

Nanjing Drum Tower Hospital

The Affiliated Hospital of Nanjing University Medical School

PROTOCOL TITLE:	
High-frequency transcranial pulsed current stimulation improves quality of life in Parkinson's disease	
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Xu Rong Department of Rehabilitation, Nanjing Drum Tower Hospital	
CONTACT PERSON:	
Li Zheng	
CONTACT NUMBER:	
15952085528	
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Section 1 General Introduction

1.1 Rationale for the Study Purpose and Population

Parkinson's disease (PD) is the second-most common neurodegenerative disorder that affects 2-3% of elderly populations ≥ 65 years of age¹, leading to disability and reduced health-related quality of life (HRQoL) that is found to be most predicted by age, gender, mood, and non-motor impairment.² Clinically, PD is characterized by both motor and non-motor symptoms. The major motor symptoms include rigidity, bradykinesia, tremor, and postural instability³. Non-motor symptoms may include cognitive and psychiatric symptoms (cognitive dysfunction, depression, anhedonia, panic attacks, hallucinations etc), sleep disorders (insomnia, excessive daytime sleepiness, restless leg syndrome, REM behaviour disorder etc), gastrointestinal disorders, sensory symptoms (pain, loss of smell etc) and autonomic dysfunction (bladder incontinence, orthostatic hypotension etc).⁴

According to epidemiological data, both the incidence and prevalence of PD have increased over the past two decades. In 2016, there were approximately 6.1 million people with PD worldwide.⁵ In China, the prevalence of PD among individuals aged 60 years and older is 1.37%⁶, corresponding to an estimated 3.62 million affected individuals nationwide. Multiple health economic analyses indicate that the average annual economic burden per patient is on the order of RMB 20,000–30,000, with direct medical expenses as the major cost component, highlighting the substantial economic impact of PD in China.⁷

Despite the increasing global burden of PD, there is currently no curative treatment. Therapeutic goals focus on reducing disability, slowing disease progression, and optimizing patients' quality of life. Standard care for motor symptoms in PD primarily consists of pharmacological dopaminergic replacement therapies, complemented by non-pharmacological interventions such as exercise, physical therapy, and occupational therapy, which are often recommended as adjunctive treatments. However, as the disease progresses, patients may develop reduced responsiveness to medication, and dopaminergic therapies can lead to motor complications, including dyskinesias and motor fluctuations⁸. Non-motor symptoms are less systematically

addressed in clinical practice and are frequently inadequately controlled by dopaminergic drugs alone⁹, in some cases, these medications may even exacerbate certain non-motor manifestations⁹. Consequently, there remains substantial unmet clinical needs in PD management, supporting the identification of novel and effective therapeutic strategies that are capable of improving both motor and non-motor symptoms, ultimately to reduce disability, disease burden and improve quality of life for individuals with PD.

1.2 Rationale for the Intervention

Brain stimulation using medical devices, both invasive and non-invasive methods, have also been explored as therapeutic options for PD. Deep brain stimulation is an established treatment for refractory motor symptoms¹⁰ in PD, but requires careful patient selection and carries surgical risks. Non-invasive brain stimulation methods including repetitive transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES)¹¹ are less risky options with a good safety profile and have shown beneficial effects on motor manifestations and selected non-motor domains^{12–15}, however responses are highly variable. Additionally, rTMS is limited in scalability due to its reliance on in-clinic delivery. Notably, transcranial direct current stimulation (tDCS), the most extensively investigated tES modality in PD, fail to demonstrate robust advantages over sham in recent meta-analyses¹⁶, underscoring the need to explore other tES modalities.

In recent years, high-frequency transcranial pulsed current stimulation (hf-tPCS) has gained increasing attention in experimental and clinical settings^{17–22}, delivering trains of pulses at predefined high frequencies to modulate cortical excitability^{23,24}. In previous research comparing tPCS to tDCS²⁰, Jaberzadeh stimulated healthy subjects with anodal a-tPCS versus anodal a-tDCS with short (50ms, 1.8Hz) or long (650ms, 0.9Hz) interpulse intervals, adjusting the stimulation time so that the total charge for all three conditions is similar. The results showed that, a-tPCS with short pulse interval had a greater effect on corticospinal excitability in the primary motor cortex compared with tDCS. Although the physiological mechanism of tPCS inducing corticospinal excitability is still unclear, Jaberzadeh hypothesized that tPCS mechanism includes both tonic effect that promotes the the depolarization / hyperpolarization of local resting membrane potential of neurons (similar to tDCS) and phasic effect where the pulses exert a phasic on-off effect on the voltage gated carrier

protein in the neuronal membrane²¹, and collectively induce enhancement in corticospinal excitability. Notably, prior hf- tPCS studies have reported improvements in motor function in PD ¹⁸

Preclinical studies further indicate that high-frequency pulse trains ($\approx 100\text{--}800\text{ Hz}$) can induce axonal conduction block, promote asynchronous firing, and suppress sustained neural activity ^{25–27}, suggesting that hf-tPCS may disrupt abnormal network synchrony. In PD, this is particularly relevant because aberrant cortical–subcortical connectivity ²⁸ and exaggerated beta-band synchrony within basal ganglia–thalamocortical circuits ²⁹ are key pathophysiological features linked to both motor and non-motor symptoms.

A previous head-modeling study comparing tPCS with tDCS ³⁰ reported that tPCS produces stronger electric fields in deeper structures, including the midbrain, pons, insula, thalamus, hypothalamus, and cerebellum, whereas tDCS predominantly modulates cortex directly under the electrodes. This greater depth of engagement is potentially advantageous for PD, in which critical circuits involve subcortical regions such as the basal ganglia, thalamus, and hypothalamus, and may also favor modulation of cerebellar networks that lie farther from the cortical surface.

In terms of safety, tPCS may have an advantage over tDCS due to the inverse relationship between frequency and impedance ³¹. The safety of tPCS had been investigated in healthy humans ^{22,32–36} and in the treatment of Parkinson’s disease ¹⁸ with no adverse events recorded. At present, international safety recommendations for tES dosing in adults generally considers that an output current between 0–2mA, and the single stimulation time is less than 40 minutes is considered relatively safe ³⁷.

1.3 Rationale for the Dose Selection

In this study, 400Hz hf-tPCS electrodes will be applied using two montages:

- (1) the vertex (anode electrode) and the mid cerebellar region (cathode electrode) to modulate the bilateral motor cortex and cerebellar activity implicated in motor functions.
- (2) the left dorsolateral prefrontal cortex (EEG:F3, anode electrode) and the right dorsolateral prefrontal cortex (EEG:F4, cathode electrode) to target the bilateral frontal cortices involved in higher level cognitive functions and limbic circuits underlying mood symptoms.

The current intensity for both montages will be at 1.0 mA, 10 min per montage per session, 5 times per week over 4 weeks, totaling 20 sessions.

Section 2. Hypothesis and Research Objectives

2.1 Hypothesis

We hypothesized that 400 Hz hf-tPCS, delivered as an adjunct to standard dopaminergic therapy, would reduce motor and non-motor symptoms, enhancing health-related quality of life (HRQoL) in individuals with PD.

2.2 Primary Objective

To evaluate the effect of hf-tPCS , combined with standard dopaminergic medication, on improving health-related Quality of Life (HRQoL) patients with Parkinson's disease, measured by the Parkinson's Disease Questionnaire Summary Index (PDQ-39 SI)

2.3 Secondary Objectives

- (1) To evaluate the safety, feasibility and tolerability of hf-tPCS in patients with PD
- (2) To evaluate the effect of hf-tPCS on improving non-motor and motor symptoms in patients with PD.

2.4 Potential Risks

Hf-tPCS may cause skin discomfort or tingling sensation to some people. Some people may have skin redness due to electrical stimulation and headache post stimulation. Treatment-emergent mania and hypomania have been reported in unipolar and bipolar depression treatment in tDCS (another tES modality) trials ³⁸⁻⁴⁰ and drug interactions with tDCS have been reported ^{41,42}, namely, antipsychotics with high D2 affinity such as Haloperidol and Risperidone have been reported to suppress tDCS-induced plasticity ⁴² while benzodiazepines were associated with an increase in depression scores when used in conjunction with tDCS ⁴¹.

2.5 Potential Benefits

hf-tPCS is a portable, scalable non-invasive brain stimulation method that can potentially alleviate non-motor and motor symptoms in patients with PD, ultimately reducing disability and improving quality of life in this medical condition that has presently no curative option.

Section 3. Study Population

3.1 Number and Nature of Subjects to be enrolled

The original protocol (version 1.0) specified a sample size of 72 participants (36 per group) diagnosed with PD according to the 2015 MDS criteria³ and Chinese PD and MDS guidelines⁴³. However, COVID-19 restrictions in Nanjing during 2020–2022 substantially impeded recruitment, and the target enrollment could not be achieved within the initially approved period (January 1, 2021 to January 1, 2022). The recruitment period was therefore extended to March 15, 2023, and the study was re-positioned as a pilot feasibility trial to inform the design of a future fully powered randomized controlled trial.

3.2 Determination of Sample Size

The revised sample size aimed for an analyzable cohort of 30 participants (15 per group), based on prior data in mild to moderate Parkinson's disease using the PDQ-39 as the primary outcome⁴⁴, assuming a standard deviation of 10 points, a two-sided α of 0.05, 80% power, and a clinically meaningful between-group difference of 11 points. Allowing for 20% attrition, the final recruitment target was set at 36 participants (18 per group).

3.3 Criteria for Recruitment and Recruitment Process

The eligible subjects will be those diagnosed with PD according to the 2015 MDS criteria³ and Chinese PD and MDS guidelines⁴³, which requires the presence of bradykinesia plus at least one of the following: resting tremor, rigidity, or postural instability; with a clear levodopa response, and absence of clinical red flags for atypical parkinsonism (e.g., rapid progression, early severe autonomic failure, early dementia). All eligible subjects will be recruited from Nanjing Drum Tower Hospital Outpatient Neurology Clinic and Rehabilitation Center who

receive services and/or medical follow-up. Information about the study and Consent Form will be provided to subjects who show interest to participate.

3.4 Inclusion Criteria

- (1) Age 50 years $\leq$ age $\leq$ 85 years;
- (2) Male or Female;
- (3) Hoehn-Yahr stage 1-3;
- (4) Mini-Mental State Examination (MMSE) score $>$ 24 points
- (5) No changes in oral medications for Parkinson's disease treatment $\geq$ 4 weeks before enrollment, and no changes in the type or dosage of medications during the study period;
- (6) Able to cooperate in study procedures including completing relevant scale assessments;
- (7) Agrees to participate in this trial and signs an informed consent form, and is willing to comply with the trial protocol.

3.5 Exclusion Criteria

- (1) Subjects who participated in other non-invasive brain stimulation clinical trials within 3 months prior to the start of this study or concurrent participation in another clinical trial;
- (2) Subjects with major psychiatric or intellectual disability that prevent them from completing the study according to the clinical trial protocol;
- (3) Subjects with unstable cardiovascular, pulmonary, renal, or cerebrovascular disease: acute myocardial infarction, unstable angina, chronic heart failure grade III-IV, severe arrhythmias such as ventricular tachycardia or ventricular fibrillation, severe carotid artery stenosis, or severe lung or kidney-related diseases;
- (4) Subjects with other neurological or musculoskeletal causes of motor impairment
- (5) Subjects with history of seizures or recent craniotomy; implanted electronic or metallic devices;
- (6) Subjects who have any condition expected to require surgery or intensive medical treatment during the study
- (7) Pregnant women

3.6 Discontinuation/ Withdrawal Criteria

Subject's participation in the study is entirely voluntary. Participants may stop participating in this study at any time. There are other circumstances where the participant will be allowed to withdraw from the study, which includes the following:

- Participant experiences serious side effects of the use of hf-tPCS
- Participant is unable to tolerate of the use of hf-tPCS
- Study closure due to safety concerns or other reasons
- Upon request of the Principal Investigators for other reasons not stated

3.7 Subject Replacement

There will be no subject replacement

3.8 Provisions for dropout cases and handling of missing data

Drop-out definition: Any participant who reports significant adverse effects, is unable tolerate the session, or asked to withdraw by request of the Principal Investigators for other reasons not stated, will be considered drop-out.

A. Dropout criteria:

1. Subjects who entered the randomized trial with informed consent and qualified screening, but failed to complete the 20-day course of treatment and observation period specified in this trial protocol will be considered as dropout cases (including those the study team deems it necessary for the subject to terminate the trial from a medical perspective)
2. Subjects who unilaterally changed the treatment plan midway, such as stopping or reducing dosage of pharmacological therapy or start using new drugs during the trials without the consent of the attending physician will be considered as dropout cases.

B. Handling of missing data:

For subjects who have dropout, the researcher will contact the subjects as soon as possible to ask for the reason for the dropout and make records of the last treatment session. Post-treatment assessments will be completed using actual available data using best effort basis, and where

applicable, statistical imputation and other assumptions will be made for the per protocol-population analyses, defined as participants who completed the intervention and had post-treatment outcome data. All relevant trial data should be properly kept on file for the dropout cases, which may be required for full analysis.

