Trial Protocol v1.1:

Cerebellar High Frequency Transcranial Pulsed Current Stimulation Increases Total Sleep Time in Chronic Insomnia: A Pilot Study

1 BACKGROUND AND RATIONALE

1.1 General Introduction

Sleep disorders are prevalent in the general population and in people suffering from depression (Murphy & Peterson, 2015; Ohayon, 2011)(Murphy & Peterson, 2015; Ohayon, 2011) with insomnia as the most common type of sleep disorder (American Psychiatric Association, 2013; Ohayon, 2002). Insomnia may itself be a disorder such as in primary insomnia, or it could also be a comorbid symptom of more complex types of sleep, medical and psychiatric disorders(Harvey, 2001). Altered states of arousal and sleep has been associated with greater risk of adverse health outcomes including higher risk of diabetes, stroke, coronary heart disease and heart attack (Bertisch et al., 2018; Nagai et al., 2010; Taylor et al., 2007; Yin et al., 2017), mental health (Sivertsen et al., 2021)as well as death (Cappuccio et al., 2010). Thus, treating insomnia may have important implications for improved general health and quality of life.

Following the COVID-19 pandemic, the World Health Organization (WHO) has reported that global prevalence of anxiety and depression increased by a massive 25% (World Health Organization, 2022). A systematic review and meta-analysis revealed that insomnia among the general population and COVID-19 patients was significantly associated with an increased risk of depression and/or anxiety disorders (Alimoradi et al., 2021). Many observational studies with large sample sizes and long follow up lengths have also reported on similar association between insomnia and depression(Ford, 1989; Leger et al., 2000). For example, the association between insomnia and the later development of depression within 1-3 years is found to be particularly strong (Riemann, 2003). While it is unclear if insomnia is a cause of depression or insomnia develops secondarily as a disorder due to a depression, evidence of their high association suggests that treating insomnia may have therapeutic benefits for depression, in addition to general health outcomes.

1.2 Rationale and Justification for the Study

The classic model of sleep-wake regulation in mammals, the first is the classic ‘bottom up’ pathway that involves the cortico-thalamo-cortical pathway involving the brain stem nuclei such as the ascending reticular activating system (ARAS) , the thalamus and cerebral cortex via releasing neurotransmitters (Jones & M. Muhlethaler, 1999; Jouvet, 1972; Moruzzi G & Magoun HW, 1949; Steriade et al., 2013). During sleep onset and maintenance, GABAergic sleep promoting neurons in the ventro-lateral preoptic area (VLPO) within the hypothalamus inhibit the wake-promoting cell groups of the ARAS and the orexin system causing their activity to progressively decreases (Berridge et al., 2012). The ARAS and the VLPO form a ‘flip-flop switch’ creating distinct wakeful-sleep states that are stabilized by orexinergic neurons, which are highly excitatory neuropeptide produced in the lateral hypothalamus (Saper et al., 2005, 2010). The other is a ‘top-down’ pathway (Chauvette et al., 2010; Le Bon-Jego, 2007; Steriade & Timofeev, 2003) where frontal cortical neurons serve as originators of synchronized slow oscillations that emerge during sleep (Marzano et al., 2013; Steriade, 2006). Given that transcranial electrical stimulation (tES) including transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) may

modulate cortical excitability (Frase et al., 2016, 2019; Hadoush et al., 2018; Minichino et al., 2014; Sheng et al., 2018; Zhou et al., 2020), and entrain endogenous oscillations (Hathaway et al., 2021; Ladenbauer et al., 2017; Marshall et al., 2006; Reato et al., 2013; Saebipour et al., 2015; Wang et al., 2020), it might represent a novel way to intervene with specific sleep-related alterations in insomnia by modulating sleep-wake regulation.

In recent years, the cerebellar cortex has been explored as a tES neuromodulation target for sleep (D'Urso et al., 2022; Grimaldi et al., 2016; Minichino et al., 2014)due to that fact that the cerebellar is thought to be involved in the modulation of sleep processes (Cunchillos & De Andrés, 1982; J. Liu et al., 2023) and it has multiple reciprocal connections with the cerebral cortex via the thalamus, pons, mesodiencephalic junction and the inferior olive(Andre & Arrighi, 2003; De Zeeuw et al., 2008). For example, the cerebellar contains vast numbers of Purkinje cells, which are GABAergic neurons that exert strong inhibitory control over the DCN (Kang et al., 2024). The DCN is the principal output structure of the cerebellum and project extensively to the thalamus and brainstem arousal systems, including components of the ARAS (Berridge et al., 2012). In a sleep study involving bipolar euthymic patients (Minichino et al., 2014), anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC) was combined with cathodal tDCS over the right cerebellar cortex (2mA, 20 min a day for 3 weeks), improved the total score of the Pittsburgh Sleep Quality Index as well as the scores in the subdomains sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance and daytime dysfunction.

In addition, preclinical studies of high frequency electrical stimulation suggest that it may lead to the enhancement of GABAergic signalling via reduced GABA reuptake (Li et al., 2004) and activation of GABAergic interneurons (Ye et al., 2022), as well as suppression of neuronal firing and spontaneous oscillations (Pyragas et al., 2013; Pyragas & Tass, 2017; Yuan et al., 2022). Therefore tES utilising higher frequency waveforms may possibly have an additional effect of reduce excessive excitatory drive and enhancement of inhibitory control, aligning with prevailing models of insomnia pathophysiology and may alleviate insomnia.

1.3 Rationale for Study Purpose

Current pharmacological treatments for clinical conditions of insomnia including benzodiazepines and benzodiazepine-receptor agonists, have been reported to have undesirable drug side-effects and also limited treatment efficiency (Riemann D & Nissen C, 2012). Patients may have poor compliance due to fears of developing potential drug dependency, resulting in low therapeutic efficacy. Another first-line treatment for insomnia is cognitive-behavioral therapy for insomnia (CBT-I) (Rossman, 2019), although it has considerable success, CBT-I requires working with a qualified therapists which may be time-consuming, inconvenient, and costly for patient.

Notedly, evidence in literature shows that in the treatment of insomnia using pharmacological options and CBT-I, about 40% of the patients do not achieve long-term remission (Qaseem et al., 2016), therefore there is a pressing need for treatment options with lower side effects, higher cost efficiency and with more convenient administration. Home-use, self-administered tES devices may provide a potential solution.

1.4 Rationale for the Dose Selection (tES waveform, montage, intensity, duration)
Transcranial electrical stimulation (tES) is a non-invasive neuromodulation technique that transmits low intensity electrical current (<2mA) to specific areas of the brain via surface electrodes that are placed on the scalp. tES alters the resting potential of the neuronal membranes in the cortex underlying the area of the electrodes and may also influence interconnected brain regions distant from the site of the electrodes through trans-synaptic activation (Chib et al., 2013). The overall therapeutic effects of tES are due to the resultant changes in excitability and spontaneous firing rates across the stimulated brain areas (Philip et al., 2017) which may also induce long-term potentiation (LTP)-like and long-term depression (LTD)-like effects that mediates neuroplasticity changes (Fritsch et al., 2010) in the central nervous system. tES has been increasingly investigated for the treatment of sleep disorders (Dondé et al., 2021; Ma et al., 2021)

According to the differences in the mode of the output electrical current, transcranial electrical stimulation (tES) (Guleyupoglu et al., 2013) may classified into various modalities including Transcranial direct current stimulation (tDCS), Transcranial alternating current stimulation (tACS), Transcranial random noise stimulation (tRNS) and Transcranial pulsed current stimulation (tPCS). Among them, tPCS is the most novel type of tES among the four, tPCS has recently gained increasing attention in experimental settings (Alon et al., 2012; Dissanayaka, Zoghi, Hill, et al., 2020; Jaberzadeh et al., 2014, 2015; Jaberzadeh & Zoghi, 2023; Sours et al., 2014), delivering pulsed currents at a predetermined frequency to the cortex. In previous research comparing tPCS to tDCS (Jaberzadeh et al., 2014), 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 this tPCS mechanism includes both tonic and phasic effect, it not only promotes the increase / decrease of spontaneous neuronal discharge rate by promoting the depolarization / hyperpolarization of local resting membrane potential of cells (the tonic effect similar to mechanism of tDCS) to induce corticospinal excitability, but at the same time, tPCS also exerts a phasic on-off effect on the voltage gated carrier protein in the neuron membrane through the characteristics of pulsed wave (Jaberzadeh et al., 2015).

In a previous head modeling study that compared tPCS with tDCS (Datta et al., 2013), support for additional benefits of tPCS included that tPCS could reach deeper brain regions, such as the midbrain, pons, insula, thalamus, and hypothalamus, while the latter seemed to mainly increase cortical excitability under the stimulating electrodes. This may be important for the treatment of insomnia as the local processes, neuronal network, hormonal influences and the biological clock that control the waking, NREM and REM states are all regulated by the hypothalamus , which situated deeper in the subcortical brain. Also, the cerebellum is located further away from the cortical surface compared to regions such as the motor cortex, tPCS with greater depth of stimulation may thus be more suitable to modulate the cerebellar compared to tDCS.

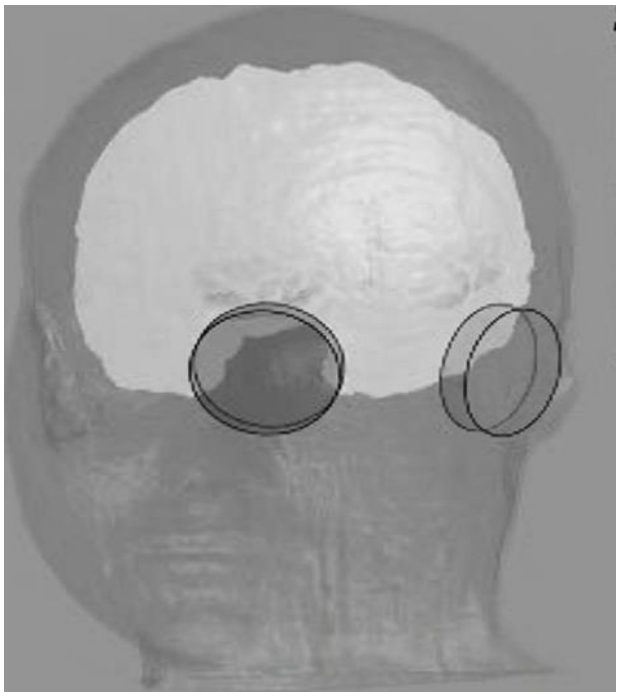
In terms of safety, tPCS may have an advantage over tDCS due to the inverse relationship between frequency and impedance (Alon et al., 2011). While there are yet no studies done involving tPCS and people with insomnia, the safety of tPCS had been investigated in healthy humans (Dissanayaka, Zoghi, Farrell, et al., 2020; Dissanayaka, Zoghi, Hill, et al., 2020; Morales-Quezada

et al., 2014, 2016; A. Vasquez et al., 2016; A. C. Vasquez et al., 2017) in the treatment of Parkinson's disease (Alon et al., 2012) and childhood Cerebral Palsy(Z. Liu et al., 2021), 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 (Antal et al., 2017).

In this study, tPCS electrodes would be applied to the bilateral cerebellar hemisphere to deliver high frequency pulsed currents (400Hz) to modulate cerebellar activity, intensity will be at 0.6mA, 30 min per session, 6 times per week over 2 weeks, totaling 12 sessions.

tPCS montage for the study

Figure :
Insomnia Montage – Electrodes over the Bilateral Cerebellar Hemispheres



1.5 Rationale for the Study Design
A prospective, single-center, randomized, double-blind, placebo-controlled (sham tPCS), pilot feasibility clinical trial design will be adopted, consisting of the following:

Target population: Adult subjects diagnosed with insomnia with or without comorbid depression

Sample size: 38 subjects

Allocation and Randomization: Participants who successfully entered the trial will be randomly allocated to the active-tPCS Group and the sham Group according to the strategy mentioned in Section 3, with 19 subjects in each group.

Study Design:

I. Recruitment at out-patient sleep clinic at Chongqing Western Hospital
II. Pre-screening/ baseline assessment using three whole-night recording of actigraphy-derived TST of ≤480 minutes (≤8 hours) using wrist actigraphy to determine if total sleep time is < 8 hours for potential participants.
III. Baseline assessment of ICD-10, SAS, SDS, PSQI questionnaire
IV. Intervention: Two consecutive weeks of treatment – 6 sessions (Mon to Sat) per week, 30-min per session of 0.6mA active tPCS, or sham tPCS stimulation, in addition to standard pharmacological therapy.
V. Post-treatment assessment of SAS, SDS, PSQI questionnaire and actigraphy recording in the final three days of intervention.

1.6 Hypothesis

The combination of tPCS and standard pharmacological therapy is effective in improving actigraphy total sleep time in people with insomnia with or without comorbid depression.

1.7 Primary Objective

The primary objective is to assess the effectiveness of the combination of tPCS and standard pharmacological therapy in improving wrist actigraphy total sleep time in people with insomnia with or without comorbid depression, compared with standard pharmacological therapy alone.

1.8 Secondary Objectives:

Key secondary outcome: To evaluate, contingent on the primary actigraphy-derived TST endpoint achieving a statistically significant between-group difference, the efficacy of tPCS combined with standard pharmacological therapy versus sham-tPCS and standard pharmacological therapy on change in the Chinese version of the Pittsburgh Sleep Quality Index (PSQI) global score

Other secondary outcomes:

I. To assess the effectiveness of the combination of tPCS and standard pharmacological therapy versus sham-tPCS and standard pharmacological therapy on changes in other actigraphy sleep measures such as sleep efficiency (SE), sleep latency (SL), total time in bed (TIB), wake after sleep onset (WASO), number of awakenings, and average awakening duration.
II. To assess the effectiveness of the combination of tPCS and standard pharmacological therapy versus sham-tPCS and standard pharmacological therapy on changes in the Chinese version of the Pittsburgh Sleep Quality Index (PSQI) subjective sleep quality , sleep latency ,

sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction .

III. To assess the effectiveness of the combination of tPCS and standard pharmacological therapy versus sham-tPCS and standard pharmacological therapy on changes in Self-rated Depression Scale (SDS) scores and Self-rated Anxiety Scale (SAS) scores.

1.9 Potential Risks

tPCS may cause skin discomfort or tingling sensation to some people. Some people may have skin redness due to allergic reaction to electrode. Few people may complain of headache post stimulation. Treatment-emergent mania and hypomania have been reported in unipolar and bipolar depression treatment in tDCS trials (Arul-Anandam et al., 2010; Brunoni et al., 2011; Chao et al., 2018). Finally, drug interactions with tDCS (another tES modality) have been reported (Brunoni et al., 2013; Nitsche et al., 2006), antipsychotics with high D2 affinity such as Haloperidol and Risperidone are known to suppress tDCS-induced plasticity (Nitsche et al., 2006) while benzodiazepines were associated with an increase in depression scores when used in conjunction with tDCS (Brunoni et al., 2013).

1.10 Potential Benefits

Use of tPCS is potentially an effective intervention for people with chronic insomnia with or without comorbid depression to improve total sleep time and may lead to further positive benefits for improving overall sleep quality, depression and anxiety.

2 STUDY POPULATION

2.1 Number and Nature of subjects to be enrolled

The original trial protocol version 1.0 planned sample size of 130 participants (65 per group) was based on a conservative power calculation assuming a standardized effect size of d = 0.55, informed by prior tACS studies reporting an approximately 33-minute increase in objective sleep duration (Ayanampudi et al., 2023). Using $\alpha = 0.05$ and 80% power, this required 104 participants, inflated to 130 to account for an anticipated 20% attrition, as calculated using G*Power 3(Faul et al., 2009).

Due to recruitment limitations, the target enrollment could not be achieved within the approved study period. The study was therefore completed as a pilot feasibility trial, consistent with its objective of informing the design of a future fully powered randomized controlled trial. The revised target focused on achieving an analyzable sample of 30 participants (15 per group)**.** Assuming an actigraphy TST standard deviation of 60 minutes, this sample size allows estimation of the between-group difference in TST with a 95% confidence interval half-width of approximately ± 43 minutes**,** which is sufficient for estimating outcome variability and planning subsequent trials. To account for potential attrition, 38 participants were enrolled.

2.2 Recruitment Criteria and Recruitment Process

The eligible subjects will be recruited from Chongqing Western Hospital Outpatient Sleep Clinic who receive services and/or medical follow-up. Information of the study and Consent Form will be provided to the subjects who show interest in the study.

2.3 Inclusion Criteria

1. Adult subjects aged between 18~65 years old, male or female;
2. Subject has been diagnosed by a qualified psychiatrist for insomnia, where the diagnosis of insomnia is based on the American Academy of Sleep Medicine (ICSD-3-TR) criteria, according to subjective and objective sleep disorders;
3. Subject has a score of 11~21 points on the 19-item Pittsburgh Sleep Quality Inventory (PSQI);
4. Participants with an average three whole-night actigraphy-derived TST of ≤480 minutes (≤8 hours) using wrist actigraphy (ActiGraph wGT3X-BT);
5. Subjects may have mild to moderately severe depressive symptoms
6. Negative pregnancy test (for women with childbearing potential)
7. Subjects must be on stable dose of medication, for at least 30 days prior to screening. Medication and dose adjustments are allowed but must be documented;
8. Able to provide written informed consent and able to comply with study protocol.

2.4 Exclusion Criteria

Any subject who meets any of the exclusion criteria at baseline will be excluded from participation in this study.

