

Acupuncture for Cognitive Impairment in Parkinson's Disease: A Randomized Controlled Trail Protocol

Junhong Zhong, Yingxue Cui, Qianqian Li, Xin Wang, Bingcong Zhao, Shaosong Wang, Jingqing Sun

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Acupuncture for Cognitive Impairment in Parkinson's Disease: A Randomized Controlled Trial Protocol

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Abstract

Background: Cognitive impairment is a common non-motor symptom of Parkinson's disease, significantly affecting patients' expected lifespan and quality of life, diminishing the well-being of family members, and placing an additional economic burden on society. Although some studies suggest that acupuncture may alleviate cognitive impairment, the existing research is limited in scale. This study aims to evaluate the clinical efficacy of acupuncture in treating cognitive impairment associated with Parkinson's disease.

Objective: Methods: This study protocol outlines a randomized, two-arm, single-center clinical trial to be conducted at Beijing Hospital of Traditional Chinese Medicine, affiliated with Capital Medical University. 72 eligible Parkinson's disease patients with cognitive impairment will be randomized equally to acupuncture or sham-acupuncture groups. The total duration of the study will be 20 weeks, consisting of an 8-week intervention period and a 12-week follow-up period. Participants will undergo acupuncture treatment three times per week. The primary outcome will be the score of (MoCA and PD-CRS). Secondary outcomes will include EEG assessments, the T&T olfactometer, routine blood tests, blood lipid levels, and the Health-Related Quality of Life Questionnaire (PDQ-39). Outcomes will be assessed at baseline, and at the 8th and 20th weeks. Methods: Discussion: This study offers clinical evidence supporting acupuncture as a potential therapeutic option for cognitive impairment in Parkinson's disease, potentially guiding future treatment strategies. Despite challenges such as controlling placebo effects and implementing sham-needle interventions, we aim to mitigate these biases through rigorous experimental design and standardized procedures. Results: Trial registration: Chinese Clinical Trial Registry?ChiCTR?ChiCTR2400087389. Registered on 26 July 2024. Conclusions: keywords:Parkinson's disease cognitive impairment; Acupuncture; EEG

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Original Manuscript

Acupuncture for Cognitive Impairment in Parkinson's Disease: A Randomized Controlled Trial Protocol

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Abstract

Background: Cognitive impairment is a common non-motor symptom of Parkinson's disease, significantly affecting patients' expected lifespan and quality of life, diminishing the well-being of family members, and placing an additional economic burden on society. Although some studies suggest that acupuncture may alleviate cognitive impairment, the existing research is limited in scale. This study aims to evaluate the clinical efficacy of acupuncture in treating cognitive impairment associated with Parkinson's disease.

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Trial registration: Chinese Clinical Trial Registry □ ChiCTR □ ChiCTR2400087389. Registered on 26 July 2024.

Keywords: Parkinson's disease cognitive impairment, Acupuncture, EEG

Funding: Beijing Hospital Management Center “peak” talent training plan team (DFL20241001)

Introduction

The global prevalence of Parkinson's disease (PD) has risen significantly, driven largely by population aging, with projections suggesting over 12 million cases worldwide by 2040 [1]. While PD is primarily characterized by motor symptoms like bradykinesia, tremor, and rigidity, cognitive dysfunction—a prevalent non-motor symptom—remains understudied despite affecting 60-80% of PD patients [2, 3]. Cognitive decline in PD, strongly associated with aging, significantly impacts life expectancy, daily functioning, and quality of life for both patients and caregivers [4]. It manifests as mild cognitive impairment (PD-MCI), marked by gradual cognitive decline detectable by patients, families, or clinicians, or progresses to Parkinson's disease dementia (PDD), characterized by deficits in at least two cognitive domains (executive function, attention, visuospatial ability, or memory) severe enough to impair daily functioning [5, 6]. Given the variability in onset, characteristics, and prevalence of cognitive deficits in PD, early identification and prediction of cognitive decline are critical. Implementing standardized screening and management protocols is essential to slow disease progression and improve patient outcomes.

Cognitive impairment in Parkinson's disease (PD) differs from Alzheimer's disease, which is

primarily characterized by memory and language deficits[7]. In PD, initial cognitive changes predominantly involve impairments in executive function, attention, memory, and visuospatial abilities[8]. Evidence suggests that cholesterol[9-11] and chronic inflammation[12-14] play roles in the pathogenesis of cognitive impairment. Additionally, olfactory dysfunction has been identified as a risk factor for cognitive decline, linked to deficits across multiple cognitive domains[15, 16]. Olfactory tests (e.g., T&T olfactometer) can detect early signs of cognitive decline, offering valuable insights for intervention. Furthermore, patients with cognitive impairment may exhibit specific brainwave slowing or electroencephalographic (EEG) markers, highlighting quantitative EEG as a promising diagnostic tool for predicting PD-related cognitive decline[2, 13]. Further research is needed to explore the correlations between blood markers, olfactory deficits, and EEG changes with cognitive impairment in PD, and to translate these findings into clinical applications for treatment and efficacy assessment.

Neuropsychological assessments are crucial for diagnosing cognitive impairment in Parkinson's disease. Global cognitive screening tools, such as the Montreal Cognitive Assessment (MoCA) and the Parkinson's Disease Cognitive Rating Scale (PD-CRS), are recommended for cognitive screening in PD patients[17]. Additionally, the assessment of health-related quality of life (HRQOL) is critical. HRQOL in Parkinson's disease patients offers a comprehensive evaluation of their overall well-being, encompassing aspects such as anxiety and depression. Given that cognitive impairment may be exacerbated by anxiety or depression, screening and management of these comorbidities are essential for patients with Parkinsonian cognitive impairment, alongside regular monitoring of cognitive function [2].

Currently, effective pharmacological treatments for cognitive impairment associated with Parkinson's disease remain elusive. Research is heavily focused on preventing dementia in patients with Parkinson's disease and mild cognitive impairment [18]. Although anti-dementia agents like cholinesterase inhibitors (ChEIs) exhibit limited efficacy, their long-term use may lead to gastrointestinal and other adverse effects [19]. Non-pharmacological interventions, including physical exercise, cognitive training, and stimulation therapies, warrant further exploration [20]. Meta-analyses indicate that physical exercise may outperform traditional therapies in certain cognitive domains [21], yet some randomized controlled trials have not demonstrated significant cognitive improvements in Parkinson's patients, coupled with considerable variability in exercise protocols complicating research efforts [22, 23]. As for cognitive training, evidence supporting enhancements in overall cognition, executive functioning, or visual processing is lacking [24]. Additionally, research in cognitive training has been impeded by issues such as low patient adherence and the complexity of system implementation in clinical settings. Stimulation therapies are regarded as a potential avenue for addressing cognitive impairment in Parkinson's disease; however, current evidence supporting their efficacy, including rTMS, tDCS, and tRNS, remains insufficient [25].

Acupuncture is thought to engage the body's regulatory systems by harmonizing yin and yang while modulating the circulation of qi and blood within the internal organs. It addresses the limitations of modern medical practices in managing various clinical conditions. Numerous studies have indicated the positive effects of acupuncture on cognitive disorders [26-29]. Specifically, acupuncture has demonstrated therapeutic benefits in enhancing cognitive functions—such as intellectual capabilities, attention, and executive functioning—in patients with Parkinson's disease (PD). These enhancements can slow disease progression and improve quality of life, positioning acupuncture as a viable non-pharmacological intervention [30]. Nevertheless, despite its prevalent use in traditional Chinese medicine, there is a paucity of robust evidence-based research on the application of acupuncture for cognitive deficits in PD. Current studies often lack standardized protocols regarding point selection, treatment frequency, and duration, leading to variability in outcomes. Furthermore, the evaluation of acupuncture's efficacy predominantly relies on subjective measures, lacking a thorough and objective assessment framework [31].