Section 4. Study Design

4.1. Randomization and Allocation

The study will adopt a simple randomization method. A study administrator uninvolved in participant enrollment, intervention delivery, outcome assessment, or data analysis will perform random sampling using IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA) statistical software to generate a random number allocation sequence that divide the numbers randomly into two groups – Group 1 : Active-hf-tPCS Group and Group 2: Sham stimulation Group. The randomization list containing which group each number corresponded to will be entered into a secured database and maintained by the independent study administrator for allocation concealment. These random numbers will then be put into opaque, sealed and identical envelopes with number marked only on the inside of the envelopes.

Subjects who meet criteria will be recruited and randomly allocated according to the selection of the envelopes by each subject, with ratio as follows Active-hf-tPCS Group (18 pax): Sham Group (18 pax). The sealed envelopes will be opened only after baseline assessments to further ensure allocation concealment.

4.2 Screening visits and Procedures

Recruitment will be performed at out-patient neurology clinic and rehabilitation centre at Nanjing Drum Tower Hospital by qualified neurologists and rehabilitation specialists in the study team according to the inclusion/exclusion criteria. The clinicians will collect basic medical and drug history and perform physical examinations as part of screening to determine whether a subject can participate in the study. Female subjects must provide pregnancy test results that was performed at a tertiary-level hospital within the past month.

4.3 Study Visits and Procedures

Visit to Nanjing Drum Tower Hospital	Visit 1	Visit 2-21	Visit 22
Timeline	Week 0	Week 1-4	Week 5
Procedure	Baseline Assessment	Intervention Period	Post-hoc Assessment
¹ Informed Consent	X		
Collect medical and drug history; pregnancy test results , if female	X		
Heart rate , blood pressure and serum test	X		X
² Modified Hoehn and Yahr Scale	X		
³ Mini-Mental State Examination (MMSE)	X		
⁴ Parkinson's Disease Quality of Life Questionnaire-39 (PDQ-39)	X		X
⁵ Movement Disorder Society– Unified Parkinson’s Disease Rating Scale (MDS-UPDRS)	X		X
⁶ Non-Motor Symptoms Scale (NMSS)	X		X
⁷ Hamilton Depression Rating Scale (HAMD)	X		X
⁸ Parkinson Fatigue Scale-16 (PFS-16)	X		X
⁹ Berg Balance Scale (BBS)	X		X

¹⁰ Timed Up and Go Test (TUGT)	X		X
¹¹ Active or Sham tPCS		X	
¹² Concomitant pharmacological therapy	X	X	X
¹³ Safety Adverse Event Form		X	
¹⁴ Multimodal MRI	X		X

¹ **Informed Consent** will be taken at screening visit, i.e. on the same day as when they are identified as a potential participant. Randomization will be performed after consent taking is completed.

² **Modified Hoehn and Yahr Scale (H&Y)** ⁴⁵: Disease stage was classified using the Modified H&Y scale a widely used clinician-rated measure of Parkinson’s disease severity. The scale ranges from Stage 1 (unilateral involvement only) to Stage 5 (wheelchair-bound or bedridden unless aided), with higher stages indicating more advanced disease.

³ **Mini-Mental State Examination (MMSE)** ⁴⁶ : The Mini-Mental State Examination (MMSE) is a widely used, standardized cognitive screening tool that assesses global cognitive function. It evaluates multiple cognitive domains, including orientation, attention and concentration, memory, language, and visuospatial abilities. The MMSE consists of 30 items, with total scores ranging from 0 to 30, where higher scores indicate better cognitive performance. It is commonly used in clinical and research settings to screen for cognitive impairment, monitor changes in cognitive status over time, and assess the effectiveness of interventions targeting cognitive function.

⁴ **Parkinson’s Disease Questionnaire-39 (PDQ-39)** ⁴⁷ :The PDQ-39 is a validated, disease-specific self-report instrument widely used in Parkinson’s disease research. The PDQ-39 comprises 39 items across eight domains: Mobility, Activities of Daily Living, Emotional Well-being, Stigma, Social Support, Cognition, Communication, and Bodily Discomfort. Each item is rated on a 5-point Likert scale (0 = never to 4 = always), with higher scores indicating worse perceived health status. Domain scores and the PDQ-39 Summary Index (PDQ SI) will be calculated according to standard scoring procedures and transformed to a 0–100 scale. The PDQ

Summary Index (PDQ-SI) will be treated as the primary quality-of-life outcome in this study. (see Appendix 1)

⁵ Movement Disorder Society–Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) ⁴⁸ :

The MDS-UPDRS is the current gold-standard instrument used to assess Parkinson’s disease severity, evaluating motor and non-motor manifestations. The MDS-UPDRS comprises four parts: Part I (Non-Motor Experiences of Daily Living), Part II (Motor Experiences of Daily Living), Part III (Motor Examination), and Part IV (Motor Complications), with higher scores indicating greater disease severity. The UPDRS I, evaluating cognitive impairment, thought disorders, mood and behavior and non-motor daily living (includes sleep disorders, fatigue, pain, and urinary or constipation issues) will be used for non-motor symptom assessment and the UPDRS III, evaluating speech and facial expression, rigidity, bradykinesia, tremor, gait and posture and postural stability, will be used for motor symptom assessment in sub-group analysis. The validated **Chinese version of the MDS-UPDRS** ⁴⁹ will be used in this study and performed by trained raters according to the standardized MDS-UPDRS protocol. (see Appendix 2)

⁶ Non-Motor Symptoms Scale (NMSS) ⁵⁰ : The NMSS is a validated instrument for comprehensive evaluation of non-motor manifestations in Parkinson’s disease. The NMSS evaluates symptoms across nine domains, including cardiovascular, sleep/fatigue, mood/cognition, perceptual problems, attention/memory, gastrointestinal, urinary, sexual function, and miscellaneous symptoms. Each item is scored based on frequency (1–4) and severity (0–3), and domain scores are summed to generate a total score ranging from 0 to 360, with higher scores indicating greater non-motor symptom burden. The validated **Chinese version of the NMSS** ⁵¹ will be administered according to standardized procedures, and total scores were used to quantify changes in non-motor symptoms. (see Appendix 3)

⁷ Hamilton Depression Rating Scale (HAMD)⁵²: Depressive symptoms will be assessed using the HAMD, a clinician-administered and validated instrument widely used to evaluate depression severity. The scale consists of 17 items assessing core depressive symptoms, including mood, guilt, insomnia, psychomotor changes, anxiety, and somatic symptoms. Items are rated on either 3-point or 5-point scales, yielding a total score ranging from 0 to 52, with higher scores

indicating more severe depressive symptoms. The validated **Chinese version of the HAMD** ⁵³ will be administered by trained raters following standardized procedures, and total scores were used to evaluate changes in depressive symptom severity. (see Appendix 4)

⁸ **Parkinson Fatigue Scale–16 (PFS-16)**⁵⁴ : Fatigue severity will be assessed using the PFS-16, a validated, disease-specific self-report instrument designed to measure the impact and physical aspects of fatigue in individuals with Parkinson’s disease. The PFS-16 comprises 16 items rated on a 5-point Likert scale (1 = strongly disagree to 5 = strongly agree). The mean score across items is calculated, with higher scores indicating greater fatigue severity. The Parkinson Fatigue Scale-16 (PFS-16) will be administered using the Chinese-language version commonly used in Parkinson’s disease research. (see Appendix 5)

⁹ **Berg Balance Scale (BBS)**⁵⁵: Balance performance will be evaluated using the BBS, a widely used clinical measure of static and dynamic balance. The BBS consists of 14 functional tasks, each scored from 0 to 4, yielding a total score ranging from 0 to 56, with higher scores indicating better balance performance. The **Chinese version of the BBS** ⁵⁶ will be administered by trained assessors following standardized testing procedures. (see Appendix 6)

¹⁰ **Timed Up and Go Test (TUGT)**⁵⁷: Functional mobility will be assessed using physical examination. Participants are asked to sit in a chair with a backrest. If using a walking aid, the participant will hold the aid in their hand, stands up, walks 3 meters in a straight line, turns around, walks to the chair, sits down, and the timing begins the moment they start to stand up. The timing ends when they return to the chair. One practice session is allowed before the formal test. The test is conducted 3 times, with a 1-minute rest in between. The average of the 3 tests is taken for analysis. The time taken to complete the task will be recorded in seconds, with longer times indicating poorer functional mobility. Reference range: ≥ 12 s: Increased risk of falling; < 10 s: Walks freely; < 20 s: Can move independently; 20-29s: Unstable mobility; > 30 s: Difficulty moving.

¹¹ **Active or Sham hf-tPCS:** A high-frequency transcranial pulsed current stimulator (**YQ-D1222; Yiqi Biotechnology Co. Ltd., Beijing, China**) will be used for both active hf-tPCS and sham stimulation group. See Section 5 Trial Material for more information on the device.

¹² **Concomitant pharmacological therapy :** All patients will receive standard anti-parkinsonian medications which may include, including levodopa preparations (e.g., Madopar), dopamine agonists (e.g., pramipexole), anticholinergics (e.g., trihexyphenidyl), and MAO-B inhibitors (e.g., rasagiline).

¹³ **Safety Adverse Event Form:** The safety adverse events form is a standardized hospital SAE reporting form that captures SAEs relating to Active and Sham hf-tPCS, such as mild and severe headache, dizziness, scalp pain, neck pain, nausea and scalp burns.

¹⁴ **Magnetic Resonance Imaging (MRI) examination:** Participants will undergo a multimodal MRI scans at baseline and post-treatment assessments using a 3-Tesla MRI scanner equipped with a standard head coil. The MRI scans include T1-weighted and T2 flair structural MRI sequence.

4.3.1 Baseline Assessment

Clinicians in the study team will be responsible for baseline assessment of all participants, within 1 week before treatment commences. The assessments to be performed include modified H&Y, MMSE, PDQ-39, MDS-UPDRS, NMSS, HAMD, PFS-16, BBS, TUGT. Heart rate, blood pressure and a serum sample test will be performed. Additionally, participants will undergo a multimodal MRI scan at baseline. Clinicians in the study team will also be responsible for recording the occurrence of any safety adverse events throughout the study. Clinicians in the study team are blinded to the group allocation.

4.3.2 Intervention

High-frequency Transcranial Pulsed Current Stimulation (hf-tPCS)

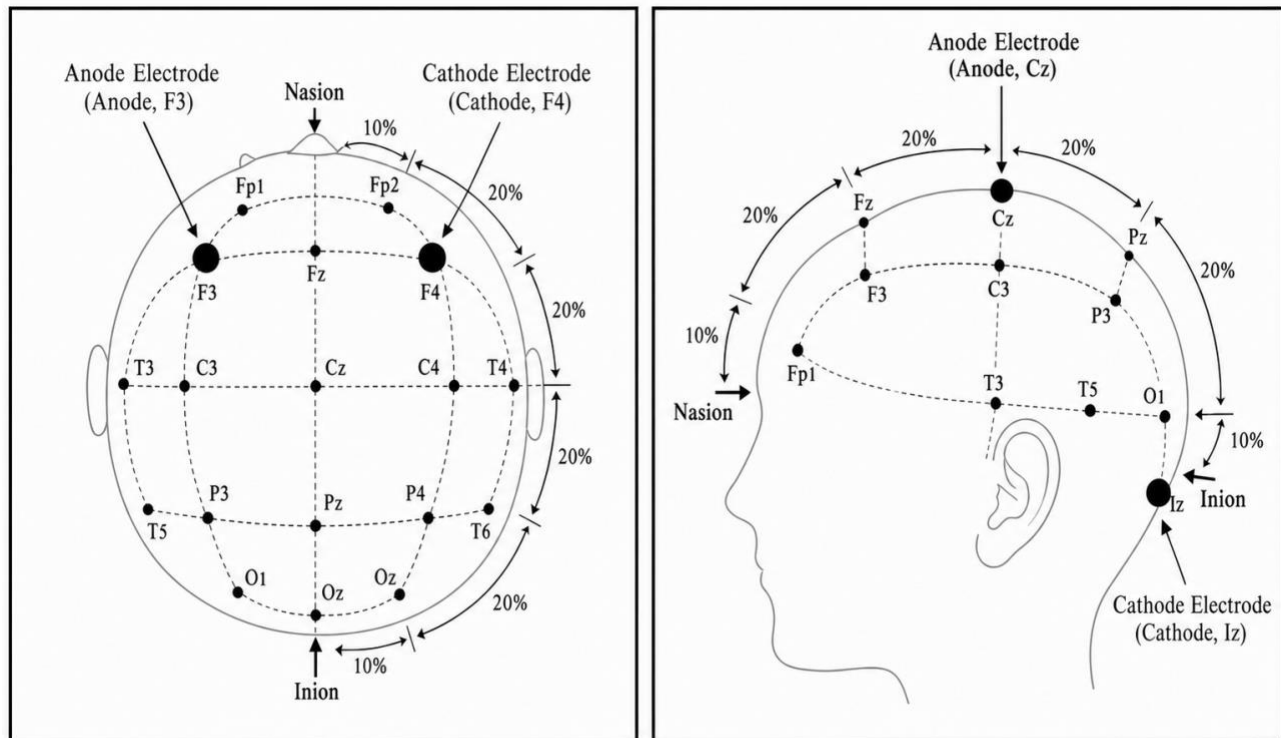
Participants in the active hf-tPCS group will receive 400 Hz stimulation at 1.0 mA for 20 minutes per day, Monday to Friday, over four consecutive weeks (20 in-clinic sessions). Sham participants will follow the same schedule, but stimulation will consist only of a brief ramp-up to 1.0 mA over 10 seconds and ramp-down over 5 seconds, with no current delivered thereafter.