1. Severe anxiety and depressive symptoms that include suicidal behaviors requiring immediate medical attention;
2. Mental illnesses including severe psychosis, bipolar disorder, schizophrenia, and mania;
3. History of brain surgery or placement of a deep brain stimulator, pacemaker or defibrillator;
4. tPCS-specific exclusions included metal in the head, history of neurosurgical procedures, ferromagnetic bioimplants, metallic paint, history of seizure disorder;
5. Clinically significant functional impairment related to cardiovascular, pulmonary, metabolic, other severe neurological disease;
6. Any medical condition that might require other medical or surgical treatment during the study period;
7. Current participation in psychological therapies such as Cognitive Behavioral Therapy (CBT);
8. Current participation in another investigational interventional study;
9. Pregnant women and breast-feeding women;
10. Night shift workers;
11. Subjects with other sleep disorders other than insomnia, such as sleep apnea and narcolepsy;
12. History of heavy alcoholic dependency, caffeine dependency or drug addicts.
13. Recent history of non-invasive brain stimulations eg. rTMS, tDCS

2.5 Provisions for dropout cases and handling of missing data

Drop-out definition: Any participant who reports significant adverse effects, are unable tolerate the session, or withdraw from the study 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 12-day course of treatment and observation period specified in this trial protocol will be considered as dropout cases.
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.

3 STUDY DESIGN

3.1 Randomization and Allocation

In accordance with China clinical research standards in "Methodology of Clinical Scientific Research of Integrated Traditional Chinese and Western Medicine (2nd edition)" , study subjects recruited from will be entered into a centralized database, and then using random sampling and allocation sequence generation by SPSS® 23.0 statistical software, be divided into two groups – active-tPCS Group and sham Group.

38 subjects who meet the inclusion criteria are numbered according to the sequence of the time of visit (from 1 to 38). SPSS® 23.0 statistical software is used to generate random numbers for the group division. The random numbers will be put into 38 opaque, sealed and identical envelopes, and their random number marked only on the inside of the envelopes.

The subjects will be randomly allocated according to the random selection of the envelopes that contain their corresponding numbers, with ratio as follows active-tPCS Group (19 pax): Sham Group (19 pax). Sequence generation and group allocation will be performed by an independent statistician who was not involved in participant enrollment, intervention delivery, outcome assessment, or data analysis.

3.2 Study Visits and Procedures

Visit to Chongqing Western Hospital	**Visit 1**	**Visit 2-13**	**Visit 14**
Timeline	**Week 0**	**Week 1-2**	**Week 3**
Procedure	**Baseline assessment**	**Intervention Period**	**Post- treatment assessment**
[1]Informed Consent	X		
[2]PSQI Questionnaire	X		X
[3]SAS Questionnaire	X		X
[4]SDS Questionnaire	X		X
[5]Actigraphy	X	X (night recordings after visit 11,12,13)	
[6]Active or Sham tPCS		X	
[7]Standard pharmacological therapy	X	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]**PQSI**- Chinese version of the Pittsburgh Sleep Quality Index (PSQI), including the global score and seven component domains, with higher scores indicating poorer sleep quality; global scores range from 0 to 21, with scores >5 indicating poor sleep quality (Buysse et al., 1989).

[3]**SDS** - Zung Self-Rating Depression Scale (SDS) (H. C. Lee et al., 1994). The SDS also comprises 20 items, evaluating affective, psychological, and somatic symptoms of depression over the past week, rated on the same 4-point Likert scale (1 = none or a little of the time, 4 = most or all of the time), with 10 items reverse-scored. The raw score (20–80) is converted to an index score (multiplied by 1.25), with ranges: <50 (normal), 50–59 (mild depression), 60–69 (moderate depression), ≥70 (severe depression).

[4]**SAS** - Zung Self-Rating Anxiety Scale (SAS) (Zung, 1971). The SAS consists of 20 items assessing emotional and somatic symptoms of anxiety over the past week. Each item is rated on a 4-point Likert scale (1 = none or a little of the time, 4 = most or all of the time), with 5 items reverse-scored. The total raw score (20–80) is converted to an index score, with higher scores indicating greater anxiety severity. Score ranges: <50 (normal), 50 – 59 (mild to moderate anxiety), 60 – 69 (marked to severe anxiety), ≥70 (extreme anxiety).

[5]**Actigraphy** – Product : ActiGraph wGT3X-BT; ActiGraph LLC, Pensacola, FL, USA. Actigraphy is a validated, non-invasive method for quantifying sleep–wake patterns and demonstrates good agreement with polysomnography for TST and sleep efficiency, particularly in naturalistic settings (Ancoli-Israel et al., 2003; Martin & Hakim, 2011). Compared to polysomnography, it has been found to have high accuracy (86%) to objectively measure sleep (Marino et al., 2013)Participants wore the actigraph on the non-dominant wrist.

Baseline Actigraphy: Subjects who signed the informed consent will collect the ActiGraph wGT3X-BT and wear it for 3 days at home for whole night actigraphic data before the start of first treatment. Baseline measurements were obtained during the week prior to first intervention, calculated as the mean value of three nights of actigraphy recordings.

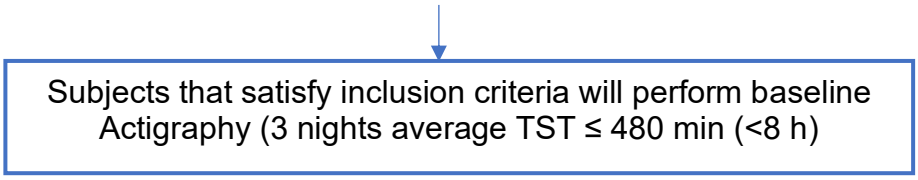
Post-treatment Actigraphy: Participants in the trial will collect the ActiGraph wGT3X-BT and wear it for 3 for whole night actigraphy data at home during the last 3 days of treatment after visit 11,12,13. Post-treatment actigraphy parameter values will be calculated as the mean value of 3-nights actigraphy recordings following the final three visits of the intervention period. Participants will return the Actiwatch at the end of the study.

[6]**Active or Sham tPCS**: Product: Transcranial pulsed current stimulator (YQ-D1111; Yiqi Biotechnology Co. Ltd., Beijing, China) . A 400-Hz tPCS waveform will be delivered via two circular silver–fiber cotton electrodes (12.56 cm^2), pre-soaked in 0.9% saline placed over the bilateral cerebellar hemispheres. In the active-tPCS group, a current amplitude of 0.6 mA was delivered throughout each session. In the sham group, current was ramped up to 0.6 mA over 10 s and ramped down over 5 s, with no stimulation delivered thereafter. All groups 30min/ session of tPCS will be performed in Chongqing Western Hospital, Monday to Saturday for 12 sessions over 2 weeks.

[7] **Standard pharmacological therapy** : All patients will receive standard pharmacological therapy which may include hypnotics (e.g., benzodiazepine or Z-drugs), selective serotonin reuptake inhibitors, atypical antidepressants and atypical antipsychotics.

3.3 Study Design

Recruit 38 subjects with chronic insomnia with / without comorbid depression from Chongqing Western Hospital Outpatient Sleep Clinic



3.3.1 Baseline Assessment

Subjects from both the Intervention and Control group will wear ActiGraph wGT3X-BT on the nondominant wrist 3whole nights one week prior to the first treatment session. The subject will ony enter the trial and be randomized to either the active-tPCS group or sham group if the average total sleep time during the 3-day period is less than ≤ 8 hours as captured by wrist Actigraphy. SAS, SDS, PSQI questionnaires will be self-completed by subjects in hospital under supervision of the study team within 1 week before treatment commences.

3.3.2 Intervention

Subjects from the active-tPCS group will receive active 400Hz tPCS, 0.6mA for 30 min/ day, Monday to Saturday, totaling 12 sessions, at a consistent time daily, during the intervention period of 2 weeks.

Subjects from the sham group will be receiving sham tPCS, for 30 min/ day, Monday to Saturday, totaling 12 sessions, at a consistent time daily. In the sham group, current was ramped up to 0.6 mA over 10 s and ramped down over 5 s, with no stimulation delivered thereafter.

All subjects will continue with their standard pharmacological therapy during the intervention period of the 2 weeks, as recommended by their attending physician.

Any adverse event will be documented and reported in accordance with institutional procedures using standardized hospital SAE reporting forms.

3.3.3 Post-treatment assessment

Active-tPCS group and Sham group: Subjects will wear the ActiGraph wGT3X-BT on the non-dominant wrist following the final 3 days of treatment period (visit 11,12,13), and 3 whole nights of actigraphy data will be collected. SAS, SDS, PSQI questionnaires will be self-completed in clinic within 1 week after the last treatment.

3.4 Blinding

The study is double-blind, where the study subjects and outcome evaluators are both blinded and do not know about the grouping. The active-tPCS and sham tPCS devices look identical in appearance but located and operated in separate treatment rooms with identical layout and furnishing. Treatment rooms were located in different areas of the hospital, and participant visits were scheduled at least two hours apart to minimize contact and prevent unblinding. Participants attended all 12 sessions in the same treatment room. Therapists administering the intervention will be blinded to group allocation.

All subjects will be tPCS naïve and receiving tPCS for the first time. They will not be aware of the difference between active and sham stimulation and will be informed by the doctors that the sensation felt is typical, therefore effectively blinding them to the different treatment conditions.

3.4.1 Assessors

Two qualified psychologists from Chongqing Western Hospital will be responsible for pre and post treatment evaluation. These assessors will not be involved in the randomization process and will be blinded to the allocation of the patients to the groups, they will also not participate in the treatment of the subjects.

3.4.2 Subjects
Adult subjects diagnosed with insomnia with or without comorbid depression

4 OUTCOME ASSESSMENT

4.1 Primary Outcome: **Actigraphy total sleep time**
Evaluation tool: Wrist Actigraphy Device (ActiGraph wGT3X-BT; ActiGraph LLC, Pensacola, FL, USA).

We will be collecting whole night actigraphy data ActiGraph wGT3X-BT 3 days before intervention commences, and in the final 3 days of treatment in both groups.

4.2 Secondary Outcomes

- Key secondary outcome : Chinese version of the Pittsburgh Sleep Quality Index (PSQI) [81] global score, evaluated only if the primary endpoint demonstrated a statistically significant between-group difference
- Other actigraphy sleep measures such as sleep efficiency (SE), sleep latency (SL), total time in bed (TIB), wake after sleep onset (WASO), number of awakenings, and average awakening duration.
- Other subcomponent scores of the Chinese version of the Pittsburgh Sleep Quality Index (PSQI) including the PSQI subjective sleep quality, sleep latency , sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction .
- Depression scores based on Self-rated Depression Scale (SDS).
- Anxiety scores based on Self-rated Anxiety Scale (SAS).

Evaluation tools: Wrist Actigraphy, PSQI, SDS, SAS,

4.2.1 Pittsburgh Sleep Quality Inventory (PSQI)

The PSQI is a self-administered 19-item questionnaire that assesses sleep quality and disturbances over the previous month. The 19 self-rated questions are grouped into seven clinically derived domains of sleep difficulties (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction). The seven subcomponents correspond to specific dimensions related to sleep quality that are generally assessed in clinical practice. Each domain is rated equally on a Likert scale that ranges from 0 to 3 and is used to generate a global score of 0–21; global PSQI scores >5 indicate poor overall sleep quality; higher scores indicating lower sleep quality.(Tsai et al., 2005)
(*See Appendix 1 for full questionnaire.)*

4.2.2 Self-rating Depression Scale (SDS)

The SDS is a 20-item questionnaire (scores range from 0 to 100, with higher scores indicating more severe depression) to measure depressive symptoms over the previous week. SDS scores are classified as normal (<50), mild depression (50 to 59), moderate to marked major depression (60 to 69), and severe to extreme major depression (>70). The raw score can be converted to an SDS Index score by multiplying the raw score times 1.25 (Lee et al., 1994; ZUNG, 1965). *(See Appendix 2 for full questionnaire.)*

4.2.3 Self-rating Anxiety Scale (SAS)

The SAS is a 20-item questionnaire (scores range from 0 to 100, with higher scores indicating more severe anxiety) to measure anxiety symptoms over the previous week.(Zung, 1971) *(See Appendix 3 for full questionnaire.)*

5 STATISTICAL ANALYSES

5.1 Determination of Sample Size

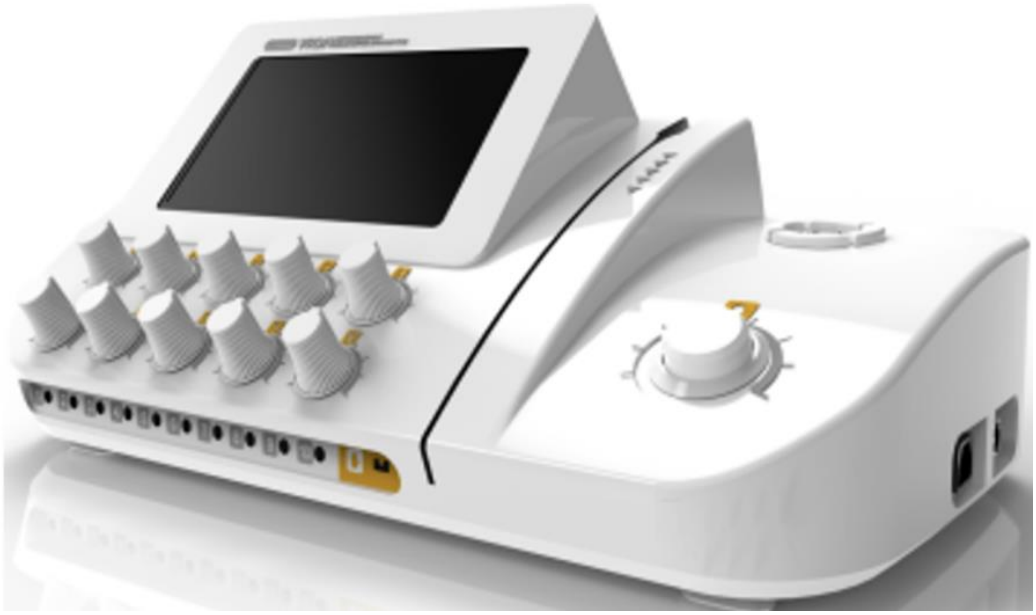
Please see Section 2.1

5.2 Statistical and Analytical Plans

All statistical analyses will be performed using IBM SPSS Statistics (version 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. Baseline between-group comparisons will be conducted using Pearson's chi-square test or Fisher's exact test for categorical variables and Welch's two-sample t-test, Wilcoxon rank-sum test, or Wilcoxon rank-sum exact test for continuous or ordinal variables, as appropriate. Normality of outcome distributions will be assessed using the Shapiro–Wilk and Kolmogorov–Smirnov tests. For normally distributed outcomes, analysis of variance (ANOVA) or analysis of covariance (ANCOVA) will be used for between-group post-intervention comparisons, with ANCOVA applied when adjustment for baseline differences is required; for non-normally distributed data, the Mann–Whitney U test or rank-based ANCOVA will be employed. Within-group changes from baseline to post-treatment will be analyzed using the

Wilcoxon signed-rank test. Exploratory associations will be examined using Pearson's correlation, Spearman's rank correlation, or Kendall's tau, as appropriate, with scatterplots used for visualization when relevant. The incidence of adverse events will be compared between groups using chi-square tests and the adverse events that occurred in this trial will be described in a table. All statistical tests will be two-sided, with $P < 0.05$ considered statistically significant. The Holm–Bonferroni correction will be applied to adjust for multiple comparisons for actigraphy and PSQI outcomes, except for actigraphy-derived total sleep time (TST), which is prespecified as the primary outcome.

6 TRIAL DEVICE



Device Model : YQ-D1111, Multi-channel Pulsed Current Stimulator, Yiqi Biotechnology Ltd, Beijing, China

Silver-fiber Cotton Electrodes *Velcro head strap*

Technical Information of the tPCS

YQ-D1111 Multi-channel Transcranial Pulsed Current Stimulator, Yiqi Biotechnology Ltd, Beijing, China:

- Intensity: 0.6mA
- Waveform: Monophasic square wave
- Frequency: 400Hz
- Electrode materials: Circular Silver-fiber Cotton Electrodes
- Electrode size: 12.56cm2
- Head Strap Material: Hypoallergenic Velcro Cloth

7 STUDY TIMELINE

19 Jun 2023- 30 Jun 2025

8 SAFETY MEASUREMENTS

8.1 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.

8.2 Safety Monitoring Plan

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.

All adverse events of tPCS in all subjects will also be logged and safety of tPCS will be monitored by the principal investigator.

8.3 Complaints Handling

If there is any complaint of the tPCS, the Principal Investigator will be informed immediately to rectify the issue. If the subject is unable to tolerate the tPCS, the study will be discontinued.

9 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 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 Chongqing Western 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.

9.1 Informed Consent

In obtaining and documenting informed consent, the investigator 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 therapist or doctor in Chongqing Western 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.

9.2 Confidentiality of Data and Patient Records

All data will be entered into a secure password-protected document in the desktop. 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.

10 PUBLICATIONS

Following approval by Ethics Committee of Chongqing Western Hospital , the study will be registered on 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 FUNDING AND RESOURCES

Grant:

National Natural Science Foundation of China (No.823B2029)
Chongqing Natural Science Foundation (No. CSTB2023NSCQ-MSX0779)
Beijing Municipal Science and Technology Commission (No.D171100007017001).

In Kind:

Chongqing Western Hospital will supply the manpower for recruitment of study subjects and carrying out ICD-10 diagnostic assessments, actigraphy assessment, PSQI, SDS and SAS questionnaires evaluation for the study subjects.

