Official Title: Repetitive Transcranial Magnetic Stimulation for Musculoskeletal Pain in Patients With Parkinson's Disease：Efficacy and Safety, Electrophysiological Mechanisms and Influence on Motor and Other Non-motor Symptoms

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Informed Consent Form

Dear Participant,

You are cordially invited to participate in a clinical research study entitled "Electroencephalographic and Functional Magnetic Resonance Imaging Characteristics of Pain in Parkinson's Disease and Therapeutic Efficacy of Transcranial Magnetic Stimulation". This investigation is scheduled to be conducted from May 2022 to March 2024 at the Second Affiliated Hospital of Soochow University. The study aims to enroll approximately 100 eligible participants. We would like to emphasize that this research protocol has undergone rigorous ethical review and has obtained official approval from the Institutional Review Board of the Second Affiliated Hospital of Soochow University (JD-LK-2021-132-02).

1. Study Objectives and Background

Parkinson's disease (PD) is a prevalent neurodegenerative disorder predominantly affecting middle-aged and elderly populations. Non-motor symptoms, including pain, depression, constipation, hyposmia, and sleep disturbances, significantly impair patients' quality of life. Among these non-motor manifestations, pain and sensory abnormalities may occur at any disease stage, potentially preceding motor symptoms by several years. Epidemiological studies indicate that 40-85% of PD patients experience pain-related symptoms, markedly exceeding the prevalence in age-matched control groups (8%-62.8%). The pathogenesis of PD-associated pain remains incompletely understood, and current clinical practice lacks effective and disease-specific therapeutic interventions. Notably, pain management in PD has been historically underrecognized, with suboptimal treatment rates. Nearly 50% of affected individuals report no prior pharmacological or physical therapeutic interventions, exacerbating functional disability and diminishing life quality. Consequently, comprehensive multidimensional evaluation of PD-related pain is imperative, necessitating integrated therapeutic strategies combining pharmacotherapy and rehabilitation modalities.

This study aims to:

1. Delineate clinical and neuroimaging characteristics of pain in PD
2. Investigate standardized assessment methodologies and underlying mechanisms of pain generation
3. Evaluate the therapeutic efficacy of transcranial magnetic stimulation (TMS) in PD-related pain management

2. Study Protocol

Upon enrollment, you will be required to: 1) Complete standardized questionnaires assessing demographic characteristics (age, education level), clinical history (disease duration, medication regimens, comorbidities), and PD-specific symptom severity. 2) Undergo comprehensive neurophysiological evaluations, including: Resting-state electroencephalogram (EEG); Functional magnetic resonance imaging (fMRI). 3) Receive stratified group allocation (Pain vs. Non-pain groups) based on quantitative assessments using the King's Parkinson's Disease Pain Scale (KPPS)

Pain-group participants electing to receive high-frequency repetitive transcranial magnetic stimulation (rTMS) will be randomly assigned to active or sham stimulation groups through a computer-generated 2:1 allocation sequence. The intervention protocol comprises daily 20-minute rTMS sessions spanning 7 consecutive days.

After treatment, you will undergo monthly clinical follow-ups for three consecutive months following treatment completion, during which standardized scale assessments will be systematically administered to monitor rTMS therapeutic efficacy in PD-related pain management. Additionally, EEG recordings will be acquired pre- and post-intervention to evaluate spatiotemporal modulation of cortical excitatory/inhibitory balance and functional network reorganization. It should be emphasized that you are requested to refrain from modifying oral PD medications during follow-up unless medically necessary.

3. Inclusion/Exclusion Criteria

Inclusion Criteria: 1) Diagnosis of idiopathic Parkinson's disease per the International Parkinson and Movement Disorder Society (MDS) clinical diagnostic criteria; 2) Stable PD medication regimens maintained for ≥2 weeks; 3) Mini-Mental State Examination (MMSE) score ≥24; Exclusion Criteria: 1) Contraindications to MRI or rTMS (Ferromagnetic implants, Elevated intracranial pressure or active intracranial infections, Severe cardiovascular comorbidities); 2) History of deep brain stimulation surgery; 3) Clinically significant tremor interfering with neurophysiological recordings; 4) Comorbid pain-inducing conditions independent of PD (Malignancy, Diabetes mellitus with peripheral neuropathy, Advanced osteoarthritis or rheumatoid arthritis confirmed by imaging/laboratory evidence).

4. Potential Benefits

Participation in this study may lead to potential clinical improvement in your

condition, though measurable therapeutic effects cannot be guaranteed. Importantly, your involvement will contribute to advancing understanding of TMS protocols, potentially enabling safer and more effective pain management strategies for future PD patients with similar clinical profiles.