In both groups, stimulation will be delivered with a transcranial pulsed current stimulator (YQ-D1222, Yiqi Biotechnology Ltd., Beijing, China) using circular silver–fiber cotton electrodes (12.56 cm²) pre-soaked in 0.9% saline and secured by an adjustable head strap. Each session will comprise two 10-minute montages separated by a 5-minute interval (total stimulation time 20 minutes/day).

In Montage 1, the anode electrode will be placed over the left dorsolateral prefrontal cortex (EEG: F3) and the cathode electrode over the right dorsolateral prefrontal cortex (EEG: F4) to target cognitive–affective non-motor circuits^{58,59}. In Montage 2, the anode electrode will be positioned at the vertex (EEG: Cz) and the cathode electrode over the midline cerebellar region (EEG: Iz) to engage cerebello–basal ganglia–cortical motor pathways⁶⁰.

In terms of current intensity, in the active-hf-tPCS group, 1 mA current stimulation will be applied for both 10-min block of the montages, that included a 10-s ramp-up to 1 mA and a 5-s ramp-down. In the sham condition, for each 10-min block, current will be ramped up to 1 mA over 10 seconds at the start of the session and then zeroized over 5 seconds. See Figure 1 for electrode placement.

Figure 1. Electrode Montage 1 and 2



Montage 1: Anode: Left Dorsolateral Prefrontal Cortex (EEG: F3); Cathode: Right Dorsolateral Prefrontal Cortex (EEG: F4).
Montage 2: Anode: Mid Motor Cortex (EEG: Cz); Cathode: Mid Cerebellar Region (EEG: Iz).

Concomitant therapy

All participants will continue with their usual anti-parkinsonian medications, including levodopa preparations (e.g., Madopar), dopamine agonists (e.g., pramipexole), anticholinergics (e.g., trihexyphenidyl), and MAO-B inhibitors (e.g., rasagiline) during the intervention period of the 4 weeks, as recommended by their attending physician. Medication dosing are required to be stable for ≥ 4 weeks before enrollment and participants are not permitted to add any new Parkinson's disease medications nor are they allowed to adjust the dosage or interval of any previously prescribed Parkinson's disease medications during the intervention period.

Any side effects of stimulation and other safety adverse event during each treatment session in clinic will be documented and reported in accordance with institutional procedures using standardized hospital SAE reporting forms.

4.3.3 Post-treatment assessment

Within one week after the final treatment session, all participants will return to clinic and undergo the following assessments by blinded clinicians in the study team: PDQ-39, MDR-UPDRS, NMSS, HAMD, PFS-16, Berg Balance Scale, TUGT. Heart rate, blood pressure and a serum sample test will be performed. Additionally, participants will undergo a post-treatment multimodal MRI scan. Recording of safety adverse events beyond the last intervention session in-clinic will be performed at post-treatment assessment.

4.3.4 Lost to follow up

Every reasonable effort will be made to maintain contact with participants throughout the study. Participants who miss scheduled visits will be contacted by telephone, text message, or other approved communication methods to reschedule assessments. At least three attempts will be made to contact participants who fail to attend a scheduled visit before they are considered lost to follow-up.

A participant will be classified as lost to follow-up if all reasonable attempts to establish contact have been unsuccessful and no outcome data can be obtained. The date and reason for loss to follow-up, if known, will be documented in the study records. Data collected up to the point of loss to follow-up will be retained and included in the analysis unless the participant requests otherwise, in accordance with applicable regulations and informed consent provisions. The number of participants lost to follow-up and the reasons, where available, will be reported in the study results and participant disposition flow diagram.

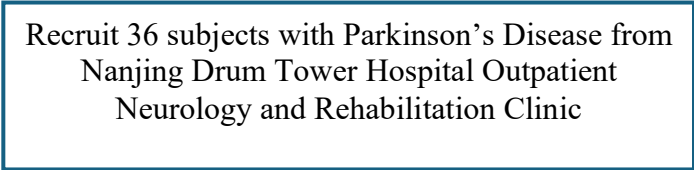
4.4 Blinding

Participants, device operators, outcome assessors, and statisticians will be blinded to treatment allocation throughout the study. Active and sham tPCS devices look identical in appearance and the allocated intervention (active hf-tPCS or sham) are programmed using pre-assigned codes, thereby maintaining operator blinding. Code assignment will be performed by a independent study administrator who is not involved in treatment administration, outcome assessment, or data analysis. To further preserve blinding, participants will be instructed not to discuss their treatment experiences with other participants or study personnel. Participants will complete all treatment sessions in the same treatment environment at a consistent time each day.

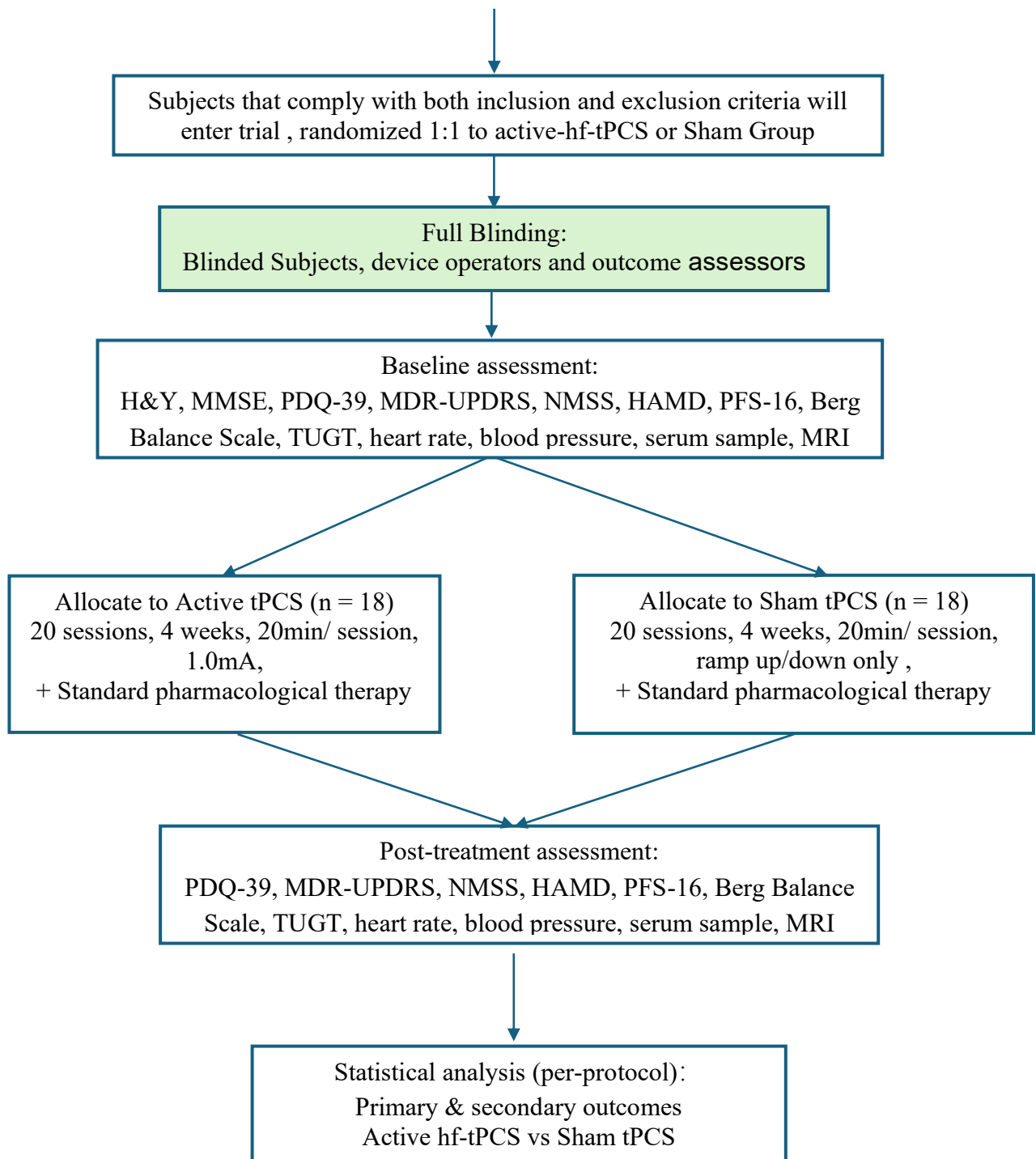
All participants are hf-tPCS naïve and will be receiving hf-tPCS for the first time, hence they will not be aware of the difference between active and sham stimulation and will be informed by the study team that the sensation felt is typical, effectively blinding them to the different treatment conditions.

Outcome assessments both at baseline and post-treatment will be performed by two blinded clinicians (neurologists or rehabilitation physicians) from Nanjing Drum Tower Hospital, with a minimum of five years relevant work experience. The outcome assessors will have no involvement in participant randomization, allocation, or intervention delivery, to ensure integrity of blinding.

4.5 Study Design Flowchart



Recruit 36 subjects with Parkinson's Disease from
Nanjing Drum Tower Hospital Outpatient
Neurology and Rehabilitation Clinic



Section 5: Trial materials

5.1 Trial Product



Device Model : YQ-D1222, Multi-channel Pulsed Current Stimulator, Yiqi Biotechnology Ltd, Beijing, China



5.1.1 Technical Information:

- Waveform: Monophasic rectangular pulse
- Frequency: 400Hz
- Electrode materials: Circular Silver-fiber Cotton Electrodes
- Electrode size: 12.56cm²
- Head Strap Material: Hypoallergenic Velcro Cloth

5.1.2 Regulatory Classification:

National Medical Product Administration (NMPA) of the People's Republic of China, Henan Food and Drug Administration Medical Device Production Permit No. 20150077, Class II, Physical Therapy and Rehabilitation Equipment

Section 6: Study Timeline

- Execution period : : January 1, 2021 – January 1, 2023 , **extended to Jan 1, 2024**
- Recruitment period : January 31, 2021 – January 1, 2022, **extended to March 15, 2023**

Section 7. Safety Measurements

7.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally

associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening.
- requires inpatient hospitalisation or prolongation of existing hospitalisation.
- results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect.

7.2 Safety Monitoring Plan

7.2.1 Observation and Recording of Adverse Events

Any adverse events occurring in participants during the trial must be carefully inquired and investigated. The nature, severity, and relevance to the high-frequency transcranial pulsed current stimulation must be determined for all adverse events. All adverse events of hf-tPCS in all subjects will be logged in the SAE reporting form, and safety of hf-tPCS will be monitored by the principal investigators.

7.2.2 Relevance Assessment: The relevance of adverse events to the high-frequency transcranial pulsed current stimulation is categorized as: definitely related, very likely related, possibly related, and definitely not related. Principal Investigators must determine whether the adverse event is related to the study intervention and provide supporting evidence for this determination.

7.2.3 Severity Assessment: Adverse events are classified into three levels of intensity or severity according to the following criteria:

- Mild: Usually transient and does not affect normal daily activities.
- Moderate: Significant discomfort affecting normal daily life; subjects experience noticeable but tolerable symptoms; treatment does not need to be discontinued.

- Severe: Inability to perform normal daily activities; subjects experience significant and intolerable symptoms; treatment needs to be discontinued.

7.2.4 Management of Adverse Events During and After the Trial:

The Principal Investigator should follow up and record the outcome of all adverse events, tracking subjects who withdraw from the trial due to adverse events and how and when the adverse events are resolved. The Principal Investigators will conduct a cumulative review of all adverse events on a regular basis, and hold an investigator meeting when necessary to evaluate the risks and risks of the study. Serious adverse events and unexpected events are promptly reported to the ethics committee, competent authorities, and sponsors in accordance with regulations.

Potential adverse reactions to the high-frequency transcranial pulsed current stimulation device include:

- Mild discomfort or pain, including mild headache and neck pain, at the electrode site (this may be due to uneven local scalp contact with the electrodes etc) - This can be resolved by pausing treatment and reattaching the electrodes)
- Redness of the scalp at the electrode site- Spontaneous remission is expected within 20 to 30 minutes of stopping stimulation. In severe cases, topical anti-allergy medications can be administered.
- Dizziness, severe headache, nausea, vomiting, severe sweating, scalp burns, palpitations, loss of appetite- Some participants may have experience such symptoms, although rare occurrence is expected - Treatment should be stopped and symptomatic treatment administered to alleviate symptoms.

7.2.5 Emergency Unblinding Procedures:

If a subject experiences a severe adverse event, the Principal Investigator may access the secured database containing the randomization list and corresponding group allocation for emergency unblinding of the subject, recording the reason and date of unblinding in the case record form. Once a subject has been unblinded, the Principal Investigators and study team must discuss and decide whether the subject should withdraw from the study.

7.3 Complaints Handling

If there is any complaint of the hf-tPCS, the Principal Investigator will be informed immediately, address the complaints and rectify the issue. If the complaints are related to participants being unable to tolerate the hf-tPCS, the study will be discontinued.