Yiqi Biotechnology Co. Ltd will supply:

- 4 units of YQ-D1111 tPCS medical devices (2 active device , 2 sham devices), by Yiqi Biotechnology Co. Ltd.
- 50 pairs of tPCS silver fiber electrodes
- 40 head straps
- 200 bottles of saline solution
- Pre-trial clinician training

REFERENCES

Alimoradi, Z., Broström, A., Tsang, H. W. H., Griffiths, M. D., Haghayegh, S., Ohayon, M. M., Lin, C.-Y., & Pakpour, A. H. (2021). Sleep problems during COVID-19 pandemic and its' association to psychological distress: A systematic review and meta-analysis. *EClinicalMedicine*, *36*, 100916. https://doi.org/10.1016/j.eclinm.2021.100916

Alon, G., Roys, S. R., Gullapalli, R. P., & Greenspan, J. D. (2011). Non-invasive electrical stimulation of the brain (ESB) modifies the resting-state network connectivity of the primary motor cortex: A proof of concept fMRI study. *Brain Research*, *1403*, 37–44. https://doi.org/10.1016/j.brainres.2011.06.013

Alon, G., Yungher, D. A., Shulman, L. M., & Rogers, M. W. (2012). Safety and Immediate Effect of Noninvasive Transcranial Pulsed Current Stimulation on Gait and Balance in Parkinson Disease. *Neurorehabilitation and Neural Repair*, *26*(9), 1089–1095. https://doi.org/10.1177/1545968312448233
American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596
Ancoli-Israel, S., Cole, R., Alessi, C., Chambers, M., Moorcroft, W., & Pollak, C. P. (2003). The Role of Actigraphy in the Study of Sleep and Circadian Rhythms. *Sleep*, *26*(3), 342–392. https://doi.org/10.1093/sleep/26.3.342
Andre, P., & Arrighi, P. (2003). Hipnic modulation of cerebellar information processing: implications for the cerebro-cerebellar dialogue. *The Cerebellum*, *2*(2), 84–95. https://doi.org/10.1080/14734220309403
Antal, A., Alekseichuk, I., Bikson, M., Brockmöller, J., Brunoni, A. R., Chen, R., Cohen, L. G., Dowthwaite, G., Ellrich, J., Flöel, A., Fregni, F., George, M. S., Hamilton, R., Haueisen, J., Herrmann, C. S., Hummel, F. C., Lefaucheur, J. P., Liebetanz, D., Loo, C. K., … Paulus, W. (2017). Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. *Clinical Neurophysiology*, *128*(9), 1774–1809. https://doi.org/10.1016/j.clinph.2017.06.001
Arul-Anandam, A. P., Loo, C., & Mitchell, P. (2010). Induction of Hypomanic Episode With Transcranial Direct Current Stimulation. *The Journal of ECT*, *26*(1), 68–69. https://doi.org/10.1097/YCT.0b013e3181a744bf
Ayanampudi, V., Kumar, V., Krishnan, A., Walker, M. P., Ivry, R. B., Knight, R. T., & Gurumoorthy, R. (2023). Personalized transcranial alternating current stimulation improves sleep quality: Initial findings. *Frontiers in Human Neuroscience*, *16*. https://doi.org/10.3389/fnhum.2022.1066453
Berridge, C. W., Schmeichel, B. E., & España, R. A. (2012). Noradrenergic modulation of wakefulness/arousal. *Sleep Medicine Reviews*, *16*(2), 187–197. https://doi.org/10.1016/j.smrv.2011.12.003
Bertisch, S. M., Pollock, B. D., Mittleman, M. A., Buysse, D. J., Bazzano, L. A., Gottlieb, D. J., & Redline, S. (2018). Insomnia with objective short sleep duration and risk of incident cardiovascular disease and all-cause mortality: Sleep Heart Health Study. *Sleep*, *41*(6). https://doi.org/10.1093/sleep/zsy047
Brunoni, A. R., Ferrucci, R., Bortolomasi, M., Scelzo, E., Boggio, P. S., Fregni, F., Dell'Osso, B., Giacopuzzi, M., Altamura, A. C., & Priori, A. (2013). Interactions between transcranial direct current stimulation (tDCS) and pharmacological interventions in the Major Depressive Episode: Findings from a naturalistic study. *European Psychiatry*, *28*(6), 356–361. https://doi.org/10.1016/j.eurpsy.2012.09.001
Brunoni, A. R., Valiengo, L., Zanao, T., de Oliveira, J. F., Bensenor, I. M., & Fregni, F. (2011). Manic Psychosis After Sertraline and Transcranial Direct-Current Stimulation. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *23*(3), E4–E5. https://doi.org/10.1176/jnp.23.3.jnpe4
Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193–213. https://doi.org/10.1016/0165-1781(89)90047-4
Cappuccio, F. P., D'Elia, L., Strazzullo, P., & Miller, M. A. (2010). Sleep Duration and All-Cause Mortality: A Systematic Review and Meta-Analysis of Prospective Studies. *Sleep*, *33*(5), 585–592. https://doi.org/10.1093/sleep/33.5.585
Chao, P.-C., Chang, C.-C., & Chang, H.-A. (2018). Hypomania Induced by Bifrontal Transcranial Direct Current Stimulation in a Patient with Bipolar Depression. *Psychiatry Investigation*, *15*(9), 914–915. https://doi.org/10.30773/pi.2018.08.11.1
Chauvette, S., Volgushev, M., & Timofeev, I. (2010). Origin of Active States in Local Neocortical Networks during Slow Sleep Oscillation. *Cerebral Cortex*, *20*(11), 2660–2674. https://doi.org/10.1093/cercor/bhq009
Chib, V. S., Yun, K., Takahashi, H., & Shimojo, S. (2013). Noninvasive remote activation of the ventral midbrain by transcranial direct current stimulation of prefrontal cortex. *Translational Psychiatry*, *3*(6), e268–e268. https://doi.org/10.1038/tp.2013.44
Cunchillos, J. D., & De Andrés, I. (1982). Participation of the cerebellum in the regulation of the sleep-wakefulness cycle. Results in cerebellectomized cats. *Electroencephalography and Clinical Neurophysiology*, *53*(5), 549–558. https://doi.org/10.1016/0013-4694(82)90067-0
Datta, A., Dmochowski, J. P., Guleyupoglu, B., Bikson, M., & Fregni, F. (2013). Cranial electrotherapy stimulation and transcranial pulsed current stimulation: A computer based high-resolution modeling study. *NeuroImage*, *65*, 280–287. https://doi.org/10.1016/j.neuroimage.2012.09.062
De Zeeuw, C. I., Hoebeek, F. E., & Schonewille, M. (2008). Causes and Consequences of Oscillations in the Cerebellar Cortex. *Neuron*, *58*(5), 655–658. https://doi.org/10.1016/j.neuron.2008.05.019

Dissanayaka, T., Zoghi, M., Farrell, M., Egan, G., & Jaberzadeh, S. (2020). The effects of a single-session cathodal transcranial pulsed current stimulation on corticospinal excitability: A randomized sham-controlled double-blinded study. *European Journal of Neuroscience*, *52*(12), 4908–4922. https://doi.org/10.1111/ejn.14916
Dissanayaka, T., Zoghi, M., Hill, A. T., Farrell, M., Egan, G., & Jaberzadeh, S. (2020). The Effect of Transcranial Pulsed Current Stimulation at 4 and 75 Hz on Electroencephalography Theta and High Gamma Band Power: A Pilot Study. *Brain Connectivity*, *10*(9), 520–531. https://doi.org/10.1089/brain.2020.0756
Dondé, C., Brunelin, J., Micoulaud-Franchi, J.-A., Maruani, J., Lejoyeux, M., Polosan, M., & Geoffroy, P. A. (2021). The Effects of Transcranial Electrical Stimulation of the Brain on Sleep: A Systematic Review. *Frontiers in Psychiatry*, *12*. https://doi.org/10.3389/fpsyt.2021.646569
D'Urso, G., Dini, M., Bonato, M., Gallucci, S., Parazzini, M., Maiorana, N., Bortolomasi, M., Priori, A., & Ferrucci, R. (2022). Simultaneous Bilateral Frontal and Bilateral Cerebellar Transcranial Direct Current Stimulation in Treatment-Resistant Depression—Clinical Effects and Electrical Field Modelling of a Novel Electrodes Montage. *Biomedicines*, *10*(7), 1681. https://doi.org/10.3390/biomedicines10071681
Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, *41*(4), 1149–1160. https://doi.org/10.3758/BRM.41.4.1149
Ford, D. E. (1989). Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA: The Journal of the American Medical Association*, *262*(11), 1479–1484. https://doi.org/10.1001/jama.262.11.1479
Frase, L., Piosczyk, H., Zittel, S., Jahn, F., Selhausen, P., Krone, L., Feige, B., Mainberger, F., Maier, J. G., Kuhn, M., Klöppel, S., Normann, C., Sterr, A., Spiegelhalder, K., Riemann, D., Nitsche, M. A., & Nissen, C. (2016). Modulation of Total Sleep Time by Transcranial Direct Current Stimulation (tDCS). *Neuropsychopharmacology*, *41*(10), 2577–2586. https://doi.org/10.1038/npp.2016.65
Frase, L., Selhausen, P., Krone, L., Tsodor, S., Jahn, F., Feige, B., Maier, J. G., Mainberger, F., Piosczyk, H., Kuhn, M., Klöppel, S., Sterr, A., Baglioni, C., Spiegelhalder, K., Riemann, D., Nitsche, M. A., & Nissen, C. (2019). Differential effects of bifrontal tDCS on arousal and sleep duration in insomnia patients and healthy controls. *Brain Stimulation*, *12*(3), 674–683. https://doi.org/10.1016/j.brs.2019.01.001
Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., & Lu, B. (2010). Direct Current Stimulation Promotes BDNF-Dependent Synaptic Plasticity: Potential Implications for Motor Learning. *Neuron*, *66*(2), 198–204. https://doi.org/10.1016/j.neuron.2010.03.035
Grimaldi, G., Argyropoulos, G. P., Bastian, A., Cortes, M., Davis, N. J., Edwards, D. J., Ferrucci, R., Fregni, F., Galea, J. M., Hamada, M., Manto, M., Miall, R. C., Morales-Quezada, L., Pope, P. A., Priori, A., Rothwell, J., Tomlinson, S. P., & Celnik, P. (2016). Cerebellar Transcranial Direct Current Stimulation (ctDCS). *The Neuroscientist*, *22*(1), 83–97. https://doi.org/10.1177/1073858414559409
Guleyupoglu, B., Schestatsky, P., Edwards, D., Fregni, F., & Bikson, M. (2013). Classification of methods in transcranial Electrical Stimulation (tES) and evolving strategy from historical approaches to contemporary innovations. In *Journal of Neuroscience Methods* (Vol. 219, Issue 2, pp. 297–311). https://doi.org/10.1016/j.jneumeth.2013.07.016
Hadoush, H., Al-Sharman, A., Khalil, H., Banihani, S. A., & Al-Jarrah, M. (2018). Sleep Quality, Depression, and Quality of Life After Bilateral Anodal Transcranial Direct Current Stimulation in Patients with Parkinson's Disease. *Medical Science Monitor Basic Research*, *24*, 198–205. https://doi.org/10.12659/MSMBR.911411
Harvey, A. G. (2001). INSOMNIA: SYMPTOM OR DIAGNOSIS? *Clinical Psychology Review*, *21*(7), 1037–1059. https://doi.org/10.1016/S0272-7358(00)00083-0
Hathaway, E., Morgan, K., Carson, M., Shusterman, R., Fernandez-Corazza, M., Luu, P., & Tucker, D. M. (2021). Transcranial Electrical Stimulation targeting limbic cortex increases the duration of human deep sleep. *Sleep Medicine*, *81*, 350–357. https://doi.org/10.1016/j.sleep.2021.03.001
Jaberzadeh, S., Bastani, A., & Zoghi, M. (2014). Anodal transcranial pulsed current stimulation: A novel technique to enhance corticospinal excitability. *Clinical Neurophysiology*, *125*(2), 344–351. https://doi.org/10.1016/j.clinph.2013.08.025
Jaberzadeh, S., Bastani, A., Zoghi, M., Morgan, P., & Fitzgerald, P. B. (2015). Anodal Transcranial Pulsed Current Stimulation: The Effects of Pulse Duration on Corticospinal Excitability. *PLOS ONE*, *10*(7), e0131779. https://doi.org/10.1371/journal.pone.0131779
Jaberzadeh, S., & Zoghi, M. (2023). Exploring sensory, motor, and pain responses as potential side or therapeutic effects of sub-2 mA, 400 Hz transcranial pulsed current stimulation. *PLOS ONE*, *18*(12), e0290137. https://doi.org/10.1371/journal.pone.0290137
Jones, B. E., & M. Muhlethaler. (1999). *Handbook of behavioral state control: cellular and molecular mechanisms.*

Jouvet, M. (1972). The role of monoamines and acetylcholine-containing neurons in the regulation of the sleep-waking cycle. In *Neurophysiology and Neurochemistry of Sleep and Wakefulness* (pp. 166–307). Springer Berlin Heidelberg. https://doi.org/10.1007/3-540-05462-6_2
Kang, Q., Talesh, A. R., Lang, E. J., & Sahin, M. (2024). Transsynaptic modulation of cerebellar nuclear cells: theta AC-burst stimulation. *Journal of Neural Engineering*, *21*(6). https://doi.org/10.1088/1741-2552/ad9ad1
Ladenbauer, J., Ladenbauer, J., Külzowä, N., De Boor, R., Avramova, E., Grittner, U., & Flöel, A. (2017). Promoting sleep oscillations and their functional coupling by transcranial stimulation enhances memory consolidation in mild cognitive impairment. *Journal of Neuroscience*, *37*(30), 7111–7124. https://doi.org/10.1523/JNEUROSCI.0260-17.2017
Le Bon-Jego, M. (2007). Persistently active, pacemaker-like neurons in neocortex. *Frontiers in Neuroscience*, *1*(1), 123–129. https://doi.org/10.3389/neuro.01.1.1.009.2007
Lee, H. C., Chiu, H. F. K., Wing, Y. K., Leung, C. M., Kwong, P. K., & Chung, D. W. S. (1994). The Zung Self-Rating Depression Scale: Screening for Depression Among the Hong Kong Chinese Elderly. *Journal of Geriatric Psychiatry and Neurology*, *7*(4), 216–220. https://doi.org/10.1177/089198879400700404
Leger, D., Guilleminault, C., Dreyfus, J. P., Delahaye, C., & Paillard, M. (2000). Prevalence of insomnia in a survey of 12 778 adults in France. *Journal of Sleep Research*, *9*(1), 35–42. https://doi.org/10.1046/j.1365-2869.2000.00178.x
Li, T., Qadri, F., & Moser, A. (2004). Neuronal electrical high frequency stimulation modulates presynaptic GABAergic physiology. *Neuroscience Letters*, *371*(2–3), 117–121. https://doi.org/10.1016/j.neulet.2004.08.050
Liu, J., Zou, G., Xu, J., Zhou, S., Qin, L., Sun, H., Zou, Q., & Gao, J.-H. (2023). State-dependent and region-specific alterations of cerebellar connectivity across stable human wakefulness and NREM sleep states. *NeuroImage*, *266*, 119823. https://doi.org/10.1016/j.neuroimage.2022.119823
Liu, Z., Dong, S., Zhong, S., Huang, F., Zhang, C., Zhou, Y., & Deng, H. (2021). The effect of combined transcranial pulsed current stimulation and transcutaneous electrical nerve stimulation on lower limb spasticity in children with spastic cerebral palsy: a randomized and controlled clinical study. *BMC Pediatrics*, *21*(1), 141. https://doi.org/10.1186/s12887-021-02615-1
Ma, H., Lin, J., He, J., Lo, D. H. T., & Tsang, H. W. H. (2021). Effectiveness of TES and rTMS for the Treatment of Insomnia: Meta-Analysis and Meta-Regression of Randomized Sham-Controlled Trials. In *Frontiers in Psychiatry* (Vol. 12). Frontiers Media S.A. https://doi.org/10.3389/fpsyt.2021.744475
Marino, M., Li, Y., Rueschman, M. N., Winkelman, J. W., Ellenbogen, J. M., Solet, J. M., Dulin, H., Berkman, L. F., & Buxton, O. M. (2013). Measuring Sleep: Accuracy, Sensitivity, and Specificity of Wrist Actigraphy Compared to Polysomnography. *Sleep*, *36*(11), 1747–1755. https://doi.org/10.5665/sleep.3142
Marshall, L., Helgadóttir, H., Mölle, M., & Born, J. (2006). Boosting slow oscillations during sleep potentiates memory. *Nature*, *444*(7119), 610–613. https://doi.org/10.1038/nature05278
Martin, J. L., & Hakim, A. D. (2011). Wrist Actigraphy. *Chest*, *139*(6), 1514–1527. https://doi.org/10.1378/chest.10-1872
Marzano, C., Moroni, F., Gorgoni, M., Nobili, L., Ferrara, M., & De Gennaro, L. (2013). How we fall asleep: regional and temporal differences in electroencephalographic synchronization at sleep onset. *Sleep Medicine*, *14*(11), 1112–1122. https://doi.org/10.1016/j.sleep.2013.05.021
Minichino, A., Bersani, F. S., Spagnoli, F., Corrado, A., De Michele, F., Calò, W. K., Primavera, M., Yang, B., Bernabei, L., Macrì, F., Vergnani, L., Biondi, M., & Delle Chiaie, R. (2014). Prefronto-Cerebellar Transcranial Direct Current Stimulation Improves Sleep Quality in Euthymic Bipolar Patients: A Brief Report. *Behavioural Neurology*, *2014*, 1–3. https://doi.org/10.1155/2014/876521
Morales-Quezada, L., Leite, J., Carvalho, S., Castillo-Saavedra, L., Cosmo, C., & Fregni, F. (2016). Behavioral effects of transcranial pulsed current stimulation (tPCS): Speed-accuracy tradeoff in attention switching task. *Neuroscience Research*, *109*, 48–53. https://doi.org/10.1016/j.neures.2016.01.009
Morales-Quezada, L., Saavedra, L. C., Rozisky, J., Hadlington, L., & Fregni, F. (2014). Intensity-dependent effects of transcranial pulsed current stimulation on interhemispheric connectivity. *NeuroReport*, *25*(13), 1054–1058. https://doi.org/10.1097/WNR.0000000000000228
Moruzzi G, & Magoun HW. (1949). *Brain stem reticular formation and activation of the EEG*. Electroencephalogr Clin Neurophysiol.
Murphy, M. J., & Peterson, M. J. (2015). Sleep Disturbances in Depression. *Sleep Medicine Clinics*, *10*(1), 17–23. https://doi.org/10.1016/j.jsmc.2014.11.009
Nagai, M., Hoshide, S., & Kario, K. (2010). Sleep Duration as a Risk Factor for Cardiovascular Disease- a Review of the Recent Literature. *Current Cardiology Reviews*, *6*(1), 54–61. https://doi.org/10.2174/157340310790231635