5. Potential Risks

As a non-invasive neurophysiological monitoring technique, EEG carries negligible procedural risks. When scanning with MRI, claustrophobic reactions may occur due to confined spatial conditions. Ferromagnetic objects could become projectile hazards under strong magnetic fields (1.5-3 Tesla), posing risks of traumatic injury or equipment damage. TMS represents a non-invasive neuromodulation technique with established safety profiles, capable of ameliorating neurological dysfunction through targeted cortical regulation. However, it should be noted that TMS does not constitute curative intervention, and therapeutic outcomes may exhibit interindividual variability, potentially resulting in suboptimal symptom relief for some participants post-treatment. Transient adverse effects associated with coil operation include auditory discomfort and self-limiting neurological manifestations (dizziness, cephalalgia). While theoretical risks of seizure induction exist with excessive stimulation parameters (prolonged duration or suprathreshold intensities), our safety-optimized protocol (unilateral 20 Hz stimulation at 80% resting motor threshold) combined with rigorous exclusion criteria significantly mitigates such occurrences. It is imperative to acknowledge that unforeseen risks inherent to neuromodulation technologies may emerge despite comprehensive precautionary measures.

6. Alternative Therapeutic Options

Non-participation or voluntary withdrawal from this study will not affect your eligibility to continue standard oral pharmacotherapy, ensuring uninterrupted therapeutic continuity.

7. Financial Considerations

All study-related expenses, including neurophysiological assessments (EEG, fMRI), serial rTMS interventions, and standardized scale evaluations, will be fully subsidized by the Department of Neurology at the Second Affiliated Hospital of Soochow University. This funding structure has undergone rigorous ethical review to eliminate financial barriers to participation.

8. Adverse Event Management

Immediate notification to the principal investigator is required upon experiencing any emergent symptoms, clinical deterioration, or unanticipated events, irrespective of perceived causality. The research team will initiate prompt clinical evaluation and implement appropriate medical interventions. All adverse events occurring during the study period, whether related to the investigational procedures or not, will be managed through the hospital's comprehensive healthcare system at no additional cost to participants. Should study-related injuries occur, affected individuals will receive prioritized medical care and legally mandated compensation through an ethically reviewed framework in strict compliance with China's Clinical Trial Quality Management Standard (GCP) and relevant biomedical regulations.

9. Protocol Termination Scenarios

Investigators reserve the right to immediately disenroll participants without prior consent under the following circumstances: (1) Continuation poses substantiated risk-benefit imbalance favoring harm; (2) Protocol deviations compromising data integrity; (3) Premature study termination mandated by regulatory authorities or safety monitoring boards.

10. Data Confidentiality

Medical records will be securely archived within hospital information systems with access restricted to authorized investigators, regulatory auditors, and IRB members. All published research outputs will utilize strictly de-identified datasets. Privacy protection measures adhere to China's Personal Information Protection Law (PIPL) and Cybersecurity Law, employing encrypted data transmission and role-based access controls.

11. Voluntary Participation & Withdrawal Rights

Enrollment constitutes fully voluntary engagement without prejudice to ongoing care. You may withdraw consent at any study phase without obligation to disclose rationale. Post-withdrawal safety assessments may be requested to ensure neurological stability, though compliance remains discretionary. Clinically significant findings emerging during the study will be promptly disclosed through structured debriefing sessions. Real-time protocol clarifications may be obtained via 24/7 research coordinator hotline. Substantial protocol modifications (e.g., newly identified safety concerns) necessitating revised informed consent documents will undergo IRB-approved amendments, with re-consenting procedures implemented prior to continued participation.

For study-related inquiries, please contact: Principal Investigator: Dr. Liu.

Contact Number: 13073361889

For ethical concerns regarding participant rights, please contact: Institutional Review Board, Second Affiliated Hospital of Soochow University. Tel: +86-512-67783682

Participant Declarations

I hereby certify that I have thoroughly reviewed this informed consent document, received comprehensive explanations, and had all questions satisfactorily addressed. I acknowledge that participation is entirely voluntary, and my decision to decline or withdraw at any stage will not compromise my medical care or legal entitlements.

I understand that investigators may discontinue my participation under the following circumstances: Requirement for alternative diagnostic/therapeutic interventions; Protocol non-adherence; Emergence of scientifically justified termination criteria

By endorsing this document, I voluntarily consent to participate in this clinical trial. I retain a countersigned copy of this agreement. Authorize controlled access to my de-identified data by authorized investigators, regulatory bodies, and audit entities for research purposes

Participant Signature: _____Date: ___
Contact Number: _____

Legally Authorized Representative Addendum *(For participants lacking decision-making capacity)*

Guardian/Legal Representative Signature: _____Date: ___
Contact Number: _____**Relationship to Participant:** _____

Impartial Witness Attestation *(Required for non-literate participants)*

I confirm witnessing the complete informed consent process, including disclosure, discussion, and documentation. The participant/representative demonstrated full comprehension of the trial's nature and implications.

Witness Signature: _____ Date: //____
Contact Number: _____

Investigator Attestation

I, the undersigned investigator, solemnly affirm: 1) Provided exhaustive explanations of the trial's objectives, procedures, risks, and benefits. 2) Ensured adequate time for document review and independent consultation. 3) Disclosed 24/7 contact protocols for emergent queries. 4) Explicitly communicated unconditional withdrawal rights. 5) Verified the participant's/representative's autonomous decision-making capacity.

Investigator Signature: _____ Date: ___

Office Tel: _____ **Mobile:** _____