Clinical Research Protocol

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Project source and number: Investigator-initiated clinical study

Immediate Effects of External Trigeminal Nerve Stimulation on Motor Dysfunction in Parkinson's Disease

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Protocol Synopsis

Study title	**Immediate Effects of External Trigeminal Nerve Stimulation on Motor Dysfunction in Parkinson's Disease**
Objective	To explore evidence for external trigeminal nerve stimulation (eTNS) in treating motor dysfunction in Parkinson's disease and to determine the optimal stimulation frequency and the profile of immediate therapeutic effects.
Study design	Within-subject design
Sample size	Thirty patients with idiopathic Parkinson's disease
Eligibility criteria	Inclusion criteria: 1. Patients with idiopathic Parkinson's disease (PD) diagnosed by two neurologists according to the Chinese diagnostic criteria for Parkinson's disease formulated in 2020 by the Chinese Parkinson's Disease and Movement Disorders Society on the basis of the MDS Clinical Diagnostic Criteria for Parkinson's Disease. 2. Hoehn and Yahr stage 1-5 in the medication ON state. 3. Mini-Mental State Examination (MMSE) score >24. 4. Stable antiparkinsonian medication for at least 1 month before the trial. 5. No history of orthopedic or musculoskeletal disorders, and no other condition that may affect balance or gait, such as ophthalmologic disease. 6. No history of epilepsy, intracranial tumor, or other neurological disease; no severe psychiatric disorder, such as schizophrenia; and no long-term use of antipsychotic medication. 7. Age 40-80 years. 8. Ability to complete all assessments and eTNS treatment and provision of written informed consent. Exclusion criteria: 1. Secondary parkinsonism or atypical parkinsonian syndrome. 2. Current use of anticholinergic medication. 3. Contraindication to non-invasive electrical neuromodulation. 4. eTNS treatment within the preceding 6 months. 5. Severe neurological, renal, cardiovascular, hepatic, or other major systemic disease. 6. Inability to complete clinical assessments or refusal to provide written informed consent.
Intervention	This within-subject study includes three 20-min stimulation conditions: 120-Hz eTNS, 40-Hz eTNS, and sham eTNS. Each patient with PD will complete all conditions in a single session in randomized order. Instrumented gait analysis using the IDEEA gait system, together with motor and gait rating scales, will be used to quantify immediate post-stimulation changes in gait and motor function relative to baseline.
Efficacy assessments	Primary outcomes: mean gait speed, mean gait length and dual-task cost (DTC). Secondary outcomes: stride length variability, percentage of double-support phase, symmetry index, and cadence. Other assessments: MDS-UPDRS Part III, Tinetti Gait Assessment, and Hoehn and Yahr staging. Safety outcome: adverse event records.
Statistical methods	Continuous variables will be analyzed using linear mixed-effects models, t tests, or analysis of variance, as appropriate.
Study duration	1 month

1. Background

Parkinson's disease (PD), the most common movement disorder, is characterized by motor symptoms including tremor, rigidity, bradykinesia, and postural instability. These symptoms substantially impair quality of life and increase the risks of falls, disability, and accidental injury, making them a major therapeutic challenge [1-2]. Although symptoms can often be controlled with medication in early disease, motor complications and waning medication response in the middle and late stages increase treatment difficulty. Deep brain stimulation (DBS) is an established therapeutic option, but its invasiveness, high cost, and complex postoperative programming limit

its broader clinical use. Therefore, a new therapeutic technology that combines efficacy with practical applicability is urgently needed for PD.

Electrical stimulation of the trigeminal nerve was first used in 1974 to evaluate neuromodulatory control of cerebral blood flow [3]. External trigeminal nerve stimulation (eTNS), a non-invasive trigeminal nerve stimulation technique, was initially developed at the University of California, Los Angeles in 2007 for the treatment of drug-resistant epilepsy [4]. Subsequent studies have suggested promising effects in PD and other movement disorders.

