Study on the Efficacy of Temporal Interference Stimulation (TIS) for Parkinson's Disease

Study Protocol

Study Title: Study on the Efficacy of Temporal Interference Stimulation (TIS) for Parkinson's Disease
Protocol Number: Version 2.2
Principal Investigator: Bin Mei
Department: Department of Neurology
Study Period: September 2025 - December 2026

Zhongnan Hospital of Wuhan University
September 4, 2025
Version: v2.2

1. Study Summary

1.1 Abstract

Study Title: Study on the Efficacy of Temporal Interference Stimulation (TIS) for Parkinson's Disease
Study Introduction: To explore the therapeutic effect of Temporal Interference Stimulation (TIS) on patients with Parkinson's disease (PD) and to further investigate the potential mechanism of TIS for treating PD.
Study Objective: Based on exploring the improvement effects of TIS on motor and non-motor symptoms in PD patients, this study aims to investigate the differences in symptom improvement resulting from TIS intervention on the subthalamic nucleus (STN).
Study Population: Planned enrollment of 24 subjects.
Study Site/Location: Zhongnan Hospital of Wuhan University / Department of Neurology
Study Intervention: TIS stimulation target is the subthalamic nucleus, with a current intensity of 2mA, base frequency of 2000Hz, frequency difference of 130Hz, and stimulation duration of 20 minutes.
Study Start/End Time: From September 4, 2025, to December 31, 2026.
Subject Participation Duration: The time from enrollment to completion of all follow-ups for each subject is 3 months.

1.2 Technical Roadmap

(To be included as a figure/flowchart)

2. Study Background

2.1 Significance of the Study

Parkinson's disease (PD) is a neurodegenerative disorder for which, to date, no curative therapy exists. Furthermore, as the disease progresses, the efficacy of existing symptomatic treatments becomes increasingly limited. Concurrently, the incidence of PD is rising annually. Given this trend, there is an urgent need to develop new therapeutic strategies to improve the future quality of life for PD patients, with non-invasive neuromodulation technologies being one such avenue. Transcranial alternating current stimulation (tACS) is a commonly used non-invasive neuromodulation method that influences brain neural activity by applying alternating current through electrodes placed on the scalp. However, this method is significantly attenuated by tissues such as the scalp and skull, making it difficult to reach deep brain regions. The proposal of the Temporal Interference Stimulation (TIS) method has made non-invasive deep brain stimulation

possible. This method involves simultaneously inputting two pairs of high-frequency stimulation signals to stimulation electrodes placed on the scalp. A strong overlapping electric field is formed in specific deep brain regions, which fluctuates at the frequency difference of the two high-frequency currents. The synthesized modulated signal overcomes issues such as insufficient depth of intervention and electric field dispersion inherent in traditional transcranial electrical stimulation. The effectiveness of the TIS modulation method has been validated in rodent models. In the field of Parkinson's disease research, TIS not only holds potential therapeutic value but also provides an important tool for exploring and validating key regulatory targets of the disease (such as the subthalamic nucleus, globus pallidus, etc.). By modulating neural activity in different brain regions, it is hoped to further clarify the core links in the pathological mechanism of PD, laying the foundation for Deep Brain Stimulation (DBS) therapy. Meanwhile, with its advantages of being non-invasive, safe, and highly repeatable, TIS has the potential to become a novel intervention for PD, offering new possibilities for expanding clinical treatment strategies.

2.2 Research Background

PD is a common progressive neurodegenerative disorder associated with severe disability and negative impacts on quality of life [1]. Although the etiology of PD is unclear, its pathological manifestation involves the loss or dysfunction of dopaminergic neurons in the substantia nigra pars compacta [2]. Typical clinical manifestations include difficulties with coordinated movements, such as asymmetric resting tremor, rigidity, and bradykinesia. These symptoms and their response to levodopa form the basis for the clinical diagnosis of PD. Postural instability and gait abnormalities occur in later stages of the disease. Although PD is incurable, numerous pharmacological treatments are available to control motor and non-motor symptoms.

PD is characterized by progressive motor dysfunction. Over the past three decades, Deep Brain Stimulation (DBS) has been used as a neurosurgical procedure to treat debilitating motor symptoms in PD patients. Although DBS of the globus pallidus internus (GPi) has proven effective, its widespread clinical application is limited, partly due to its invasiveness and treatment-related adverse effects [3-5]. Moreover, because its efficacy varies significantly among individuals, the choice of stimulation target is crucial for surgical outcomes. How to accurately determine the most suitable DBS target for an individual patient before surgery remains a significant clinical challenge.