Section 8. Quality Control and Data Security

8.1 Quality control and quality assurance

All members of the study team will be trained on high-frequency transcranial pulsed current stimulation medical device, whether or not they are the device operators, and will conduct clinical research only after training. Study team members will undergo training for clinical trial procedures, including performing informed consent, patient communication, data handling, SAE handling and maintenance of blinding procedures among the study team.

8.2 Data Security Monitoring

All data will be entered into a secure password-protected document in the desktop. Access to the data will only be open to the study investigators. Hardcopy of the data forms will be stored in a locked cupboard in the department for up to 7 years post-trial.

Section 9. Statistical Methods

9.1 Determination of Sample Size

Please see Section 3.2

9.2 Statistical and Analytical plans

All statistical analyses will be performed using IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA) and R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Analyses will follow the per-protocol principle, defined as participants who completed the intervention and had post-treatment outcome data. Normality will be assessed with the Shapiro–Wilk test and Kolmogorov–Smirnov test at baseline and post-treatment.

Baseline between-group comparisons will be conducted using the Independent sample t-tests, Welch’s two-sample t-test, Wilcoxon rank-sum test, or Wilcoxon rank-sum exact test for continuous or ordinal variables, as appropriate. Pearson’s chi-square test or Fisher’s exact test will be used for categorical variables, as appropriate.

Post-treatment between group comparison will be conducted using analysis of variance (ANOVA) or analysis of covariance (ANCOVA) for normally distributed outcomes, as appropriate; the Wilcoxon rank-sum test or rank-based ANCOVA will be employed for non-normally distributed data, as appropriate. Exploratory within-group pre–post changes will be conducted using the Paired samples t-tests or the Wilcoxon signed-rank test, as appropriate. Exploratory correlations among selected outcomes will be assessed using Pearson Correlation Coefficient, Spearman’s Rank correlation coefficient and Kendall’s Tau, as appropriate.

The number and incident of adverse events will be calculated by grouping and summarized descriptively. Between-group differences in SAE incidence will be evaluated using Pearson’s chi-square test or Fisher’s exact test, as appropriate. All tests will be two-sided with $\alpha = 0.05$. Differences at $p < 0.05$ will be statistically significant and its 95% confidence interval was calculated. Bonferroni correction was applied to adjust for multiple comparison across domain scores, except for Parkinson Disease Questionnaire-Summary Index (PDQ-SI), which is prespecified as the primary outcome of the study

Section 10. Ethical Considerations

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice (GCP) and the applicable regulatory requirements. This final Clinical Trial Protocol, including the final version of

the Participant Information Sheet and Consent Form, must be approved in writing by the Ethics Committee of Nanjing Drum Tower Hospital, prior to enrolment of any patient into the study. The Principal Investigator is responsible for informing the Ethics Committee of Chongqing Western Hospital of any amendments to the protocol or other study-related documents, as per local requirement.

The Clinical Trial will be implemented after the ethics committee approves the trial protocol. Before each subject is enrolled in this study, the investigators are responsible for fully and comprehensively introducing the purpose, procedures and possible risks of this study to the subject or his or her agent, and signing a written informed consent form. Subjects should be informed that they have the right to withdraw from this study at any time, and the informed consent should be retained as a clinical research document for future reference.

10.1 Informed Consent

In obtaining and documenting informed consent, the investigators will comply with the GCP guidelines and to the ethical principles that have their origin in the Declaration of Helsinki. Potential participant will be identified by their attending neurologists in Nanjing Drum Tower Hospital, and if inclusion criteria met, consent will be signed in the presence of a witness. Consent taking will take place in the clinic room or rehab outpatient room. The study investigator will sign the consent and make sure that study information is correctly given to the study participant.

10.2 Confidentiality of Data and Patient Records

All data will be entered into a secure password-protected document in the desktop. The personal privacy and data confidentiality of the subjects will be protected during the research process. Identifiable patient data will be anonymized. Access to the data will only be open to the study investigators. Hardcopy of the data forms will be stored in a locked cupboard in the department for up to 7 years.

Section 11. Publications

Following approval by Ethics Committee of Nanjing Drum Tower Hospital , the study will be registered with the Chinese Clinical Trials Registry (www.chictr.org.cn) by the Principal Investigator. Study results will be published in peer-reviewed scientific literature regardless of the

trial's outcome. The CONSORT 2025 Statement will be adhered to in publication of study findings to ensure that international standards of authorship and publication are met

11.1 Retention of trial documents

All trial documents will be entered into a secure password-protected document in the desktop at Nanjing Drum Tower Hospital, Neurology department. Hardcopy of the data forms will be stored in a locked cupboard in the department for up to 7 years.

Section 12. Funding and Resources

12.1 Grant:

General Topic of Nanjing Health Bureau (YKK21103), Horizontal Project (2020-131-02)
National Natural Science Foundation of China (No.823B2029)

12.2 In Kind:

Yiqi Biotechnology Co. Ltd will supply:

- 2 units of YQ-D1222 hf-tPCS medical devices by Yiqi Biotechnology Co. Ltd.
- 40 pairs of hf-tPCS silver fiber electrodes
- 40 head straps
- 200 bottles of saline solution
- Pre-trial clinician training

Section 13. References

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Principal Investigator Statement:

I agree to abide by the review opinions of the Ethics Committee and start clinical trials after approval, promptly report to the Ethics Committee any changes in clinical trial activities, as well as unexpected issues involving risks to subjects or other personnel, and execute the trial after re-

obtaining ethics review approval. Comply with the requirements of the ethics committee for follow-up review and final review during the study.

I agree to conduct clinical trials in strict accordance with the design and specific regulations of this protocol.

I understand that I may interrupt or terminate this clinical trial at any time if it is in the best interests of the subjects.

I agree that I will personally conduct or supervise this clinical trial and certify that all researchers at my institution who assist me in conducting this clinical trial understand their responsibilities in this clinical trial.

During the execution of this clinical trial, I will strictly abide by current GCP and the Declaration of Helsinki. We also promise that the entire testing process will comply with moral, ethical and scientific principles.

During the execution of clinical trials, I will strictly abide by all laws and regulations related to clinical trials and protect the rights and interests of subjects.

I agree to maintain adequate and accurate medical records and ensure that these medical records are readily available for audit and inspection in accordance with relevant laws and regulations.

Name (Print) Signature Date

Appendix 1: PDQ-39 (Parkinson's Disease Quality of Life Questionnaire)

Due to Parkinson's disease, how often have the following occurred in the past month?

(Never = 0, Occasionally = 1, Sometimes = 2, Often = 3, Always = 4)

1. Mobility

1. Difficulty doing leisure activities?
2. Difficulty looking after your home (e.g., cooking, housework)?
3. Difficulty carrying shopping bags?
4. Difficulty walking 800 meters?
5. Difficulty walking 90 meters?
6. Difficulty moving around the house as you wish?
7. Difficulty getting around in public places?
8. Need someone to accompany you when going out?
9. Afraid or worried about falling in public?
10. Confined indoors? *Score (raw score + percentage)*

2. Activities of Daily Living

1. Difficulty washing yourself?
2. Difficulty dressing yourself?
3. Difficulty fastening buttons or tying shoelaces?
4. Difficulty writing clearly?
5. Difficulty using chopsticks or a spoon to eat?
6. Difficulty drinking from a cup without spilling? *Score (raw score + percentage)*

3. Emotional Well-being

1. Feeling depressed?
2. Feeling lonely or isolated?
3. Feeling like crying or tearful?
4. Feeling angry or bitter?
5. Feeling anxious?
6. Feeling worried about the future? *Score (raw score + percentage)*

4. Stigma

1. Feeling you need to hide your Parkinson's from people?
2. Avoiding eating or drinking in public?
3. Feeling embarrassed in public due to having Parkinson's?
4. Worried about how others will react to you? *Score (raw score + percentage)*

5. Social Support

1. Feeling that your condition has caused problems in your close relationships?

2. Lacking the support you need from your spouse or partner?
3. Lacking the support you need from family or close friends? *Score (raw score + percentage)*

6. Cognition

1. Unexpectedly falling asleep during the day?
2. Difficulty concentrating (e.g., when reading or watching TV)?
3. Feeling that your memory is poor?
4. Having distressing dreams or hallucinations? *Score (raw score + percentage)*

7. Communication

1. Difficulty speaking?
2. Feeling unable to communicate with others properly?
3. Feeling ignored by others? *Score (raw score + percentage)*

8. Bodily Discomfort

1. Experiencing painful muscle cramps or spasms?
2. Experiencing joint or body pain?
3. Experiencing uncomfortable sensations of heat or cold? *Score (raw score + percentage)*

Appendix 2: Unified Parkinson's Disease Rating Scale (UPDRS)

Assessment Time: _____ On/Off State: _____

Part I – Mental, Behavioral and Mood

1. Intellectual Impairment 0 = None 1 = Mild, consistent forgetfulness, partial recollection of events, no other difficulties 2 = Moderate memory loss, disorientation, moderate difficulty solving complex problems, mild but definite impairment at home, occasional encouragement needed 3 = Severe memory loss with time and (often) place disorientation; severe difficulty solving problems 4 = Severe memory loss, only person orientation retained; unable to make judgments or solve problems; requires more assistance

2. Thought Disorder (*due to dementia or drug toxicity*) 0 = None 1 = Vivid dreaming 2 = "Benign" hallucinations with insight intact 3 = Occasional or frequent hallucinations or delusions, without insight; may interfere with daily activities 4 = Persistent hallucinations, delusions, or florid psychosis; unable to care for self

3. Depression 0 = None 1 = Periods of sadness or guilt, more than normal, never sustained for more than one week 2 = Sustained depression lasting more than one week 3 = Sustained depression with autonomic symptoms (insomnia, anorexia, weight loss, loss of interest) 4 = Sustained depression with autonomic symptoms and suicidal thoughts or intent

4. Motivation / Initiative 0 = Normal 1 = Less assertive than usual; more passive 2 = Loss of initiative or interest in elective activities 3 = Loss of initiative or interest in routine daily activities 4 = Withdrawn; complete loss of motivation

Part II – Activities of Daily Living (*Specify "On" or "Off"*)

5. Speech (Receptive) 0 = Normal 1 = Mildly affected; no difficulty being understood 2 = Moderately affected; sometimes asked to repeat 3 = Severely affected; frequently asked to repeat 4 = Frequently unintelligible

6. Salivation 0 = Normal 1 = Slight but definite excess; may have nocturnal drooling 2 = Moderately excessive saliva; may have minimal drooling 3 = Marked excess saliva with drooling 4 = Marked drooling; requires constant tissue or handkerchief

7. Swallowing 0 = Normal 1 = Rare choking 2 = Occasional choking 3 = Requires soft food 4 = Requires nasogastric tube or gastrostomy

8. Handwriting 0 = Normal 1 = Slightly slow or small 2 = Moderately slow or small; all words legible 3 = Severely affected; not all words legible 4 = Most words illegible

9. Cutting Food and Handling Utensils 0 = Normal 1 = Somewhat slow and clumsy but no help needed 2 = Can cut most foods, though slowly and clumsily; some help needed 3 = Requires help cutting food but can feed self slowly 4 = Requires feeding

10. Dressing 0 = Normal 1 = Slightly slow; no help needed 2 = Occasionally needs help with buttons or sleeves 3 = Considerable help needed but can do some things independently 4 = Completely dependent

11. Hygiene 0 = Normal 1 = Slightly slow; no help needed 2 = Needs help with showering/bathing or very slow with hygiene 3 = Requires help washing face, brushing teeth, combing hair, bathing 4 = Requires Foley catheter or other mechanical aids

12. Turning in Bed and Adjusting Bed Clothes 0 = Normal 1 = Somewhat slow and clumsy; no help needed 2 = Can turn independently with great difficulty 3 = Can initiate but cannot complete turning or adjusting sheets 4 = Completely dependent

13. Falling (*unrelated to freezing*) 0 = None 1 = Rare falls 2 = Occasional falls 3 = Average of once daily 4 = More than once daily

14. Freezing When Walking 0 = None 1 = Rare; may have start hesitation 2 = Occasional freezing 3 = Frequent; occasionally falls due to freezing 4 = Frequently falls due to freezing

15. Walking 0 = Normal 1 = Mild difficulty; may not swing arms or tends to drag feet 2 = Moderate difficulty; little or no assistance needed 3 = Severe walking difficulty; requires assistance 4 = Cannot walk at all even with assistance

16. Tremor 0 = None 1 = Slight; not always present 2 = Moderate; bothersome 3 = Severe; interferes with many activities 4 = Marked; interferes with most activities

17. Sensory Complaints Related to Parkinsonism 0 = None 1 = Occasional numbness, tingling, or mild aching 2 = Frequent numbness, tingling, or mild aching; not distressing 3 = Frequent painful sensations 4 = Excruciating pain

Part III – Motor Examination

18. Speech (Expressive) 0 = Normal 1 = Slight loss of expression, diction, or volume 2 = Monotone, slurred but understandable; moderate impairment 3 = Marked impairment; difficult to understand 4 = Unintelligible

19. Facial Expression 0 = Normal 1 = Minimal hypomimia; could be normal "poker face" 2 = Slight but definite abnormal diminution of facial expression 3 = Moderate hypomimia; lips parted some of the time 4 = Masked or fixed face; lips parted ≥ 0.6 cm; completely lost expression