A key milestone was a double-blind, placebo-controlled clinical trial published in 2017 [5], which evaluated the immediate effects of electrical stimulation of intrinsic auricular muscle zones (IAMZs) on motor symptoms in PD. IAMZ stimulation involves the auriculotemporal branch of the trigeminal nerve and also activates the C2 spinal nerve, facial nerve, and vagus nerve. The trial enrolled 24 patients with PD (Hoehn and Yahr stage >=2) in two groups. In the first group (n=10), 10 min of stimulation at 130 Hz with a 100-us pulse width improved contralateral symptoms by 35% (UPDRS Part III decrease of 5.9 points; p=0.0003). In the second group (n=14), UPDRS scores decreased by 31% after 20 min of stimulation ($p<0.001$), and the effect persisted for up to 30 min after stimulation. Stimulation improved tremor, rigidity, and bradykinesia, with prominent bilateral effects superior to dry needling and sham stimulation. This study provided the first clinical evidence that trigeminal nerve stimulation may modulate motor symptom improvement in PD.

Another encouraging development is that, in 2023, a portable tongue stimulation device was approved by the FDA as an adjunctive treatment for gait impairment caused by multiple sclerosis; the lingual nerve is a branch of the mandibular division of the trigeminal nerve. The FDA evaluated the effectiveness of the PoNS device on the basis of two clinical studies [6-7]. In a real-world study of 150 patients with multiple sclerosis and gait impairment [8], interim results showed that lingual nerve electrical stimulation combined with home-based rehabilitation significantly improved gait and balance scores and improved quality of life. These findings suggest substantial potential for trigeminal nerve electrical stimulation in improving movement disorder symptoms.

In 2023, investigators also reported that trigeminal nerve stimulation activated intracranial dopaminergic neurons and regulated dopamine release in mice [9]. In a mouse model of traumatic brain injury, 7 days of TNS (60 min/day; 40 Hz, 0.2 mA, 200-us pulse width) improved cognitive impairment and significantly increased hippocampal dopamine levels. Activation of dopaminergic neurons in the substantia nigra pars compacta/ventral tegmental area was observed using genetically encoded dopamine sensors. These findings indicate that TNS can activate dopaminergic neurons and promote intracranial dopamine release, potentially improving regulation of the basal ganglia-thalamo-cortical circuit and correcting motor abnormalities in PD.

Together, these studies indicate substantial potential for eTNS in modulating motor dysfunction in PD. However, high-quality evidence supporting this conclusion remains insufficient, and clinical trials of eTNS for PD remain scarce. By integrating clinical efficacy assessment with mechanistic exploration, this study aims to evaluate eTNS as a non-invasive treatment strategy for PD and to provide a foundation for future clinical application.

2. Study Objective

To explore evidence for eTNS in treating motor dysfunction in Parkinson's disease and to determine the optimal stimulation frequency and the characteristics of immediate and longer-term therapeutic effects.

3. Study Design, Principles, and Procedures

3.1 Overall design

This is a clinical trial conducted primarily at Xi'an Central Hospital. A within-subject design will be used. Thirty patients with PD will be enrolled. Three 20-min stimulation conditions will be administered: 120-Hz eTNS, 40-Hz eTNS, and sham eTNS. Each participant will complete all conditions in one session, with the order randomized. Instrumented gait parameters will be collected after each stimulation condition. Motor function scales will be assessed at baseline and after completion of the experiment, including MDS-UPDRS Part III, Tinetti Gait Assessment, and Hoehn and Yahr staging.

The gait protocol includes three main walking tasks performed under both single-task (ST) and dual-task (DT) conditions: 12-meter walking, a 10-meter modified Timed Up and Go test, and a 3-meter Timed Up and Go test. The experiment will be conducted in a well-lit, flat corridor in the medication ON state, 1-2 h after administration of antiparkinsonian medication, to ensure optimal medication effect. Instrumented gait analysis using the IDEEA gait system, together with motor and gait scales, will be used to quantify immediate changes in gait and motor function after stimulation relative to baseline. The study workflow is shown in Figure 1.

