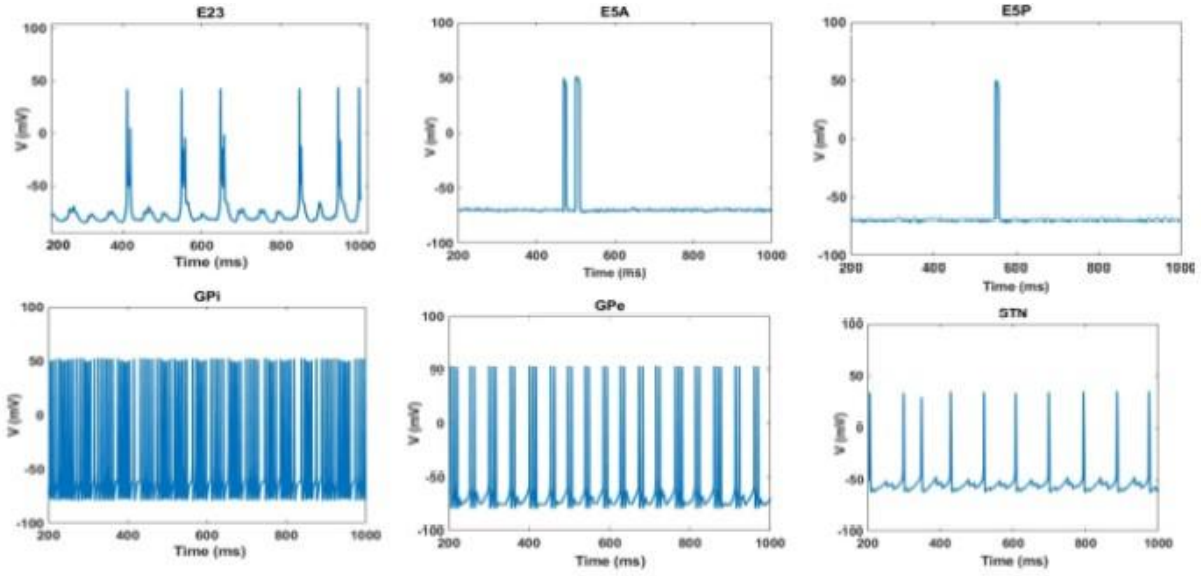
Various neural models to assess the neuron's response to input stimuli and for spectral analysis of the experimental recordings from the neurons of the GP in PD patients [16]. In this study, we have calculated the power spectrum to investigate the beta oscillations of the neurons of the M1-BG-Th network model, which is another characteristic of Parkinson's disease. Neurological brain diseases such as PD lead to an increase in beta oscillations and neuron synchrony caused by changes in the strength of synaptic connections of neurons and input currents from different parts of the brain to the neurons of the network model of the M1-BG-Th. Beta oscillations and synchrony of neurons are another characteristic of Parkinson's disease, which shows different physiological and pathological conditions. Synchronized and excessive oscillations of M1-BG-Th network model neurons disrupt the performance of network model neurons in the ability to transmit motor information [4, 5]. In this study, we have obtained the power spectrum to examine the beta oscillations of the M1- BG-Th, which is another feature of the PD.