20. Resting Tremor (*face, lips, chin, RUE, LUE, RLE, LLE — rate each separately*) 0 = None 1 = Slight; occasionally present 2 = Low amplitude, persistent; or moderate amplitude, intermittent 3 = Moderate amplitude; present most of the time 4 = Large amplitude; present most of the time

21. Action or Postural Tremor of Hands (*RUE, LUE — rate each separately*) 0 = None 1 = Slight; present with action 2 = Moderate amplitude; present with action 3 = Moderate amplitude; present with action and posture-holding 4 = Large amplitude; interferes with feeding

22. Rigidity (*patient seated and relaxed; assess major joints; rate neck, RUE, LUE, RLE, LLE*) 0 = None 1 = Slight; or only detectable with mirror movements/activation 2 = Mild to moderate 3 = Marked; full range of motion 4 = Severe; range of motion restricted

23. Finger Taps (*thumb-to-index; each hand separately*) 0 = Normal (≥ 15 in 5 sec) 1 = Mild slowing or reduction in amplitude (11–14 in 5 sec) 2 = Moderate impairment; definite early fatigue; occasional pauses (7–10 in 5 sec) 3 = Severe impairment; frequent hesitation or pauses (3–6 in 5 sec) 4 = Can barely perform (0–2 in 5 sec)

24. Hand Movements (*open/close fist; each hand separately*) 0 = Normal 1 = Mild slowing or reduced amplitude 2 = Moderate impairment; definite early fatigue; occasional pauses 3 = Severe impairment; frequent hesitation or pauses at initiation 4 = Can barely perform

25. Rapid Alternating Movements (*pronation/supination; each hand separately*) 0 = Normal 1 = Mild slowing or reduced amplitude 2 = Moderate impairment; definite early fatigue; occasional pauses 3 = Severe impairment; frequent hesitation or pauses 4 = Can barely perform

26. Leg Agility (*heel taps; each leg separately*) 0 = Normal 1 = Mild slowing or reduced amplitude 2 = Moderate impairment; definite early fatigue; occasional pauses 3 = Severe impairment; frequent hesitation or pauses 4 = Can barely perform

27. Arising from Chair (*arms folded across chest*) 0 = Normal 1 = Slow; may need more than one attempt 2 = Pushes self up from arms of seat 3 = Tends to fall back; may require multiple attempts but can arise without help 4 = Unable to arise without assistance

28. Posture 0 = Normal erect 1 = Not quite erect; slightly stooped — could be normal for older person 2 = Moderately stooped; definitely abnormal; may lean slightly to one side 3 = Severely stooped with kyphosis; may lean moderately to one side 4 = Marked flexion; extremely abnormal posture

29. Gait 0 = Normal 1 = Walks slowly; may shuffle with short steps; no festination or propulsion 2 = Walks with difficulty; little or no assistance; some festination, short steps, or propulsion 3 = Severely impaired; requires assistance 4 = Cannot walk even with assistance

30. Postural Stability (*response to sudden backward displacement at shoulders; eyes open, feet apart*) 0 = Normal 1 = Retropulsion; recovers unaided 2 = Absent postural response; would fall if not caught 3 = Very unstable; tends to lose balance spontaneously 4 = Unable to stand without assistance

31. Body Bradykinesia/Hypokinesia 0 = None 1 = Minimal slowing; deliberate; could be normal; amplitude may be decreased 2 = Mild degree of slowness and poverty of movement;

clearly abnormal; or reduced amplitude 3 = Moderate slowness; poverty or small amplitude 4 = Marked slowness; poverty or small amplitude

Part IV – Complications of Therapy

A. Dyskinesias

32. Duration (*proportion of waking day that dyskinesias are present*) 0 = None 1 = 1–25% 2 = 26–50% 3 = 51–75% 4 = 76–100%

33. Disability (*degree of disability from dyskinesias*) 0 = Not disabling 1 = Mildly disabling 2 = Moderately disabling 3 = Severely disabling 4 = Completely disabling

34. Painful Dyskinesias 0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Marked

35. Early Morning Dystonia 0 = Absent | 1 = Present

B. Clinical Fluctuations

36. "Off" periods predictable by dose timing? 0 = No | 1 = Yes

37. "Off" periods unpredictable? 0 = No | 1 = Yes

38. "Off" periods come on suddenly (within seconds)? 0 = No | 1 = Yes

39. Proportion of waking day spent in "Off" state 0 = None | 1 = 1–25% | 2 = 26–50% | 3 = 51–75% | 4 = 76–100%

C. Other Complications

40. Anorexia, nausea, or vomiting? 0 = No | 1 = Yes

41. Sleep disturbances (insomnia or hypersomnia)? 0 = No | 1 = Yes

42. Symptomatic orthostasis? (*record BP, pulse, weight*) 0 = No | 1 = Yes

Total Score: _____

Appendix 3: Non-Motor Symptoms Scale for Parkinson's Disease (NMSS)

#	Symptom	Score
1	Drooling during the day	
2	Reduced or loss of taste or smell	
3	Difficulty swallowing, choking when drinking, or history of choking	
4	Feeling unwell (dizziness)	
5	Constipation (fewer than 3 bowel movements/week) or straining	
6	Fecal incontinence	
7	Feeling that bowels do not empty completely	
8	Difficulty controlling urination, urgency to rush to toilet	
9	Frequent urge to urinate after urinating	
10	Unexplained pain (not from known causes such as arthritis)	
11	Unexplained weight change (not from dieting)	
12	Recent difficulty with memory or forgetfulness	
13	Loss of interest in surroundings or activities	
14	Seeing or hearing things you know are not really there	
15	Difficulty concentrating or staying focused	
16	Feeling sad, low, or depressed	
17	Feeling anxious, frightened, or panicky	
18	Loss of interest in sex or hypersexuality	
19	Difficulty with sexual activity despite trying	
20	Dizziness, lightheadedness, or weakness when standing from lying or sitting	
21	Falls	
22	Feeling drowsy during activities (work, driving, eating)	
23	Difficulty falling asleep or insomnia	
24	Very vivid or frightening dreams	
25	Talking or moving during sleep as if acting out dreams	
26	Unpleasant sensations in legs at night or at rest, with urge to move	
27	Swelling of legs	
28	Excessive sweating	
29	Double vision	
30	Believing something is happening that others say does not exist	

Appendix 4: Hamilton Depression Rating Scale (HAMD)

#	Item	Scoring Criteria	0	1	2	3	4
1	Depressed mood	0=Absent; 1=Only on questioning; 2=Spontaneously reported; 3=Evident in expression/voice without questioning; 4=Almost entirely expressed through non-verbal cues					
2	Guilt	0=Absent; 1=Self-reproach, feels they let people down; 2=Feels they have committed a sin or ruminates on past errors; 3=Believes illness is punishment or has guilt delusions; 4=Guilt delusions with accusatory/threatening hallucinations					
3	Suicide	0=Absent; 1=Life not worth living; 2=Wishes to be dead; 3=Suicidal ideas; 4=Serious suicidal acts					
4	Initial insomnia	0=No difficulty; 1=Complains of difficulty falling asleep (>30 min); 2=Nightly difficulty					
5	Middle insomnia	0=Absent; 1=Restless/disturbed sleep; 2=Waking during the night					
6	Delayed insomnia	0=Absent; 1=Wakes early but can return to sleep; 2=Cannot return to sleep					
7	Work and interests	0=Absent; 1=Only reported on questioning; 2=Spontaneous loss of interest in activities; 3=Less than 3 hours of activity in hospital; 4=Stopped working; unable to do ward activities without help					
8	Psychomotor retardation	0=Normal; 1=Slight retardation; 2=Obvious retardation; 3=Interview difficult; 4=Complete stupor					
9	Agitation	0=None; 1=Slight restlessness; 2=Obvious restlessness or fidgeting; 3=Cannot sit still; 4=Hand-wringing, hair/lip biting					
10	Anxiety (psychic)	0=None; 1=On questioning; 2=Spontaneous; 3=Evident from expression; 4=Obvious panic					
11	Anxiety (somatic)	Physiological symptoms: dry mouth, bloating, diarrhea, palpitations, headache, hyperventilation, urinary frequency, sweating. 0=Absent; 1=Mild; 2=Moderate; 3=Severe; 4=Incapacitating					
12	Gastrointestinal symptoms	0=None; 1=Reduced appetite but eats without encouragement; 2=Needs prompting or laxatives/digestive aids					
13	General somatic symptoms	0=Absent; 1=Heaviness in limbs, back, head; muscle aches; fatigue; 2=Clearly present					
14	Sexual symptoms	Reduced libido, menstrual disturbances. 0=Absent; 1=Mild; 2=Severe; N/A if not applicable					
15	Hypochondriasis	0=Absent; 1=Over-concern with body; 2=Repeated health concerns; 3=Hypochondriacal delusions; 4=Delusions with hallucinations					
16	Weight loss	A (history): 0=No loss; 1=Probable loss; 2=Definite loss. B (measured): 0=<0.5 kg/week; 1=>0.5 kg/week; 2=>1 kg/week					

#	Item	Scoring Criteria	0	1	2	3	4
17	Insight	0=Acknowledges depression; 1=Acknowledges illness but blames diet/environment/overwork; 2=Completely denies being ill					
Total Score							

Appendix 5: Parkinson Fatigue Scale (PFS-16)

For each of the 16 items below, rate from: Strongly Disagree (1) / Disagree (2) / Neither Agree nor Disagree (3) / Agree (4) / Strongly Agree (5)

#	Statement	Score
1	I need to rest during the day.	
2	Fatigue limits my activities.	
3	I tire more easily than other people.	
4	Fatigue is one of my worst symptoms.	
5	I feel completely exhausted.	
6	Fatigue makes me less sociable.	
7	Fatigue makes things take longer to accomplish.	
8	I feel heavy.	
9	I could do more if I were not fatigued.	
10	Everything I do is an effort.	
11	I feel fatigued most of the time.	
12	I feel my energy is completely drained.	
13	Fatigue makes daily life difficult.	
14	I feel fatigued even without doing anything.	
15	Due to fatigue, I do less during the day than usual.	
16	Due to fatigue, I want to lie down and rest at any time and anywhere.	
Total Score		

Appendix 6: Berg Balance Scale (BBS)

Test Item	Instructions	Scoring Criteria	Score
1. Sitting to Standing	"Please stand up; try not to use your hands."	4 = Stands independently without using hands and is stable; 3 = Stands using hands independently; 2 = Stands using hands after several attempts; 1 = Needs minimal help to stand or stabilize; 0 = Needs moderate to maximal assistance	
2. Standing Unsupported	"Please stand for 2 minutes without holding on."	4 = Safely stands 2 min; 3 = Stands 2 min with supervision; 2 = Stands 30 sec unsupported; 1 = Needs several attempts; 0 = Cannot stand 30 sec	
3. Sitting Unsupported (feet on floor)	"Sit with arms folded for 2 minutes."	4 = Sits safely 2 min; 3 = Sits 2 min with supervision; 2 = Sits 30 sec; 1 = Sits 10 sec; 0 = Cannot sit 10 sec without back support	
4. Standing to Sitting	"Please sit down."	4 = Sits safely with minimal use of hands; 3 = Controls descent using hands; 2 = Uses back of legs against chair to control descent; 1 = Sits independently but uncontrolled descent; 0 = Needs help to sit	
5. Transfers	Set up chairs for transfer		

经颅脉冲电刺激改善帕金森病患者的健康相关 生活质量：一项双盲、随机、真假刺激对照的 先导性研究

临床研究方案

课题来源：徐蓉

课题编号：ZR175-2021

负责人：徐蓉

承担科室：康复医学科

联系人：李政

联系电话：15952085528

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南京大学医学院附属鼓楼医院制

方案摘要

项目名称	经颅脉冲电刺激改善帕金森病患者的健康相关生活质量：一项双盲、随机、真假刺激对照的先导性研究
研究目的	先导性研究经颅脉冲电刺激对原发性帕金森病治疗的有效性和安全性
研究设计	采用单中心、双盲、随机、真假刺激对照试验设计
病例总数	使用临床试验1：1对照、20%富余的原则，总病例数选定为36例，试验组与对照组各18例
病例选择	入选标准 （1）符合2016年版中国帕金森病的诊断标准； （2）年龄（50岁≤年龄≤85岁）； （3）性别不限； （4）Hoehn-Yahr分期 1~3期； （5）MMSE评分>24分； （6）在入组前 4 周内，帕金森病治疗的口服药物没有变化，在整个研究期间，药物的种类或剂量也没有任何改变； （7）可顺利配合完成相关量表评估； （8）同意参加本试验并签署知情同意书，愿意服从本试验方案。
	排除标准 （1）在本研究开始前 3 个月内曾参与过其他非侵入性脑刺激临床试验的受试者，或同时参与过其他临床试验的受试者； （2）患有严重精神疾病或智力障碍，且根据临床试验方案无法完成本研究的受试者；