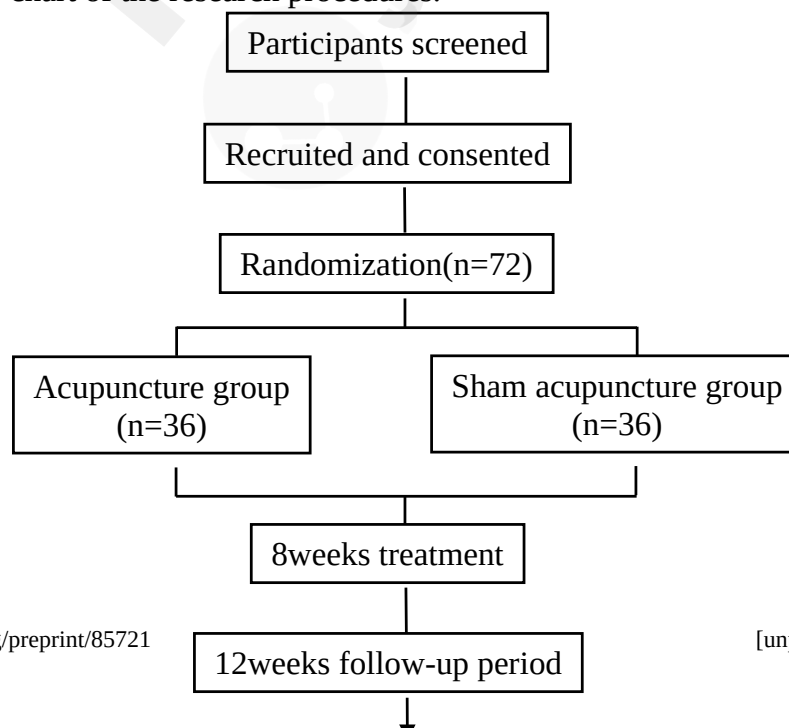
This study aims to assess the impact of acupuncture on cognitive function enhancement in patients with cognitive impairment due to Parkinson's disease through a randomized controlled trial. The objective is to identify the optimal acupuncture treatment protocol to enhance the efficacy's stability and reproducibility. A comprehensive efficacy evaluation framework will be established by integrating neuropsychological assessments (e.g., MoCA, PD-CRS), EEG, biomarkers (e.g., blood counts, lipid levels), and quality of life surveys (e.g., PDQ-39). We will investigate the effects of acupuncture on brain function in these patients via neuroimaging techniques like EEG, providing a scientific foundation for understanding acupuncture's mechanisms of action. Additionally, addressing the challenge of controlling the placebo effect in acupuncture studies, this research will employ sham acupuncture to rigorously manage this variable and ensure the scientific integrity and reliability of the findings. By achieving these objectives, the study aspires to bridge existing research gaps, offer robust evidence for acupuncture's role in treating cognitive impairment in Parkinson's disease, and facilitate its integration into clinical practice.

Methods

Trial design

This study is a single-center, prospective, two-arm randomized controlled trial (RCT) to be conducted at the Beijing Hospital of Traditional Chinese Medicine, affiliated with Capital Medical University. Eligible participants will be screened and will provide informed consent prior to enrollment. Participants will be randomly allocated to either the treatment group or the control group in a 1:1 ratio. All participants will undergo standard pharmacological treatment for 8 weeks, with the intervention group receiving additional acupuncture therapy. The primary outcomes will evaluate cognitive function using the Montreal Cognitive Assessment Scale (MoCA) and the Parkinson's Disease Cognitive Rating Scale (PD-CRS). Secondary outcomes will include measurements of brain wave activity through electroencephalography (EEG), assessments of complete blood count and lipid profiles, evaluations using the Parkinson's Disease Questionnaire (PDQ-39), and olfactory function measured by the T&T olfactometer. Data will be collected at baseline, immediately post-intervention, and 12 weeks after the intervention. The trial will maintain blinding for participants, assessors, and data analysts throughout its duration. Detailed procedural information is presented in Figures 1 and 2 and Table 1. This protocol complies with the SPIRIT checklist [32] and the Declaration of Helsinki [33]. Approval has been obtained from the Ethics Committee of Beijing Hospital of Traditional Chinese Medicine, and the study is registered with the Chinese Clinical Trial Registry (ChiCTR) (registration number: ChiCTR2400087389).

Figure 1 Flow chart of the research procedures.



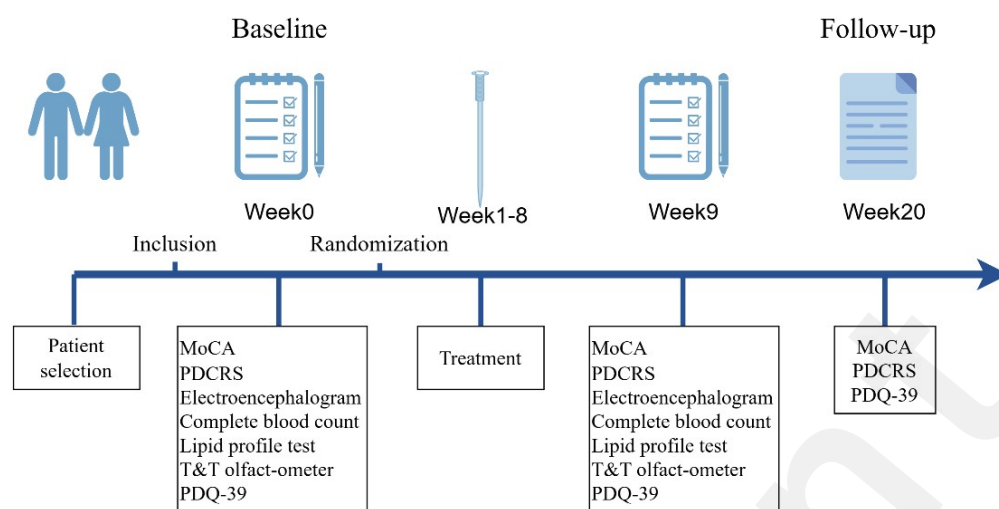


Figure 2 Graphical abstract of study design and study procedures.

Table 1 Schedule for enrolment, intervention, and assessment.

Time point	Baseline	Treatment	Follow-up
	Week0	Week9	Week20
Enrolment			
Eligibility screen	✓		
Informed consent	✓		
Randomization	✓		
Allocation	✓		
Assessment			
MoCA	✓	✓	✓
PDCRS	✓	✓	✓
Electroencephalogram	✓	✓	
T&T olfact-ometer	✓	✓	
Complete blood count	✓	✓	
Lipid profile	✓	✓	
PDQ-39	✓	✓	✓
Other assessment			
Patients' expectations assessment		✓	
Treatment effect self-assessment		✓	
Blinding assessment		✓	
Patients' compliance assessment		✓	
Participants safety			
Adverse event		✓	

Participants

Participants diagnosed with Parkinson's disease (PD) according to the Movement Disorder

Society Clinical Diagnostic Criteria for PD (2016)[34] will be recruited from the Beijing Hospital of Traditional Chinese Medicine, affiliated with Capital Medical University. Given that the median age of PD onset is 60 years, with some cases arising before the age of 45[35], and recognizing that age significantly contributes to cognitive decline in PD[36], the trial will include individuals aged 30 to 85. Recruitment will utilize diverse strategies, such as posting flyers within the hospital, leveraging social media platforms like WeChat, and advertising in local newspapers, along with word-of-mouth outreach. These methods aim to effectively engage potential participants for the study. Through the outpatient acupuncture and moxibustion departments, eligible participants who meet the criteria will be enrolled.