Nitsche, M. A., Lampe, C., Antal, A., Liebetanz, D., Lang, N., Tergau, F., & Paulus, W. (2006). Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex. *European Journal of Neuroscience*, *23*(6), 1651–1657. https://doi.org/10.1111/j.1460-9568.2006.04676.x
Ohayon, M. M. (2002). Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Medicine Reviews*, *6*(2), 97–111. https://doi.org/10.1053/smrv.2002.0186
Ohayon, M. M. (2011). Epidemiological Overview of sleep Disorders in the General Population. *Sleep Medicine Research*, *2*(1), 1–9. https://doi.org/10.17241/smr.2011.2.1.1
Philip, N. S., Nelson, B. G., Frohlich, F., Lim, K. O., Widge, A. S., & Carpenter, L. L. (2017). Low-Intensity Transcranial Current Stimulation in Psychiatry. *American Journal of Psychiatry*, *174*(7), 628–639. https://doi.org/10.1176/appi.ajp.2017.16090996
Pyragas, K., Novičenko, V., & Tass, P. A. (2013). Mechanism of suppression of sustained neuronal spiking under high-frequency stimulation. *Biological Cybernetics*, *107*(6), 669–684. https://doi.org/10.1007/s00422-013-0567-1
Pyragas, K., & Tass, P. A. (2017). Suppression of spontaneous oscillations in high-frequency stimulated neuron models. *Lithuanian Journal of Physics*, *56*(4), 223–238. https://doi.org/10.3952/physics.v56i4.3419
Qaseem, A., Kansagara, D., Forciea, M. A., Cooke, M., & Denberg, T. D. (2016). Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. *Annals of Internal Medicine*, *165*(2), 125–133. https://doi.org/10.7326/M15-2175
Reato, D., Gasca, F., Datta, A., Bikson, M., Marshall, L., & Parra, L. C. (2013). Transcranial Electrical Stimulation Accelerates Human Sleep Homeostasis. *PLoS Computational Biology*, *9*(2), e1002898. https://doi.org/10.1371/journal.pcbi.1002898
Riemann, D. (2003). Primary insomnia: a risk factor to develop depression? *Journal of Affective Disorders*, *76*(1–3), 255–259. https://doi.org/10.1016/S0165-0327(02)00072-1
Riemann D, & Nissen C. (2012). *Sleep and Psychotropic Drugs. In: Morin CM, Espie CA (eds). Oxford handbook of sleep and sleep disorders*. Oxford University Press: Oxford.
Rossman, J. (2019). Cognitive-Behavioral Therapy for Insomnia: An Effective and Underutilized Treatment for Insomnia. *American Journal of Lifestyle Medicine*, *13*(6), 544–547. https://doi.org/10.1177/1559827619867677
Saebipour, M. R., Joghataei, M. T., Yoonessi, A., Sadeghniiat-Haghighi, K., Khalighinejad, N., & Khademi, S. (2015). Slow oscillating transcranial direct current stimulation during sleep has a sleep-stabilizing effect in chronic insomnia: a pilot study. *Journal of Sleep Research*, *24*(5), 518–525. https://doi.org/10.1111/jsr.12301
Saper, C. B., Fuller, P. M., Pedersen, N. P., Lu, J., & Scammell, T. E. (2010). Sleep State Switching. *Neuron*, *68*(6), 1023–1042. https://doi.org/10.1016/j.neuron.2010.11.032
Saper, C. B., Scammell, T. E., & Lu, J. (2005). Hypothalamic regulation of sleep and circadian rhythms. *Nature*, *437*(7063), 1257–1263. https://doi.org/10.1038/nature04284
Sheng, J., Xie, C., Fan, D., Lei, X., & Yu, J. (2018). High definition-transcranial direct current stimulation changes older adults' subjective sleep and corresponding resting-state functional connectivity. *International Journal of Psychophysiology*, *129*, 1–8. https://doi.org/10.1016/j.ijpsycho.2018.05.002
Sivertsen, B., Hysing, M., Harvey, A. G., & Petrie, K. J. (2021). The Epidemiology of Insomnia and Sleep Duration Across Mental and Physical Health: The SHoT Study. *Frontiers in Psychology*, *12*. https://doi.org/10.3389/fpsyg.2021.662572
Sours, C., Alon, G., Roys, S., & Gullapalli, R. P. (2014). Modulation of Resting State Functional Connectivity of the Motor Network by Transcranial Pulsed Current Stimulation. *Brain Connectivity*, *4*(3), 157–165. https://doi.org/10.1089/brain.2013.0196
Steriade, M. (2006). Grouping of brain rhythms in corticothalamic systems. *Neuroscience*, *137*(4), 1087–1106. https://doi.org/10.1016/j.neuroscience.2005.10.029
Steriade, M., & Timofeev, I. (2003). Neuronal Plasticity in Thalamocortical Networks during Sleep and Waking Oscillations. *Neuron*, *37*(4), 563–576. https://doi.org/10.1016/S0896-6273(03)00065-5
Steriade, Mircea M, & Robert W. McCarley. (2013). *Brainstem control of wakefulness and sleep.* . Springer Science & Business Media.
Taylor, D. J., Mallory, L. J., Lichstein, K. L., Durrence, H. H., Riedel, B. W., & Bush, A. J. (2007). Comorbidity of Chronic Insomnia With Medical Problems. *Sleep*, *30*(2), 213–218. https://doi.org/10.1093/sleep/30.2.213
Tsai, P.-S., Wang, S.-Y., Wang, M.-Y., Su, C.-T., Yang, T.-T., Huang, C.-J., & Fang, S.-C. (2005). Psychometric Evaluation of the Chinese Version of the Pittsburgh Sleep Quality Index (CPSQI) in Primary Insomnia and Control Subjects. *Quality of Life Research*, *14*(8), 1943–1952. https://doi.org/10.1007/s11136-005-4346-x
Vasquez, A. C., Thibaut, A., Morales-Quezada, L., Leite, J., & Fregni, F. (2017). Patterns of brain oscillations across different electrode montages in transcranial pulsed current stimulation. *NeuroReport*, *28*(8), 421–425. https://doi.org/10.1097/WNR.0000000000000772

Vasquez, A., Malavera, A., Doruk, D., Morales-Quezada, L., Carvalho, S., Leite, J., & Fregni, F. (2016). Duration Dependent Effects of Transcranial Pulsed Current Stimulation (tPCS) Indexed by Electroencephalography. *Neuromodulation: Technology at the Neural Interface*, *19*(7), 679–688. https://doi.org/10.1111/ner.12457
Wang, H. X., Wang, L., Zhang, W. R., Xue, Q., Peng, M., Sun, Z. C., Li, L. P., Wang, K., Yang, X. T., Jia, Y., Zhou, Q. L., Xu, Z. X., Li, N., Dong, K., Zhang, Q., Song, H. Q., Zhan, S. Q., Min, B. Q., Fan, C. Q., … Wang, Y. P. (2020). Effect of Transcranial Alternating Current Stimulation for the Treatment of Chronic Insomnia: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Clinical Trial. *Psychotherapy and Psychosomatics*, *89*(1), 38–47. https://doi.org/10.1159/000504609
World Health Organization. (2022, March 2). *COVID-19 pandemic triggers 25% increase in prevalence of anxiety and depression worldwide*. WHO News.
Ye, X., Feng, Z., Wang, Z., Zheng, L., Yuan, Y., Hu, Y., & Xu, Y. (2022). Activating Interneurons in Local Inhibitory Circuits by High-Frequency Stimulations at the Efferent Fibers of Pyramidal Neurons in Rat Hippocampal CA1 Region. *Brain Sciences*, *12*(10), 1350. https://doi.org/10.3390/brainsci12101350
Yin, J., Jin, X., Shan, Z., Li, S., Huang, H., Li, P., Peng, X., Peng, Z., Yu, K., Bao, W., Yang, W., Chen, X., & Liu, L. (2017). Relationship of Sleep Duration With All-Cause Mortality and Cardiovascular Events: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. *Journal of the American Heart Association*, *6*(9). https://doi.org/10.1161/JAHA.117.005947
Yuan, Y., Feng, Z., Yang, G., Ye, X., & Wang, Z. (2022). Suppression of Neuronal Firing Following Antidromic High-Frequency Stimulations on the Neuronal Axons in Rat Hippocampal CA1 Region. *Frontiers in Neuroscience*, *16*. https://doi.org/10.3389/fnins.2022.881426
Zhou, Q., Yu, C., Yu, H., Zhang, Y., Liu, Z., Hu, Z., Yuan, T.-F., & Zhou, D. (2020). The effects of repeated transcranial direct current stimulation on sleep quality and depression symptoms in patients with major depression and insomnia. *Sleep Medicine*, *70*, 17–26. https://doi.org/10.1016/j.sleep.2020.02.003
ZUNG, W. W. K. (1965). A Self-Rating Depression Scale. *Archives of General Psychiatry*, *12*(1), 63. https://doi.org/10.1001/archpsyc.1965.01720310065008
Zung, W. W. K. (1971). A Rating Instrument For Anxiety Disorders. *Psychosomatics*, *12*(6), 371–379. https://doi.org/10.1016/S0033-3182(71)71479-0

Trial Protocol Amendment Date： ___NOV 05, 2023___

Principal Investigator： ____Hao Fengyi___

Signature： _____

Appendix 1 – Informed Consent Form (Original Mandarin)

(Translated to English)

Informed Consent Form

Dear Mr./Ms. _____,

We would like to invite you to participate in a study investigating the effects of **Modulation of Total Sleep Time by Cerebellar Transcranial Pulsed Current Stimulation (tPCS) in People with Chronic Insomnia with and without Comorbid Depression: A Pilot Study**. This study has been reviewed and approved by the Ethics Committee of Chongqing Western Hospital.

This informed consent form provides information about the purpose, procedures, potential benefits, risks, inconveniences, and your rights as a participant. Please read it carefully and decide whether to participate after thoughtful consideration. When the researchers explain and discuss this consent form with you, you may ask questions at any time and request clarification for anything you do not understand. You may also discuss your decision with your family members, friends, or your attending physician before deciding.

The principal investigator of this study is **Xiaojiang Jiang (Chongqing Western District Hospital)**.

1. Why is this study being conducted?

Existing evidence suggests that cerebellar activity is closely related to sleep states. Research has shown that external electrical modulation, particularly high-frequency electrical stimulation, can modulate cerebellar activity to support sleep-wake regulation.

Currently, medications for treating arousal or sleep disorders mainly act by altering aminergic, cholinergic, or GABAergic neurotransmitters in the brainstem arousal system. However, these medications often have adverse side effects and limited therapeutic efficacy. For example, drugs used to treat insomnia, such as benzodiazepines and benzodiazepine receptor agonists, carry the risk of tolerance. Patients are often concerned about the potential risk of dependence, leading to poor treatment adherence and reduced effectiveness.

For patients diagnosed with primary insomnia, this issue can be particularly severe, as there is no clear etiology and drug treatment is often based on trial and error. This means patients may experience various medication side effects before an effective solution is found. Another first-line treatment for insomnia is cognitive behavioral therapy (CBT). Although it has achieved considerable success, it requires working with trained therapists, which can be time-consuming, inconvenient, and costly.

It is noteworthy that evidence in the literature indicates that approximately **40% of patients do not achieve long-term remission** with medication or cognitive behavioral therapy. Therefore, there is an urgent need for treatment options with fewer side effects, better cost-effectiveness, and greater convenience. **Home-based, self-administered devices** may provide a potential solution.

2. How many people will participate in this study?

A total of **38 participants** are planned to be recruited for this study.

3. What does participation in this study involve?

Baseline data will be collected one week before treatment. Participants will then receive two consecutive weeks of treatment—a total of 12 sessions (Monday to Saturday), each lasting 30 minutes, using transcranial pulsed current stimulation (current intensity: 0.6 mA). Treatment efficacy will be evaluated after two weeks.

The following data will be collected one week before treatment:

1. Objective sleep indicators measured by an actigraphy device, including sleep onset latency, sleep efficiency, and wake after sleep onset.
2. Subjective sleep indicators measured using the Pittsburgh Sleep Quality Index (PSQI), including sleep initiation, sleep maintenance, and sleep quality.
3. Depression scores measured using the Self-Rating Depression Scale (SDS).
4. Anxiety scores measured using the Self-Rating Anxiety Scale (SAS**)** in patients with major depressive disorder accompanied by insomnia.

The test results will be provided to you after the completion of treatment.

4. How long will the study last?

The study will last 2 weeks, comprising 12 treatment sessions.

Baseline data will be collected one week before treatment.

Post treatment data will be collected as follows:

- Actigraphy measurements will be collected on the evenings of the last three treatment sessions.
- Within one week after the final treatment session, post-treatment PSQI, SDS, SAS, and health-related data will be collected.

5. What are the risks of participating in this study?

Possible risks include:

- The possibility that the study may not improve your clinical symptoms
- Time commitment (questionnaires: approximately 20 minutes each, 2 times; tPCS treatment: 30 minutes per session, 12 sessions total)
- Possible psychological discomfort
- Possible discomfort at the stimulation site including skin redness , itchiness , scalp pain
- Possible mild headache , neck pain
- In rare cases , more serious risks such as nausea, seizures, severe headache, dizziness

If you feel uncomfortable, you may refuse to answer questions or discontinue treatment at any time.

6.What are the potential benefits of participating?

Potential benefits include receiving free transcranial pulsed current stimulation treatment, as well as sleep monitoring reports and questionnaire assessment reports.

Your participation will help researchers obtain more reliable data, contributing to future understanding and scientific diagnosis of such conditions. The results of this study may help identify more scientifically sound treatment options for you and other patients with similar conditions.

7. Is participation mandatory?

Your participation in this study is entirely **voluntary**. If you do not wish to participate, you may refuse without any negative impact on your current or future medical care. Physicians will continue to provide routine medical treatment.

Even if you agree to participate, you may withdraw from the study at any time by informing the researchers. Your withdrawal will not affect your access to normal medical services. In principle, after your withdrawal, the researchers will securely store your previously collected information until final destruction, and it will not be further used or disclosed.

During the study, if any new information arises that may affect your decision to continue participating, we will inform you promptly.

8. Are there any costs or compensation for participation?

The costs associated with actigraphy, questionnaire assessments, and transcranial pulsed current stimulation treatment will be fully covered by the study. You will not be required to pay any fees. No financial compensation will be provided.

9.Will participants receive payment?

No payment will be provided to participants.

10.What happens if a study-related injury occurs?

If you are injured as a result of participating in this study, please inform the researchers as soon as possible. Necessary medical measures will be provided. In accordance with relevant Chinese laws and regulations, the study sponsor will bear the corresponding medical expenses and provide appropriate financial compensation.

11.Will my information be kept confidential?

If you decide to participate, your participation and personal data will be kept **confidential**. Samples collected from you will be identified using a research code rather than your name. Without your permission, any information that could identify you will not be disclosed to anyone outside the research team.

All research staff and related parties are required to keep your identity confidential. Your records will be stored in locked filing cabinets and accessed only by researchers. When necessary, government regulatory authorities or ethics committee members may review your personal data at the research site in accordance with regulations. When the study results are published, no identifying information will be disclosed.

12.Who should I contact if I have questions or difficulties?

If you have any questions related to this study, please contact **Xiaojiang Jiang** at **023-81913165**. If you have questions regarding your rights and interests, you may contact the **Ethics Committee of Chongqing Western District Hospital**.

Participant Signature Page

Informed Consent Statement

I have been informed of the purpose, background, procedures, risks, and benefits of this study. I have had sufficient time and opportunity to ask questions, and I am satisfied with the answers provided.

I have been informed whom to contact if I have questions, concerns, suggestions regarding the study, or if I would like to obtain further information or provide assistance to the study.

I have read this informed consent form and agree to participate in this study.

I understand that I may choose not to participate or may withdraw from the study at any time without providing a reason.

I understand that if my condition worsens, if I experience serious adverse events, or if the study physician believes that continued participation is not in my best interest, he/she may decide to withdraw me from the study without my consent. The sponsor or regulatory authorities may also terminate the study during its course. If this occurs, the physician will inform me promptly and discuss alternative options with me.

I will receive a copy of this informed consent form signed by both myself and the researcher.

Participant Name: _____ Contact Information: _____

Participant Signature: _____ Date: _____

Researcher Statement

I confirm that I have explained the details of this study to the participant, particularly the potential risks and benefits of participation.