	(3) 患有不稳定的心血管、肺部、肾脏或脑血管疾病: 急性心肌梗死、不稳定型心绞痛、慢性心功能不全III~IV级、严重心律失常(如室性心动过速或室颤)、严重的颈动脉狭窄或严重的肺部或肾脏相关疾病的受试者; (4) 有其他神经或肌肉骨骼导致运动障碍原因的受试者; (5) 有癫痫病史或近期接受过颅骨手术的受试者, 植入了电子或金属装置的受试者; (6) 在研究期间预计需要手术或重症医疗治疗的受试者; (7) 孕妇。
治疗方案	(1) 真刺激-tPCS组: 试验组采用易奇YQ-D1222设备。频率400Hz的单向正脉冲方波, 使用两对金属导电电极接触头部。 a. 受试者的头部需要使用生理盐水完全打湿, 然后再放上金属电极。如果头部有破损, 需要离开破损处2cm的距离。 b. 在方案1中, 阳极电极将置于左侧背外侧前额叶皮层(脑电图定位: F3), 阴极电极置于右侧背外侧前额叶皮层(脑电图定位: F4), 以靶向调控认知-情感非运动环路。在方案2中, 阳极电极将定位于颅顶中央(脑电图定位: Cz), 阴极电极置于小脑中上部中线区(脑电图定位: Oz正下方的Iz), 以激活小脑-基底节-皮质运动通路。 (2) 假刺激-tPCS组: 导电电极安置方案同真刺激组, 但刺激仅包括 10秒内缓慢升至 1.0mA, 然后在 5 秒内缓慢下降, 之后不再有电流输出。治疗时间整体为20分钟, 其中方案1刺激10分钟, 方案2刺激10分钟, 每天1次, 每周5次, 2周为一个疗程, 共2个疗程。

疗效评定	有效性评价指标（主要疗效指标和次要疗效指标） （1）主要疗效指标：帕金森病生活质量问卷（PDQ-39） （2）次要疗效指标：统一帕金森病评定量表（MDS-UPDRS）、帕金森病非运动症状评价量表（NMSS）、汉密尔顿抑郁量表（HAMD）、帕金森疲劳量表（PFS-16）、平衡量表（BERG）、起立-行走计时测试（TUGT）、头颅MRI神经影像学数据。
	安全性评价指标 （1）生命体征观察； （2）不良事件。
统计方法	病例报告表的数据采用双人双份录入，经核查确认无误后锁定数据库。所有统计分析将采用 IBM SPSS Statistics 23.0（IBM Corp., Armonk, NY, USA）及 R 软件 4.2.2 版本（R Foundation for Statistical Computing, Vienna, Austria）完成。分析遵循方案分析（per-protocol, PP）原则，纳入标准为完成干预且具备治疗后结局数据的受试者。基线及治疗后数据的正态性将通过 Shapiro - Wilk 检验与 Kolmogorov - Smirnov 检验进行评估。 组间基线比较中，针对连续变量或有序变量，将根据数据特征选择独立样本 t 检验、Welch 两样本 t 检验、Wilcoxon 秩和检验或 Wilcoxon 秩和精确检验；针对分类变量，则根据实际情况选用 Pearson 卡方检验或 Fisher 精确检验。 治疗后组间比较：针对正态分布的结局指标，将依据数据特征选用方差分析（ANOVA）或协方差分析（ANCOVA）；针对非正态分布数据，则根据实际情况采用 Mann - Whitney U 检验或基于秩的协方差分析（rank-based ANCOVA）。组内治疗前后变化的探索性分析：将根据数据分布特征，选择配对样本 t 检验或 Wilcoxon 符号秩检验。所选结局指标间的探索性相关性分析：将依据变量类型及分布特征，选用

	Pearson 相关系数、Spearman 等级相关系数或 Kendall's Tau 进行评估。 不良事件的发生例数及发生率将按组进行描述性统计分析。严重不良事件（SAE）的组间发生率差异，将依据数据特征采用 Pearson 卡方检验或 Fisher 精确检验进行比较。所有检验均为双侧检验，检验水准 α 设定为 0.05。当 $P<0.05$ 时，差异具有统计学意义，并计算其 95%置信区间。对于各领域评分的多重比较，除预先指定为研究主要疗效指标的帕金森病生活质量问卷（PDQ-39）外，其余均采用 Bonferroni 校正进行调整。
研究期限	2021-1 至 2024-1

一、研究背景

1、改善帕金森病患者健康相关生活质量的研究意义

帕金森病（PD）是仅次于阿尔茨海默病的第二常见神经退行性疾病，影响着 65 岁及以上老年人群体中的 2~3%^[1]，会导致残疾以及健康相关生活质量（HRQoL）的下降^[2]。帕金森病临床表现为运动性和非运动性症状。主要的运动性症状包括僵硬、运动迟缓、震颤和姿势不稳^[3]。非运动性症状可能包括认知和精神症状（认知功能障碍、抑郁、欣快感缺失、恐慌发作、幻觉等）、睡眠障碍（失眠、白天过度嗜睡、不安腿综合征、快速眼动睡眠行为障碍等）、胃肠疾病、感觉症状（疼痛、嗅觉丧失等）以及自主神经功能障碍（尿失禁、体位性低血压等）^[4]。

据统计数据显示，PD 的发病率和患病率在过去 20 年迅速上升。2016 年，全世界约有 610 万 PD 患者^[5]。中国 60 岁以上人群 PD 的患病率约为 1.37%^[6]，这意味着全国约有 362 万患者。多项健康经济分析结果表明，每位患者的平均年经济负担约为 2 ~ 3 万元人民币，其中直接医疗费用是主要成本组成，这突显了帕金森病在我国造成的巨大经济影响^[7]。

尽管全球范围内 PD 的患病率不断增加，但目前尚无根治性方法。治疗目标在于减轻残疾程度、延缓病情进展以及提高患者生活质量。临床上，帕金森病的标准治疗主要包括药物类多巴胺能药物替代疗法，辅以非药物干预措施，如运动训练、物理治疗和作业治疗等辅助治疗手段。然而，随着病情的发展，患者可能会对药物反应减弱，而长期多巴胺能药物治疗可能会导致运动并发症，包括运动障碍和运动波动等现象^[8]。非运动症状在临床实践中较少得到系统性处理，且往往仅靠多巴胺类药物难以得到充分控制，在某些情况下，药物甚至可能会加重某些非运动症状的表现^[9]。因此，帕金森病的治疗方面仍存在大量未得到满足的临床需求，这促使我们去寻找更有效的治疗策略，这些策略能够改善患者的运动和运动非运动症状，最终以减轻帕金森病患者的残疾程度、疾病负担，并提高其生活质量。

2、干预措施的依据

利用医疗设备（包括侵入式和非侵入式方法）进行大脑刺激也被用于帕金森病的临床治疗和研究。脑深部电刺激术（DBS）是治疗帕金森病难治性运动症状的成熟疗法^[10]，但需要进行严格地患者筛选，且存在手术风险。非侵入式大脑刺激方法，如重复经颅磁刺激（rTMS）和经颅电刺激（tES）^[11]，风险较低，安全性良好，并对患者的运动功能障碍和某些非运动功能障碍显示出有益效果^[12-15]，但治疗对患者的反应

性差异很大,且 rTMS 的治疗使用扩展性受到其依赖于院内使用的限制。值得注意的是,目前应用于帕金森病中研究最广泛的 tES 方式中,经颅直流电刺激(tDCS)在最近的荟萃分析中未能证明其优于假刺激^[16],这突显了探索其他 tES 方式的必要性和迫切性。

近年来,高频经颅脉冲电刺激(hf-tPCS)在实验和临床环境中受到了越来越多的关注^[17-22],它通过设定的高频脉冲序列来调节大脑皮层的兴奋性^[23,24]。之前针对 tPCS 与 tDCS 进行比较的研究中^[20],Jaberzadeh 在健康受试者中进行阳极 a-tDCS 及脉冲间隔短(50ms, 1.8Hz)或长(650ms, 0.9Hz)的阳极 a-tPCS 的刺激,并通过调整刺激时间使得所有三种情况的总电荷相似。结果表明,短脉冲间隔的 a-tPCS 对初级运动皮层的皮质脊髓兴奋性的影响比 tDCS 更大。尽管 tPCS 诱导皮质脊髓兴奋性的生理机制仍不清楚,但 Jaberzadeh 假设 tPCS 的机制包括两种效应:1)促进神经元局部静息膜电位去极化/超极化的持续效应(类似于 tDCS),2)脉冲对神经元膜上的电压门控载体蛋白产生阶段性开-关效应^[21],从而共同增强皮质脊髓兴奋性。值得注意的是,此前的 hf-tPCS 研究已表明,该疗法能够改善帕金森病患者的运动功能^[18]。

临床前基础研究进一步证明,高频率脉冲序列($\approx 100 - 800$ Hz)能够导致轴突传导阻滞、促进异步放电,并抑制持续的神经活动^[25-27]。这表明 hf-tPCS 可能是通过破坏异常的网络同步性来起到临床治疗作用的。在帕金森病中,这一点尤为重要,因为异常的皮层-海马-皮层回路^[28]以及基底神经节-丘脑-皮层回路^[29]内 β 频段同步性的过度增强是与运动和非运动症状都相关的关键病理生理特征。

一项比较 tPCS 与 tDCS 的研究表明,tPCS 在更深的脑结构中(包括中脑、脑桥、岛叶、丘脑、下丘脑和小脑)能产生更强的电场,而 tDCS 主要作用于电极下方的皮层区域^[30]。这种更深程度的介入可能对 PD 有优势,因为关键的电路涉及皮层下区域,如基底神经节、脑桥和下丘脑,并且也可能有利于对距离皮层表面更远的小脑网络的调节。

在安全性方面,tPCS 可能比 tDCS 更具优势,这是因为频率与阻抗之间存在反比关系^[31]。tPCS 的安全性已在健康人群^[22, 32-36]以及帕金森病治疗^[18]中得到验证。目前,针对成年人 tES 剂量的国际安全建议通常认为,输出电流在 $0 \sim 2$ mA 之间,单次刺激时间少于 40 分钟被认为是相对安全的^[37]。

3、剂量选择的依据

在本研究中, 将应用 400Hz 的 hf-tPCS, 使用两种电极组合进行治疗:

(1) 颅顶中央(脑电图定位: Cz, 阳极电极)和小脑中上部中线区(脑电图定位: Oz 正下方的 Iz, 阴极电极), 以调节与运动功能相关的双侧运动皮层和小脑活动。

(2) 左背外侧前额叶皮层(脑电图: F3, 阳极电极)和右背外侧前额叶皮层(脑电图: F4, 阴极电极), 以针对涉及高级认知功能的双侧额叶皮层以及情绪症状所涉及的边缘回路。

本次实验中, 两个电极的电流强度均为 1.0 mA, 每次干预总时间 20 分钟, 每种组合刺激 10 分钟, 每周进行 5 次, 持续 4 周, 总计 20 次。

4、科学研究假说

我们假设, 将 400 Hz 的 hf-tPCS 联合药物作为 PD 患者的治疗方案, 可减轻 PD 患者的运动和非运动症状, 从而提高与健康相关的生活质量(HRQoL)。

二、研究目的

1、主要研究目标

评估 hf-tPCS 联合药物治疗对 PD 患者健康相关生活质量(HRQoL)的影响, 以帕金森病问卷总结指数(PDQ-39 SI)作为评估指标。

2、次要研究目标

- (1) 评估 hf-tPCS 在帕金森病患者中的安全性、可行性和耐受性
- (2) 评估 hf-tPCS 对帕金森病患者非运动症状和运动症状改善的效果。
- (3) 通过头颅 MRI 神经影像学数据探究 hf-tPCS 对帕金森病患者治疗的可能机制。

三、随机化方案和盲法

试验单位采用简单随机化方法, 统计师和实验设计者参与分组, 由统计师采用随机数字表获得随机数字, 作出分组(真刺激组和假刺激组)规定, 由实验设计者确定各亚组的处理方案。随机号、组别标记的分配表和组别标记的处理方案一式三份, 分别由实验设计者和统计师保存。实验设计者、统计师均不参加临床试验操作。临床医师负责按纳入标准招募受试对象, 按就诊先后次序分配序列号, 受试对象姓名和序列号由临床医师负责记录并保管; 康复治疗师负责按照分配序列号和组别标记的处理方

案实施康复治疗干预；临床医师负责所有受试者的查体和各项量表的评估并记录各种不良事件的发生及结局。主要终点指标测量完毕后由其他统计师在盲态下对数据进行分析，并提交实验设计者以分析试验结果并完成试验报告。

所有受试者均采用同一型号机器进行治疗，机器设定不同程序，程序分别设定为：根据简单随机化分组结果，真刺激组受试者给予固定脉宽 140us,频率 400Hz 的单向正脉冲方波进行经颅脉冲电治疗，其中一对电极的阳极电极放置于初级运动皮层 Cz 位置，阴极电极放置在小脑中上部中线区（Iz），治疗 10 分钟；另一对电极阳极电极放置在 F3 上，阴极电极放置在 F4 上，治疗 10 分钟。假刺激组给予导电电极同样安置方案，但设置电极在前 10s 有电流刺激，10s 后刺激电流为 0。治疗师告诉所有受试者治疗中没有特殊感觉，所有治疗在一个安静的独立空间，不同受试者间隔 15 分钟以上，避免相互交流。

鉴于本研究性质已调整为先导性研究（Pilot Study），样本量是根据 PDQ-39 量表计算得出的，假设标准差（SD）为 10 分，这是基于先前关于轻度至中度帕金森病的数据得出的结论。在双侧 $\alpha = 0.05$ 、80%的样本量效能以及预期的 PDQ -39 量表临床有意义的组间差异为 11 分的基础上，每组需要 15 名参与者。考虑到 20% 的失访率，目标入组人数增加到每组 18 名参与者（总样本量为 36）。