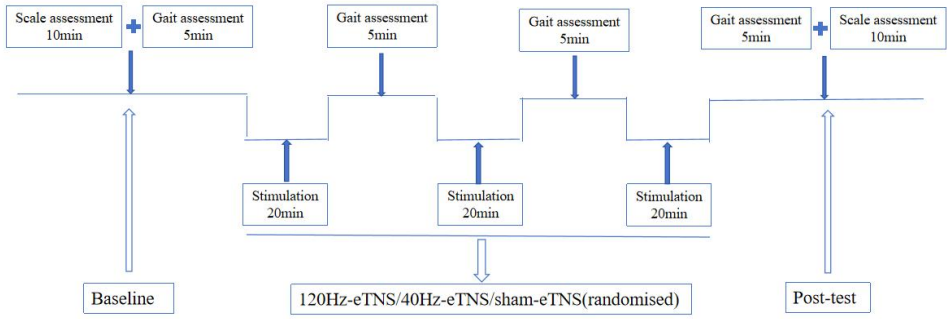


Figure 1. Study workflow

3.2 Randomization and blinding

Block randomization will be used, with five blocks and a block size of six participants. Each block will contain six possible stimulation sequences. Study personnel will print and seal the randomization results in opaque envelopes. After participant enrollment, stimulation order will be assigned sequentially. The three stimulation devices will be labeled Device A, Device B, and Device C. The devices will have identical appearances, with A/B/C labels on the back. The allocation key will be sealed in opaque envelopes. After enrollment, study personnel will inform the eTNS operator of the assigned sequence using combinations of A/B/C. The eTNS operator will administer the stimulation.

3.3 Sample size

Sample size was calculated using G*Power 3.1.9.7. On the basis of a similar within-subject tVNS-PD study [10], an effect size of Cohen's d=0.43 (medium effect) was identified. For this trial, the expected effect size was adjusted to Cohen's d=0.56, which remains within the medium effect range. With alpha=0.05 (two-sided), power=0.80, four repeated measurements, and correlation coefficient r=0.5, the estimated sample size was approximately 27. Allowing for a 10% dropout rate, 30 participants will be recruited.

3.4 Trigeminal nerve stimulation

This study will use non-invasive electrical stimulation of the trigeminal nerve. The stimulation device consists of a main unit, electrode wires, and electrode pads and is compact and portable. Before stimulation, the stimulation site will be cleaned with alcohol to remove excess keratin and oil, conductive gel will be applied,

and electrode pads will be placed over the frontal nerve territory of the ophthalmic division of the trigeminal nerve, as shown in Figure 2. Sensory and pain thresholds will be measured, and the mean of the two values will be used as the subsequent stimulation intensity.



Figure 2. Trigeminal nerve stimulation site

Contraindications include ulceration or open wounds at the stimulation site and hyperalgesia.

This treatment is a non-invasive physical therapy and is relatively safe; no serious related adverse reactions have been reported to date. Possible adverse reactions include skin discomfort at the electrode site and occasional mild headache or dizziness.

If tingling or skin redness occurs, symptoms may be relieved by reducing stimulation intensity or stopping treatment. Tingling will disappear as current decreases, and skin redness usually resolves after treatment cessation. If other adverse reactions occur, the device may be stopped immediately and study personnel notified. Appropriate symptomatic management will be provided promptly. Adverse event assessment is described in Section 7.

4. Observation Items and Assessment Time Points

Assessment item	Before trial	During trial
Inclusion and exclusion criteria	Yes	
Written informed consent	Yes	
Demographic data	Yes	
Medical history	Yes	
Levodopa equivalent daily dose (LEDD)	Yes	
Instrumented gait parameters	Yes	
MDS-UPDRS Part III	Yes	
Hoehn and Yahr staging	Yes	
Tinetti Gait Assessment	Yes	
Mini-Mental State Examination (MMSE)	Yes	
Self-reported eTNS-related response questionnaire		Yes

5. Participant Selection

5.1 Inclusion criteria

- Patients with idiopathic PD diagnosed by two neurologists according to the Chinese diagnostic criteria for Parkinson's disease formulated in 2020 by the Chinese Parkinson's Disease and Movement Disorders Society on the basis of the MDS Clinical Diagnostic Criteria for Parkinson's Disease.
- Hoehn and Yahr stage 1-5 in the medication ON state.
- MMSE score >24.
- Stable antiparkinsonian medication for at least 1 month before the trial; the trial will be conducted in the MED-ON state.
- No history of orthopedic or musculoskeletal disorders, and no other condition that may affect balance or gait, such as ophthalmologic disease.
- No history of epilepsy, intracranial tumor, or other neurological disease; no severe psychiatric disorder, such as schizophrenia; and no long-term use of antipsychotic medication.
- Age 40-80 years.
- Ability to complete all assessments and eTNS treatment and provision of written informed consent.