Researcher Name: _____ Contact Information: _____

Researcher Signature: _____ Date: _____

经颅脉冲电流刺激（tPCS）对失眠患者总睡眠时间的影响：一项先导研究

1. 研究背景与依据

1.1 总体介绍

睡眠障碍在普通人群以及抑郁症患者中均十分常见（Murphy & Peterson, 2015；Ohayon, 2011），其中失眠是最常见的一种睡眠障碍类型（American Psychiatric Association, 2013；Ohayon, 2002）。失眠本身可以作为一种独立疾病存在（如原发性失眠），也可能作为更复杂的睡眠障碍、躯体疾病或精神疾病的共病症状出现（Harvey, 2001）。觉醒与睡眠状态的异常与多种不良健康结局风险增加相关，包括糖尿病、卒中、冠心病和心肌梗死风险升高（Bertisch 等, 2018；Nagai 等, 2010；Taylor 等, 2007；Yin 等, 2017），心理健康问题（Sivertsen 等, 2021），甚至死亡风险增加（Cappuccio 等, 2010）。因此，治疗失眠对改善整体健康状况和生活质量具有重要意义。

新冠疫情（COVID-19）之后，世界卫生组织（WHO）报告全球焦虑和抑郁的患病率显著上升，增幅高达 25%（World Health Organization, 2022）。一项系统综述和荟萃分析表明，普通人群及 COVID-19 患者中的失眠与抑郁和/或焦虑障碍风险显著增加密切相关（Alimoradi 等, 2021）。此外，多项具有大样本量和长期随访的观察性研究也报告了失眠与抑郁之间的类似关联（Ford, 1989；Leger 等, 2000）。例如，失眠与 1–3 年内抑郁症后续发生之间的关联尤为显著（Riemann, 2003）。尽管目前尚不清楚失眠是抑郁的致因，还是抑郁继发导致失眠，但二者之间高度相关的证据表明，治疗失眠不仅可能改善总体健康结局，也可能对抑郁症状产生治疗获益。

1.2 睡眠–觉醒调控的神经生物学机制

哺乳动物睡眠–觉醒调控的经典模型包括两条主要通路。第一条是经典的“自下而上”通路，涉及皮层–丘脑–皮层回路，包括脑干核团（如上行网状激活系统，ARAS）、丘脑和大脑皮层，通过神经递质释放实现调控（Jones & Muhlethaler, 1999；Jouvet, 1972；Moruzzi & Magoun, 1949；Steriade 等, 2013）。在入睡和睡眠维持过程中，下丘脑腹外侧视前区（VLPO）内的 GABA 能睡眠促进神经元抑制 ARAS 和食欲素系统中促进觉醒的神经元群，使其活动逐渐下降（Berridge 等, 2012）。ARAS 与 VLPO 共同构成一个“翻转开

关（flip-flop switch）”机制，在食欲素能神经元的稳定作用下维持清醒与睡眠之间的清晰转换，而食欲素是一种由外侧下丘脑产生的高度兴奋性神经肽（Saper 等, 2005, 2010）。第二条通路为“自上而下”调控通路（Chauvette 等, 2010；Le Bon-Jego, 2007；Steriade & Timofeev, 2003），其中额叶皮层神经元作为同步慢波振荡的起源，在睡眠过程中逐渐出现（Marzano 等, 2013；Steriade, 2006）。

鉴于经颅电刺激（tES），包括经颅直流电刺激（tDCS）和经颅交流电刺激（tACS），能够调节皮层兴奋性（Frase 等, 2016, 2019；Hadoush 等, 2018；Minichino 等, 2014；Sheng 等, 2018；Zhou 等, 2020），并可对内源性脑振荡产生同步与诱导作用（Hathaway 等, 2021；Ladenbauer 等, 2017；Marshall 等, 2006；Reato 等, 2013；Saebipour 等, 2015；Wang 等, 2020），因此其可能成为通过调节睡眠–觉醒机制来干预失眠相关异常状态的一种新型治疗手段。

1.3 小脑作为神经调控靶点的科学依据

近年来，小脑皮层逐渐被探索为 tES 的潜在睡眠调控靶点（D’Urso 等, 2022；Grimaldi 等, 2016；Minichino 等, 2014），这是因为越来越多证据表明小脑参与睡眠过程的调节（Cunchillos & De Andrés, 1982；刘杰 等, 2023），并且小脑通过丘脑、脑桥、中脑–间脑交界区以及下橄榄核与大脑皮层存在广泛的双向连接（Andre & Arrighi, 2003；De Zeeuw 等, 2008）。例如，小脑包含大量浦肯野细胞，这些细胞为 GABA 能神经元，对小脑深核（DCN）具有强烈的抑制性调控作用（Kang 等, 2024）。DCN 是小脑的主要输出结构，广泛投射至丘脑及脑干觉醒系统，包括 ARAS 的多个组成部分（Berridge 等, 2012）。既往研究显示，采用左侧背外侧前额叶皮层（DLPFC）阳极 tDCS 联合右侧小脑皮层阴极 tDCS（2 mA，每日 20 分钟，持续 3 周），显著改善了双相障碍缓解期患者的匹兹堡睡眠质量指数（PSQI）总分及睡眠质量、入睡潜伏期、睡眠时间等多项指标（Minichino 等, 2014）。

此外，临床前高频电刺激研究表明，其可能通过减少 GABA 再摄取（Li 等, 2004）和激活 GABA 能中间神经元（Ye 等, 2022）增强 GABA 能信号传导，同时抑制神经元放电和自发振荡活动（Pyragas 等, 2013；Pyragas & Tass, 2017；Yuan 等, 2022）。因此，采用较高频率波形的 tES 可能在降低过度兴奋性驱动、增强抑制性控制方面具有额外作用，这与当前失眠的病理生理模型相一致，并可能有助于缓解失眠症状。

1.4 现有治疗局限性与临床需求

目前用于临床失眠治疗的药物方案（如苯二氮卓类及苯二氮卓受体激动剂）已被报道

存在不良药物副作用及疗效有限等问题（Riemann & Nissen, 2012）。患者还可能因担心产生药物依赖而依从性较差，从而影响治疗效果。另一种一线治疗方案为失眠的认知行为治疗（CBT-I）（Rossman, 2019）。尽管 CBT-I 疗效确切，但其通常需要由合格治疗师实施，过程可能较为耗时、不便且费用较高。

值得注意的是，文献证据显示，无论是药物治疗还是 CBT-I，约有 40% 的失眠患者未能获得长期缓解（Qaseem 等, 2016）。因此，亟需开发副作用更低、成本效益更高且使用更便捷的治疗方案。可居家使用、由患者自我管理的 tES 设备有望成为一种潜在解决方案。

1.5 技术选型与参数设定依据

根据输出电流模式的不同，经颅电刺激（tES）可分为多种形式（Guleyupoglu 等, 2013），包括经颅直流电刺激（tDCS）、经颅交流电刺激（tACS）、经颅随机噪声刺激（tRNS）以及经颅脉冲电流刺激（tPCS）。其中，tPCS 是最新的一种形式，近年来在实验研究中逐渐受到关注（Alon 等, 2012；Dissanayaka, Zoghi, Hill 等, 2020；Jaberzadeh 等, 2014, 2015；Jaberzadeh & Zoghi, 2023；Sours 等, 2014）。tPCS 通过向大脑皮层输送预设频率的脉冲电流发挥作用。

在一项将 tPCS 与 tDCS 进行比较的研究中（Jaberzadeh 等, 2014），结果显示在总电荷量相当的前提下，采用短脉冲间隔（50 ms，1.8 Hz）的 a-tPCS 相比 tDCS 在初级运动皮层对皮质脊髓兴奋性的增强作用更为显著。Jaberzadeh 等人提出，tPCS 的作用机制可能同时包含持续性（tonic）效应和相位性（phasic）效应。头部电场建模研究也支持 tPCS 具有额外优势，即可能作用于更深层的脑区，包括中脑、脑桥、岛叶、丘脑及下丘脑（Datta 等, 2013）。这一点对失眠治疗意义重大，因为调控睡眠-觉醒周期的关键结构（如下丘脑）位于深部皮层下。

在本研究中，tPCS 电极将置于双侧小脑半球，采用高频脉冲电流（400 Hz）以调控小脑活动；刺激强度设定为 0.6 mA，每次刺激 30 分钟，每周 6 次，连续 2 周，共计 12 次刺激疗程。本研究的 tPCS 电极放置设计见图 1。

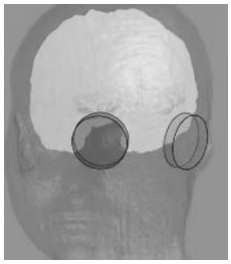


图 1. 失眠治疗刺激布置——双侧小脑半球电极布置

1.6 研究假设

本研究假设：在失眠患者中，tPCS 联合标准药物治疗相较于单纯药物治疗，能更有效地改善患者的客观总睡眠时间（基于腕式体动记录仪数据）。

1.7 研究目的

1. 主要目的：评估 tPCS 联合标准药物治疗对比单纯标准药物治疗（假刺激对照），在改善失眠患者 腕式体动记录仪导出的总睡眠时间（TST） 方面的有效性。

2. 次要目的：

核心次要目的：如果主要目标治疗组间有显著差异， 评估 tPCS 联合标准药物治疗对比单纯标准药物治疗（假刺激对照），在改善睡眠质量（PSQI） 总分的变化

- 评估其他客观睡眠指标的变化（睡眠效率 SE、入睡潜伏期 SL、卧床总时间 TIB、入睡后清醒时间 WASO、觉醒次数等）。
- 评估主观睡眠质量（PSQI 各因子分）的变化。
- 评估抑郁症状（SDS）及焦虑症状（SAS）的变化。

2. 研究对象

2.1 样本量与入组性质

本研究初始样本量估算参考了 V. Ayanampudi 等（2023）关于 tACS 改善睡眠的同类研究（其结果显示客观 TST 增加约 33 分钟），但在项目实施阶段，预实验结果提示本研究采用的 tPCS 干预临床效应强于既往 tACS 报道（预实验观察到 TST 延长约为 60 分钟），基于统计学中“效应量增强可相应降低所需样本量”的原理，并参照先导性试验常规设计标准，课题组对样本量进行了计算：在假设 TST 标准差为 60 分钟的前提下，设定目标分析样本量为 30 例（每组 15 例），该规模可将组间 TST 差异的 95% 置信区间半宽控制在 ±43 分钟以内（计算依据：$1.96 \times 60 \times \sqrt{1/15 + 1/15} \approx 42.9$），满足对参数估计精度的需求；此外，考虑到失眠伴抑郁群体约 20% 的潜在脱落率，最终确定实际入组 38 名受试者。

2.2 招募与筛选

符合条件的受试者将从重庆西区医院睡眠门诊及相关科室接受诊疗或随访的人群中招募。研究人员将向有意向参与的患者提供详细的研究信息说明，并在签署知情同意书后启

动筛选流程。

2.3 纳入标准

1. 年龄 18–65 岁的成年受试者，性别不限；

2. 由合格精神科医师依据《国际疾病分类第十版》（ICD-10）与美国睡眠医学学会《国际睡眠障碍分类》第三版文本修订本（ICSD-3-TR）结合主观和客观睡眠障碍评估，确诊为失眠；

3.19 项匹兹堡睡眠质量指数（PSQI）评分 11–21 分；

3. 基线期经腕式体动记录仪（ActiGraph wGT3X-BT）连续三整夜监测，平均总睡眠时间（TST）≤480 分钟（≤8 小时）；

4. 有生育可能的女性需提供妊娠试验阴性结果；

5. 筛查前至少 30 天内药物剂量稳定；**允许在维持原有药物方案及剂量稳定的前提下入组**，需完整记录研究期间用药情况；

6. 能够提供书面知情同意，并能够遵循研究方案完成全部研究流程。

2.4 排除标准

1. **重大安全风险**：存在严重的焦虑或抑郁症状，并伴有需要立即医学干预的自杀风险或行为；

2. **重性精神疾病**：患有严重的精神疾病（如精神分裂症、双相情感障碍躁狂发作等）；

3. **tPCS 禁忌证**：头颅内有金属异物、铁磁性植入物；既往脑部手术史；癫痫病史；体内植入有深部脑刺激器、心脏起搏器或除颤器；

4. **严重躯体共病**：存在不稳定的心血管、呼吸系统、代谢性疾病等导致的功能障碍；

5. **其他睡眠障碍**：合并除失眠以外的其他原发性睡眠障碍（如中重度阻塞性睡眠呼吸暂停、发作性睡病等）；

6. **特殊人群**：妊娠期或哺乳期女性；夜班工作者或昼夜节律紊乱者；

7. **物质依赖**：有严重的酒精依赖、咖啡因依赖或药物滥用史；

8. **治疗冲突**：当前正在接受心理治疗（如 CBT-I）；参与其他临床研究；近期（3 个月内）接受过其他无创脑刺激治疗。

2.5 脱落与数据处理

脱落定义：在研究过程中出现严重不良反应、无法耐受刺激过程或受试者主动撤回知情同意。

缺失数据处理：研究人员将尽力联系脱落受试者记录原因。统计分析将遵循符合方案集（Per-Protocol）原则，纳入完成干预并具有治疗后结局数据的受试者进行分析。

3. 研究设计与实施流程

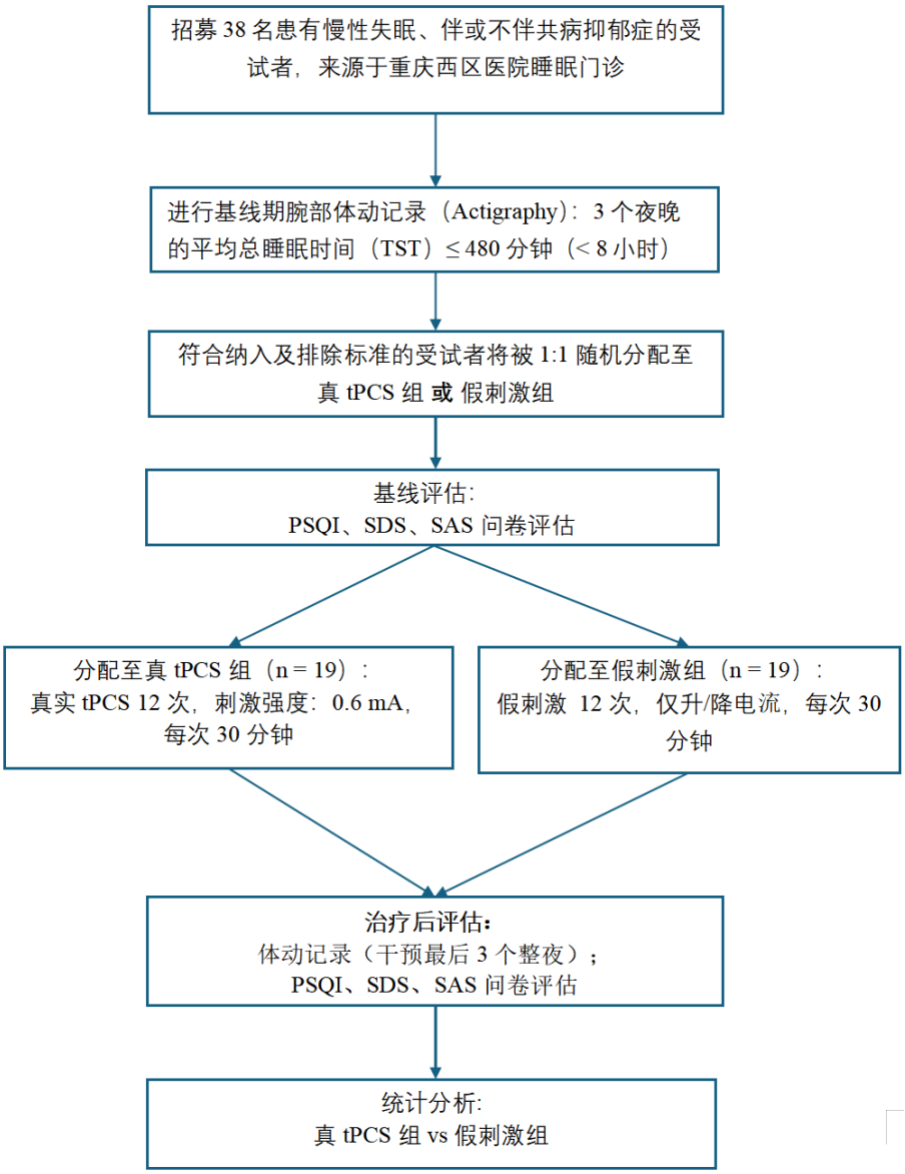


图 2. 研究流程图

3.1 总体设计与随机化

本研究采用前瞻性、单中心、随机、双盲、假刺激对照（Sham-controlled） 设计。

分组：符合纳入标准的 38 名受试者将按就诊顺序编号（1–38），并按 1:1 比例随机分配至真刺激组（Active tPCS） 或 假刺激组（Sham），每组各 19 例。

随机化实施：由一名不参与研究操作的独立统计学人员使用 SPSS® 23.0 生成随机序列。

分配隐匿：随机结果置于不透明、密封信封中，受试者入组后领取对应信封。

3.2 盲法设计

本研究采用双盲设计，受试者与评估人员均不知晓分组情况。

设备盲法：真、假设备外观完全一致。

操作盲法：设备放置于布局相同的独立治疗室，由不参与评估的治疗人员操作。

受试者盲法：受试者均为 tPCS 初次使用者，且假刺激方案包含模拟的皮肤感觉，有效维持盲法。

评估盲法：由重庆西区医院两名具备资质的心理学家负责评估，他们不参与随机化及干预实施。

3.3 干预措施

所有受试者在维持原有标准药物治疗的基础上，接受 tPCS 干预。

频率：每周 6 次（周一至周六），连续 2 周，共 12 次。

真刺激组：400 Hz，0.6 mA，持续 30 分钟。

假刺激组：电流在 10 秒内升至 0.6 mA，5 秒内降至 0 mA，剩余时间无输出（模拟皮下感觉）。

地点：所有治疗均在重庆西区医院进行。

3.4 研究访视流程表

表 1. 研究访视流程

研究阶段	时间点	主要内容
筛选/基线	第 0 周	1. 签署知情同意书 2. 佩戴体动记录仪（连续 3 晚，TST ≤ 8h） 3. 完成基线量表（PSQI, SAS, SDS）
干预期	第 1-2 周	1. 接受 12 次 tPCS 治疗（真/假） 2. 维持标准药物治疗
治疗后评估	第 2 周结束前	1. 佩戴体动记录仪（干预最后 3 晚，即第 11-13 次访视后） 2. 完成治疗后量表（PSQI, SAS, SDS）