The non-invasive deep brain stimulation technique, Temporal Interference Stimulation (TIS), offers a non-invasive method to alter neuronal activity in deep brain nuclei, potentially treating motor symptoms in PD [6]. TIS is a non-invasive approach targeting deep brain structures that has shown promise in improving PD motor symptoms in previous proof-of-concept studies. The principle of TIS involves placing two pairs of transcranial stimulation electrodes on the scalp, each generating a high-frequency current with a slightly different frequency. The human cerebral cortex does not respond to these high-frequency currents. However, when these currents interfere in the deep brain (i.e., the target region), they generate a low-frequency electric stimulation (the difference between the two high frequencies), similar to tDCS, thereby affecting deep brain areas. TI stimulation has shown potential in modulating DBS-related brain regions such as the subthalamic nucleus and globus pallidus in animal models and preliminary clinical studies. Thus, it achieves stimulation of deep brain nuclei while minimizing activation of superficial cortical areas. The breakthrough of TIS also lies in its flexibility in stimulating targets; by changing the current ratio between electrode pairs,

the stimulation target location can be adjusted without altering electrode positions. This makes it highly suitable for future clinical applications involving deep nucleus modulation and personalized treatment plan development for PD patients.

An exploratory study conducted by team members showed that using Transcranial Inductive Stimulation (TIS) to stimulate the unilateral subthalamic nucleus (STN) in PD patients led to an alleviation of motor symptoms when comparing pre- and post-treatment conditions [7]. In a more recent exploratory study on TIS stimulation of the right globus pallidus internus (GPi), TIS was confirmed to be feasible and safe for alleviating motor symptoms, especially bradykinesia and tremor, in mild PD patients; symptom relief was more significant on the left side compared to the right (especially for bradykinesia). PD patients with more severe bradykinesia and tremor before stimulation experienced greater improvement after TIS [6]. Current research results indicate that TIS has the potential to improve motor symptoms in PD patients. However, in the aforementioned two studies, some patients still did not respond to TIS stimulation. To further investigate the improvement effects of TIS stimulation on PD patients, this study plans to enroll 24 Parkinson's disease patients, using TIS to stimulate the STN, to explore the efficacy of TIS stimulation in treating PD motor symptoms. This study aims to investigate the impact of TIS on PD patients' motor symptoms, gait and postural control abilities, as well as the effects of TIS stimulation on brain activation and related brain networks. It also aims to provide validation of effectiveness and a new physical treatment method for the clinical application of TIS in treating PD motor symptoms.

References

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2.3 Expected Outcomes of the Study

TIS promotes improvement in motor symptoms, gait, and postural control in PD patients.
Relevant brain areas are activated in PD patients after TIS treatment, and connectivity within related brain networks is enhanced.
Elucidation of the physiological basis and stimulation effect patterns of TIS for improving PD symptoms, promoting the optimization of non-invasive modulation therapy for PD from an empirical selection approach towards a data-driven, mechanism-explicit pathway.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

The TIS treatment process may involve the following adverse events, including: headache, fatigue, itching at the stimulation site, etc. Furthermore, as a new technology, its long-term effects are not yet clear.

2.4.2 Known Potential Benefits

TIS is a non-invasive brain neuromodulation technology, offering improved treatment safety for subjects compared to invasive treatments. It enables stimulation of deep brain nuclei, making it more likely for subjects to benefit compared to superficial stimulation therapies, with potential effects including improvement of Parkinson's motor symptoms, gait, and postural control abilities.

2.4.3 Potential Risk/Benefit Assessment

TIS is a non-invasive brain neuromodulation technology that can provide Parkinson's patients with additional therapeutic options without interfering with conventional treatments. The breakthrough of TI technology is also reflected in the flexibility of its stimulation targets; the stimulation target location can be adjusted by changing the current ratio between electrode pairs without altering electrode positions. This makes it highly suitable for future clinical applications involving multi-target (simultaneous/sequential) modulation and the development of personalized diagnosis and treatment plans for PD patients. Therefore, based on the above, it is considered that the potential benefits of conducting this study outweigh the potential risks.

3. Principal Investigator Information

3.1 Principal Investigator Name, Qualifications, Contact Information

No.	Name	GCP Trained?	Role in Study (e.g., PI, Sub-I, CRC)
1	Bin Mei	Yes	PI
2	Yang Pan	Yes	Sub-I

3.2 Key Participant Information

No.	Name	Gender	Age	Title	Specialty	GCP Trained?	Role in Study
1	Bin Mei	Male	51	Chief Physician	Neurology	Yes	PI

No.	Name	Gender	Age	Title	Specialty	GCP Trained?	Role in Study
2	Yang Pan	Female	39	Chief Physician	Neurology	Yes	Sub-I
3	Yingfeng Xia	Male	36	Attending Physician	Neurology	Yes	Investigator
4	Chuang Nie	Female	28	Resident Physician	Neurology	Yes	Investigator
5	Xin Tu	Female	29	Research Assistant	Neurology	Yes	Data Manager

4. Study Objectives

To investigate the effects of TIS on motor symptoms, gait, and postural control in PD patients, and to explore its impact on brain activation and related brain networks in patients. To provide a more targeted and predictive basis for target selection in subsequent TIS treatment for PD patients, enhance TIS efficacy, promote the clinical translation and application of this technology in the field of Parkinson's disease, and utilize its non-invasive advantage to explore the evaluation of stimulating different targets on the treatment effect of PD.

5. Study Design

5.1 Overall Design

This study plans to enroll 24 PD subjects. Subjects will receive TIS stimulation targeting the subthalamic nucleus for 7 consecutive days. Prior to stimulation, all subjects will undergo assessments including MDS-UPDRS, MoCA, Timed Up and Go (TUG) test, as well as MRI scans, 64-channel EEG, and blood serum collection. Immediately after the first treatment and at the one-month follow-up, MDS-UPDRS assessments will be performed along with functional MRI scans, 64-channel EEG, and blood serum collection.

5.2 Definition of Study Endpoints

5.2.1 Efficacy Endpoints

Primary Efficacy Endpoints:

(1) Change in the Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS Part III) scores before treatment, immediately after a single treatment session, and at 1 month.

(2) Changes in brain activation and network functional connectivity before and after treatment, assessed by comparing pre- and post-treatment fMRI and 64-channel EEG to determine the effects of TIS on brain activation and network functional connectivity.

Secondary Efficacy Endpoints:

(1) Change in MDS-UPDRS Part II scores from baseline immediately after a single treatment and at 1 month.

(2) Montreal Cognitive Assessment (MoCA) scores before and after treatment.

(3) Change in Timed Up and Go (TUG) test performance from baseline before and after a single treatment and at the 1-month follow-up.

5.3 Determination of Sample Size

This study plans to enroll 24 subjects.

6. Study Population

6.1 Inclusion Criteria

(1) Adult male or female, aged 40 years or older.

(2) Diagnosed with idiopathic Parkinson's disease according to brain bank criteria, with age at onset after 40 years.

(3) Previous or current treatment with dopaminergic replacement therapy (e.g., levodopa) with good response.

(4) Hoehn and Yahr (H&Y) stage 1.5 - 2.5.

(5) Able to walk independently without aids for at least 5 minutes.

(6) No severe freezing of gait (FOG) episodes.

(7) Disease duration ≥ 2 years since diagnosis, stable condition, able to cooperate with study assessments and interventions.

(8) Stable medication dosage for at least 4 weeks prior to the experiment.

(9) Signed informed consent, with the subject or legal guardian able to understand and willing to participate in the study.

6.2 Exclusion Criteria

(1) Presence of other neurological disorders affecting the experiment.

(2) Mild or greater cognitive impairment (MoCA score ≤ 23).

(3) Orthopedic or other health conditions that may affect gait or balance.

(4) Contraindications unsuitable for MRI scanning, such as claustrophobia.

(5) History of taking antipsychotic drugs, antidepressant drugs, or other drugs that may affect dopamine levels.

(6) History of other severe psychiatric disorders.

(7) History of epilepsy, traumatic brain injury, or contraindications such as metal implants in the brain or heart (e.g., stimulators, pacemakers).

(8) History of electroconvulsive therapy (ECT).

(9) Currently participating in other gait and balance-related intervention training.

(10) Physician-diagnosed cardiovascular exercise risk factors.

6.3 Subject Recruitment

(1) Recruitment Channels

Medical Institutions: Recruitment through referrals from professionals in departments like Neurology at Zhongnan Hospital of Wuhan University.

Online Promotion: Dissemination of study recruitment information via the WeChat public account of the Neurology Department at Zhongnan Hospital of Wuhan University and related forums.

(2) Recruitment Process

Subject Assessment: Preliminary assessment of interested participants via telephone or online questionnaire to confirm eligibility based on inclusion criteria.

Appointment for Interview: Schedule an interview with preliminarily eligible participants to 详细介绍 study purpose, procedures, potential risks and benefits in detail.
Informed Consent: After confirming understanding, participants need to sign the informed consent form.
Assessment and Enrollment: Professional assessments, including motor symptom evaluation (MDS-UPDRS Part III) and cognitive function (MoCA) assessment, will be conducted on willing participants to determine final enrollment.

(3) Participant Benefits

Health Assessment: All participants will receive comprehensive health assessments and related health advice.
Treatment Plan: Participants will receive TIS intervention during the study, potentially obtaining effective treatment.
Compensation: Considering participants' time and transportation costs, the study will provide a certain amount of financial compensation.

(4) Ethics and Privacy Protection

All participant information will be kept strictly confidential and used solely for the purposes of this study.
The study will follow the review and approval of the Ethics Committee to ensure participants' rights and safety.

7. Study Intervention
7.1 Administration of Study Intervention
7.1.1 Description of Study Intervention
The medical device used in this study is as follows:

Product Name: Non-invasive Brain Neuromodulation Stimulator NervioX
Manufacturer: Suzhou Dome Medical Technology Co., Ltd.
Model/Specifications: TES NEURO-800
Structure/Composition: The TES NEURO-800 product consists of a stimulator main unit, electrode adapter, algorithm and control software (optional accessory), stimulation electrode cables (optional accessory), electrode cap (optional accessory), and animal electrodes (optional accessory). The NVX-36T amplifier is part of the computer system used for training systems, clinical and scientific research. Each channel has a DC cascading input and an individual 24-bit ADC for EEG sampling up to 10,000 times per second. An internal high-resolution direct digital synthesizer (DDS) current stimulator is used to generate DC or AC current through any EEG electrode or set of electrodes. Application software sets up experiments, records EDF+, BDF+, and stimulation. Software libraries are available for user application self-design.

This study device has completed safety regulation and electromagnetic compatibility testing at qualified testing institutions.

(Note: Details about the EEG device seem to be missing in the original text. The translation reflects this.)

7.1.2 Dosage and Administration Method

This study plans to enroll 24 Parkinson's disease subjects. Subjects will receive stimulation targeting the subthalamic nucleus (frequency difference = 130Hz) for a duration of 20 minutes, with a 30-second ramp-up at the beginning and a 30-second ramp-down at the end. The impedance at the four stimulation electrodes will be maintained at ≤10 kΩ throughout. The intervention will last for 7 consecutive days. The stimulation frequency difference is fixed for subjects. The stimulation current may be adjusted based on individual tolerance and clinical practical diagnosis and treatment needs, as it varies greatly among individuals.

7.2 Study Schedule

Procedure	Screening Period	Treatment Period I	Treatment Period II	Follow-up Period
Visit Timepoint	V0	V1	V2	V3
-7 to 0 days	Day 1	Day 2-7	1 Month After	
Time Window	/		+2 days	+2 days
Sign Informed Consent	X			
Demographics	X			
Medical History	X			
Inclusion/Exclusion Criteria	X			
Randomization		X		
MDS-UPDRS	X	X		X
Timed Up and Go Test	X	X		X
64-channel EEG	X	X		X
MRI Scan	X	X		X
Blood Serum	X	X		X
TI Intervention		X	X	
Adverse Events		X	X	

Procedure	Screening Period	Treatment Period I	Treatment Period II	Follow-up Period
Concomitant Medications	X	X	X	X

7.3 Study Procedures

1) Visit 0 Screening Period (-7 to 0 days):

Sign informed consent form.
Collect demographic data (date of birth, gender, etc.).
Record medical history and concomitant medications.
Determine inclusion/exclusion criteria.
Perform MDS-UPDRS, Timed Up and Go (TUG) test, 64-channel EEG.
Perform MRI scans (T1 structural image, diffusion tensor imaging, and resting-state functional MRI).
Collect blood serum samples.

2) Treatment Period (7 days +2 days window)

TI intervention will be administered for 7 consecutive days, once daily for 20 minutes each session.
Visit 1 Treatment Period I (First Treatment)

Perform 20 minutes of TI intervention.
Assess MDS-UPDRS scale, perform functional MRI scan, 64-channel EEG, and collect blood serum immediately after the first treatment.
Record adverse events and study disease concomitant medications.

Visit 2 Treatment Period II (Day 2-7 +2 days window)

Perform 20 minutes of TIS intervention.
Record adverse events and study disease concomitant medications.

3) Visit 3 Follow-up Period (1 month after +2 days window)

Perform MDS-UPDRS, Timed Up and Go (TUG) test, 64-channel EEG.
Perform MRI scans (T1 structural image, diffusion tensor imaging, and resting-state functional MRI).
Collect blood serum samples.
Record medical history and concomitant medications.

8. Study Endpoint Evaluation

8.1 Primary Endpoint Evaluation

(1) Changes in motor symptoms in PD patients: By comparing changes in MDS-UPDRS Part III scores before treatment, immediately after, 30 minutes, and 60 minutes after a single treatment session.
(2) Changes in brain activation and network functional connectivity: By comparing changes in brain

activation and network functional connectivity before and after treatment, using fMRI and 64-channel EEG to determine the impact of TIS on brain activation and network functional connectivity in PD patients.

8.2 Secondary Endpoint Evaluation

Changes in motor symptoms in PD patients after the first treatment: By comparing MDS-UPDRS Part III scores before treatment, immediately after, and the day after the first treatment session.

8.3 Safety and Other Evaluations

Safety analysis will be based on the Safety Analysis Set (SS). The safety endpoints of this study include known anticipated adverse events related to TI technology and other adverse events, including serious adverse events, that occur during the study period. The number of cases, number of occurrences, and incidence rates of adverse events/serious adverse events will be calculated separately, and a detailed list will be provided.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Adverse Event (AE) Definition

Any untoward medical occurrence in a clinical study subject, whether or not related to this study, is termed an Adverse Event (AE).

8.4.2 Serious Adverse Event (SAE) Definition

The following events occurring during the clinical research process are termed Serious Adverse Events (SAEs):

Death.
Life-threatening illness or injury.
Permanent impairment of a body structure or function.
Requiring hospitalization or prolongation of hospitalization.
Requiring medical or surgical intervention to prevent permanent impairment of a body structure or function.
Events causing fetal distress, fetal death, or congenital abnormalities, birth defects, etc.

8.4.3 Adverse Event Classification

8.4.3.1 Event Severity

Mild: The subject can tolerate it, does not affect the study intervention treatment, does not require special treatment, and has no impact on the subject's health.
Moderate: The subject finds it difficult to tolerate, requires suspension of the study intervention treatment or special handling, and has a direct impact on the subject's health.
Severe: Life-threatening to the subject, causing death or disability, requiring immediate cessation of the study intervention treatment or emergency handling.

8.4.3.2 Relationship to Study Intervention

The investigator should assess the relationship between the adverse event and TI treatment, classifying it according to the following criteria:
Related to Treatment: (1) There is a reasonable temporal relationship between the two; (2) The event is a known risk of the treatment intervention or can be explained by the mechanism of the treatment intervention; (3) The harm decreases or disappears after stopping treatment; (4) The

harm reappears upon re-treatment; (5) Cannot be explained by other influencing factors. Meeting all five criteria is judged as "Definitely Related"; meeting two criteria is judged as "Possibly Related". Unrelated to Treatment: (1) There is no reasonable temporal relationship between the two; (2) The adverse event is a type that this treatment intervention is unlikely to cause; (3) The adverse event can be explained by concomitant device/drug use, progression of the subject's condition, or other treatment influences. Meeting all three criteria is judged as "Definitely Unrelated"; meeting one criterion is judged as "Possibly Unrelated".

8.4.3.3 Expected Adverse Reactions and Suspected Unexpected Serious Adverse Reactions

The examination methods used in this study (MRI scanning) comply with international standards and are widely used in clinical research. They may cause minor side effects in subjects, such as feeling warm or increased heart rate, most of which do not cause serious impact. They are common clinical methods, and their potential health risks are within clinically acceptable limits. If psychological discomfort or other reactions occur during the study, subjects can contact the research doctor at any time for timely handling. Furthermore, follow-up surveys may involve some personal privacy issues for subjects, potentially causing anxiety or psychological discomfort. If necessary, researchers will refer subjects to a psychological counselor or clinician for relevant consultation.

Additionally, TIS is a non-invasive brain neuromodulation stimulator that may have effects on improving motor symptoms. The TIS treatment process may involve the following adverse events, including: headache, fatigue, itching at the stimulation site, etc. If such symptoms occur, subjects can promptly report to the trial staff and receive prompt handling. If a subject experiences a rapid decline in motor function during the study, that subject will be handled as a dropout, and appropriate diagnostic and therapeutic methods will be selected for treatment based on their confirmed condition.

9. Statistical Analysis

9.1 General Methods

A biostatistician will formulate the statistical analysis plan based on the study protocol, refining it into a document before database lock.

The statistical software used for analysis will be SPSS version 28.0 or above. All statistical tests will be two-sided, and a P-value less than 0.05 will be considered statistically significant (unless otherwise specified).

Descriptive statistics for quantitative measures will include mean, standard deviation, maximum, minimum, median, 25th and 75th percentiles. Categorical measures will be described using frequencies and proportions.

For between-group comparisons, analyses will be performed according to the measure type as needed. Comparisons of quantitative data between groups will use independent samples t-test (if variance is homogeneous and distribution is normal) or Wilcoxon rank-sum test based on data distribution. Categorical data will use chi-square test or Fisher's exact test (if chi-square test is not applicable). Ordinal data will use Wilcoxon rank-sum test or CMH test.

10. Privacy and Confidentiality

All personal information involved in this study is confidential. Subjects' original data will be encrypted and stored at the research center. Questionnaire and cognitive function task data will be stored in locked filing cabinets. All information provided by subjects will be used solely by members of this project team for scientific research purposes. This information may include name, address, phone number, medical history, and information obtained during study visits. All subject data will be identified by a study ID number rather than the subject's real name. Information that can identify a subject will not be disclosed to members outside the research team unless permission is obtained from the individual subject. All research team members are required to keep subject identities confidential. To ensure the study is conducted according to regulations, government regulatory authorities or Ethics Committee members may, when necessary and in accordance with regulations, inspect subject personal information at the research site. When the results of this study are published, no individual subject information will be disclosed.

The results of this study may be registered on public websites such as the Chinese Clinical Trial Registry. The research results will be jointly owned by the participating research units.

11. Conflict of Interest Statement

There are no relevant conflicts of interest in this study.

Protocol Signature Page

I have carefully reviewed this study protocol and acknowledge that it covers all necessary content required to conduct the study. I will conduct the research in accordance with this protocol.

I will provide copies of this protocol and all related materials to all personnel assisting me in this research. I will discuss these materials with them to ensure they fully understand the information regarding the trial.

Research Site	**Principal Investigator**	**Date**
Zhongnan Hospital of Wuhan University		

Patient Informed Consent Form

Protocol Title: Study on the Efficacy of Temporal Interference Stimulation (TIS) for Parkinson's Disease
Informed Consent Form Version: 2.2, Version Date: September 4, 2025
Research Institution: Zhongnan Hospital of Wuhan University
Principal Investigator: Bin Mei

You are being invited to participate in a clinical study. This informed consent form provides you with information to help you decide whether to participate. Please read it carefully. If you have any questions, please ask the investigator responsible for this study.

What are the background and purpose of the study?

Study Background: Parkinson's disease (PD) is a common progressive neurodegenerative disorder associated with severe disability and negative impacts on quality of life. Although the etiology of PD

is unclear, its pathological manifestation involves the loss or dysfunction of dopaminergic neurons in the substantia nigra pars compacta. Typical clinical manifestations include difficulties with coordinated movements, such as asymmetric resting tremor, rigidity, and bradykinesia. These symptoms and their response to levodopa form the basis for the clinical diagnosis of PD. Postural instability and gait abnormalities occur in later stages of the disease. Although PD is incurable, numerous pharmacological treatments are available to control motor and non-motor symptoms. PD is characterized by progressive motor dysfunction. Over the past three decades, Deep Brain Stimulation (DBS) has been used as a neurosurgical procedure to treat debilitating motor symptoms in PD patients. Although DBS of the globus pallidus internus (GPi) has proven effective, its widespread clinical application is limited, partly due to its invasiveness and treatment-related adverse effects.

Based on the non-invasive deep brain stimulation technique, Temporal Interference Stimulation (TIS), it offers a non-invasive method to alter neuronal activity in deep brain nuclei, potentially treating motor symptoms in PD. Non-invasive deep brain stimulation (Temporal Interference Stimulation, TI) is a non-invasive method targeting deep brain structures that has shown promise in improving PD motor symptoms in previous proof-of-concept studies. The principle of TI involves placing two pairs of transcranial stimulation electrodes on the scalp, each generating a high-frequency current with a slightly different frequency. The human cerebral cortex does not respond to these high-frequency currents. However, when these currents interfere in the deep brain (i.e., the target region), they generate a low-frequency electric stimulation (the difference between the two high frequencies), similar to transcranial direct current stimulation (tDCS), thereby affecting deep brain areas. Thus, it achieves stimulation of deep brain nuclei while minimizing activation of superficial cortical areas. The breakthrough of TI also lies in its flexibility in stimulating targets; by changing the current ratio between electrode pairs, the stimulation target location can be adjusted without altering electrode positions. This makes it highly suitable for future clinical applications involving deep nucleus modulation and personalized treatment plan development for PD patients.

An exploratory study by team members, stimulating the unilateral subthalamic nucleus (STN) of PD patients with TI, observed alleviation of motor symptoms when comparing pre- and post-treatment conditions. In a recent exploratory study on TI stimulation of the right GPi, TI was feasible and safe for alleviating motor symptoms, especially bradykinesia and tremor, in mild PD patients; symptom relief was more significant on the left side compared to the right (especially for bradykinesia). PD patients with more severe bradykinesia and tremor before stimulation experienced greater improvement after TI. Current research results indicate that TI has the potential to improve motor symptoms in PD patients. However, in these two studies, some patients still did not respond to TI stimulation. To further explore the differences between PD patients who respond and those who do not respond to TI stimulation, this study plans to enroll 16 Parkinson's patients to investigate the impact of TI on PD patients' motor symptoms, gait and postural control abilities, as well as the effects of TI stimulation on brain activation and related brain networks, providing validation of effectiveness and a new physical therapy method for the clinical application of TI in treating PD motor symptoms.

Study Objective: To explore the effects of non-invasive deep brain stimulation on motor symptoms, gait, and postural control abilities in PD patients, as well as the impact of TI stimulation on brain activation and related brain networks.

Study Device: The medical device used in this study is the non-invasive brain neuromodulation stimulator NervioX, developed by Suzhou Dome Medical Technology Co., Ltd. It consists of a stimulator main unit, electrode adapter, algorithm and control software (optional accessory), stimulation electrode cables (optional accessory), electrode cap (optional accessory), and animal electrodes (optional accessory). Currently, the product is still in the experimental research and development stage and has not received marketing approval from the National Medical Products Administration. However, the product has completed safety regulation and electromagnetic compatibility testing at qualified testing institutions, and the test results are qualified.

If I participate in the study, what do I need to do?

If you agree to participate in this study, we will assign you a number and establish a medical record file. During the study process, we need to comprehensively evaluate your condition, personality traits, sleep issues, etc., which will be conducted by professional healthcare personnel using clinical scale assessments and related examinations.

【Clinical Scales】

The clinical scales you need to complete include the MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the Montreal Cognitive Assessment (MoCA).

【Motor Function Assessment】

Motor Function Assessment: Doctors will assess your motor function using the Timed Up and Go (TUG) task.

【MRI Scans, Blood Collection】

Doctors will perform MRI scans and collect blood samples for you. This examination has no radioactivity. You only need to lie quietly and complete specific cognitive tasks while trying to keep your body still. MRI data will be collected using the MRI scanner at the imaging center, including T1 structural images (scan duration about 6 minutes), diffusion tensor imaging (scan duration about 15 minutes), and resting-state functional MRI (total scan duration about 9 minutes). The purpose is to evaluate whether there are visible structural changes and invisible structural and functional state changes in your brain.

For MRI scans, you are required to undergo the examination at the lead unit of this study, Zhongnan Hospital of Wuhan University.

【Process and Duration】

After signing the informed consent, the doctor will ask you some basic information such as personal details, medical history, Parkinson's medication use, etc. At the same time, arrangements will be made for your MDS-UPDRS and MoCA assessments, and the Timed Up and Go test. Additionally, you will undergo MRI scans, 64-channel EEG, and blood collection at Zhongnan Hospital of Wuhan University. Your Parkinson's medication use will be recorded. This study requires that your anti-Parkinson medication regimen remain unchanged from within 30 days before signing the

informed consent until your participation in the entire trial period. If the above assessment results indicate you are suitable for this study, you will formally enter the study to receive treatment.
During the treatment phase, the doctor will use a randomization system to assign you to a group. You may be assigned to Group A to receive TIS stimulation of the subthalamic nucleus, once daily for 7 days, or you may be assigned to Group B to receive TIS stimulation of the globus pallidus, once daily for 7 days. The probability of being assigned to any group is the same, and the grouping result is not subject to human intervention. You will follow the grouping result to receive TIS stimulation targeting the right subthalamic nucleus or globus pallidus, with a current intensity of 2mA, base frequency of 2000Hz, frequency difference of 130Hz, and stimulation duration of 20 minutes. Before stimulation, you will undergo MDS-UPDRS, MoCA, Timed Up and Go test assessments, as well as MRI scans and blood collection. Immediately after the first treatment and at the 3-month follow-up, MDS-UPDRS assessments will be performed along with functional MRI scans, 64-channel EEG, and blood collection. During this period, your Parkinson's medication use and any physical discomfort will be recorded.

As a research subject, you need to provide truthful information about your medical history and current physical condition; inform the research doctor of any discomfort you experience during this study; during the study period, you must not change your Parkinson's medication or its dosage on your own; inform the research doctor if you are currently participating in any other research; if you or your spouse becomes pregnant during the study period, please promptly inform your research doctor. The research doctor will also answer any related questions you have during the clinical trial process.

The research doctor will contact you by phone to remind you of hospital appointment times. To ensure contact can be made, please inform the doctor in advance if you change your phone number or have similar situations.

Your participation in this study is expected to last approximately three months. This study plans to enroll 16 subjects.