Inclusion Criteria

To qualify for participation in the study, individuals must satisfy the following criteria:

- (1) A confirmed diagnosis of Parkinson's disease (PD) as per the Movement Disorder Society's Clinical Diagnostic Criteria for Parkinson's Disease (2016) [34];
- (2) Age range of 30 to 85 years, irrespective of gender;
- (3) A score below 26 on the Montreal Cognitive Assessment Scale (MoCA) [37];
- (4) A score under 80.5 on the Parkinson's Disease Cognitive Rating Scale (PDCRS), where scores between 73.5 and 80.5 suggest mild cognitive impairment (PD-MCI), and scores of 73.5 or lower indicate Parkinson's disease dementia (PDD) [38];
- (5) Capability to comply with and complete the necessary evaluations and treatments, with no oral cognitive-enhancing medications taken within the 30 days preceding enrollment;
- (6) Submission of written informed consent.

Exclusion Criteria

The criteria for exclusion are as follows:

- (1) Individuals diagnosed with Parkinsonian superimposed syndrome or secondary Parkinsonism due to traumatic brain injury, epilepsy, or other primary causes linked to cognitive impairment;
- (2) Individuals with severe cardiovascular, hepatic, or renal conditions, as well as those with deafness, epilepsy, or blindness;
- (3) Individuals presenting with comorbid severe depression, anxiety, or schizophrenia;
- (4) Individuals with consciousness or mental disorders that hinder their ability to engage in the treatment;
- (5) Individuals unable to participate in acupuncture or cognitive function training interventions.

Drop out criteria

Participants will be disqualified from the study if they satisfy any of the following criteria:

- (1) Voluntary withdrawal from the study treatment;
- (2) The onset of severe adverse events or reactions (any new significant medical occurrence, including symptoms or side effects);
- (3) The development of serious illnesses, such as disability, cancer, or organ failure, necessitating critical interventions as assessed by qualified specialists;
- (4) Concurrent receipt of other acupuncture or moxibustion treatments.

Sample size calculation

This research utilized a randomized controlled trial (RCT) design, where the experimental group underwent acupuncture treatment, while the control group received sham acupuncture. The primary outcome was assessed using the Montreal Cognitive Assessment (MoCA) score of the participants. Literature indicates that the control group's average MoCA score was 15.67 ± 5.16 . It was predicted that the acupuncture group would exhibit a 3.44 point rise in MoCA scores [39], with a two-tailed α of 0.05 and an 80% statistical power. The required sample size was determined by the following

formula.

This calculation indicates that 36 participants were required in each group, accounting for the 1:1 randomization ratio, resulting in a minimum of 72 participants in total.

Randomization and Blinding

This study utilized simple randomization to create a random number table based on the sample size, employing SPSS 25.0 software. Group allocation codes were placed in sealed envelopes, which were tamper-proof once opened. Participants will be enrolled sequentially according to their assigned

$$n = \frac{2(z_{\alpha} + z_{\beta})^2 * \sigma^2}{\delta^2}$$

numbers, with group assignment dictated by the code within the envelope. Random assignments will be conducted via phone by an individual not involved in the study. Participants will remain blinded to their group allocation. While treatment providers will not be blinded due to the intervention's nature, outcome evaluators and data scientists will remain unaware of group assignments.

Baseline assessment

Before the study begins, a comprehensive set of baseline descriptive data will be gathered from all participants, encompassing demographic factors such as gender and age. This information will yield essential insights into the participants' initial characteristics, thereby enhancing the precision of the study's findings.

Interventions

Acupuncture protocols were established following an extensive review of both literature and clinical practices. Acupuncturists involved were mandated to possess a valid Chinese medicine practice license, and two practitioners received specialized training tailored to the trial to ensure a clear understanding of their responsibilities within the study.

Additionally, all participants will undergo standard pharmacological treatment for 8 weeks. Current mechanistic studies on Parkinson's disease categorize primary pharmacological interventions into several classes: Levodopa, Catechol-O-methyltransferase inhibitors (such as entacapone), Monoamine oxidase-B inhibitors (including rasagiline and selegiline), Dopamine agonists (like pramipexole), and Anticholinergics (for example, trihexyphenidyl). The first three classes are prevalent in clinical settings, associated with side effects such as delusions, somnolence, and dyskinesias, which do not impair cognition[40]. In contrast, the latter two classes have been linked to cognitive decline[41, 42], making them less suitable for older patients with Parkinson's disease. This trial will meticulously document participants' medication regimens before enrollment to mitigate potential confounding effects and biases on cognitive function. Participants must refrain from using any oral medications designed to enhance cognitive function for 30 days prior to enrollment.

Treatment Group

Licensed acupuncturist administered treatment.

The localization of acupuncture points was based on the 2006 National Standard of the People's Republic of China (GB/T 12346-2006), "Names and Localization of Acupoints". The needling procedure followed the methods outlined in the "Acupuncture and Moxibustion" textbook, part of the national curriculum for Traditional Chinese Medicine (TCM) in universities. Participants received Huatuo-brand disposable sterile acupuncture needles (0.3×40 mm), which were inserted into the designated acupoints to a depth of 15–30 mm. The needles were flat tonic and flat drainage to elicit the sensation of "qi" (characterized by pain, numbness, swelling, and heaviness), after which the

needles were retained for 30 minutes. Participants in the treatment group will receive acupuncture three times per week for a duration of 8 weeks.

The specific acupuncture points used were: Baihui (DU20), Sishencong (EX-HN1), Fengfu (DU16), Fengchi (GB20), Dazhui (DU14), Shendao (DU11), Zhiyang (DU9), Jinsuo (DU8), Mingmen (DU4), Yaoyangguan (DU3), Neiguan (PC6), Sanyinjiao (SP6), and Taixi (KI3). With precise information outlined in Figure 3 and Table 2.

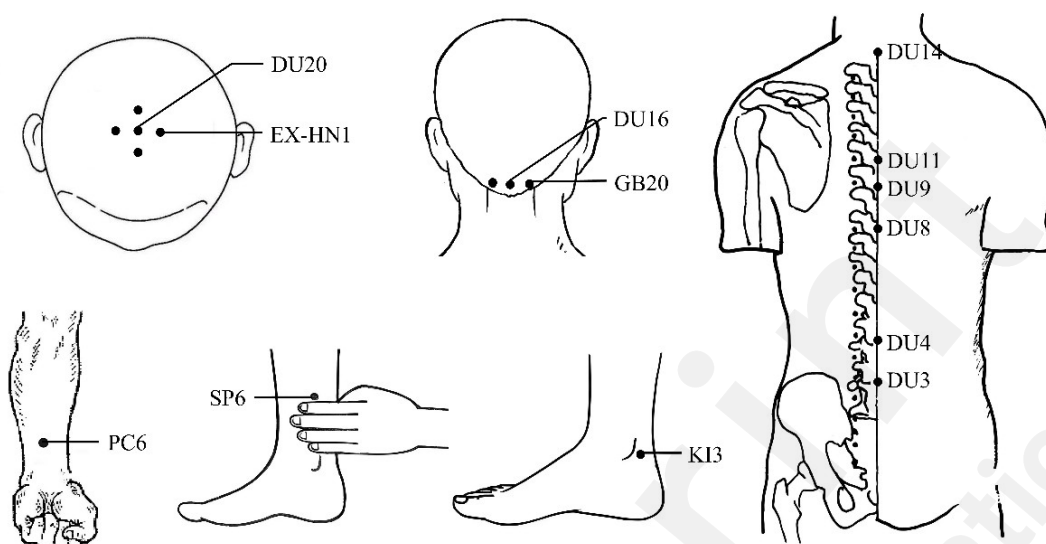


Figure 3 Location of acupoints

Table 2 Location of acupoints

Acupoints	Location
Baihui (DU20)	On the midline of the head, 7 cun directly above the midpoint of the posterior hairline.
Sishencong (EX-HN1)	On the parietal region, 1 cun anterior, posterior and lateral to Baihui, 4 acupoints totally.
Fengfu (DU16)	1 cun directly above the midpoint of the posterior hairline, in the depression below the external occipital protuberance.
Fengchi (GB20)	At the level of Fengfu, in the depression between the upper ends of the sternocleidomastoid trapezius muscles.
Dazhui (DU14)	On the posterior midline, in the depression below the spinous process of the 7th cervical vertebra.
Shendao (DU11)	On the posterior midline, in the depression below the spinous process of the 5th thoracic vertebra.
Zhiyang (DU9)	On the posterior midline, in the depression below the spinous process of the 7th thoracic vertebra.
Jinsuo (DU8)	On the posterior midline, in the depression below the spinous process of the 9th thoracic vertebra.
Mingmen (DU4)	On the posterior midline, in the depression below the spinous process of the 2nd lumbar vertebra.
Yaoyangguan (DU3)	On the posterior midline, in the depression below the spinous process of the 4th lumbar vertebra.
Neiguan (PC6)	On the line joining Daling and Quze, between the tendons of palmaris longus and flexor carpi radialis muscle.

Sanyinjiao (SP6)	Posterior to the mesial border of the tibia, and 3 cun above the tip of the medial malleolus.
Taixi (KI3)	In the depression between the tip of the medial malleolus and the Achilles tendon.

Control Group

Acupuncture was administered by a licensed physician with specialized expertise in acupuncture and moxibustion.

Needle Selection: A pragmatic placebo needle was employed. Conventionally, acupuncture control has been organized into two main groups: (1) Sham acupuncture that involve needles penetrating the skin, which applied to nonacupoints or shallowly to acupoints. However, Several studies[43] have shown that sham acupuncture may also lead to therapeutic and neurobiological responses at different levels of the central nervous system, as it is hard to find a non-influential skin site not close to other acupoints. (2) Placebo acupuncture, which is nonpenetrating. Such as Streitberger, Park, and Japanese devices. Nevertheless, the design and handling of these placebo needles are more complex than standard acupuncture needles. These dissimilarities have been found to have implications for blinding[44]. Therefore, none of the above control methods were selected in this trial. Pragmatic placebo needle belongs to a type of placebo acupuncture, a technique implemented solely using blunt needle tips and a basic adhesive pad for securing it, which is more convenient to operate than other placebo acupuncture. Pragmatic placebo needle has demonstrated no notable difference from actual acupuncture regarding needle penetration, pain, sensation, and acceptability, making it a valid control in acupuncture studies[45]. The pragmatic placebo needle retained for a duration of 30 minutes. Patients in the control group received acupuncture three times a week over the course of eight weeks. The acupuncture points selected for the control group were identical to those utilized in the treatment group.

Upon conclusion of the trial, the control group was provided with compensatory acupuncture treatment. The treatment regimen was identical to that of the experimental group, with a duration of eight weeks.

Outcome measurements

Table 3 summarized the primary and secondary endpoints.

Table 3 Primary and secondary endpoints

Primary endpoints

- 1.Changes in MoCA after 8, 20 weeks
- 2.Changes in PDCRS after 8, 20 weeks

Secondary endpoints

- 1.Changes in Electroencephalographic Evaluation after 8 weeks
- 2.Changes in Complete Blood Count after 8 weeks
- 3.Changes in Lipid Profile after 8 weeks
- 4.Changes in T&T Olfactometry Test after 8 weeks
- 5.Changes in PDQ-39 after 8, 20 weeks

Primary Outcome Measurement

The primary outcome measure of this study was a neuropsychological assessment of overall cognitive functioning. This assessment was conducted by a qualified neuropsychological assessor utilizing the MoCA and PD-CRS neuropsychological scales.

1. Montreal Cognitive Assessment (MoCA)

The MoCA comprises 30 items, yielding scores between 0 and 30, and evaluates eight cognitive domains: memory, delayed recall, attention, executive function, language, visuospatial skills, and orientation. An extra point was added to the overall score for those with fewer than 12 years of schooling to reduce educational bias. A score of 26 or more is categorized as normal, scores from 15

to 25 denote mild cognitive impairment, and scores of 15 or under suggest dementia[37].

2. Parkinson's Disease Cognitive Rating Scale (PDCRS)

The PD-CRS is recognized as a highly effective instrument for assessing cognitive impairment in individuals with Parkinson's disease (PD), particularly in identifying early cognitive deficits linked to the condition. The scale includes seven tasks evaluating "subfrontal cortex" functions (such as sustained attention, working memory, alternating and motor verbal fluency, clock drawing, and both immediate and delayed free-recall verbal memory) along with two tasks assessing "instrumental cortex" functions (including antagonistic naming and clock replication) [38].

Secondary Outcome Measurement

1. Electroencephalographic Assessment

A 32-channel digital video EEG system from Nicolette Biomedical Corporation (USA) was employed as follows:

Participants were instructed to relax in a seated position with a comfortable posture. After scalp sterilization, electrode pads were affixed according to the internationally accepted 10-20 system (Figure 4). The purpose, methodology, and content of the evoked experimental test were explained to the participants, who underwent training on the test instructions until they demonstrated proficiency prior to formal testing. EEG data were recorded while the participant remained relaxed, alert, and undisturbed in a chair with back support. Both eyes were directed horizontally at the center of a stimulus display located 80 cm away, with a horizontal viewing angle of 3.6° and a vertical viewing angle of 2.5°. The recording session lasted for 20 minutes, during which evoked experimental tests were administered, interspersed with 30-second breaks to alleviate participant fatigue. The testing environment was controlled, with the lights on and only the tester and participants present to minimize external noise and environmental influences on the results. E-Prime software facilitated the test administration.

The testing protocol is outlined below (Figure 5):

1. Resting State Eyes Closure: The subject was instructed to close their eyes, keep their body still and relaxed, avoid moving the eyeballs or squeezing the eyelids, and maintain mental relaxation, refraining from thinking or becoming drowsy. The lights were turned off, and EEG recordings were initiated, marking "eyes closed" for a 5-minute resting state collection.

2. Resting State Eyes Open: The subject was instructed to open their eyes and keep their body still and relaxed, focusing on the cross logo displayed on the computer screen while minimizing blinking. Mental relaxation was emphasized, with the subject instructed to avoid thinking. The lights were turned on, and EEG recordings were initiated, marking "eyes open" for a 5-minute resting state collection.

3. Calculation Task: The lights were turned off, and the subject was instructed to close their eyes and silently count backwards from 100, subtracting 7 consecutively until reaching 0. The subject was asked to remain silent and still throughout the task. EEG recording began once the calculation started, with the task marked as "100-7." EEG was collected for 60 seconds, after which the recording was stopped, followed by the cessation of the calculation task and inquiry of the result.

4. Attention test: Attention Test: The lights were turned on, and the subject was instructed to open their eyes and focus on the computer screen to sustain a high level of concentration during the attention test. EEG recording was initiated, and data were collected for 3 minutes. The recording was then terminated, and the computer screen was turned off.

5. The procedure was repeated once.

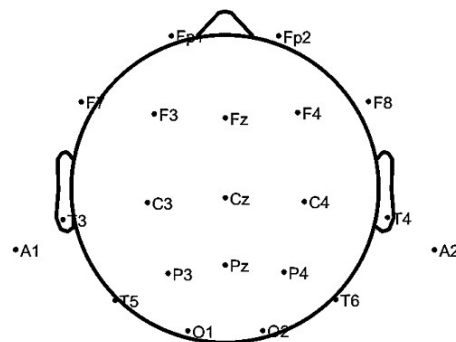


Figure 4: Channel Locations

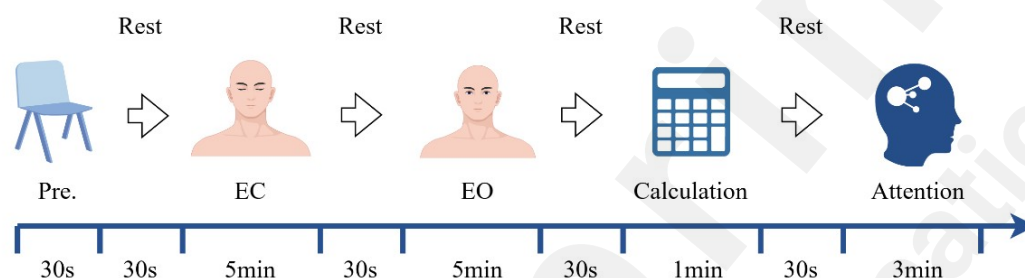


Figure 5: Electroencephalography procedure. Pre.: Preparation; EO: Eyes Closure; EO: Eyes Open.

2. Complete Blood Count (CBC)

A complete blood count (CBC) was performed, including the assessment of lymphocyte count and the neutrophil-lymphocyte ratio (NLR).

3. Lipid Profile

Venous blood was collected from the participants following an overnight fast, and lipid levels were measured. The lipid profile included measurements of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1 (Apo A1), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (Apo B).

4. T&T Olfactometry Test

The T&T Olfactometry system (T&T Olfactometer), manufactured by Daiichi Pharmaceutical Industries, Ltd., was utilized for the olfactory identification threshold test. Five odorants were employed in this test: β -phenylethanol, methylcyclopentenone, isovaleric acid, γ -undecalactone, and a fecal odorant. Each odorant was divided into 7 to 8 concentration gradients, which were sequentially diluted by a factor of 10 in descending order. The recognition threshold refers to the smallest concentration where the odor can be accurately detected. The average recognition thresholds for the five odorants were calculated. Based on the mean recognition threshold results, olfactory function was classified into the following categories: normal, mild olfactory loss, moderate olfactory loss, severe olfactory loss, and anosmia (complete loss of the sense of smell).

5. Health-Related Quality of Life – Parkinson's Disease Quality of Life Questionnaire (PDQ-39)

The Parkinson's Disease Quality of Life Questionnaire (PDQ-39) was administered to assess the overall quality of life in patients with Parkinson's disease. The questionnaire consists of 39 items distributed across eight domains: physical discomfort (3 items), communication (3 items), cognition (4 items), social support (3 items), humiliation (4 items), mental health (6 items), daily living

behaviors (6 items), and motor function (10 items). Every item is rated from 0 to 4, where higher scores reflect a poorer quality of life.

Patients' expectations about acupuncture treatment

To assess whether participants' expectations influence acupuncture outcomes, each participant will complete the Acupuncture Expectations Questionnaire prior to the intervention. The survey features seven questions, evaluated using a 4-level Likert scale.

Treatment effect self-assessment

End-of-therapy contentment is gauged via a 4-point Likert assessment. Patients will be asked, "How have your Parkinson's disease (PD) symptoms in the past week compared to baseline?" Response options include "cured," "improved," "unchanged," and "worsened."

Blinding assessment

During enrollment, subjects will be advised of the equiprobable allocation to either acupuncture treatment or sham acupuncture treatment. To evaluate the blinding's success, they will be asked to guess the type of acupuncture they received after completing the final session. The question posed will be: "Which type of acupuncture do you think you have undergone?" Participants choose from three alternatives.: acupuncture, sham acupuncture, or uncertain.

Patients' compliance assessment

All participants will receive a card indicating the date and time of each trial. Theacupuncturist will inform the participant of the time and place of the treatment via cellphone the day before each treatment. Participants'compliance will be recorded at the end of the treatment. Attrition and corresponding rationales are documented over a 20-week observation period.

Trial status

Participant enrollment is ongoing. The first participant was enrolled on October 1, 2024, and recruitment is anticipated to be completed by October 2025.

Adverse events

All adverse events will be systematically documented, including a detailed description, severity, duration, and the required treatment. All serious adverse events will be promptly reported to the chief investigator for timely intervention. All serious negative effects necessitate reporting to the RMIT Human Research Ethics Committee (HREC), which will make the final determination regarding the termination of the trial.

Assessment of Safety

The safety of acupuncture for cognitive impairment in Parkinson's disease was assessed by closely monitoring patients throughout the treatment process for any signs of discomfort or abnormal reactions, including needle retention, needle breakage, bleeding, hematomas, infections, allergies, and other adverse events.

Statistical Analysis

All analyses followed intention-to-treat (ITT) principles. They included all randomized subjects (n=72). Statistical analyses were performed using SPSS version 25.0 (IBM, USA) for descriptive statistics and between-group comparisons. R version 4.3.1 (R Foundation) was used for linear mixed-effects modeling, multiple imputation, and sensitivity analysis. The significance level for two-sided tests was set at 0.05.

We calculated individual and total scores for the Montreal Cognitive Assessment Scale (MoCA)

and the Parkinson's Disease Cognitive Rating Scale (PD-CRS). We computed absolute power spectral values (ASP) and slow-fast power ratios (SPR) for common EEG bands (e.g., delta, theta, alpha, and beta). We determined the mean olfactory recognition thresholds using the T&T olfactometer. We also calculated values such as the neutrophil-to-lymphocyte ratio (NLR), total cholesterol (CHO), and the total score of the Parkinson's Disease Quality of Life Questionnaire (PDQ-39). Demographic characteristics included age, gender. Baseline characteristics were summarized with descriptive statistics, including mean and standard deviation for continuous variables. For skewed distributions, we reported the median, 25th, and 75th percentiles. For categorical variables, we listed the number and percentage of subjects in each category. We analyzed the baseline characteristics across different groups utilizing independent samples t-tests for continuous variables that followed a normal distribution, Mann-Whitney U-tests for those that did not, and chi-square tests for categorical variables. If notable variations were detected ($p < 0.05$), these factors were included as covariates in the primary analysis.

The main analyses used Linear Mixed-Effects Models (LMM). These models included fixed effects (group, time, group×time interaction) and random individual intercepts. Covariates were age, gender. We assessed the assumptions of the LMM. Residual normality was assessed with the Shapiro-Wilk test, while homogeneity of variance was confirmed using Levene's test. Secondary analyses were conducted using the Per-Protocol Set ($n=XX$) to verify result robustness.

Missing data were handled using Multiple Imputation by Chained Equations (MICE). We generated five complete datasets. Imputation variables included group, time point, and baseline characteristics. MICE predicted missing values through iterative modeling, reflecting the uncertainty of missing data. We applied False Discovery Rate (FDR) correction to secondary outcomes (e.g., EEG metrics, blood metrics) within the same category to control false positives. To assess the robustness of the primary analyses, we performed sensitivity analyses: 1) Worst-case analysis: assuming that missing subjects in the acupuncture group had outcomes worsening to baseline levels. Missing subjects in the sham acupuncture group had outcomes improving to the best observed values. 2) Pattern-mixture models: stratifying the analyses by missingness patterns (completed follow-up vs. lost to follow-up). This evaluated the impact of different missingness patterns on the results. 3) Complete case analysis: We analyzed only subjects with no missing data and compared these results with the multiple imputation results.

Data Collection Methods and Study Monitoring

Procedures for data collection and management will be created in partnership with statisticians and lead investigators, resulting in the establishment of a secure, centralized database. During the acupuncture treatment process, adverse reactions will be systematically monitored and documented, with appropriate interventions implemented promptly as required. In the event of serious adverse events, the "Serious Adverse Event Report Form" will be completed and immediately submitted to the Ethics Committee and the Clinical Supervision and Management team for review to assess whether trial termination is warranted. The Scientific Management Committee and statisticians retain full study data access.

Confidentiality

To protect patient privacy and safety, numerical identifiers will replace participant names. The personal details of all participants will remain completely confidential and will not be shared with any person or entity without clear consent.

Ethics and dissemination

This trial was approved by the Research Ethics Committee of Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, and registered with the Chinese Clinical Trial Registry (ChiCTR2400087389). Should the protocol undergo any amendments, it will be presented

to both the Ethics Committee and the Registry Center. Prior to taking part in the study, all participants must provide their signature on a voluntary informed consent form.

The findings of this research will be showcased at various academic conferences and published in scholarly journals. Original paper documents and electronic data will be kept for at least five years following publication, with appropriate justification available to the corresponding author upon request.

Discussion

Acupuncture, as a potential adjunctive therapy, has shown promise in improving cognitive functions in patients with Parkinson's Disease (PD). This study further supports the effectiveness of acupuncture in enhancing specific cognitive domains such as memory and executive function.

This research will provide clinical evidence that acupuncture may improve cognitive functions in PD patients. By utilizing both the MoCA and PDCRS scales, we were able to assess overall cognitive function as well as specific cognitive domains like executive function, visuospatial abilities, attention, language, and memory. These findings have significant implications for clinical practice: acupuncture could serve as a non-pharmacological adjunctive treatment, offering a promising option for PD patients, especially those experiencing cognitive decline.

Studies suggest that acupuncture modulates brain activity through mechanisms such as promoting cerebral blood flow, reducing neuroinflammation, and fostering neurogenesis [46, 47]. It is particularly effective in regulating dopamine function, which is crucial for cognitive functions in PD patients. Functional neuroimaging studies, including fMRI and EEG, have shown that acupuncture can alter connectivity in brain networks associated with cognitive control and memory, particularly in areas like the prefrontal cortex and hippocampus [48, 49]. Additionally, research has found that acupuncture treatment can ameliorate behavioral deficits in PD model mice, potentially by modulating olfactory function [50]. Acupuncture may also inhibit lipid peroxidation levels in dopaminergic neurons, protecting them from oxidative damage and thereby aiding in the treatment of neurodegenerative diseases [51].

In this study, we focused on changes in EEG patterns, particularly in the θ and δ frequency bands, which are associated with cognitive deficits in PD patients. Following acupuncture treatment, the increase in α and β wave activity and the decrease in θ and δ activity may reflect improvements in cognitive processing and enhanced synchronization of brain networks. The latter also links EEG changes to cognitive improvements in neurodegenerative diseases [52, 53]. Future research should delve deeper into the relationship between acupuncture-induced EEG changes and cognitive function, as EEG could serve as a useful biomarker for monitoring treatment efficacy.

Common adverse events include localized pain, bruising, or temporary dizziness, particularly in PD patients. Given their risk of falls and other complications, any adverse reactions could significantly impact the feasibility of acupuncture treatment. Therefore, future studies should include comprehensive safety monitoring and clearly inform patients of potential risks. Since acupuncture is generally considered safe when performed by trained professionals, research should focus on risks specific to the PD patient population and explore ways to mitigate these risks.

Our results are promising but come with several limitations. First, the study's restricted participant number curtails the results' statistical robustness and scope. Larger-scale, multicenter clinical trials are needed to validate these results and assess their applicability across different patient groups. Additionally, potential biases, such as patient expectations, placebo effects, and treatment adherence, were not fully addressed in this study. Although we controlled for the use of cognitive medications, patient adherence to the acupuncture regimen was not strictly monitored, which may have influenced the outcomes. Due to the high frequency of acupuncture treatments (three times per week), some patients may have experienced reduced adherence, potentially limiting the external validity of the findings. Lastly, while we minimized bias through randomization and blinding, the patient selection criteria based on specific inclusion criteria may not fully represent the broader PD

population. Future studies should aim to overcome these limitations to provide more robust evidence.

Our study suggests that acupuncture may be an effective intervention for improving cognitive impairment in Parkinson's Disease (PD), but further research is needed to establish clear clinical guidelines. Future studies should focus on determining the optimal treatment frequency, duration, and patient selection criteria, as well as exploring the effects of fewer sessions or shorter treatment durations while improving patient adherence. Additionally, combining acupuncture with other treatments, such as medications or cognitive rehabilitation, may enhance overall efficacy. Given the small sample size and short follow-up period of this study, larger-scale, multicenter clinical trials with extended follow-up periods are recommended to validate the efficacy of acupuncture. Furthermore, integrating imaging techniques like fMRI and PET to explore the neurobiological mechanisms of acupuncture could provide deeper insights into its effects on brain function.

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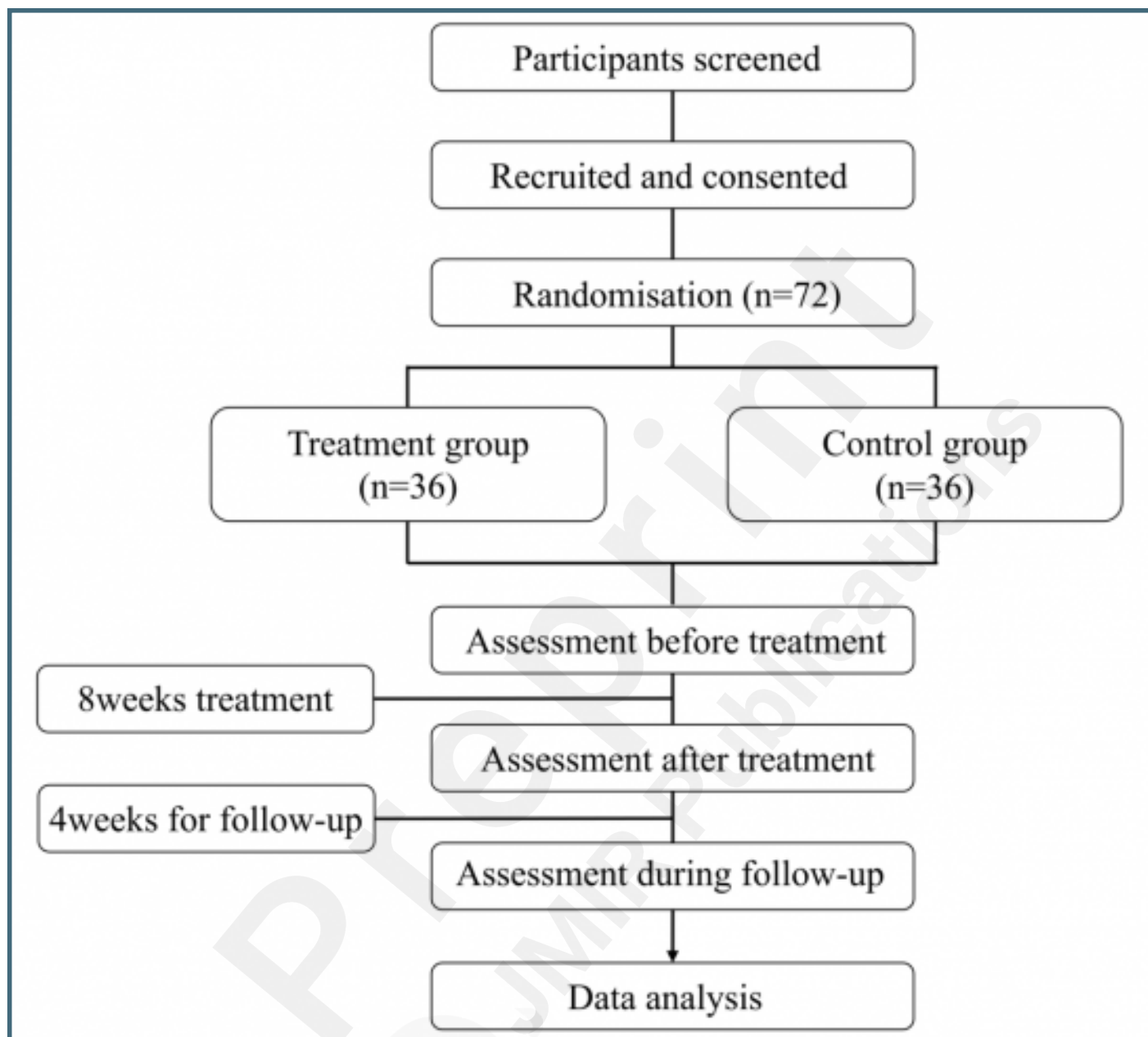
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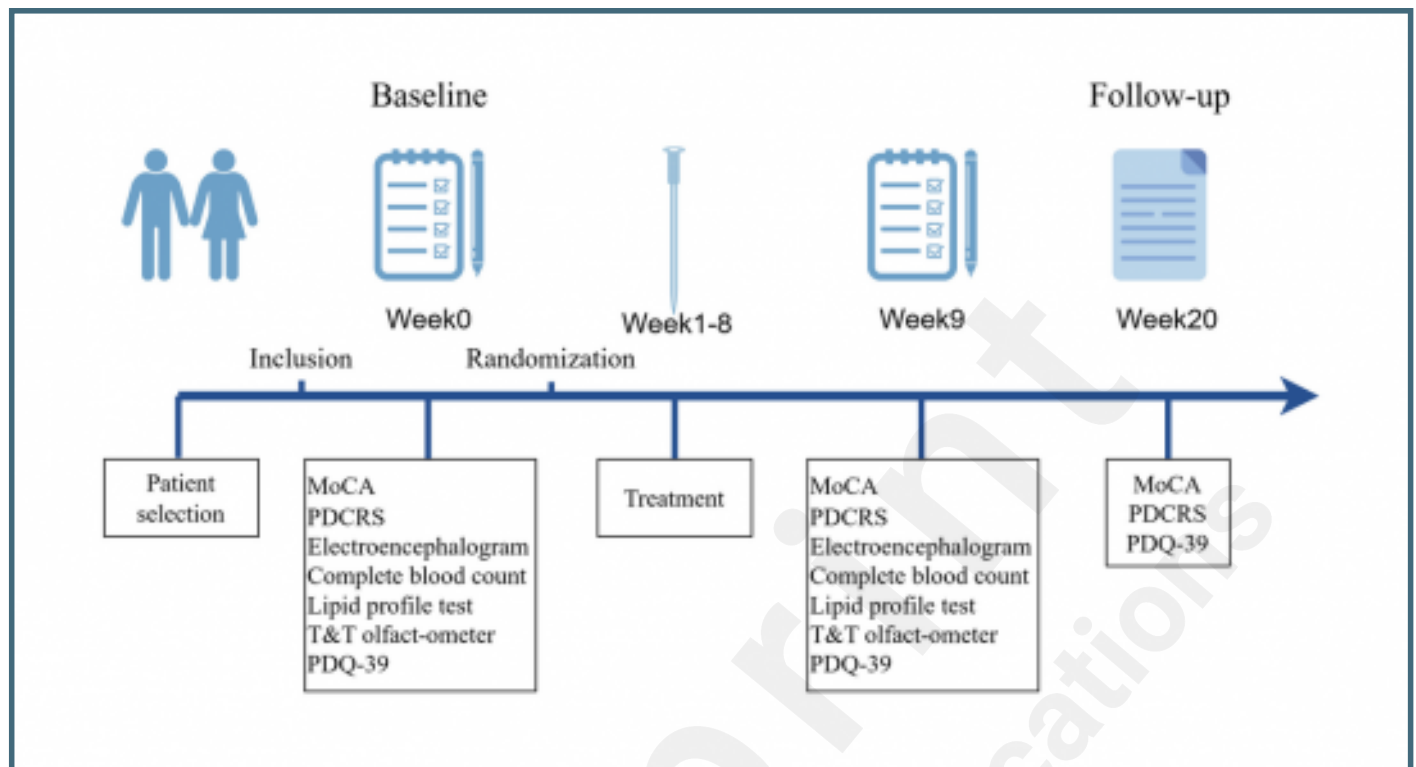
Supplementary Files

Figures

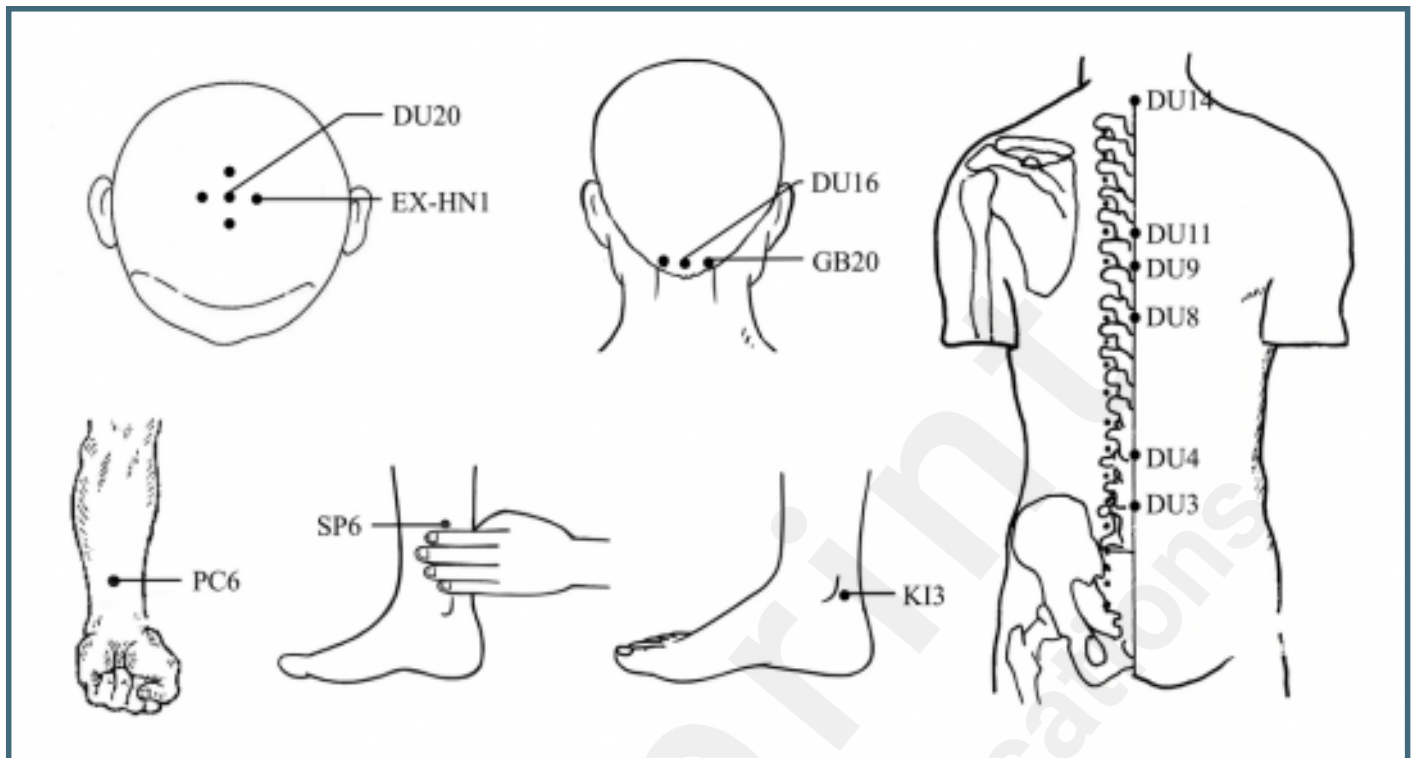
Flow chart of the research procedures.



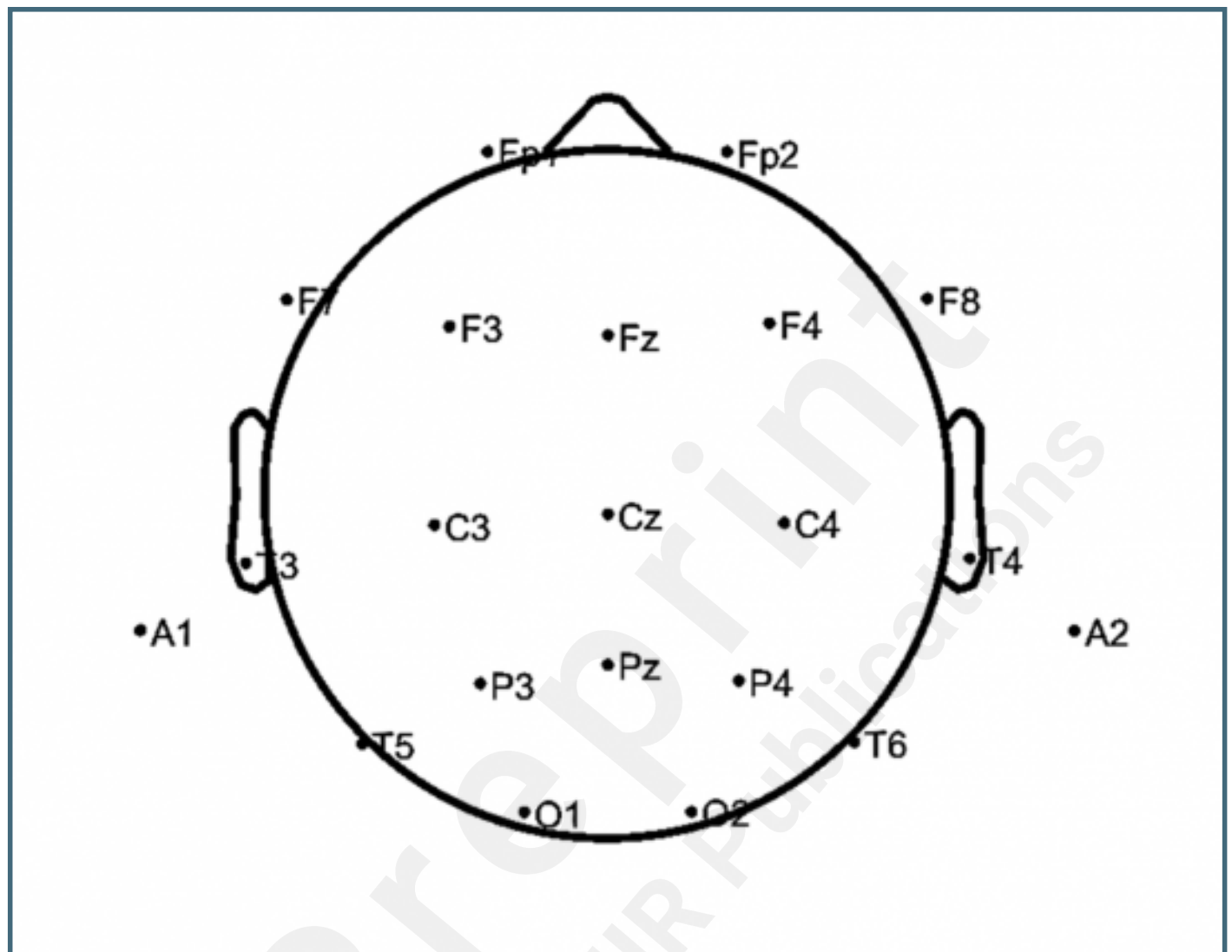
Graphical abstract of study design and study procedures.



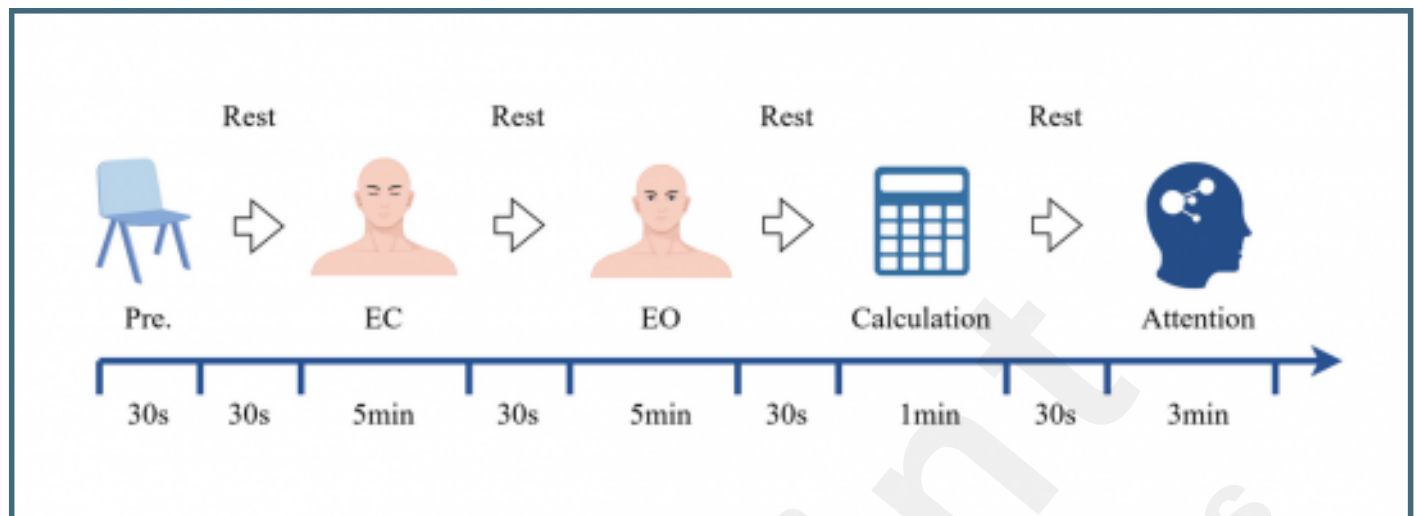
Location of acupoints.



Channel Locations.



Electroencephalography procedure.



Schedule for enrolment, intervention, and assessment.

Time point	Baseline Period	After treatment	
	0 week	8 weeks	12 weeks
Enrolment			
Eligibility screen	✓		
Informed consent	✓		
Randomization	✓		
Allocation	✓		
Assessment			
MoCA	✓	✓	✓
PDCRS	✓	✓	✓
Electroencephalogram	✓	✓	
Complete blood count	✓	✓	
Lipid profile	✓	✓	
T&T olfactometry test	✓	✓	
PDQ-39	✓	✓	✓
Other assessment			
Patients' expectations assessment		✓	
Treatment effect self-assessment		✓	
Blinding assessment		✓	
Patients' compliance assessment		✓	
Participants safety			
Adverse event		✓	

Location of acupoints.

Acupoints	Location
Baihui (DU20)	On the midline of the head, 7 cun directly above the midpoint of the posterior hairline.
Sishencong (EX-HN1)	On the parietal region, 1 cun anterior, posterior and lateral to Baihui, 4 acupoints totally.
Fengfu (DU16)	1 cun directly above the midpoint of the posterior hairline, in the depression below the external occipital protuberance.
Fengchi (GB20)	At the level of Fengfu, in the depression between the upper ends of the sternocleidomastoid trapezius muscles.
Dazhui (DU14)	On the posterior midline, in the depression below the spinous process of the 7th cervical vertebra.
Shendao (DU11)	On the posterior midline, in the depression below the spinous process of the 5th thoracic vertebra.
Zhiyang (DU9)	On the posterior midline, in the depression below the spinous process of the 7th thoracic vertebra.
Jinsuo (DU8)	On the posterior midline, in the depression below the spinous process of the 9th thoracic vertebra.
Mingmen (DU4)	On the posterior midline, in the depression below the spinous process of the 2nd lumbar vertebra.
Yaoyangguan (DU3)	On the posterior midline, in the depression below the spinous process of the 4th lumbar vertebra.
Neiguan (PC6)	On the line joining Daling and Quze, between the tendons of palmaris longus and flexor carpi radialis muscle
Sanyinjiao (SP6)	Posterior to the mesial border of the tibia, and 3 cun above the tip of the medial malleolus.
Taixi (KI3)	In the depression between the tip of the medial malleolus and the Achilles tendon.

Primary and secondary endpoints.

Primary endpoints

- 1.Changes in MoCA after 8, 12 weeks
- 2.Changes in PDCRS after 8, 12 weeks

Secondary endpoints

- 1.Changes in Electroencephalographic Evaluationafter after 8 weeks
- 2.Changes in Complete Blood Count after 8 weeks
- 3.Changes in Lipid Profile after 8 weeks
- 4.Changes in T&T Olfactometry Test after 8 weeks
- 5.Changes in PDQ-39 after 8, 12 weeks