5.2 Exclusion criteria

- Secondary parkinsonism or atypical parkinsonian syndrome.
- Current use of anticholinergic medication.
- Contraindication to non-invasive electrical neuromodulation.
- eTNS treatment within the preceding 6 months.
- Severe neurological, renal, cardiovascular, hepatic, or other major systemic disease.
- Inability to complete clinical assessments or refusal to provide written informed consent.

5.3 Withdrawal/exclusion after enrollment

- Participant is found after enrollment not to meet inclusion criteria or to meet exclusion criteria.
- Stimulation is not administered according to the protocol, or incomplete data affect efficacy or safety evaluation.
- Poor compliance, voluntary withdrawal during treatment, use of treatments prohibited by the protocol, or unauthorized change of treatment during the study.
- Serious adverse event or complication occurs, making continued treatment inappropriate and requiring trial discontinuation.

5.4 Criteria for study termination

- A serious adverse event occurs and continued participation is inappropriate.
- The study is terminated by the investigator, sponsor, regulatory authority, or ethics committee.
- The investigator determines that withdrawal is in the participant's best interest for safety reasons.
- The participant withdraws informed consent.

6. Treatment Plan

Design: within-subject design.

Participants: 30 patients with PD.

Stimulation conditions: 120-Hz eTNS, 40-Hz eTNS, and sham eTNS.

6.1 Stimulation parameters

Condition	Parameters
120-Hz eTNS	Frequency 120 Hz; pulse width 250 us; duty cycle 30 s on/30 s off.
40-Hz eTNS	Frequency 40 Hz; pulse width 250 us; duty cycle 30 s on/30 s off.
Sham eTNS	120 Hz, 250 us, 30 s on/30 s off; double-ramp paradigm, with current delivered only at intervention onset (0-15 s) and midway through the session (15 s at minute 10).

Stimulation site: bilaterally above the medial ends of the eyebrows, corresponding to the terminal frontal nerve branches of the ophthalmic division of the trigeminal nerve.

Treatment duration: 20 min. Current intensity will be titrated according to each participant's individual tolerance threshold within a range of 0-6 mA.

Procedure: Each participant will complete all stimulation conditions in one session, with the order randomized. Instrumented gait parameters will be analyzed before and after stimulation, and MDS-UPDRS Part III, Hoehn and Yahr staging, and Tinetti Gait Assessment will be assessed to determine immediate changes in gait and motor function after stimulation relative to baseline.

7. Adverse Event Monitoring

7.1 Definition of adverse events

An adverse event is any unfavorable medical occurrence in a participant during the clinical trial, regardless of whether it has a causal relationship with treatment. An adverse event may be any unfavorable or unintended sign, including abnormal laboratory findings, symptom, or intercurrent illness occurring during treatment, whether or not related to treatment. This includes:

- All suspected adverse events.
- All adverse reactions caused by improper trigeminal nerve stimulation procedures.
- Clearly unrelated diseases, including exacerbation of pre-existing conditions.
- Injuries or accidents.
- Abnormal findings on physiological or physical examination that require clinical treatment or further investigation.
- Abnormal laboratory findings that require clinical treatment or further investigation.

7.2 Collection of adverse event information

Study physicians will report all adverse events directly observed or spontaneously reported by participants using concise medical terminology. After treatment, participants will also be asked about adverse events. Potential adverse reactions include skin tingling, pruritus, drowsiness, dry eyes, and muscle spasm.

7.3 Observation and recording of adverse events

The parties responsible for recording, handling, and reporting adverse events and serious adverse events include the investigator, the project-responsible institution, the clinical monitor, and the participant. All study personnel involved in participant treatment are responsible for recording and reporting adverse events and serious adverse events, regardless of whether a causal relationship with clinical study procedures is suspected. Events will be recorded in source documents and case report forms with signature and date.

All adverse reactions or adverse events, whether or not related to the study treatment, will be recorded in detail. Records will include a detailed description of the adverse event or serious adverse event; time of onset; time of resolution; duration in days or hours; severity and frequency; treatment measures, dose, course, and rationale; treatment outcome; assessment of causal relationship with the investigational treatment; follow-up status; and all relevant clinical materials, such as laboratory reports and electrocardiograms, in the source documents.