Are there risks in the study?
The examination methods used in this study (MRI scans) and blood collection comply with international standards and are widely used in clinical diagnosis and treatment. They may cause minor side effects in you, such as feeling warm or increased heart rate, most of which do not cause serious impact. Additionally, the study may involve some personal privacy issues for you, which could cause anxiety or psychological discomfort. If necessary, researchers will refer you to a psychological counselor or clinician for relevant consultation. The non-invasive deep brain stimulation (TI) process may involve the following adverse reactions, including: headache, fatigue, itching at the stimulation site, switching to mania, suicidal tendencies, etc. If such symptoms occur, you can promptly report them to the research doctor and receive prompt handling.

What are the possible benefits of participating?
This study may alleviate your Parkinson's condition, or it may not benefit you. Furthermore, we hope that the information you provide from participating in this study may benefit you or others with similar needs in the future.

Are there costs or compensation for participating?

Costs: You will receive study-related examinations and assessments free of charge, including MRI scans, 64-channel EEG, scale assessments, motor function assessments, and blood sample collection. All costs associated with non-invasive deep brain stimulation will also be covered by research funds. The study will not cover your medication costs or examination fees unrelated to the study.

Compensation: During your participation in this trial, the study provides a transportation allowance of 200 RMB and a nutrition subsidy of 50 RMB. The subsidy will be disbursed in a lump sum when you return to the hospital for follow-up visits.

What happens if I am harmed due to participation?

If you experience complications or other injuries during this trial, the doctor will accurately record the situation and determine whether the adverse event is related to the procedures required by the study. For adverse events caused by study-required procedures that cause you harm, you can receive active treatment at your research institution, and/or receive corresponding compensation according to relevant Chinese laws and regulations. However, this study will not pay for costs unrelated to the research.

Is my information confidential?

If you decide to participate in this study, your participation and personal information within the study will be kept confidential. Information that can identify you will not be disclosed to members outside the research team unless your permission is obtained. All research team members are required to keep your identity confidential. The information and data generated by this study's procedures do not involve external transfer. Your research-related medical records will be stored in locked filing cabinets within this medical institution, accessible only to researchers. To ensure the study is conducted according to regulations, government regulatory authorities or Ethics Committee members may, when necessary and in accordance with regulations, inspect your personal information at the research site. When the results of this study are published, no individual information about you will be disclosed.

Do I have to participate?

You can voluntarily choose to participate or not participate in this study, or notify the researcher at any time to withdraw from the study. Your data will not be included in the study results, and your medical treatment and rights will not be affected as a result. Participation in this study is entirely voluntary. If you do not participate, it will not have any impact on the medical services you receive at this hospital.

If you require other treatments, if you do not comply with the study plan, if injury related to the research occurs, or if there are other reasons that continuing participation might increase the risk of harm to you from participating in the study, the research physician may terminate your further participation in this study.

Who should I contact if I need more information?

You can learn about information related to this study and research progress at any time. If new safety information related to this study arises, we will also notify you promptly. If you have questions related to this study, or if you experience any discomfort or injury during the study, or have questions regarding participant rights in this study, you can contact Dr. Pan at 19291751431.

This study has been reviewed and approved by the Medical Ethics Committee of Zhongnan Hospital of Wuhan University. If you have any questions or concerns regarding your rights and health as a participant in this study, you can contact the institutional Ethics Committee at telephone number: 027-67812787; Contact person: Teacher Hu.

Informed Consent Form Signature Page

I have read this informed consent form.

I have had the opportunity to ask questions and all questions have been answered.

I understand that participation in this study is voluntary.

I can voluntarily choose to participate or not participate in this study, or withdraw at any time after notifying the researcher without discrimination or retaliation, and my medical treatment and rights will not be affected as a result.

If I require other treatments, if I do not comply with the study plan, if injury related to the research occurs, or if there are other reasons that continuing participation might increase the risk of harm to me from participating in the study, the research physician may terminate my further participation in this study.

I will receive a signed copy of this "Informed Consent Form."

Subject Name: _____

Subject Signature: _____

Date: _____ Year _____ Month _____ Day

Legal Representative Name: _____

Legal Representative Signature: _____

Date: _____ Year _____ Month _____ Day

Witness Name: _____

Witness Signature: _____

Date: _____ Year _____ Month _____ Day

(Note: Witness signature is required if the subject is illiterate; legal representative signature is required if the subject lacks/ has limited capacity for civil conduct.)

I have accurately informed the subject about this document, requested him/her to carefully read this informed consent form, and carefully answered any questions or doubts raised.

Investigator Name: _____

Investigator Signature: _____

Date: _____ Year _____ Month _____ Day