4. 结局指标与评估工具

4.1 主要结局指标

客观总睡眠时间（TST）

工具：腕式体动记录仪（ActiGraph wGT3X-BT；ActiGraph LLC，美国）。

方法：对比干预前 3 晚与干预最后 3 晚（访视 11、12、13 后夜间）的平均 TST。体动记录仪是一种经验证的客观测量方法，其准确率约为 86%（Marino 等, 2013）。

4.2 次要结局指标

1．**其他客观睡眠参数**（基于体动记录仪）：包括睡眠效率（SE）、入睡潜伏期（SL）、卧床总时间（TIB）、入睡后清醒时间（WASO）、觉醒次数等。

2．**主观睡眠质量（PSQI）**：采用中文版匹兹堡睡眠质量指数。PSQI 总分 >5 分提示睡眠质量较差（Buysse 等, 1989）。

3．**抑郁症状（SDS）**：采用 Zung 自评抑郁量表。原始分乘以 1.25 转换为指数分，≥50 分提示存在抑郁症状（Lee 等, 1994）。

4．**焦虑症状（SAS）**：采用 Zung 自评焦虑量表。指数分 ≥50 分提示存在焦虑症状（Zung, 1971）。

5. 统计分析

5.1 分析策略

所有统计分析将使用 IBM SPSS Statistics (v23.0) 及 R 软件 (v4.2.2) 完成。分析将基于符合方案集，即完成干预并具有治疗后数据的受试者。

5.2 统计方法

统计软件与分析集所有统计分析计划使用 IBM SPSS Statistics (v23.0) 及 R 软件 (v4.2.2) 进行，分析基于符合方案集。

基线分析时，通过 Shapiro-Wilk 或 K-S 检验评估正态性；对于连续变量，正态分布用 t 检验，非正态用 Wilcoxon 秩和检验及 Wilcoxon 秩和精确检验；分类变量用卡方检验或 Fisher 精确检验。

疗效分析组间比较采用协方差分析 (ANCOVA)；若数据不满足正态性，则采用秩协方差分析 (Rank ANCOVA)。

多重校正时，次要结局指标采用 Holm-Bonferroni 校正；探索性分析采用 FDR (Benjamini-Hochberg) 校正；主要结局指标不校正。

对于不良事件的比较，采用卡方检验或 Fisher 精确检验。

对于真刺激组，治疗后 TST 与 SDS/SAS 评分之间的探索性关联，若数据服从正态分布，将采用 Pearson 相关系数分析；若不服从正态分布，采用非参数 Kendall 秩相关系数检验或 Spearman 秩相关系数检验。

显著性设置为双侧 $P < 0.05$。

6. 试验设备

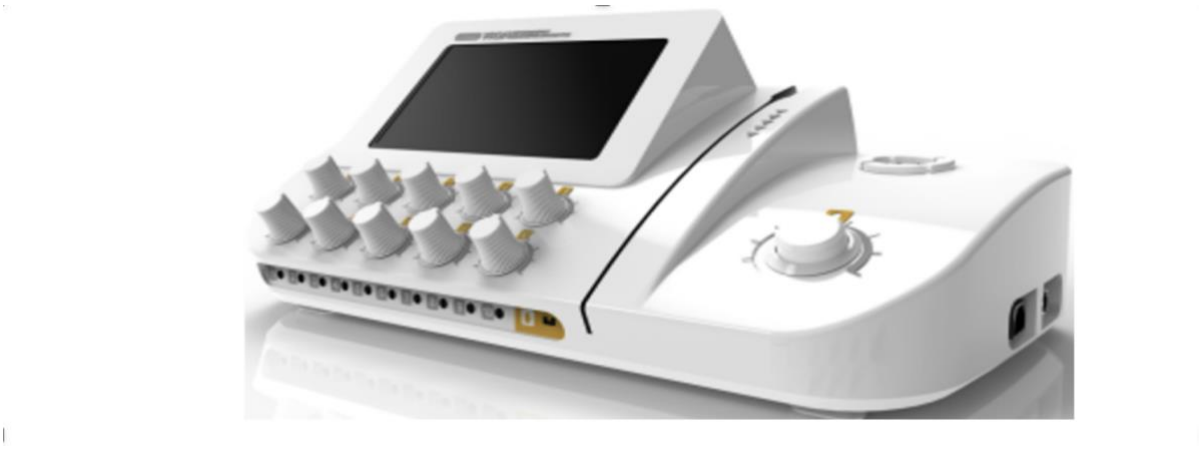
YQ-D1111 经颅脉冲电流刺激仪（北京易奇生物技术有限公司，见图 3）

波形：单相方波

频率：400 Hz

强度：0.6 mA

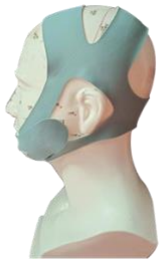
电极：圆形银纤维棉电极（面积 12.56 cm^2），需预先浸润于 0.9% 生理盐水。



设备型号: YQ-D1111 经颅脉冲电流刺激仪（北京易奇生物技术有限公司，北京，中国）

图 3. 试验设备图

银纤维棉电极



7. 研究时间

研究周期：2023 年 6 月 19 日 – 2025 年 6 月 30 日。

发表：研究结果将遵循 CONSORT 2025 声明发表于同行评议期刊。

8. 安全性与伦理

8.1 风险评估与监测

tPCS 总体安全性良好，潜在风险包括轻微的头皮刺痛、一过性头痛或皮肤发红。既往 tDCS 研究提示极少数情况可能影响情绪（如躁狂风险），尽管 tPCS 尚无此类报告，本研究仍将密切监测。

不良事件（AE）记录：所有 AE 将被完整记录。

严重不良事件（SAE）处理：如发生 SAE（如危及生命、需住院），立即停止干预并上报伦理委员会。

终止标准：如受试者无法耐受刺激或出现明显不适，将终止其参与。

8.2 伦理考量

本研究遵循《赫尔辛基宣言》及 GCP 规范。

知情同意：所有受试者在入组前均需签署知情同意书。

隐私保护：所有数据匿名化处理，仅限授权研究人员访问。

9. 经费与资源

本研究由重庆西区医院提供场地、人员及评估支持；本研究获得国家自然科学基金（编号：823B2029）, 重庆自然科学基金 （编号：CSTB2023NSCQ-MSX0779）和北京市科学技术委员会（编号：D171100007017001）的资助，资助经费用于承担与研究相关的各项费用，包括经颅脉冲电流刺激设备的租赁费用、活动记录仪的购置费用、评估量表的使用费用以及研究过程相关的操作性支出。

References:

Alimoradi, Z., Broström, A., Tsang, H. W. H., Griffiths, M. D., Haghayegh, S., Ohayon, M. M., Lin, C.-Y., & Pakpour, A. H. (2021). Sleep problems during COVID-19 pandemic and its' association to psychological distress: A systematic review and meta-analysis. *EClinicalMedicine*, *36*, 100916. https://doi.org/10.1016/j.eclinm.2021.100916

Alon, G., Roys, S. R., Gullapalli, R. P., & Greenspan, J. D. (2011). Non-invasive electrical stimulation of the brain (ESB) modifies the resting-state network connectivity of the primary motor cortex: A proof of concept fMRI study. *Brain Research*, *1403*, 37–44. https://doi.org/10.1016/j.brainres.2011.06.013

Alon, G., Yungher, D. A., Shulman, L. M., & Rogers, M. W. (2012). Safety and Immediate Effect of Noninvasive Transcranial Pulsed Current Stimulation on Gait and Balance in Parkinson Disease. *Neurorehabilitation and Neural Repair*, *26*(9), 1089–1095. https://doi.org/10.1177/1545968312448233

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

Ancoli-Israel, S., Cole, R., Alessi, C., Chambers, M., Moorcroft, W., & Pollak, C. P. (2003). The Role of Actigraphy in the Study of Sleep and Circadian Rhythms. Sleep, 26(3), 342–392. https://doi.org/10.1093/sleep/26.3.342

Andre, P., & Arrighi, P. (2003). Hipnic modulation of cerebellar information processing: implications for the cerebro-cerebellar dialogue. The Cerebellum, 2(2), 84–95. https://doi.org/10.1080/14734220309403

Antal, A., Alekseichuk, I., Bikson, M., Brockmöller, J., Brunoni, A. R., Chen, R., Cohen, L. G., Dowthwaite, G., Ellrich, J., Flöel, A., Fregni, F., George, M. S., Hamilton, R., Haueisen, J., Herrmann, C. S., Hummel, F. C., Lefaucheur, J. P., Liebetanz, D., Loo, C. K., … Paulus, W. (2017). Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. Clinical Neurophysiology, 128(9), 1774–1809. https://doi.org/10.1016/j.clinph.2017.06.001

Arul-Anandam, A. P., Loo, C., & Mitchell, P. (2010). Induction of Hypomanic Episode With Transcranial Direct Current Stimulation. The Journal of ECT, 26(1), 68–69. https://doi.org/10.1097/YCT.0b013e3181a744bf

Ayanampudi, V., Kumar, V., Krishnan, A., Walker, M. P., Ivry, R. B., Knight, R. T., & Gurumoorthy, R. (2023). Personalized transcranial alternating current stimulation improves sleep quality: Initial findings. Frontiers in Human Neuroscience, 16. https://doi.org/10.3389/fnhum.2022.1066453

Berridge, C. W., Schmeichel, B. E., & España, R. A. (2012). Noradrenergic modulation of wakefulness/arousal. Sleep Medicine Reviews, 16(2), 187–197. https://doi.org/10.1016/j.smrv.2011.12.003

Bertisch, S. M., Pollock, B. D., Mittleman, M. A., Buysse, D. J., Bazzano, L. A., Gottlieb, D. J., & Redline, S. (2018). Insomnia with objective short sleep duration and risk of incident cardiovascular disease and all-cause mortality: Sleep Heart Health Study. Sleep, 41(6). https://doi.org/10.1093/sleep/zsy047

Brunoni, A. R., Ferrucci, R., Bortolomasi, M., Scelzo, E., Boggio, P. S., Fregni, F., Dell'Osso, B., Giacopuzzi, M., Altamura, A. C., & Priori, A. (2013). Interactions between transcranial direct current stimulation (tDCS) and pharmacological interventions in the Major Depressive Episode: Findings from a naturalistic study.

European Psychiatry, 28(6), 356–361. https://doi.org/10.1016/j.eurpsy.2012.09.001

Brunoni, A. R., Valiengo, L., Zanao, T., de Oliveira, J. F., Bensenor, I. M., & Fregni, F. (2011). Manic Psychosis After Sertraline and Transcranial Direct-Current Stimulation. The Journal of Neuropsychiatry and Clinical Neurosciences, 23(3), E4–E5. https://doi.org/10.1176/jnp.23.3.jnpe4

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Research, 28(2), 193–213. https://doi.org/10.1016/0165-1781(89)90047-4

Cappuccio, F. P., D'Elia, L., Strazzullo, P., & Miller, M. A. (2010). Sleep Duration and All-Cause Mortality: A Systematic Review and Meta-Analysis of Prospective Studies. Sleep, 33(5), 585–592. https://doi.org/10.1093/sleep/33.5.585

Chao, P.-C., Chang, C.-C., & Chang, H.-A. (2018). Hypomania Induced by Bifrontal Transcranial Direct Current Stimulation in a Patient with Bipolar Depression. Psychiatry Investigation, 15(9), 914–915. https://doi.org/10.30773/pi.2018.08.11.1

Chauvette, S., Volgushev, M., & Timofeev, I. (2010). Origin of Active States in Local Neocortical Networks during Slow Sleep Oscillation. Cerebral Cortex, 20(11), 2660–2674. https://doi.org/10.1093/cercor/bhq009

Chib, V. S., Yun, K., Takahashi, H., & Shimojo, S. (2013). Noninvasive remote activation of the ventral midbrain by transcranial direct current stimulation of prefrontal cortex. Translational Psychiatry, 3(6), e268–e268. https://doi.org/10.1038/tp.2013.44

Cunchillos, J. D., & De Andrés, I. (1982). Participation of the cerebellum in the regulation of the sleep-wakefulness cycle. Results in cerebellectomized cats. Electroencephalography and Clinical Neurophysiology, 53(5), 549–558. https://doi.org/10.1016/0013-4694(82)90067-0

Datta, A., Dmochowski, J. P., Guleyupoglu, B., Bikson, M., & Fregni, F. (2013). Cranial electrotherapy stimulation and transcranial pulsed current stimulation: A computer based high-resolution modeling study. NeuroImage, 65, 280–287. https://doi.org/10.1016/j.neuroimage.2012.09.062

De Zeeuw, C. I., Hoebeek, F. E., & Schonewille, M. (2008). Causes and Consequences of Oscillations in the Cerebellar Cortex. Neuron, 58(5), 655–658. https://doi.org/10.1016/j.neuron.2008.05.019

Dissanayaka, T., Zoghi, M., Farrell, M., Egan, G., & Jaberzadeh, S. (2020). The effects of a single-session cathodal transcranial pulsed current stimulation on corticospinal excitability: A randomized sham-controlled double-blinded study. European Journal of Neuroscience, 52(12), 4908–4922. https://doi.org/10.1111/ejn.14916

Dissanayaka, T., Zoghi, M., Hill, A. T., Farrell, M., Egan, G., & Jaberzadeh, S. (2020). The Effect of Transcranial Pulsed Current Stimulation at 4 and 75 Hz on Electroencephalography Theta and High Gamma Band Power: A Pilot Study. Brain Connectivity, 10(9), 520–531. https://doi.org/10.1089/brain.2020.0756

Dondé, C., Brunelin, J., Micoulaud-Franchi, J.-A., Maruani, J., Lejoyeux, M., Polosan, M., & Geoffroy, P. A. (2021). The Effects of Transcranial Electrical Stimulation of the Brain on Sleep: A Systematic Review. Frontiers in Psychiatry, 12. https://doi.org/10.3389/fpsyt.2021.646569

D'Urso, G., Dini, M., Bonato, M., Gallucci, S., Parazzini, M., Maiorana, N., Bortolomasi, M., Priori, A., & Ferrucci, R. (2022). Simultaneous Bilateral Frontal and Bilateral Cerebellar Transcranial Direct Current Stimulation in Treatment-Resistant Depression—Clinical Effects and Electrical Field Modelling of a Novel Electrodes Montage. Biomedicines, 10(7), 1681. https://doi.org/10.3390/biomedicines10071681

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using GPower 3.1: Tests for correlation and regression analyses. Behavior Research Methods, 41(4), 1149–1160. https://doi.org/10.3758/BRM.41.4.1149

Ford, D. E. (1989). Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? JAMA: The Journal of the American Medical Association, 262(11), 1479–1484. https://doi.org/10.1001/jama.262.11.1479

Frase, L., Piosczyk, H., Zittel, S., Jahn, F., Selhausen, P., Krone, L., Feige, B., Mainberger, F., Maier, J. G., Kuhn, M., Klöppel, S., Normann, C., Sterr, A., Spiegelhalder, K., Riemann, D., Nitsche, M. A., & Nissen, C. (2016). Modulation of Total Sleep Time by Transcranial Direct Current Stimulation (tDCS). Neuropsychopharmacology, 41(10), 2577–2586. https://doi.org/10.1038/npp.2016.65

Frase, L., Selhausen, P., Krone, L., Tsodor, S., Jahn, F., Feige, B., Maier, J. G., Mainberger, F., Piosczyk, H., Kuhn, M., Klöppel, S., Sterr, A., Baglioni, C., Spiegelhalder, K., Riemann, D., Nitsche, M. A., & Nissen, C. (2019). Differential effects of bifrontal tDCS on arousal and sleep duration in insomnia patients and healthy controls. Brain Stimulation, 12(3), 674–683. https://doi.org/10.1016/j.brs.2019.01.001

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., & Lu, B. (2010). Direct Current Stimulation Promotes BDNF-Dependent Synaptic Plasticity: Potential Implications for Motor Learning. Neuron, 66(2), 198–204. https://doi.org/10.1016/j.neuron.2010.03.035

Grimaldi, G., Argyropoulos, G. P., Bastian, A., Cortes, M., Davis, N. J., Edwards, D. J., Ferrucci, R., Fregni, F., Galea, J. M., Hamada, M., Manto, M., Miall, R. C., Morales-Quezada, L., Pope, P. A., Priori, A., Rothwell, J., Tomlinson, S. P., & Celnik, P. (2016). Cerebellar Transcranial Direct Current Stimulation (ctDCS). The Neuroscientist, 22(1), 83–97. https://doi.org/10.1177/1073858414559409

Guleyupoglu, B., Schestatsky, P., Edwards, D., Fregni, F., & Bikson, M. (2013). Classification of methods in transcranial Electrical Stimulation (tES) and evolving strategy from historical approaches to contemporary innovations. In Journal of Neuroscience Methods (Vol. 219, Issue 2, pp. 297–311). https://doi.org/10.1016/j.jneumeth.2013.07.016

Hadoush, H., Al-Sharman, A., Khalil, H., Banihani, S. A., & Al-Jarrah, M. (2018). Sleep Quality, Depression, and Quality of Life After Bilateral Anodal Transcranial Direct Current Stimulation in Patients with Parkinson's Disease. Medical Science Monitor Basic Research, 24, 198–205. https://doi.org/10.12659/MSMBR.911411

Harvey, A. G. (2001). INSOMNIA: SYMPTOM OR DIAGNOSIS? Clinical Psychology Review, 21(7), 1037–1059. https://doi.org/10.1016/S0272-7358(00)00083-0

Hathaway, E., Morgan, K., Carson, M., Shusterman, R., Fernandez-Corazza, M., Luu, P., & Tucker, D. M. (2021). Transcranial Electrical Stimulation targeting limbic cortex increases the duration of human deep sleep. Sleep Medicine, 81, 350–357. https://doi.org/10.1016/j.sleep.2021.03.001

Jaberzadeh, S., Bastani, A., & Zoghi, M. (2014). Anodal transcranial pulsed current stimulation: A novel technique to enhance corticospinal excitability. Clinical Neurophysiology, 125(2), 344–351. https://doi.org/10.1016/j.clinph.2013.08.025

Jaberzadeh, S., Bastani, A., Zoghi, M., Morgan, P., & Fitzgerald, P. B. (2015). Anodal Transcranial Pulsed Current Stimulation: The Effects of Pulse Duration on Corticospinal Excitability. PLOS ONE, 10(7), e0131779. https://doi.org/10.1371/journal.pone.0131779

Jaberzadeh, S., & Zoghi, M. (2023). Exploring sensory, motor, and pain responses as potential side or therapeutic effects of sub-2 mA, 400 Hz transcranial pulsed current stimulation. PLOS ONE, 18(12), e0290137. https://doi.org/10.1371/journal.pone.0290137

Jones, B. E., & M. Muhlethaler. (1999). Handbook of behavioral state control: cellular and molecular mechanisms.

Jouvet, M. (1972). The role of monoamines and acetylcholine-containing neurons in the regulation of the sleep-

waking cycle. In Neurophysiology and Neurochemistry of Sleep and Wakefulness (pp. 166–307). Springer Berlin Heidelberg. https://doi.org/10.1007/3-540-05462-6_2

Kang, Q., Talesh, A. R., Lang, E. J., & Sahin, M. (2024). Transsynaptic modulation of cerebellar nuclear cells: theta AC-burst stimulation. Journal of Neural Engineering, 21(6). https://doi.org/10.1088/1741-2552/ad9ad1

Ladenbauer, J., Ladenbauer, J., Külzowä, N., De Boor, R., Avramova, E., Grittner, U., & Flöel, A. (2017). Promoting sleep oscillations and their functional coupling by transcranial stimulation enhances memory consolidation in mild cognitive impairment. Journal of Neuroscience, 37(30), 7111–7124. https://doi.org/10.1523/JNEUROSCI.0260-17.2017

Le Bon-Jego, M. (2007). Persistently active, pacemaker-like neurons in neocortex. Frontiers in Neuroscience, 1(1), 123–129. https://doi.org/10.3389/neuro.01.1.1.009.2007

Lee, H. C., Chiu, H. F. K., Wing, Y. K., Leung, C. M., Kwong, P. K., & Chung, D. W. S. (1994). The Zung Self-Rating Depression Scale: Screening for Depression Among the Hong Kong Chinese Elderly. Journal of Geriatric Psychiatry and Neurology, 7(4), 216–220. https://doi.org/10.1177/089198879400700404

Leger, D., Guilleminault, C., Dreyfus, J. P., Delahaye, C., & Paillard, M. (2000). Prevalence of insomnia in a survey of 12 778 adults in France. Journal of Sleep Research, 9(1), 35–42. https://doi.org/10.1046/j.1365-2869.2000.00178.x

Li, T., Qadri, F., & Moser, A. (2004). Neuronal electrical high frequency stimulation modulates presynaptic GABAergic physiology. Neuroscience Letters, 371(2–3), 117–121. https://doi.org/10.1016/j.neulet.2004.08.050

Liu, J., Zou, G., Xu, J., Zhou, S., Qin, L., Sun, H., Zou, Q., & Gao, J.-H. (2023). State-dependent and region-specific alterations of cerebellar connectivity across stable human wakefulness and NREM sleep states. NeuroImage, 266, 119823. https://doi.org/10.1016/j.neuroimage.2022.119823

Liu, Z., Dong, S., Zhong, S., Huang, F., Zhang, C., Zhou, Y., & Deng, H. (2021). The effect of combined transcranial pulsed current stimulation and transcutaneous electrical nerve stimulation on lower limb spasticity in children with spastic cerebral palsy: a randomized and controlled clinical study. BMC Pediatrics, 21(1), 141. https://doi.org/10.1186/s12887-021-02615-1

Ma, H., Lin, J., He, J., Lo, D. H. T., & Tsang, H. W. H. (2021). Effectiveness of TES and rTMS for the Treatment of Insomnia: Meta-Analysis and Meta-Regression of Randomized Sham-Controlled Trials. In Frontiers in Psychiatry (Vol. 12). Frontiers Media S.A. https://doi.org/10.3389/fpsyt.2021.744475

Marino, M., Li, Y., Rueschman, M. N., Winkelman, J. W., Ellenbogen, J. M., Solet, J. M., Dulin, H., Berkman, L. F., & Buxton, O. M. (2013). Measuring Sleep: Accuracy, Sensitivity, and Specificity of Wrist Actigraphy Compared to Polysomnography. Sleep, 36(11), 1747–1755. https://doi.org/10.5665/sleep.3142

Marshall, L., Helgadóttir, H., Mölle, M., & Born, J. (2006). Boosting slow oscillations during sleep potentiates memory. Nature, 444(7119), 610–613. https://doi.org/10.1038/nature05278

Martin, J. L., & Hakim, A. D. (2011). Wrist Actigraphy. Chest, 139(6), 1514–1527. https://doi.org/10.1378/chest.10-1872

Marzano, C., Moroni, F., Gorgoni, M., Nobili, L., Ferrara, M., & De Gennaro, L. (2013). How we fall asleep: regional and temporal differences in electroencephalographic synchronization at sleep onset. Sleep Medicine, 14(11), 1112–1122. https://doi.org/10.1016/j.sleep.2013.05.021

Minichino, A., Bersani, F. S., Spagnoli, F., Corrado, A., De Michele, F., Calò, W. K., Primavera, M., Yang, B., Bernabei, L., Macrì, F., Vergnani, L., Biondi, M., & Delle Chiaie, R. (2014). Prefronto-Cerebellar Transcranial Direct Current Stimulation Improves Sleep Quality in Euthymic Bipolar Patients: A Brief

Report. Behavioural Neurology, 2014, 1–3. https://doi.org/10.1155/2014/876521

Morales-Quezada, L., Leite, J., Carvalho, S., Castillo-Saavedra, L., Cosmo, C., & Fregni, F. (2016). Behavioral effects of transcranial pulsed current stimulation (tPCS): Speed-accuracy tradeoff in attention switching task. Neuroscience Research, 109, 48–53. https://doi.org/10.1016/j.neures.2016.01.009

Morales-Quezada, L., Saavedra, L. C., Rozisky, J., Hadlington, L., & Fregni, F. (2014). Intensity-dependent effects of transcranial pulsed current stimulation on interhemispheric connectivity. NeuroReport, 25(13), 1054–1058. https://doi.org/10.1097/WNR.0000000000000228

Moruzzi G, & Magoun HW. (1949). Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol.

Murphy, M. J., & Peterson, M. J. (2015). Sleep Disturbances in Depression. Sleep Medicine Clinics, 10(1), 17–23. https://doi.org/10.1016/j.jsmc.2014.11.009

Nagai, M., Hoshide, S., & Kario, K. (2010). Sleep Duration as a Risk Factor for Cardiovascular Disease- a Review of the Recent Literature. Current Cardiology Reviews, 6(1), 54–61. https://doi.org/10.2174/157340310790231635

Nitsche, M. A., Lampe, C., Antal, A., Liebetanz, D., Lang, N., Tergau, F., & Paulus, W. (2006). Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex. European Journal of Neuroscience, 23(6), 1651–1657. https://doi.org/10.1111/j.1460-9568.2006.04676.x

Ohayon, M. M. (2002). Epidemiology of insomnia: what we know and what we still need to learn. Sleep Medicine Reviews, 6(2), 97–111. https://doi.org/10.1053/smrv.2002.0186

Ohayon, M. M. (2011). Epidemiological Overview of sleep Disorders in the General Population. Sleep Medicine Research, 2(1), 1–9. https://doi.org/10.17241/smr.2011.2.1.1

Philip, N. S., Nelson, B. G., Frohlich, F., Lim, K. O., Widge, A. S., & Carpenter, L. L. (2017). Low-Intensity Transcranial Current Stimulation in Psychiatry. American Journal of Psychiatry, 174(7), 628–639. https://doi.org/10.1176/appi.ajp.2017.16090996

Pyragas, K., Novičenko, V., & Tass, P. A. (2013). Mechanism of suppression of sustained neuronal spiking under high-frequency stimulation. Biological Cybernetics, 107(6), 669–684. https://doi.org/10.1007/s00422-013-0567-1

Pyragas, K., & Tass, P. A. (2017). Suppression of spontaneous oscillations in high-frequency stimulated neuron models. Lithuanian Journal of Physics, 56(4), 223–238. https://doi.org/10.3952/physics.v56i4.3419

Qaseem, A., Kansagara, D., Forciea, M. A., Cooke, M., & Denberg, T. D. (2016). Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. Annals of Internal Medicine, 165(2), 125–133. https://doi.org/10.7326/M15-2175

Reato, D., Gasca, F., Datta, A., Bikson, M., Marshall, L., & Parra, L. C. (2013). Transcranial Electrical Stimulation Accelerates Human Sleep Homeostasis. PLoS Computational Biology, 9(2), e1002898. https://doi.org/10.1371/journal.pcbi.1002898

Riemann, D. (2003). Primary insomnia: a risk factor to develop depression? Journal of Affective Disorders, 76(1–3), 255–259. https://doi.org/10.1016/S0165-0327(02)00072-1

Riemann D, & Nissen C. (2012). Sleep and Psychotropic Drugs. In: Morin CM, Espie CA (eds). Oxford handbook of sleep and sleep disorders. Oxford University Press: Oxford.

Rossman, J. (2019). Cognitive-Behavioral Therapy for Insomnia: An Effective and Underutilized Treatment for Insomnia. American Journal of Lifestyle Medicine, 13(6), 544–547. https://doi.org/10.1177/1559827619867677

Saebipour, M. R., Joghataei, M. T., Yoonessi, A., Sadeghniiat-Haghighi, K., Khalighinejad, N., & Khademi, S.

(2015). Slow oscillating transcranial direct current stimulation during sleep has a sleep-stabilizing effect in chronic insomnia: a pilot study. Journal of Sleep Research, 24(5), 518–525. https://doi.org/10.1111/jsr.12301

Saper, C. B., Fuller, P. M., Pedersen, N. P., Lu, J., & Scammell, T. E. (2010). Sleep State Switching. Neuron, 68(6), 1023–1042. https://doi.org/10.1016/j.neuron.2010.11.032

Saper, C. B., Scammell, T. E., & Lu, J. (2005). Hypothalamic regulation of sleep and circadian rhythms. Nature, 437(7063), 1257–1263. https://doi.org/10.1038/nature04284

Sheng, J., Xie, C., Fan, D., Lei, X., & Yu, J. (2018). High definition-transcranial direct current stimulation changes older adults' subjective sleep and corresponding resting-state functional connectivity. International Journal of Psychophysiology, 129, 1–8. https://doi.org/10.1016/j.ijpsycho.2018.05.002

Sivertsen, B., Hysing, M., Harvey, A. G., & Petrie, K. J. (2021). The Epidemiology of Insomnia and Sleep Duration Across Mental and Physical Health: The SHoT Study. Frontiers in Psychology, 12. https://doi.org/10.3389/fpsyg.2021.662572

Sours, C., Alon, G., Roys, S., & Gullapalli, R. P. (2014). Modulation of Resting State Functional Connectivity of the Motor Network by Transcranial Pulsed Current Stimulation. Brain Connectivity, 4(3), 157–165. https://doi.org/10.1089/brain.2013.0196

Steriade, M. (2006). Grouping of brain rhythms in corticothalamic systems. Neuroscience, 137(4), 1087–1106. https://doi.org/10.1016/j.neuroscience.2005.10.029

Steriade, M., & Timofeev, I. (2003). Neuronal Plasticity in Thalamocortical Networks during Sleep and Waking Oscillations. Neuron, 37(4), 563–576. https://doi.org/10.1016/S0896-6273(03)00065-5

Steriade, Mircea M, & Robert W. McCarley. (2013). Brainstem control of wakefulness and sleep. . Springer Science & Business Media.

Taylor, D. J., Mallory, L. J., Lichstein, K. L., Durrence, H. H., Riedel, B. W., & Bush, A. J. (2007). Comorbidity of Chronic Insomnia With Medical Problems. Sleep, 30(2), 213–218. https://doi.org/10.1093/sleep/30.2.213

Tsai, P.-S., Wang, S.-Y., Wang, M.-Y., Su, C.-T., Yang, T.-T., Huang, C.-J., & Fang, S.-C. (2005). Psychometric Evaluation of the Chinese Version of the Pittsburgh Sleep Quality Index (CPSQI) in Primary Insomnia and Control Subjects. Quality of Life Research, 14(8), 1943–1952. https://doi.org/10.1007/s11136-005-4346-x

Vasquez, A. C., Thibaut, A., Morales-Quezada, L., Leite, J., & Fregni, F. (2017). Patterns of brain oscillations across different electrode montages in transcranial pulsed current stimulation. NeuroReport, 28(8), 421–425. https://doi.org/10.1097/WNR.0000000000000772

Vasquez, A., Malavera, A., Doruk, D., Morales-Quezada, L., Carvalho, S., Leite, J., & Fregni, F. (2016). Duration Dependent Effects of Transcranial Pulsed Current Stimulation (tPCS) Indexed by Electroencephalography. Neuromodulation: Technology at the Neural Interface, 19(7), 679–688. https://doi.org/10.1111/ner.12457

Wang, H. X., Wang, L., Zhang, W. R., Xue, Q., Peng, M., Sun, Z. C., Li, L. P., Wang, K., Yang, X. T., Jia, Y., Zhou, Q. L., Xu, Z. X., Li, N., Dong, K., Zhang, Q., Song, H. Q., Zhan, S. Q., Min, B. Q., Fan, C. Q., … Wang, Y. P. (2020). Effect of Transcranial Alternating Current Stimulation for the Treatment of Chronic Insomnia: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Clinical Trial. Psychotherapy and Psychosomatics, 89(1), 38–47. https://doi.org/10.1159/000504609

World Health Organization. (2022, March 2). COVID-19 pandemic triggers 25% increase in prevalence of anxiety and depression worldwide. WHO News.

Ye, X., Feng, Z., Wang, Z., Zheng, L., Yuan, Y., Hu, Y., & Xu, Y. (2022). Activating Interneurons in Local Inhibitory Circuits by High-Frequency Stimulations at the Efferent Fibers of Pyramidal Neurons in Rat

Hippocampal CA1 Region. Brain Sciences, 12(10), 1350. https://doi.org/10.3390/brainsci12101350

Yin, J., Jin, X., Shan, Z., Li, S., Huang, H., Li, P., Peng, X., Peng, Z., Yu, K., Bao, W., Yang, W., Chen, X., & Liu, L. (2017). Relationship of Sleep Duration With All-Cause Mortality and Cardiovascular Events: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. Journal of the American Heart Association, 6(9). https://doi.org/10.1161/JAHA.117.005947

Yuan, Y., Feng, Z., Yang, G., Ye, X., & Wang, Z. (2022). Suppression of Neuronal Firing Following Antidromic High-Frequency Stimulations on the Neuronal Axons in Rat Hippocampal CA1 Region. Frontiers in Neuroscience, 16. https://doi.org/10.3389/fnins.2022.881426

Zhou, Q., Yu, C., Yu, H., Zhang, Y., Liu, Z., Hu, Z., Yuan, T.-F., & Zhou, D. (2020). The effects of repeated transcranial direct current stimulation on sleep quality and depression symptoms in patients with major depression and insomnia. Sleep Medicine, 70, 17–26. https://doi.org/10.1016/j.sleep.2020.02.003

ZUNG, W. W. K. (1965). A Self-Rating Depression Scale. Archives of General Psychiatry, 12(1), 63. https://doi.org/10.1001/archpsyc.1965.01720310065008

Zung, W. W. K. (1971). A Rating Instrument For Anxiety Disorders. Psychosomatics, 12(6), 371–379. https://doi.org/10.1016/S0033-3182(71)71479-0

研究计划书方案修正日期：_____2023 年 11 月 05 日_____

研究者姓名：_____郝凤仪_____

研究者签字：_____

附录 1. 匹兹堡睡眠质量指数量表（PSQI）

指导语:下面一些问题是关于您最近 1 个月的睡眠状况，这仅仅与您的睡眠习惯有关。请选择或填写最符合您近 1 个月白天和晚上实际情况的选项，并尽可能地做精确回答。其中划有横杠的部分是需要自己填写。

2. 近 1 个月，您晚上上床睡觉通常是____点钟。

3. 近 1 个月，您每晚通常要多长时间才能入睡（从上床到入睡）:_____分钟。

4. 近 1 个月，您每天早上通常_____点钟起床。

5. 近 1 个月，您每晚实际睡眠的时间为_____小时（注意:不等同于卧床时间，可以有小数）。

从下列问题中选择一个最符合您的情况的选项作为答案，并划“√”。

6. 近 1 个月，您是否因下列情况影响睡眠而烦恼，并描述其程度:

A．不能在 30 分钟内入睡:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

B．在晚上睡眠过程中醒来或早醒（凌晨醒后不容易再次入睡）:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