7.4 Severity grading

When completing the adverse event form, investigators will describe event intensity as mild, moderate, or severe:

- Mild: does not affect normal participant function.
- Moderate: affects normal participant function to some extent.
- Severe: clearly affects normal participant function.

7.5 Assessment of relationship to study intervention

Investigators will assess the possible relationship between adverse events and the investigational product or medication using the following five-level classification:

- Definitely related: the reaction occurs in a reasonable temporal sequence after product use, is consistent with the known reaction profile of the suspected product, disappears after discontinuation, and cannot be explained by the participant's clinical condition or other causes.
- Probably related: the reaction occurs in a reasonable temporal sequence after product use, is consistent with the known reaction profile of the suspected product, clearly improves after discontinuation, and cannot be explained by the participant's clinical condition or other causes.
- Possibly related: the reaction occurs in a reasonable temporal sequence after product use, is not highly consistent with the known reaction profile of the suspected product, does not improve after discontinuation, and may be explained by the participant's clinical condition or other causes; the reaction improves after improvement of the disease state or elimination of other causes.
- Definitely unrelated: the reaction does not occur in a reasonable temporal sequence after product use, is not consistent with the known reaction profile of the suspected product, can be explained by the participant's clinical condition or other causes, and improves after improvement of the disease state or elimination of other causes.

Events classified in the first three categories will be counted as adverse events related to the investigational product and used to calculate the adverse event incidence.

7.6 Prevention and management of adverse events

Before electrical stimulation, the local skin will be prepared and the electrode pads placed firmly against the skin to reduce impedance between the skin and electrodes. Stimulation intensity will then be increased slowly from zero. Excessive stimulation intensity may cause local skin tingling, which can be relieved by slightly reducing the intensity.

If skin allergy occurs at the electrode site, or if symptoms do not resolve after stimulation cessation, the attending physician will be contacted for clinical observation and treatment until recovery to normal or baseline status, stabilization, or another condition judged reasonable by the investigator. If an adverse event has not resolved by the end of the study, investigators will continue necessary treatment, reporting, and documentation. Special circumstances may be handled according to the opinions of the relevant administrative authorities.

8. Statistical Analysis

Data will be analyzed using descriptive statistics. Continuous variables will first be assessed for normality. Normally distributed continuous variables will be presented as mean +/- standard deviation; non-normally distributed variables will be presented as median and interquartile range [M (Q1, Q3)]. Categorical variables will be presented as frequencies and percentages. Independent-samples t tests will be used to compare differences in age, height, and MMSE score between groups, and chi-square tests will be used to compare sex distribution between groups.

To compare the effects of different interventions on primary endpoints across measurement time points, a linear mixed-effects model will be used. Stimulation type will be included as a fixed factor, pre- versus post-stimulation as the time factor, and the relevant PD grouping factor will also be included. The model will include a random intercept for each participant, and model parameters will be estimated using maximum likelihood. F tests or t tests will be used to test the significance of fixed effects and determine the effects of stimulation type, time, and grouping factors on each assessment index. Likelihood ratio tests will be used to assess the contribution of random effects.

All analyses will be performed using SPSS Statistics 27.0 (IBM Corp., USA). Two-sided $p<=0.05$ will be considered statistically significant.

9. Ethics

The clinical study will comply with the Declaration of Helsinki of the World Medical Association and other relevant regulations. Before study initiation, the protocol will be approved by the ethics committee before implementation. Before enrollment, investigators are responsible for fully explaining the study purpose, procedures, potential benefits, and risks to each participant or legally authorized representative. Written informed consent will be obtained. Participants will be informed that they may withdraw from the study at any time. The informed consent form will be retained as a clinical study document for reference. Participant privacy and data confidentiality will be protected throughout the study.

10. Study Personnel

Name	Title/Specialty	GCP training	Role in this trial
Zhengli Di	Chief Physician / Neurology	Yes	Study design
Zhiqin Liu	Chief Physician / Neurology	Yes	Data analysis
Xuejuan Yang	Associate Professor / Biomedical Engineering	No	Device technical support
Gejuan Zhang	Chief Physician / Neurology	No	Participant recruitment
Rong Li	Resident Physician / Biomedical Engineering	No	Participant recruitment and management

11. References

[1] Duty S, Jenner P. Animal models of Parkinson's disease: a source of novel treatments and clues to the cause of the disease. Br J Pharmacol. 2011;164(4):1357-1391.