四、研究人群

1、入组对象的数量及类型

原始方案（版本 1.0）规定样本量为 72 名参与者（每组 36 名），这些参与者依据 2015 年 MDS 标准^[3]及 2016 版中国 PD 诊断标准^[43]来确诊帕金森病。然而，2020 年至 2022 年期间南京地区的新冠疫情限制措施极大地阻碍了招募工作，目标招募人数未能在最初批准的期间内（2021 年 1 月 1 日至 2022 年 1 月 1 日）完成。因此，招募期延长至 2023 年 3 月 15 日，并且该研究重新定位为一项先导性研究，为未来进行有效的随机对照试验的设计提供参考依据。

2、样本量确认

修订后的样本量旨在形成一个可进行分析的 30 人研究群体（每组 15 人），这是基于针对轻度至中度帕金森病的先前研究数据（以 PDQ-39 作为主要指标）得出的结论^[44]，假设标准差为 10 分，双侧 α 值为 0.05，80%的样本量，以及临床有意义

的组间差异为 11 分。考虑到 20%的流失率，最终的招募目标设定为 36 名参与者（每组 18 名）。

3、入组筛查流程

符合条件的受试者需符合 2015 年 MDS 标准^[3]及 2016 年中国帕金森病和运动障碍指南^[43]的诊断标准，同时没有非典型帕金森病的临床症状标志（如快速进展、早期严重自主神经功能障碍、早期痴呆）。所有符合条件的受试者将从南京鼓楼医院神经内科门诊和康复中心招募，这些受试者已接受服务和/或医疗随访。有关研究的信息和同意书将提供给有兴趣参与的受试者。

4、入选标准

- （1）符合2016年版中国帕金森病的诊断标准；
- （2）年龄（50岁≤年龄≤85岁）；
- （3）性别不限；
- （4）Hoehn-Yahr分期 1~3期；
- （5）MMSE评分>24分；
- （6）在入组前 4 周内，帕金森病治疗的口服药物没有变化，在整个研究期间，药物的种类或剂量也没有任何改变；
- （7）可顺利配合完成相关量表评估；
- （8）同意参加本试验并签署知情同意书，愿意服从本试验方案。

5、排除标准

- （1）在本研究开始前 3 个月内曾参与过其他非侵入性脑刺激临床试验的受试者，或同时参与过其他临床试验的受试者；
- （2）患有严重精神疾病或智力障碍，且根据临床试验方案无法完成本研究的受试者；
- （3）患有不稳定的心血管、肺部、肾脏或脑血管疾病：急性心肌梗死、不稳定型心

绞痛、慢性心功能不全III~IV级、严重心律失常（如室性心动过速或室颤）、严重的颈动脉狭窄或严重的肺部或肾脏相关疾病的受试者；

（4）有其他神经或肌肉骨骼导致运动障碍原因的受试者；

（5）有癫痫病史或近期接受过颅骨手术的受试者，植入了电子或金属装置的受试者；

（6）在研究期间预计需要手术或重症医疗治疗的受试者；

（7）孕妇。

6、退出标准

受试者参与本研究完全是自愿的。参与者可在任何时候停止参与本研究。还有其他情况下允许参与者退出研究，具体包括以下情况：

- ☐ 参与者因使用 hf-tPCS 而出现严重的副作用
- ☐ 参与者无法耐受使用 hf-tPCS
- ☐ 因安全问题或其他原因导致研究终止
- ☐ 应主要研究者的要求出于未提及的其他原因退出研究

7、针对脱落的处理及缺失数据的处理办法

脱落定义：任何报告出现严重不良反应、无法耐受该实验环节，或因未说明的其他原因被主要研究者要求退出的参与者，都将被视为脱落。

A 脱落标准：1.在获得知情同意并通过资格筛查后参与随机试验的受试者，若未能完成本试验方案中规定的 20 天治疗及观察期，则将被视为脱落病例（包括研究团队从医学角度认为受试者有必要终止试验的情况）。2.那些中途擅自更改治疗方案的受试者，比如在试验过程中停止或减少药物治疗的剂量，或者在未获得主治医生同意的情况下开始使用新药物，都将被视为脱落病例。

B 缺失数据的处理：

对于中途退出的受试者，研究人员应尽快与他们取得联系，询问退出的原因，并记录最后一次治疗情况。在可用数据允许的情况下，将使用最佳努力原则完成治疗后的评估，并在适用的情况下，为符合方案人群的分析（定义为完成干预且有治疗后结果数据的参与者）进行统计推断和其他假设。所有相关的试验数据都应妥善保存在档

案中，以备退出病例的完整分析之用。

五、研究设计

1、研究流程及随访图

	Visit1	Visit2	Visit3
时间	0 周	1-4 周	5 周
流程	基线评估	干预阶段	干预后评估
知情同意	X		
收集既往史、药物治疗	X		
心率、血压	X		X
改良版 H&Y 分期	X		
MMSE	X		
PDQ - 39	X		X
MDS-UPDRS	X		X
NMSS	X		X
HAMD	X		X
PFS-16	X		X
BERG	X		X
TUGT	X		X
真/假刺激 tPCS		X	
联合药物使用	X	X	X
安全不良事件表		X	
多模态 MRI	X		X

(1) 基线评估

研究团队中的临床医生将负责对所有参与者进行基线评估，评估将在治疗开始前 1 周内进行。所进行的评估包括改良的 H&Y 分期、MMSE、PDQ-39、MDS-UPDRS、NMSS、HAMD、PFS-16、BERG、TUGT。并进行心率、血压监测。此外，参与者在基线阶段还将接受多模态磁共振成像扫描。研究团队中的临床医生还将负责记录整个研究期间任何安全不良事件的发生情况。研究团队中的临床医生对组别分配情况保持保密。

(2) 干预

高频经颅脉冲电刺激

参与高频经颅脉冲电刺激（真刺激-tPCS 组）的受试者将每天接受 400 Hz、1.0mA 刺激，持续 20 分钟，从周一至周五，共持续四周（20 次门诊治疗）。假刺激组的

受试者将遵循相同的日程安排,但刺激仅包括 10 秒内缓慢升至 1.0mA,然后在 5 秒内缓慢下降,之后不再有电流输出。

在两组实验中,刺激均通过一种经颅脉冲电刺激器(YQ-D1222,易奇生物技术有限公司,中国北京)进行,使用的是圆形银纤维棉电极(面积 12.56 mm²),这些电极事先浸泡在 0.9%的生理盐水中,并通过可调节的头带固定。每次刺激过程包括两个 10 分钟的阶段,中间间隔 5 分钟(每天总刺激时间 20 分钟)。

在方案 1 中,阳极电极置于 F3,阴极电极置于 F4,以靶向调控认知-情感非运动环路^[58,59]。在方案 2 中,阳极电极置于 Cz,阴极电极置于 Iz,以激活小脑-基底节-皮质运动通路^[60]。

在电流强度设置上,真刺激-tPCS 组中,两个 10 分钟的刺激阶段均采用 1 mA 电流刺激,包含 10 秒的电流上升(从零递增至 1 mA)和 5 秒的电流下降(从 1 mA 递减至零)过程。在假刺激条件下,每个 10 分钟阶段开始时,电流先在 10 秒内升至 1 mA,随后在 5 秒内归零。电极放置方式详见图 1。

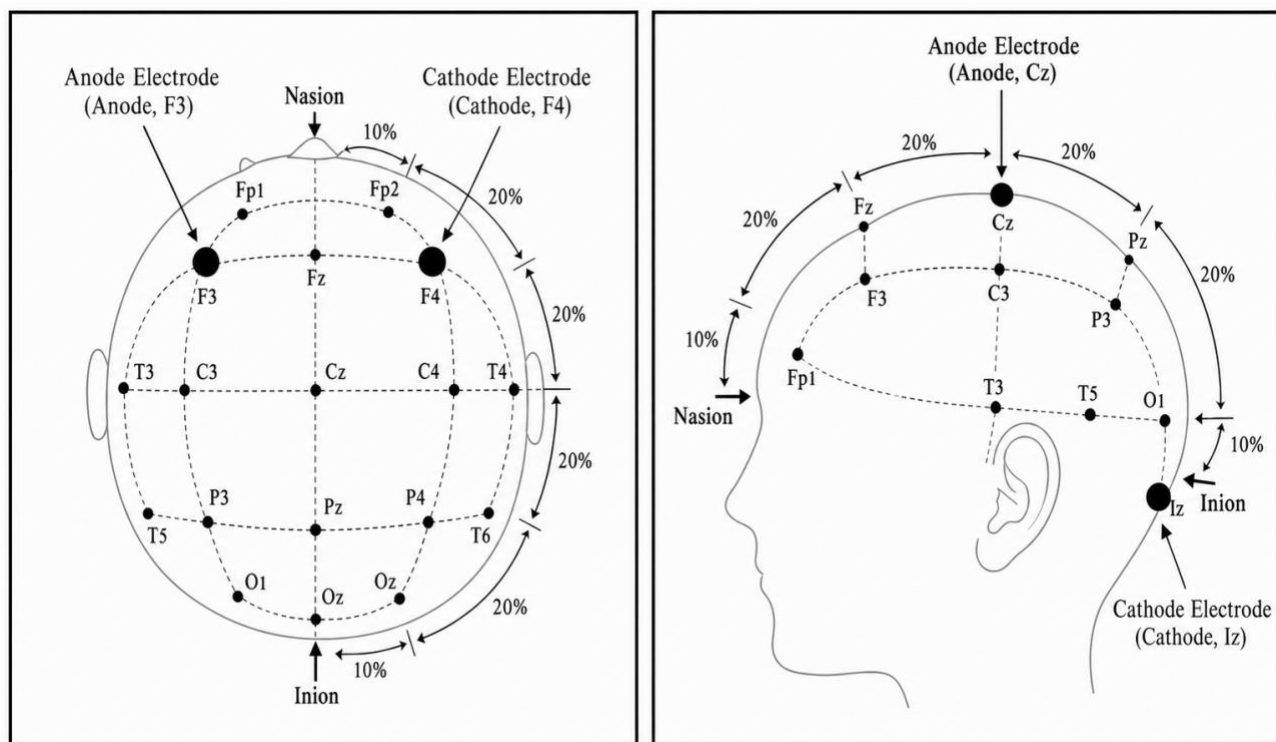


图 1. 电极片放置方案

注: 方案 1: 阳极: 左侧背外侧前额叶皮层(脑电图: F3); 阴极: 右侧背外侧前额叶皮层(脑电图: F4)。

方案 2: 阳极: 中央运动皮层(脑电图: Cz); 阴极: 小脑中上部中线区域(脑电图: Oz 正下方的 Iz)

(3) 联合治疗

所有受试者在 4 周干预期间, 将继续遵其既往常规服用的帕金森病治疗药物, 包括左旋多巴制剂(如美多芭)、多巴胺受体激动剂(如普拉克索)、抗胆碱能药物(如苯海索)及单胺氧化酶 B (MAO-B) 抑制剂(如雷沙吉兰)。入组前需保持药物剂量稳定 ≥ 4 周; 干预期间, 受试者不得新增任何抗帕金森病药物, 亦不得调整原处方抗帕金森病药物的剂量或用药间隔。

每次临床治疗过程中出现的刺激相关不良反应及其他安全性不良事件, 将依据机构规程, 使用标准化医院严重不良事件 (SAE) 报告表进行记录与上报。

(4) 干预后评估

最后一次治疗结束后 1 周内, 所有受试者需返回研究中心, 由研究团队中采用盲法的临床医生完成以下评估: PDQ-39、MDS-UPDRS、NMSS、HAMD、PFS-16、BERG 及 TUGT。同时进行心率、血压测量, 并完成治疗后多模态磁共振扫描。治疗后评估阶段需记录最后一次干预治疗后在研究中心内发生的安全性不良事件。

(5) 失访处理

研究全程将采取一切合理措施与受试者保持联络。对于未按时参加预定访视的受试者, 研究人员将通过电话、短信或其他经批准的通讯方式联系, 以重新安排评估。对于未出席预定访视的受试者, 需至少尝试三次联络, 若仍无法取得联系, 则判定为失访。若经所有合理联络尝试仍无法与受试者取得联系, 且无法获取任何结局数据, 则判定该受试者为失访。失访日期及已知原因需记录于研究档案中。依据适用法规及知情同意书条款, 除非受试者提出要求, 否则失访前收集的所有数据均需保留并纳入分析。研究结果及受试者流程处置图中, 需报告失访人数及可追溯的失访原因。