C．晚上起床上洗手间:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

D．晚上睡觉时出现不舒服的呼吸:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

E．晚上睡觉出现大声咳嗽或鼾声:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

F．晚上睡觉感到寒冷:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

G．晚上睡觉感到太热:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

H．晚上睡觉做恶梦:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

I．晚上睡觉身上出现疼痛不适:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

J．其他影响睡眠的问题

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

7. 近 1 个月，总的来说，您认为自己的睡眠质量:

（1）很好

（2）较好

（3）较差

（4）很差

8. 近 1 个月，您服用催眠药物（包括医院和药店购买的药物）的情况:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

9. 近 1 个月，您是否在开车、吃饭、或参加社会活动时时常感到困倦:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

10. 近 1 个月，您在积极完成事情上是否感到精力不足:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

11. 您是与人同睡一床，或有室友:

（1）没有;

（2）同伴或室友在另以房间;

（3）同伴在同一房间但不同床;

（4）同伴在同一床上。

如果您是与人同睡一床或有室友，请询问他您在过去一个月里是否出现以下情况:

A 在您睡觉时，有无打鼾声:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

B 在您睡觉时，呼吸之间有没有长时间停顿:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

在您睡觉时，您的腿是否有抽动或痉挛:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

C 在您睡觉时，是否出现不能辨认方向或混乱状态:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

D 在您睡觉时，是否有其他睡觉不安宁的情况，如果有，请描述这个问题:_____

并描述其程度:

（1）无

（2）<1 次/周

（3）1-2 次/周

（4）≥3 次/周

PSQI 用于评定被试最近 1 个月的睡眠质量。由 19 个自评和 5 个他评条目构成，其中第 19 个自评条目和 5 个他评条目不参与计分，在此仅介绍参与计分的 18 个自评条目（详见附问卷）。18 个条目组成 7 个成份，每个成份按 0～3 等级计分，累积各成份得分为 PSQI 总分，总分范围为 0~21，得分越高，表示睡眠质量越差。被试者完成试问需要 5～10 分钟。各成份含意及计分方法如下：

A. 睡眠质量

根据条目 6 的应答计分“很好”计 0 分，“较好”计 1 分，“较差”计 2 分，“很差”计 3 分。

B. 入睡时间

1. 条目 2 的计分为“≤15 分”计 0 分，“16～30 分”计 1 分，“31~60”计 2 分，“≥60 分”计 3 分。

2. 条目 5a 的计分为“无”计 0 分，“<1 次/周”计 1 分, “1-2 次/周”计 2 分,“≥3 次/周”计 3 分。

3. 累加条目 2 和 5a 的计分，若累加分为“0”计 0 分，“1~2”计 1 分，“3~4”计 2 分，“5~6”

计 3 分。

C. 睡眠时间

根据条目 4 的应答计分，“>7 小时”计 0 分，“6~7”计 1 分，“5~6”计 2 分，“<5 小时”计 3 分。

D. 睡眠效率

1. 床上时间=条目 3（起床时间）-条目 1（上床时间）

2. 睡眠效率=条目 4（睡眠时间）/床上时间×100%

3. 成分 D 计分位，睡眠效率>85%计 0 分，75~84%计 1 分，65~74%计 2 分，<65%计 3 分。

E. 睡眠障碍

根据条目 5b 至 5j 的计分为“无”计 0 分，“<1 周/次”计 1 分，“1~2 周/次”计 2 分，“≥3 周/次”计 3 分。累加条目 5b 至 5j 的计分，若累加分为“0”则成分 E 计 0 分，“1~9”计 1 分，“10~18”计 2 分，“19~27”计 3 分。

F. 催眠药物

根据条目 7 的应答计分，“无”计 0 分，“<1 周/次”计 1 分，“1~2 周/次”计 2 分，“≥3 周/次”计 3 分。

G. 日间功能障碍

1、根据条目 8 的应答计分，“无”计 0 分，“<1 周/次”计 1 分，“1~2 周/次”计 2 分，“≥3 周/次”计 3 分。

2、根据条目 9 的应答计分，“没有”计 0 分，“偶尔有”计 1 分，“有时有”计 2 分，“经常有”计 3 分。

3、累加条目 8 和 9 的得分，若累加分为“0”则成分 G 计 0 分，“1~2”计 1 分，“3~4”计 2 分，“5~6”计 3 分。

PSQI 总分=成分 A+成分 B+成分 C+成分 D+成分 E+成分 F+成分 G。

得分 0～5 分，表示睡眠质量：很好。

得分 6～10 分，表示睡眠质量：较好。

得分 11～15 分，表示睡眠质量：一般。

得分 16～21 分，表示睡眠质量：差。

附录 2. 抑郁自评量表 SDS

填表注意事项:下面有二十条文字，请仔细阅读每一条，然后根据您最近 2 周的实际情况在适当的方格里面划一个钩“√”。

1、我觉得闷闷不乐，情绪低沉（忧郁）

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

2、我觉得一天中早晨最好（晨重夜轻）

A 没有或很少时间有。（4 分）

B 有时有（3 分）

C 大部分时间有。（2 分）

D 绝大部分或全部时间都有。（1 分）

3、一阵阵哭出来或觉得想哭（易哭）

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

5、我晚上睡眠不好（睡眠障碍）

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

5、我吃得跟平常一样多（食欲减退）

A 没有或很少时间有。（4 分）

B 有时有（3 分）

C 大部分时间有。（2 分）

D 绝大部分或全部时间都有。（1 分）

6、我与异性密切接触时和以往一样感到愉快（性兴趣减退）

A 没有或很少时间有。（4 分）

B 有时有（3 分）

C 大部分时间有。（2 分）

D 绝大部分或全部时间都有。（1 分）

7、我发觉我的体重在下降（体重减轻）

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

8、我有便秘的苦恼（便秘）

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

9、心跳比平常快（心悸）

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

10、我无缘无故地感到疲乏（易倦）

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

11、我的头脑和平常一样清楚（思考困难）

A 没有或很少时间有。（4 分）

B 有时有（3 分）

C 大部分时间有。（2 分）

D 绝大部分或全部时间都有。（1 分）

12、我觉得经常做的事情并没有困难（能力减退）

A 没有或很少时间有。（4 分）

B 有时有（3 分）

C 大部分时间有。（2 分）

D 绝大部分或全部时间都有。（1 分）

14、我觉得不安而平静不下来（不安）

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

14、我对未来抱有希望（绝望）

A 没有或很少时间有。（4 分）

B 有时有（3 分）

C 大部分时间有。（2 分）

D 绝大部分或全部时间都有。（1 分）

15、我比平常容易生气激动（易激惹）

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

16、我觉得做出决定是容易的（决断困难）

A 没有或很少时间有。（4 分）

B 有时有（3 分）

C 大部分时间有。（2 分）

D 绝大部分或全部时间都有。（1 分）

17、我觉得自己是个有用的人，有人需要我（无用感）

A 没有或很少时间有。（4 分）

B 有时有（3 分）

C 大部分时间有。（2 分）

D 绝大部分或全部时间都有。（1 分）

18、我的生活过得很有意思（生活空虚感）

A 没有或很少时间有。（4 分）

B 有时有（3 分）

C 大部分时间有。（2 分）

D 绝大部分或全部时间都有。（1 分）

19、我认为如果我死了，别人会生活得更好（无价值感）

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

20、平常感兴趣的事我仍然感兴趣（兴趣丧失）

A 没有或很少时间有。（4 分）

B 有时有（3 分）

C 大部分时间有。（2 分）

D 绝大部分或全部时间都有。（1 分）

抑郁自评量表（SDS）由 W.K.Zung 编制于 1965 年。本量表含有 20 个反映抑郁主观感受的项目，每个项目按症状出现的频度分为四级评分，其中 10 个为正向评分，10 个为反向评分。

若为正向评分题，依次评为 1、2、3、4 分；反向评分题则评为 4、3、2、1。待评定结束后，把 20 个项目中的各项分数相加，即得总粗分，然后将粗分乘以 1.25 以后取整数部分，就得标准分。按照中国常模结果，SDS 标准分的分界值为 53 分，其中 53-62 分为轻度抑郁，63-72 分为中度抑郁，73 分以上为重度抑郁。

附录 3. 焦虑自评量表 SAS

填表注意事项:下面有二十条文字，请仔细阅读每一条，然后根据您最近 2 周的实际情况在适当的方格里面划一个钩“√”。

4、我觉得比平常容易紧张和着急

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

5、我无缘无故地感到害怕

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

6、我容易心里烦乱或觉得惊恐

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

7、我觉得我可能将要发疯

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

5、我觉得一切都很好，也不会发生什么不幸

A 没有或很少时间有。（4 分）

B 有时有（3 分）

C 大部分时间有。（2 分）

D 绝大部分或全部时间都有。（1 分）

8、我手脚发抖打颤

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

9、我因为头痛、头颈痛和背痛而苦恼

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

10、我感觉容易衰弱和疲乏

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

9、我觉得心平气和，并且容易安静坐着

A 没有或很少时间有。（4 分）

B 有时有（3 分）

C 大部分时间有。（2 分）

D 绝大部分或全部时间都有。（1 分）

11、我觉得心跳得很快

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

12、我因为一阵阵头晕而苦恼

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

13、我有晕倒发作，或觉得要晕倒似的

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

13、我吸气呼气都感到很容易

A 没有或很少时间有。（4 分）

B 有时有（3 分）

C 大部分时间有。（2 分）

D 绝大部分或全部时间都有。（1 分）

12. 我的手脚麻木和刺痛

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

13. 我因为胃痛和消化不良而苦恼

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

14. 我常常要小便

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

17、我的手是干燥温暖的

A 没有或很少时间有。（4 分）

B 有时有（3 分）

C 大部分时间有。（2 分）

D 绝大部分或全部时间都有。（1 分）

15. 我脸红发热

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

19、我容易入睡，并且一夜睡得很好

A 没有或很少时间有。（4 分）

B 有时有（3 分）

C 大部分时间有。（2 分）

D 绝大部分或全部时间都有。（1 分）

16. 我做恶梦

A 没有或很少时间有。（1 分）

B 有时有（2 分）

C 大部分时间有。（3 分）

D 绝大部分或全部时间都有。（4 分）

SAS 采用 4 级评分，主要评定症状出现旳频度，其标准为:“1”表示没有或很少有，；“2”表示有时有；“3”表示大部分时间有；“4”表示绝大部分或全部时间都有。

20 个条目中有 15 项是用负性词陈述的，按上述 1~4 顺序评分。其余 5 项目(第 5，9，13，17， 19）是用正性词陈述的，按 4～1 顺序反向计分。

SAS 的主要统计指标为总分。将 20 个项目的各个得分相加，即得粗分；用粗分乘以 1.25

以后取整数部份，就得到标准分，或者可以查表作相同的转换。按照中国常模结果，SAS 标准分的分界值为 50 分，其中 50—59 分为轻度焦虑，60—69 分为中度焦虑，70 分以上为重度焦虑。

附录 4. 知情同意书

知情同意书

尊敬的 _____ 先生/女士：

我们诚挚地邀请您参加一项题为“经颅脉冲电流刺激（tPCS）对失眠患者总睡眠时间的影响：一项先导研究”的临床研究。本研究已通过重庆西区医院伦理委员会的审查和批准。

本知情同意书将向您介绍本研究的目的、步骤、潜在获益、风险、不便之处以及作为受试者的权益。请您仔细阅读，并在慎重考虑后决定是否参加。当研究人员向您讲解和讨论本知情同意书时，您可以随时提问，并要求对不理解的地方进行解释。在做出决定前，您也可以与家人、朋友或您的主治医生讨论。

本研究的项目负责人是**蒋晓江**（重庆西区医院）。

1. 为什么要进行这项研究？

现有证据表明小脑活动与睡眠状态密切相关。研究显示，外部电调节（特别是高频电刺激）可以调节小脑活动以支持睡眠-觉醒调节。

目前，治疗唤醒或睡眠障碍的药物主要通过改变脑干唤醒系统中的胺类、胆碱能或 GABA 能神经递质来发挥作用。然而，这些药物往往伴有不良副作用且疗效有限。例如，用于治疗失眠的苯二氮卓类药物和苯二氮卓受体激动剂存在耐受风险。患者常因担心潜在的药物依赖风险，导致治疗依从性差，进而降低了疗效。

对于被诊断为原发性失眠的患者，这一问题尤为严重，因为缺乏明确病因，药物治疗往往基于“试错法”。这意味着患者在找到有效方案前，可能要经历各种药物副作用。另一种失眠的一线治疗方案是认知行为治疗（CBT）。尽管通过合格治疗师实施的 CBT 取得了相当大的成功，但其过程耗时、不便且费用较高。

值得注意的是，文献证据显示，无论是药物治疗还是认知行为治疗，约有 40% 的患者无法获得长期缓解。因此，亟需开发副作用更低、成本效益更高且使用更便捷的治疗方案。居家使用、由患者自我管理的设备可能提供一种潜在的解决方案。

2. 有多少人将参加这项研究？

本研究计划共招募 **38 名** 受试者。

3. 参加本研究涉及哪些内容？

研究将在治疗前一周收集基线数据。随后受试者将接受连续 2 周的治疗，共 12 次（周一至周六），每次 30 分钟，使用经颅脉冲电流刺激（电流强度：0.6 mA）。治疗 2 周后将评估疗效。

在治疗前一周，我们将收集以下数据：

1. **客观睡眠指标**：由腕式体动记录仪测量，包括入睡潜伏期、睡眠效率和入睡后清醒时间。

2. **主观睡眠指标**：采用匹兹堡睡眠质量指数（PSQI）测量，包括入睡情况、睡眠维持及睡眠质量。

3. **抑郁评分**：采用自评抑郁量表（SDS）测量。

4. **焦虑评分**：采用自评焦虑量表（SAS）测量。

测试结果将在治疗完成后提供给您。

4. 研究将持续多久？

本研究将持续 2 周，包含 12 次治疗。

基线数据将在治疗前一周收集。

治疗后数据收集安排如下：

5. **体动记录仪测量**：将在最后 3 次治疗的当晚进行收集。

6. **问卷及健康数据**：在最后一次治疗结束后的一周内，将收集治疗后的 PSQI、SDS、SAS 及健康相关数据。

7. 参加本研究有什么风险？

可能的风险包括：

1. 研究可能无法改善您的临床症状；

2. 时间投入（填写问卷：约 20 分钟/次，共 2 次；tPCS 治疗：30 分钟/次，共 12 次）；

3. 可能的心理不适；

4. 刺激部位可能出现的不适，包括皮肤发红、瘙痒、头皮痛；

5. 可能出现轻微头痛、颈痛；

6. 极罕见情况下，可能出现较严重的风险，如恶心、癫痫发作、剧烈头痛、头晕。

如果您感到不适，您可以随时拒绝回答问题或停止治疗。

8. 参加本研究有什么潜在获益？

潜在的获益包括获得免费的经颅脉冲电流刺激治疗，以及睡眠监测报告和问卷评估报告。

您的参与将帮助研究者获取更可靠的数据，有助于未来对该类疾病的理解和科学诊断。本研究的结果可能有助于为您及其他具有类似病情的患者找到更科学的治疗方案。

9. 必须参加吗？

您参加本研究完全是自愿的。如果您不愿参加，可以拒绝，这不会对您目前或未来的医疗护理产生任何负面影响。医生将继续为您提供常规医疗治疗。

即使您同意参加，您也可以随时通知研究者退出研究。您的退出不会影响您获得正常的医疗服务。原则上，在您退出后，研究者将安全存储您此前收集的信息直至最终销毁，且不会再进行进一步使用或披露。

在研究期间，如果出现任何可能影响您继续参与决定的新信息，我们将及时告知您。

10. 参加研究有费用或补偿吗？

与体动记录仪、问卷评估及经颅脉冲电流刺激治疗相关的费用将由本研究全额承担。您无需支付任何费用。本研究不提供经济补偿。

11. 受试者会收到报酬吗？

受试者将不会获得报酬。

12. 如果发生研究相关伤害怎么办？

如果您因参加本研究而受伤，请尽快通知研究者。我们将提供必要的医疗措施。根据中国相关法律法规，申办方将承担相应的医疗费用并提供适当的经济补偿。

13. 我的信息会保密吗？

如果您决定参加，您的参与情况及个人资料将严格保密。从您处收集的样本将使用研究编码而非您的姓名进行标识。未经您的许可，任何能识别您身份的信息都不会透露给研究团队以外的人员。

所有研究人员及相关方均有义务对您的身份保密。您的记录将存放在上锁的文件柜中，仅限研究人员查阅。必要时，政府监管部门或伦理委员会成员可能会按规定在研究中心查阅您的个人数据。当研究结果发表时，将不会披露任何身份信息。

14. 有问题或困难联系谁？

如果您有任何与本研究相关的问题，请联系 **蒋晓江**，电话：**023-81913165**。

如果您有关于受试者权益的问题，可以联系 **重庆西区医院伦理委员会**。

签字页

知情同意声明

我已被告知本研究的目的、背景、程序、风险和获益。我有充足的时间和机会进行提问，并对所获得的解答感到满意。

我已被告知如果我有关于本研究的问题、顾虑、建议，或者我想获取更多信息或为研究提供协助时应联系谁。

我已阅读本知情同意书，并同意参加本研究。

我理解我可以选择不参加，或在任何时间无需提供理由退出研究。

我理解如果我的病情恶化、发生严重不良事件，或者研究医生认为继续参与不符合我的最佳利益，他/她可能会在未征得我同意的情况下决定让我退出研究。申办方或监管机构也可能在研究过程中终止本研究。如果发生这种情况，医生将及时通知我并与我讨论替代方案。

我将收到一份由我和研究者双方签字的本知情同意书副本。

受试者姓名： _____ **联系方式：** _____

受试者签字： _____ **日期：** _____

研究者声明

我确认已向受试者解释了本研究的详细情况，特别是参与研究的潜在风险和获益。

研究者姓名： _____ **联系方式：** _____

研究者签字： _____ **日期：** _____