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Informed Consent Form

Informed Consent Form

Version: V1.0 Version Date: March 3, 2026

Part I. Information Sheet

Dear Patient,

You are invited to participate in a clinical study of non-invasive external trigeminal nerve stimulation (eTNS) for Parkinson's disease. Before deciding whether to participate, please read the following information carefully. It explains the purpose of the study, the study procedures and duration, and the possible benefits, risks, and discomforts associated with participation. You may discuss this information with your family or friends before making your decision. When the investigator explains and discusses this informed consent form with you, you may ask questions at any time and request clarification of anything you do not understand.

[Study Title]

Immediate Effects of External Trigeminal Nerve Stimulation on Motor Dysfunction in Parkinson's Disease

[Study Overview]

Parkinson's disease (PD) is a common neurodegenerative disorder. Its motor symptoms mainly include tremor, rigidity, bradykinesia, and postural and balance impairment. According to the China Parkinson's Disease Report 2025, as of 2021, the number of people with PD in China had reached 5.07 million, accounting for approximately 43.14% of the global PD population; the incidence of PD in China is also higher than the global average. At present, PD cannot be cured. Pharmacotherapy remains the mainstay of treatment. Although medications can improve symptoms in the early stage, motor complications and reduced treatment efficacy may occur as patients age and the disease progresses. Worsening gait impairment not only reduces quality of life but is also closely associated with falls and disability, making it a major challenge in PD management.

Non-invasive eTNS has attracted increasing attention because of its potential to improve motor dysfunction. Animal studies suggest that this therapy may promote intracranial dopamine release and modulate dopaminergic neuronal activity, with potential benefits for both motor and non-motor symptoms of PD. A related device has been cleared by the U.S. Food and Drug Administration as an adjunctive treatment for motor dysfunction caused by multiple sclerosis, supporting a possible mechanism for improving gait and balance.

This study will investigate whether short-term non-invasive eTNS can produce immediate modulatory effects on motor function in PD.

[Summary of Study Procedures]

1. Study design and procedures:

This exploratory clinical trial will compare the short-term efficacy of acute non-invasive eTNS at different stimulation frequencies in patients with PD and identify a preferred stimulation paradigm. This part of the study is designed as an exploratory, randomized, within-subject controlled clinical trial. Patients with idiopathic PD (Hoehn and Yahr stage ≤5) will be recruited. Each participant will receive three stimulation conditions: 120-Hz eTNS, 40-Hz eTNS, and sham stimulation. Each condition will last 20 minutes. Each participant will complete all three stimulation conditions in a single experimental visit, with the order randomized. Instrumented gait analysis and motor rating scales will be used to quantify immediate changes in gait after stimulation relative to

baseline. The study aims to identify the stimulation mode with superior immediate effects on PD-related motor dysfunction. The entire visit will take approximately 2.5–3 hours.

1) Please provide the study physician with information relevant to your eligibility for this study as completely and accurately as possible. The study physician can confirm your participation only if you meet all eligibility requirements. If you choose to participate, you will be asked to sign and date this informed consent form. After enrollment, participants will be randomly assigned to different treatment sequences, and a clinically appropriate study protocol will be provided. After you sign the informed consent form, the investigators will collect demographic information and ask in detail about your medical history, diseases you have had, and family history.

2) If you meet the criteria and are enrolled, baseline clinical data will first be recorded, including but not limited to general personal information, medical history, handedness, medication history, hereditary diseases, and past medical history.

3) You will then undergo the acute stimulation experiment. Instrumented analysis will be used to quantitatively assess gait parameters, together with gait and motor rating scales, to evaluate immediate changes in gait after stimulation compared with baseline. Before the experiment, please take your usual medications as prescribed, so that testing can be conducted in the MED-ON state 1.5–2 hours after administration of antiparkinsonian medication.