Ⅲ.Results

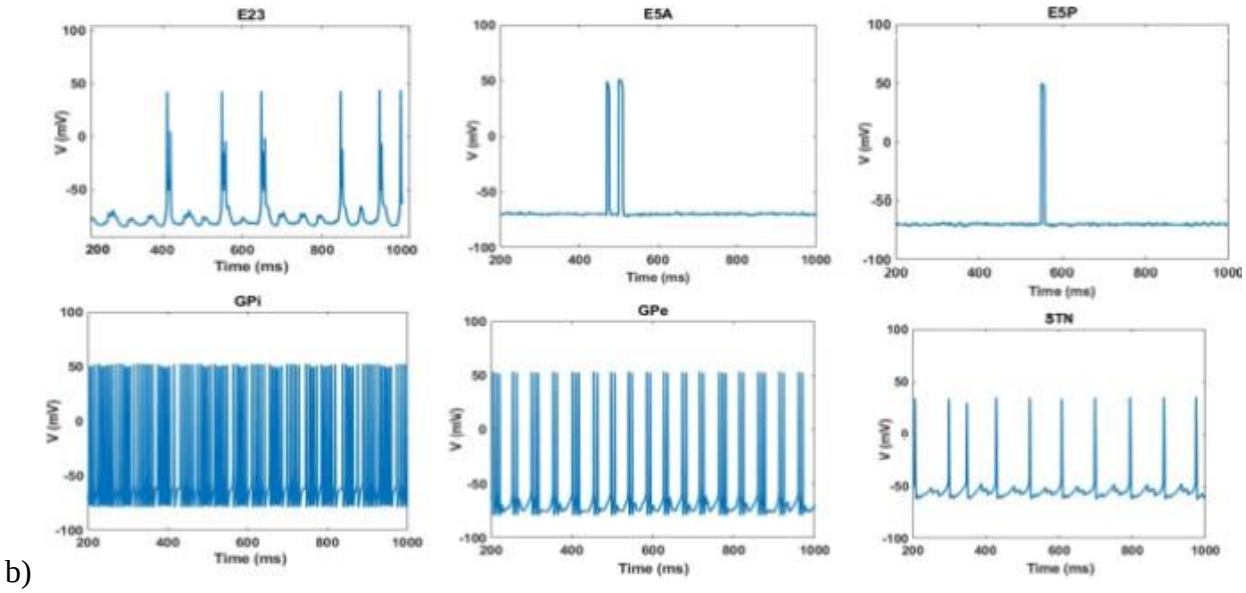
Since excitatory input is applied to M1 neurons in the direct and indirect brain path through Th neurons, in this paper, unlike Yu et al. (2023), we have examined the complete model of the M1-BG-Th while considering the connections between Th and M1 neurons. On the other hand, since inhibitory and excitatory connections between neurons and the number of connections between them are important in the function of the M1-BG-Th network model and play an important role in examining characteristics of healthy and parkinsonian states, we have also applied them in M1-BG - Th model. To investigate the treatment of PD with electrical and optogenetic stimulations, we have studied the firing rate of neurons and the beta oscillations of the neurons without applying stimulation for the M1-BG-Th network model. Yu et al., have done the simulation in Neuron software, whereas, we have implemented all the simulation steps with MATLAB software to access the parameters and data of neurons of the M1-BG-Th network model.

A. Firing characteristics of the neurons of the M1-BG-Th model in healthy and PD states

Neuronal firing characteristics play a crucial role in understanding neurological disorders, especially Parkinson's disease (PD). The M1-BG-Th network model consists of neurons of the STN, GPe, GPi, E23, E5A and E5P. The changes in firing rates and patterns between the healthy and PD states significantly impact motor control and are key indicators of dysfunction in the motor circuitry. In the healthy state (Fig. 3a), the M1 neurons (E23, E5A, and E5P) exhibit a random and sparse discharge pattern, while BG neurons (STN, GPe, and GPi) fire irregularly and asynchronously. This firing behavior ensures a balanced inhibitory-excitatory interaction in the M1-BG-Th network, leading to normal motor function. GPi neurons provide appropriate inhibitory input to Th neurons, preventing.



a)



b)

Fig.**3** Firing rate of the M1-BG-Th network model neurons. a) healthy state. b) PD state.

Excessive excitation. The neurons relay proper excitatory input to M1 neurons, maintaining normal motor activity. STN and GPe maintain irregular and asynchronous firing, ensuring a dynamic and adaptive motor control system. This normal firing pattern allows the network to function efficiently, preventing abnormal oscillatory activity and motor dysfunction.

In PD (Fig. 3b), there are significant alterations in neuronal firing rates and patterns, leading to pathological activity in the M1-BG-Th network. M1 neurons (E23, E5A, and E5P) show increased firing rates and synchrony. This excessive excitatory activity contributes to the generation of pathological motor commands, Beta oscillations (13–30 Hz) play a crucial role in motor control, and their abnormal enhancement is a hallmark of Parkinson's disease (PD). These oscillations are linked to motor impairments such as rigidity and bradykinesia. To analyze beta oscillatory activity in both healthy and PD states, the Power Spectrum (PS) of key neurons in the M1-BG-Th network (STN, GPe, GPi, and E23) was calculated, with results presented in (Fig. 4). In leading to symptoms like rigidity and tremors. GPi neurons fire in a bursting pattern. This abnormal burst activity results in excessive inhibition of the Th neurons, disrupting the normal relay of excitatory signals to M1. GPe neurons fire more regularly, reducing their ability to regulate STN activity. This change weakens the indirect pathway, leading to excessive excitatory input from STN to GPi. STN neurons show increased discharge frequency, leading to stronger excitatory input to GPi, which further exacerbates the excessive inhibition of Th.

B. Beta oscillations of the M1-BG-Th model in healthy and PD states

the healthy state, beta oscillations in the M1-BG-Th network exhibit a broad and unstructured spectral distribution without distinct peaks. This absence of prominent beta activity suggests that: STN, GPe, and GPi neurons do not show excessive synchronization, allowing smooth motor execution. E23 neurons in M1 display low amplitude beta activity (PS range: 0–30), which is within normal physiological limits. The lack

of dominant beta rhythms reflects the ability of the network to flexibly modulate motor commands without excessive inhibition or excitation.

In the Parkinsonian state, the M1-BG-Th network exhibits abnormally strong and synchronized beta oscillations, characterized by distinct peaks in the PS of STN, GPe, GPi, and E23 neurons (Fig. 4). The key changes include: STN, GPe, and GPi neurons show enhanced beta peaks, indicating increased synchronization within the basal ganglia. GPi neurons exhibit strong beta-band activity, leading to excessive inhibition of the thalamus, which disrupts normal motor output. E23 neurons in M1 also show increased beta oscillations, though within a lower PS range (0–30). This suggests that cortical activity is influenced by abnormal basal ganglia rhythms, contributing to impaired voluntary movement. The increase in beta oscillations in PD is primarily due to the dysfunction of the cortico-basal ganglia-thalamic loop, which results in excessive excitation of the STN due to reduced GPe inhibition, leading to enhanced beta-band activity in STN and GPi. Overactive GPi neurons impose excessive inhibition on the thalamus, reducing excitatory output to M1. M1 neurons (E23) adopt the abnormal beta rhythm, reinforcing pathological oscillations and contributing to motor deficits such as bradykinesia and rigidity. Clinical Implications of Beta Oscillations in PD Increased beta synchronization is associated with movement difficulties, as excessive beta oscillations reduce the flexibility of motor control.

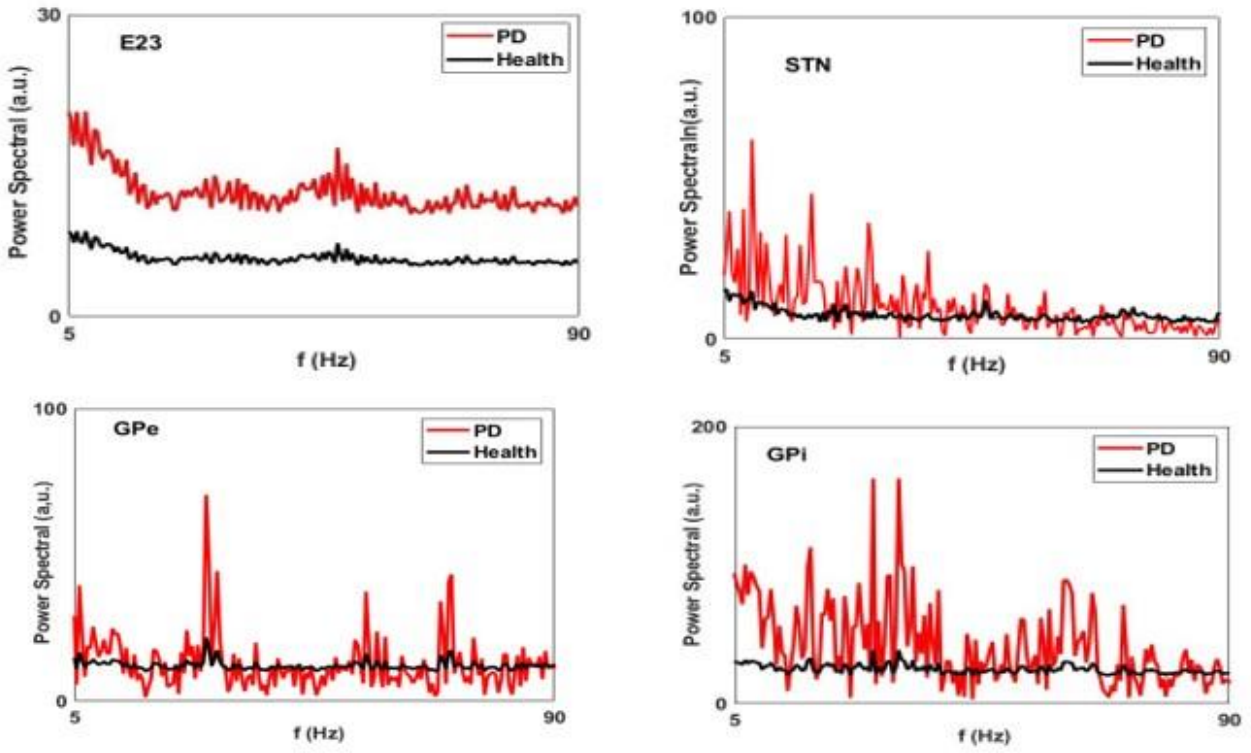


Fig.4 Beta oscillations of the E23, STN, GPe, and GPi for healthy and PD states.

C. AFR of the M1-BG-Th model in healthy and PD states

The Average Firing Rate (AFR) represents the number of spikes generated by neurons in a given period, providing insights into network activity in both healthy and Parkinsonian (PD) states. By analyzing AFR in different neurons of the M1-BG-Th network model, we can understand how PD alters neural dynamics. The

results of this analysis are presented in Table 1. In the healthy state, the AFR of neurons in the M1-BG-Th network follows a balanced pattern, ensuring proper motor function. M1 neurons (E23, E5A, E5P) fire at a moderate rate, supporting controlled and flexible movement.BG neurons (STN, GPe, GPi) maintain normal activity, contributing to the proper regulation of thalamic output. GPi neurons provide appropriate inhibitory control over Th neurons, allowing the thalamus to deliver proper excitatory input to M1. This balanced AFR distribution ensures smooth motor control, preventing excessive or deficient neural excitation.

Table. 1 AFR of the M1-BG-Th network model neurons in healthy and PD states

M1-BG-Th network model neurons	AFR of the healthy state	AFR of the PD state
STN	100	180
GPe	390	490
GPi	1030	980
E23	60	230
E5A	20	80
E5P	10	40

In PD, AFR increases for all neurons except GPi, leading to network dysfunction. STN neurons show increased AFR, resulting in excessive excitatory input to GPi, disrupting normal inhibitory control. GPe neurons fire at a higher rate, reducing their ability to regulate STN activity, and further amplifying STN overactivity. M1 neurons (E23, E5A, E5P) exhibit increased AFR, contributing to abnormal motor commands and pathological activity. GPi neurons exhibit reduced AFR (inhibitory state), impairing their ability to suppress Th neurons effectively. The neurons receive insufficient inhibition from GPi, leading to a failure in delivering appropriate excitatory input to M1. This abnormal AFR distribution disrupts motor signal processing, resulting in increased beta oscillations, excessive synchronization, and the hallmark motor symptoms of PD (tremors, rigidity, and bradykinesia).

Ⅳ. CONCLUSION

Neurological brain diseases lead to disturbances in the function of the brain's neural network. In this study, the M1-BG-Th network model including BG neurons (STN, GPe, and GPi), Th neurons, and M1 neurons (E23, E5A, E5P, and E5B) for healthy and diseased (PD) brain neurons is considered. Since the firing rate of network neurons and beta oscillations are important parameters for network model of the M1-BG-Th network model, we have examined both parameters for healthy and Parkinsonian states and finally, we have obtained AFR for the neurons of the network model of the M1-BG-Th. Based on the obtained results, in the healthy state, BG neurons fire irregularly and M1 neurons fire randomly and sparsely. In the PD state, the firing of BG neurons is bursting, regular, and incremental. Also, this fire increase is observed for M1 neurons. Fewer beta oscillations are seen in the healthy state, but for the PD state, these oscillations have been increased and have distinct peaks. On the other hand, the AFR in the Parkinsonian state is raised for all the neurons except GPi, which leads to disruption in the performance of the M1-BG-Th network and creates pathological activities. Therefore, our proposed model has been able to show the abnormal characteristics of neurodegenerative diseases. Which paves the way for the treatment of neurological brain diseases with electrical and optogenetic stimulations.

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