2、盲法

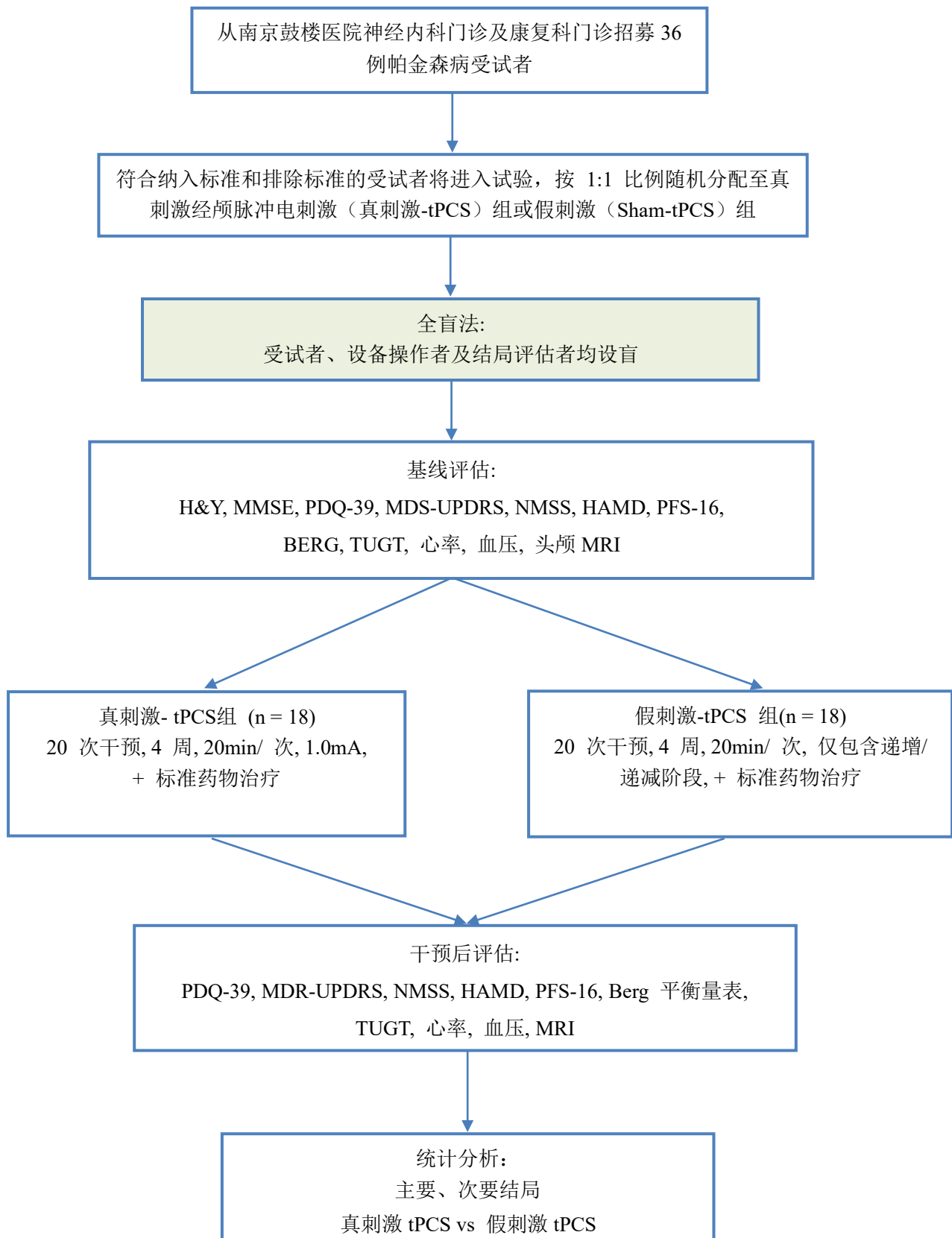
在整个研究过程中, 参与者、设备操作员、结果评估人员和统计学家均对治疗分配情况保持盲态。真/假刺激-tPCS 设备外观完全相同, 所分配的干预措施(真刺激或假刺激)通过预先设定的代码进行编程, 从而确保操作员的盲态。代码分配将由一名独立的研究管理员执行, 该管理员不参与治疗实施、结果评估或数据分析。为进一步

维持盲法，将要求参与者不得与其他参与者或研究工作人员讨论其治疗体验。所有治疗环节将在相同的治疗环境中，每天固定时间完成。

所有受试者均为 hf-tPCS 的初治接触者，系首次接受该干预，因此无法区分真/假刺激。研究团队将告知受试者其感受到的刺激体验为典型反应，从而有效维持对治疗分组的盲态。

基线及治疗后结局评估由南京鼓楼医院 2 名具有至少 5 年相关工作经验的盲态临床医生（神经内科或康复科医师）完成。为确保盲法的完整性，结局评估人员不得参与受试者的随机化、分组或干预实施过程。

3、研究设计流程



六、实验材料

1、试验用产品



设备型号：YQ-D1222，多通道脉冲电流刺激仪，北京易奇生物科技有限公司



银纤维棉质电极

魔术贴头套

(1) 技术参数

波形：单相矩形脉冲

频率：400 Hz

电极材料：圆形银纤维棉质电极

电极尺寸: 12.56 cm²

头带材质: 低致敏性魔术贴布料

(2) 监管分类:

中华人民共和国国家药品监督管理局 (NMPA), 河南省药品监督管理局医疗器械生产许可证编号: 20150077, 第二类, 物理治疗及康复设备。

七、研究时间

- 研究实施时间: 2021 年 1 月 1 日—2023 年 1 月 1 日, 延长至 2024 年 1 月 1 日
- 征募观察对象时间: 2021 年 1 月 31 日—2022 年 1 月 1 日, 延长至 2023 年 3 月 15 日

八、安全监查

1、定义

不良事件 (Adverse Event, AE) 指在接受药品给药的患者或临床研究受试者中发生的任何非预期医学事件, 该事件与所施治疗不一定存在因果关联。因此, 不良事件 (AE) 可涵盖与药物 (试验用药物) 使用存在时间关联性的任何不利且非预期的体征 (含异常实验室检查结果)、症状或疾病, 无论其是否与该药物 (试验用药物) 存在关联。

严重不良事件 (Serious Adverse Event, SAE) 指在任何剂量下发生的非预期医学事件, 满足以下任一情形:

- • 导致死亡;
- • 危及生命;
- • 需住院治疗或延长现有住院时长;
- • 造成持续性或显著的残疾/失能, 或引发先天性畸形/出生缺陷。

2、安全监查计划

(1) 不良事件的观察与记录

试验期间受试者发生的所有不良事件均需进行仔细询问与调查。需明确所有不良

事件的性质、严重程度及其与 hf-tPCS 的相关性。所有受试者中与 hf-tPCS 相关的不良事件均应记录于严重不良事件 (SAE) 报告表中, 且由主要研究者负责监测 hf-tPCS 的安全性

(2) 相关性评估

不良事件与高频经颅脉冲电刺激的相关性分为以下等级: 肯定相关、很可能相关、可能相关、肯定不相关。主要研究者需判断不良事件与研究干预措施的相关性, 并为该判断提供支持依据。

(3) 严重程度评估: 不良事件依据以下标准分为三个强度/严重程度等级:

- 轻度: 通常为一过性, 不影响正常日常活动;
- 中度: 存在显著不适, 影响正常日常生活, 受试者出现可感知但可耐受的症状, 无需终止治疗;
- 重度: 无法开展正常日常活动, 受试者出现显著且难以耐受的症状, 需终止治疗。

(4) 试验期间及试验后不良事件的管理

主要研究者需跟进并记录所有不良事件的转归, 追踪因不良事件退出试验的受试者, 以及不良事件的解决方式与时间节点。主要研究者将定期对所有不良事件进行累积性审查, 并在必要时召开研究者会议, 评估研究的风险。严重不良事件及非预期事件需依据规定及时向伦理委员会、监管部门及申办方报告。

高频经颅脉冲电刺激装置的潜在不良反应包括:

- 电极部位轻度不适或疼痛 (含轻度头痛、颈痛): 可能因电极与局部头皮接触不均等因素所致, 可通过暂停治疗并重新贴附电极缓解。
- 电极部位头皮发红: 停止刺激后 20-30 分钟内可自行缓解; 严重时给予局部抗过敏药物。
- 头晕、剧烈头痛、恶心、呕吐、大量出汗、头皮灼伤、心悸、食欲减退: 部分受试者可能出现此类症状 (发生率较低), 需立即停止治疗并给予对症处理以缓解症状。

(5) 紧急揭盲程序:

若受试者发生严重不良事件, 主要研究者可访问存储随机化列表及对应分组信息的加密数据库, 对该受试者实施紧急揭盲, 并在病例报告表中记录揭盲原因与日期。

受试者一旦被揭盲, 主要研究者及研究团队须讨论并决策其是否应退出研究。

九、质量控制和数据安全

1、质量控制与质量保证

研究团队所有成员(无论是否为设备操作人员)均需接受高频经颅脉冲电刺激医疗器械相关培训, 经培训合格后方可开展临床研究工作。研究团队成员还需接受临床试验流程专项培训, 涵盖知情同意的执行、受试者沟通、数据管理、严重不良事件(SAE)处置及研究团队内部盲法程序的维护等内容

2、研究数据安全

所有数据将被录入桌面端受密码保护的安全文档中。仅限研究负责人访问这些数据。数据表的纸质副本将在试验结束后存放于部门的上锁柜子中, 保存期限最长为 7 年。

十、统计方法

1、样本量的确定: 参见前文。

2、统计与分析方案

所有统计分析将采用 IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA) 及 R 软件 4.2.2 版本 (R Foundation for Statistical Computing, Vienna, Austria) 完成。分析遵循方案分析(per-protocol, PP)原则, 纳入标准为完成干预且具备治疗后结局数据的受试者。基线及治疗后数据的正态性将通过 Shapiro - Wilk 检验与 Kolmogorov - Smirnov 检验进行评估。

组间基线比较中, 采用标准化均数差 (standardized mean differences, SMDs) 评估两组基线特征的平衡性。SMD 的计算方法为两组均值或比例之差除以合并标准差。

治疗后组间比较: 针对正态分布的结局指标, 将依据数据特征选用方差分析 (ANOVA) 或协方差分析 (ANCOVA); 针对非正态分布数据, 则根据实际情况采用 Mann - Whitney U 检验或基于秩的协方差分析 (rank-based ANCOVA)。组内治疗前后变化的探索性分析: 将根据数据分布特征, 选择配对样本 t 检验或 Wilcoxon 符号秩检验。所选结局指标间的探索性相关性分析: 将依据变量类型及分布特征, 选用 Pearson 相关系数、Spearman 等级相关系数或 Kendall's Tau 进行评估。

不良事件的发生例数及发生率将按组进行描述性统计分析。严重不良事件（SAE）的组间发生率差异，将依据数据特征采用 Pearson 卡方检验或 Fisher 精确检验进行比较。所有检验均为双侧检验，检验水准 α 设定为 0.05。当 $P < 0.05$ 时，差异具有统计学意义，并计算其 95% 置信区间。对于各领域评分的多重比较，除预先指定为研究主要疗效指标的帕金森病生活质量问卷（PDQ-39）外，其余均采用 Bonferroni 校正进行调整。

十一、伦理设计

本研究将严格遵循《赫尔辛基宣言》确立的伦理原则，同时符合《药物临床试验质量管理规范》（GCP）及适用的法规要求。在任何受试者入组前，本临床试验最终方案（含受试者知情同意书及知情同意表格的最终版本）必须获得南京鼓楼医院伦理委员会的书面批准。

临床试验将在伦理委员会批准试验方案后启动实施。每位受试者入组前，研究人员须向受试者本人或其法定代理人充分、全面地告知本研究的目的、试验流程及潜在风险，并签署书面知情同意书。需明确告知受试者有权随时退出本研究，且知情同意书作为临床研究核心文件予以存档，以备后续核查。

1、知情同意

在知情同意的获取与记录环节，研究者须严格遵循《赫尔辛基宣言》确立的伦理原则及《药物临床试验质量管理规范》（GCP）指南。潜在受试者由南京鼓楼医院经治医师筛选识别，符合纳入标准者需在见证人在场的情况下签署知情同意书。知情同意签署操作需在门诊诊室或康复门诊室完成。研究负责人需签署知情同意书，并确保向受试者准确传递研究相关信息。

2、数据与受试者记录的保密性：

所有研究数据需录入桌面端受密码保护的安全文档系统。研究全程需严格保护受试者的个人隐私及数据机密性。

可识别的受试者个人数据需进行匿名化处理。数据访问权限仅限本研究的研究者团队成员。纸质版数据表单需存放于科室专用上锁文件柜中，保存期限不超过 7 年。

十二、研究成果发表

本研究经南京鼓楼医院伦理委员会批准后，由主要研究者在中国临床试验注册中心（www.chictr.org.cn）完成注册。研究结果无论阳性或阴性，均需在同行评审的科学期刊上发表。研究成果发表需严格遵循《CONSORT 2025 声明》，确保符合国际作者署名及出版规范。

十三、研究经费与资源

1、资助项目：

南京市卫生健康委员会一般课题（项目编号：YKK21103）、横向合作项目（项目编号：ZR175-2021）。

2、实物支持

易奇生物科技有限公司将提供以下支持：

- 易奇生物科技有限公司生产的 YQ-D1222 型 hf-tPCS 医疗器械 2 台
- hf-tPCS 银纤维电极 40 对
- 头带 40 条
- 生理盐水 200 瓶
- 试验前临床医师培训

十四、参加人员

姓名	职称/专业	任务	GCP培训（时间）
徐蓉	副主任医师	临床研究设计	2018-4
李政	主治医师	临床病人筛查、治疗方案制定	2021-5
洪文军	主治医师	数据统计分析	2021-5
许碧云	高级统计师	统计指导	-
艾冬梅	主管技师	数据收集	2018-4
赵春霞	技师	数据收集	-

十五、参考文献

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