2. Inclusion and exclusion criteria:

To participate in this study, you must meet the following criteria:

Idiopathic PD diagnosed by two neurologists according to the Chinese diagnostic criteria for Parkinson’s disease formulated in 2020 by the Chinese Parkinson’s Disease and Movement Disorders Society based on the MDS Clinical Diagnostic Criteria for Parkinson’s disease;

Hoehn and Yahr stage 1–5 in the medication ON state;

Mini-Mental State Examination (MMSE) score >24;

Stable antiparkinsonian medication for at least 1 month before the trial;

Age 40–80 years;

No history of epilepsy, intracranial tumors, or other neurological disorders; no severe psychiatric disorders such as schizophrenia; and no long-term use of antipsychotic medications;

No history of orthopedic or musculoskeletal disorders and no other conditions that may affect balance or gait, such as ophthalmologic disorders;

Ability to cooperate with all assessments and eTNS treatment, and provision of written informed consent.
You must also not meet any of the following criteria:

Secondary parkinsonism or atypical parkinsonian syndromes;

Current use of anticholinergic medications;

Contraindications to non-invasive electrical neuromodulation;

Previous non-invasive eTNS treatment within the past 6 months;

Severe neurological, renal, cardiovascular, hepatic, or other major systemic disease;

Inability to complete clinical assessments or refusal to provide written informed consent**.**

3. Study discontinuation and withdrawal:

The investigator has the right to discontinue your participation in this study under any of the following circumstances: 1) you are found not to meet the eligibility criteria; 2) for your health, the investigator determines that another treatment would be more beneficial to you; 3) other safety factors are identified during the study and you are considered unsuitable for continued participation; 4) discontinuation is required by laws or regulations; or 5) the entire study is terminated.

You have the right to decide freely whether to participate, to be informed, to provide consent, and to withdraw. Participation is voluntary, and withdrawal during the study will not result in any loss of rights or benefits. If you wish to withdraw, your decision will be fully respected. The investigator will make a scientific decision based on your best interests. If you withdraw, you may continue to receive routine medical care from your physician.

[Confidentiality]

Your information will be entered into the database in coded form. The code will not contain any personally identifiable information. All information about you, your family, and your household will be kept confidential, and your privacy and your family's privacy will be protected. However, your study data may be inspected by relevant authorities, including the ethics committee and the food and drug regulatory authority, but the contents will not be publicly disclosed.

[Compensation and Medical Care for Study-Related Injury]

After you sign the informed consent form, all non-invasive eTNS treatments provided as part of this study will be free of charge. Costs related to routine medication treatment will be your responsibility. If you are injured due to the electrical stimulation device, we will provide clinical follow-up until the adverse event resolves, meaning recovery to normal or baseline status, stabilization of the condition, or another status considered reasonable by the investigator. If the adverse event has not resolved by the end of the entire study, we will continue to provide necessary treatment, reporting, and documentation, or provide appropriate compensation or indemnification in accordance with national laws.

[Potential Benefits and Risks]

Potential direct benefits to participants: During the study, your condition may improve substantially, which would be a direct medical benefit of participation. In addition, you will be offered the opportunity to participate free of charge in the research team's subsequent long-course non-invasive eTNS study for PD. You will also be offered free brain magnetic resonance imaging and/or electroencephalography examinations before and after the long-course treatment.

Expected societal benefits: The results from all participants may improve understanding of the efficacy of non-invasive eTNS for PD and contribute useful new information to medicine.

Risks: Non-invasive eTNS is a non-invasive physical therapy and is relatively safe. No related serious adverse reactions have been reported to date. During treatment, you may experience local numbness or tingling of the skin, itching or redness at the electrode site, or similar discomfort. These symptoms generally disappear quickly after reducing the stimulation intensity or pausing treatment. If you experience any discomfort or other unexpected event, please inform your responsible study physician immediately. We will respond carefully and promptly.

[Participant Rights]

If you have any questions or concerns during the study, please contact your study physician, Dr. Rong Li (telephone: 15529957876). This study protocol has been approved by the hospital ethics committee. If there is any violation of the study protocol during the study, participants may file a complaint directly with the Ethics Committee of Xi'an Central Hospital. Telephone: 029-62812604.

[Voluntary Participation]

Your participation in this study is voluntary. You may withdraw at any time and for any reason. If you choose not to participate, your and your family's rights to health care or other services will not be affected. If you have any questions during the study, please contact the investigators.

Part II. Consent Statement

I have carefully read this informed consent form. The study staff have explained it to me in detail and answered my questions. I fully understand the information above and agree to participate in this study.

Participant name/signature (print):	**Date:**
Legally authorized representative name/signature (if applicable, print):	Date: