

Acupuncture for Mild Cognitive Impairment in Vascular Parkinsonism: A Prospective, Randomized, Controlled Trial Protocol

Ziru Yu^{1-3,*}, Ying Wang^{3,*}, Xu Wang^{4,5}, Yanlong Xie⁶, Yingdong Wang³, Limeng Li³, Wenxiu Qin¹⁻³, Qingjie Kong¹⁻³, Peng Zhang^{1,2}, Junfeng Xu^{1,2}

¹Department of Acupuncture and Moxibustion, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, People's Republic of China; ²Department of Acupuncture and Moxibustion, National Clinical Research Center for Chinese Medicine, Tianjin, People's Republic of China; ³Graduate School, Tianjin University of Traditional Chinese Medicine, Tianjin, People's Republic of China; ⁴Department of Medical Imaging, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, People's Republic of China; ⁵Department of Medical Imaging, National Clinical Research Center for Chinese Medicine, Tianjin, People's Republic of China; ⁶Department of Acupuncture and Moxibustion, Affiliated Hospital of Tianjin Academy of Traditional Chinese Medicine, Tianjin, People's Republic of China

*These authors contributed equally to this work

Correspondence: Peng Zhang; Junfeng Xu, Department of Acupuncture and Moxibustion, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, No. 314, Anshan West Road, Nankai District, Tianjin, People's Republic of China, Email zhangpeng13@163.com; 13002246377@163.com

Purpose: Vascular parkinsonism (VP) is a form of secondary parkinsonism caused by cerebrovascular disease and is typically associated with progressive cognitive decline, which greatly disrupts patients' daily lives and well-being. Vascular parkinsonism with mild cognitive impairment (VP-MCI) represents an early and potentially reversible stage of cognitive dysfunction, and an important window for early intervention. However, effective therapies for VP-MCI remain limited. Acupuncture is a non-pharmacological intervention that has shown potential benefits for motor and cognitive functions in vascular-related disorders. This study aims to evaluate the effectiveness and safety of acupuncture in patients with VP-MCI and to explore possible mechanisms.

Patients and Methods: This is a prospective, two-center, randomized, controlled, and assessor-blinded clinical trial. A total of 105 patients with VP-MCI and 12 healthy controls will be enrolled. Patients will be randomly assigned to acupuncture, sham acupuncture, or waiting-list groups. Participants in the intervention groups will receive verum or sham acupuncture three times per week for 8 weeks (24 sessions in total), with each session lasting 30 minutes. Patients in the waiting-list group will receive acupuncture after completion of the trial. The primary outcome is the Montreal Cognitive Assessment (MoCA). Secondary outcomes include the Mini-Mental State Examination (MMSE), Part III of the Unified Parkinson's Disease Rating Scale (UPDRS-III), Activities of Daily Living (ADL), Transcranial Color-Coded Doppler (TCCD), serum neurofilament light chain (sNfL) levels, and diffusion tensor imaging (DTI).

Discussion: This trial is designed to provide clinical evidence for the efficacy of acupuncture in alleviating cognitive impairment in VP-MCI, and to explain its underlying mechanism. The findings are expected to support acupuncture as a potential complementary therapy for the early management of VP-MCI.

Keywords: vascular parkinsonism, cognitive function, acupuncture, neurofilament light chain, diffusion tensor imaging

Introduction

Parkinsonism, a clinical manifestation defined by bradykinesia, rest tremor, rigidity, or postural instability, is most typically brought on by idiopathic Parkinson's disease (PD).¹ However, secondary factors account for a significant proportion of the cases. Vascular parkinsonism (VP) is a unique pathological type caused by cerebrovascular disease, accounting for around 4.4–12% of all parkinsonism patients.² Population aging coupled with increasing prevalence of cerebrovascular disease has led to the growing burden of VP.³

A neuropathological feature of PD is the loss of dopaminergic neurons in the substantia nigra pars compacta, accompanied by the formation of Lewy bodies composed of misfolded α -synuclein.⁴ In contrast, the pathophysiology of VP is less well defined. It is thought to result from a combination of cerebrovascular changes and neurodegenerative alterations. Vascular injury may disrupt the cortico-basal ganglia connection, thereby impairing the cortico-striato-pallido-thalamo-cortical motor circuit.⁵ These pathological differences give rise to distinct clinical subtypes of VP. Acute or subacute post-stroke VP is relatively uncommon and involves direct damage to the nigrostriatal pathway. It is often associated with asymmetric symptoms and partial responsiveness to dopaminergic therapy.^{6,7} The more common insidious-onset VP is characterized by symmetric gait instability of the lower limbs as well as a high incidence of non-motor symptoms, especially cognitive dysfunction and dysuria. This subtype has preserved dopamine transporter function and therefore limited response to dopaminergic treatment.⁸

A number of cardiovascular and cerebrovascular risk factors have been found to contribute to the development of the VP. These are old age, hypertension, hyperlipidemia, heart disease, type 2 diabetes, and smoking.⁹ These metabolic states can damage the operation of the neurovascular unit through causing vascular endothelial damage and destabilizing the blood-brain barrier, thereby leading to a worsening of white matter pathology. The accompanying dysregulated immune responses then further promote the development of VP.¹⁰

Neuropathological alterations in VP are intimately related to cerebral small vessel disease, most commonly presenting as lacunar infarctions and white matter lesions (WMLs). Brain MRI in VP patients frequently reveals extensive periventricular WMLs. These are accompanied by lacunes, mostly in the basal ganglia, as well as enlargement of the lateral and third ventricles.¹¹ Previously, WMLs were considered a normal aspect of aging. WMLs are now recognized for their role in disrupting white matter tracts and impairing cortico-subcortical connectivity.¹² It may account for a key mechanism for characteristic cognitive deficits of VP.

Patients with VP exhibit a combination of motor and non-motor symptoms, largely determined by the extent of cerebrovascular pathology. Cognitive impairment is one of the most prominent non-motor features, particularly in the insidious-onset subtype. Approximately 73.5% of patients develop cognitive impairment, with progression to dementia reported in 60–80% of cases.^{13–15} Cognitive impairment in VP typically reflects subcortical dysfunction and is characterized by deficits in executive function, attention, planning, judgment, abstract thinking, and verbal fluency.¹⁶ Previous research has indicated that cognitive impairment is more common and severe in VP than in PD, with greater impairments in working memory, attention, and language function.^{9,16} A crucial therapeutic window for early intervention is heightened by mild cognitive impairment (MCI), the prodromal stage of dementia. Unfortunately, current treatment options for cognitive impairment in VP remain inadequate. Most approaches are largely adapted from therapies for vascular cognitive impairment. N-methyl-D-aspartate receptor antagonists and cholinesterase inhibitors are commonly used, but their efficacy is modest. They are also frequently accompanied by side effects, including gastrointestinal discomfort, dizziness, and cardiovascular complications.¹⁷

Acupuncture, as a traditional Chinese medical therapy, has been shown to improve qi and blood circulation, mental regulation, and cognitive performance. Evidence indicates that acupuncture modulates brain regions associated with cognition, therefore enhancing cognitive abilities, promoting quality of daily life, and delaying the progression of dementia.¹⁸ These beneficial effects may be mediated by mechanisms involving the attenuation of inflammatory responses, reduction of oxidative stress, normalization of central cholinergic pathway activity, mitigation of excitotoxicity within the central nervous system, and modulation of brain-derived neurotrophic factor levels and plasticity of synaptic connections.^{19–23} However, there are few high-quality randomized controlled trials (RCTs) directly on vascular parkinsonism with mild cognitive impairment (VP-MCI). Most existing studies have focused on broader categories of vascular cognitive impairment or PD-related cognitive decline, and hence their findings may not be relevant to VP-MCI. Moreover, previous studies have mostly used clinical outcome measures, with limited use of biological or neuroimaging measures to investigate the mechanisms of cognitive changes in VP. Diffusion tensor imaging (DTI) and serum neurofilament light chain (sNfL) provide complementary measures of white matter microstructural integrity and neuroaxonal damage, respectively, and this may enhance the mechanistic explanation of clinical outcomes. Therefore, this study aims to evaluate the efficacy of acupuncture in patients with VP-MCI and to explore the possible underlying mechanisms.

Materials and Methods

Study Design

The Ethics Committee of First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (approval number: TYLL2025[K] No.024) and the Ethics Committee of Affiliated Hospital of Tianjin Academy of Traditional Chinese Medicine (approval number: LLKY2025-77) have both provided their approval. The trial has been registered in International Traditional Medicine Clinical Trial Registry (number: ITMCTR2025001041). This study will be held in conformity with the guidelines of the Declaration of Helsinki and has been reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT). This is a prospective, two-center, randomized, controlled, and assessor-blinded clinical trial. Eligible patients will be randomized to one of three groups: acupuncture, sham acupuncture, or the waiting-list group. Figure 1 shows a detailed flowchart for this trial.

Participant and Recruitment

Recruitment will take place in the aforementioned two hospitals. Recruitment information will be distributed via a variety of approaches, including posters and social networking sites like WeChat. Participants interested in this trial will be given details about the purpose of the research, methods, potential risks and benefits. If patients decide to join after receiving

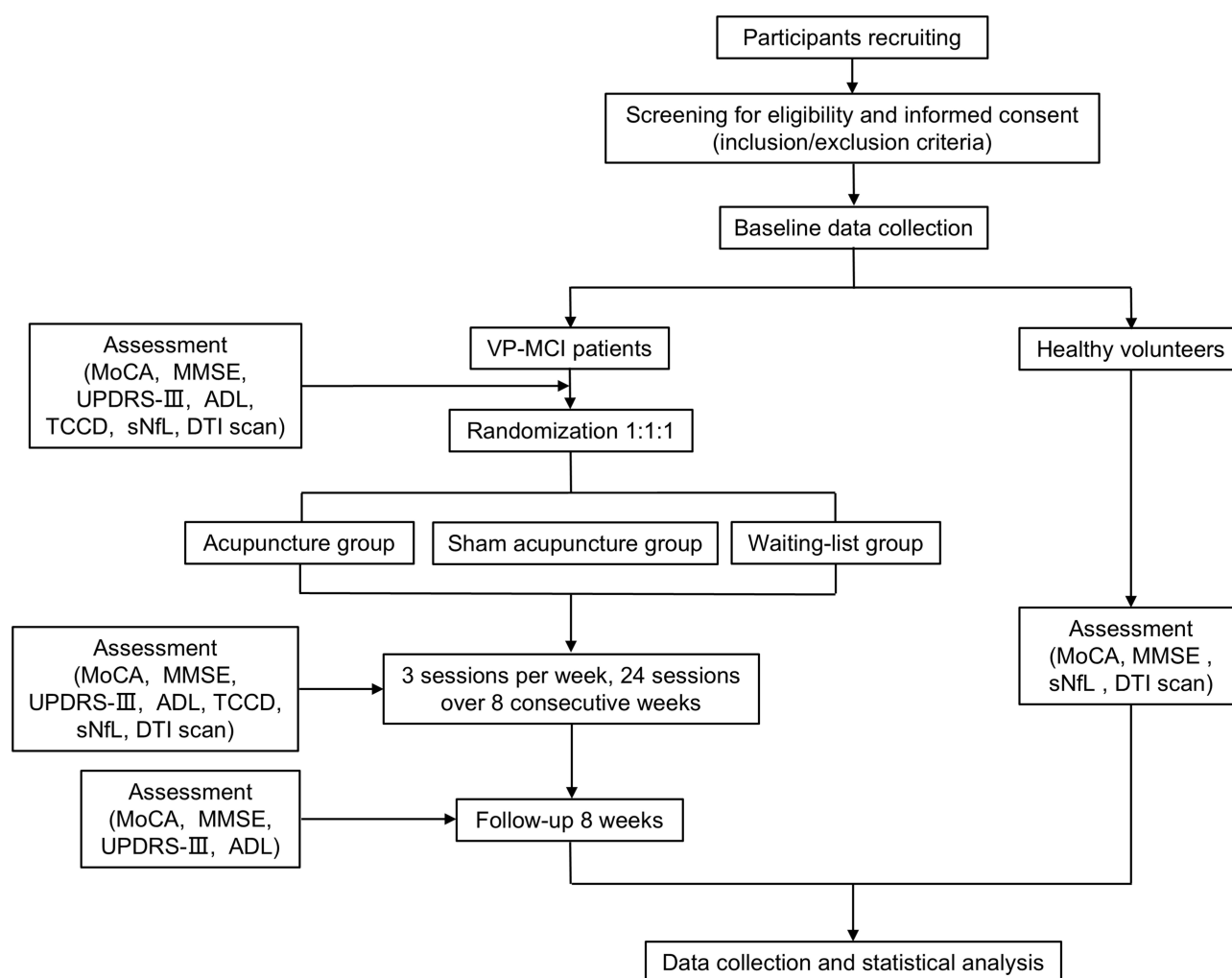


Figure 1 Flowchart of trial process.

Abbreviations: VP-MCI, vascular parkinsonism with mild cognitive impairment; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; UPDRS-III, Part III of the Unified Parkinson's Disease Rating Scale; ADL, Activities of Daily Living; TCCD, Transcranial Color-Coded Doppler; sNfL, serum neurofilament light chain; DTI, diffusion tensor imaging.

this information, they will go through a preliminary clinical assessment with qualified Traditional Chinese Medicine (TCM) practitioners who have at least five years of clinical experience. Eligible patients will have to fill out a written informed consent form.

Eligibility Criteria

Diagnostic Criteria: The diagnosis of VP has been determined using previous clinical criteria.⁷ The following criteria will be considered: (1) The presence of parkinsonian syndrome, characterized by bradykinesia and no less than one of the following kinds of symptoms: resting tremor, muscular rigidity, or postural instability (excluding that caused by primary visual, vestibular, cerebellar, or proprioceptive abnormalities). (2) Evidence of cerebrovascular disorders, either indicated by neuroimaging findings or manifested as focal signs and symptoms resulting from stroke. (3) A clear temporal relationship between conditions (1) and (2), meaning that parkinsonian features appear acutely after a stroke or gradually within one year of the cerebrovascular event. (4) Exclusion of parkinsonism caused by repeated head trauma, encephalitis, frontal lobe tumors, normal-pressure hydrocephalus, or the use of antipsychotic medications.

Inclusion Criteria for VP-MCI patients: (1) Men and women between the ages of 40 and 80; (2) Meeting the diagnostic criteria for VP; (3) $20 < \text{Mini-Mental State Examination (MMSE) score} \leq 24$; (4) $20 < \text{Montreal Cognitive Assessment (MoCA) score} \leq 26$; (5) Right-handed; (6) Willingness to give written, informed consent in order to participate in this study.

Exclusion Criteria for VP-MCI patients: (1) The existence of cognitive impairment before VP was diagnosed; (2) Coexisting disorders of the central nervous system; (3) Brain surgery history; (4) History of suicidal ideation or tendency, severe psychiatric disorders (eg, schizophrenia), or treatment with antipsychotic medications; (5) Presence of other severe organic diseases or conditions that could interfere with the assessment of cognitive function; (6) Contraindications to MRI or inability to cooperate with the examination for other reasons; (7) Using drugs that are known to impair cognitive function, either presently or in the past.

Inclusion Criteria for healthy subjects: (1) Men or women aged 40 to 80 years; (2) Able to provide a valid health examination report within the past six months; (3) Right-handed; (4) Willingness to give written, informed consent in order to participate in this study.

Exclusion Criteria for healthy subjects: (1) History of brain surgery; (2) Presence of any central nervous system disorders; (3) History of suicidal tendencies, severe psychiatric disorders (eg, schizophrenia), or prior treatment with antipsychotic medications; (4) Using drugs that are known to impair cognitive function, either presently or in the past; (5) Contraindications to MRI or inability to cooperate with the examination for other reasons.

Withdrawal and Termination Criteria

Withdrawal Criteria: (1) Participants who stop taking part in the study for any reason; (2) Participants who cannot be contacted due to relocation or changes in contact information; (3) Individuals concurrently participating in other research projects; (4) Participants who fail to comply with study assessments or demonstrate poor adherence.

Termination Criteria: (1) Participants who experience adverse reactions and are deemed by the researcher to be unfit to proceed with the study; (2) Participants who develop serious adverse events, complications, or disease deterioration requiring emergency medical intervention.

During the trial, investigators will retain all original study records and document in detail the reasons and timing for any participant's withdrawal or study termination.

Randomization and Allocation Concealment

A random sequence of numbers will be generated using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Eligible participants will be assigned with a 1:1:1 ratio to the acupuncture, sham acupuncture, or waiting-list groups. A research assistant at each clinical site, who is independent of other study activities, will carry out the randomization process. To guarantee the allocation remains concealed, the randomization results will be kept in opaque, sealed envelopes with sequential numbers.

Blinding

Participants will remain unaware of which group they are in and will be treated in an independent space to prevent chatting among them. However, blinding of the waiting-list group is not feasible. The acupuncturists will not be blinded during the procedure because of the nature of the operation. The treatment allocation will be kept hidden from outcome assessors and statisticians throughout the trial. This process is maintained to prevent bias during data collection and statistical analysis. Unblinding will be conducted by the study center upon completion of data analysis. In the event of any serious adverse events or medical emergencies, emergency unblinding will be carried out.

Intervention

Standard Treatment

All patients will receive standard treatment, including therapy for parkinsonian syndromes (eg, anticholinergics and dopamine receptor agonists) and management of stroke and its associated risk factors (eg, antiplatelet therapy, blood pressure control, blood glucose management, and lipid regulation). Medication dosages will remain unchanged unless medical adjustments are necessary. Any changes will be recorded in the case report forms (CRFs). Additionally, no non-pharmacological therapies, other than acupuncture, will be provided during the trial.

Acupuncture Group

Participants in this group will get verum acupuncture intervention. They will be placed in the supine position. Sterile, disposable needles from Huatuo (Suzhou, China) will be used. These needles are 0.25 mm in diameter and 40 mm in length. The treatment protocol includes twelve acupoints: Neiguan (PC6), Renzhong (GV26), Baihui (GV20), Sishencong (EX-HN1), Fengchi (GB20), Wangu (GB12), Tianzhu (BL10), Sibai (ST2), Shenmen (HT7), Fenglong (ST40), Sanyinjiao (SP6), and Taichong (LR3).²⁴ All bilateral acupoints will be needled on both sides. The locations and procedures for manipulating the acupoints are detailed in [Table S1](#). The needles will be kept for 30 minutes. Participants will receive acupuncture sessions on three occasions weekly over eight weeks.

Sham Acupuncture Group

Ten non-acupoints will receive sham acupuncture. The non-acupoints in this group will be chosen based on sites located off the meridians but adjacent to the acupoints used in the acupuncture group, which is a commonly adopted method in sham acupuncture design.²⁵ Superficial needling will be applied at these non-acupoints without eliciting the Deqi sensation. The locations and procedures for manipulating the non-acupoints are detailed in [Table S2](#). [Figure 2](#) shows the specific layout and positions of the selected non-acupoints. The qualifications and requirements for acupuncturists will be identical to those in the acupuncture group.

Waiting-List Group

Participants assigned to the waiting-list group will only receive standard treatment during the first 16 weeks after randomization. After the waiting period, they will be compensated with verum acupuncture therapy, with the same treatment procedure as the acupuncture group, following the waiting period.

Healthy Control Group

Healthy volunteers will be recruited to undergo the same DTI scanning protocol. Their data will serve as baseline references, allowing precise identification of specific white matter changes in patients with VP-MCI following acupuncture treatment.

Outcomes Measurement

We will record baseline demographic and clinical characteristics for all participants, including age, sex, education background, illness duration, treatment history, and current concomitant medications. The detailed timeline for the assessment is presented in [Table 1](#).

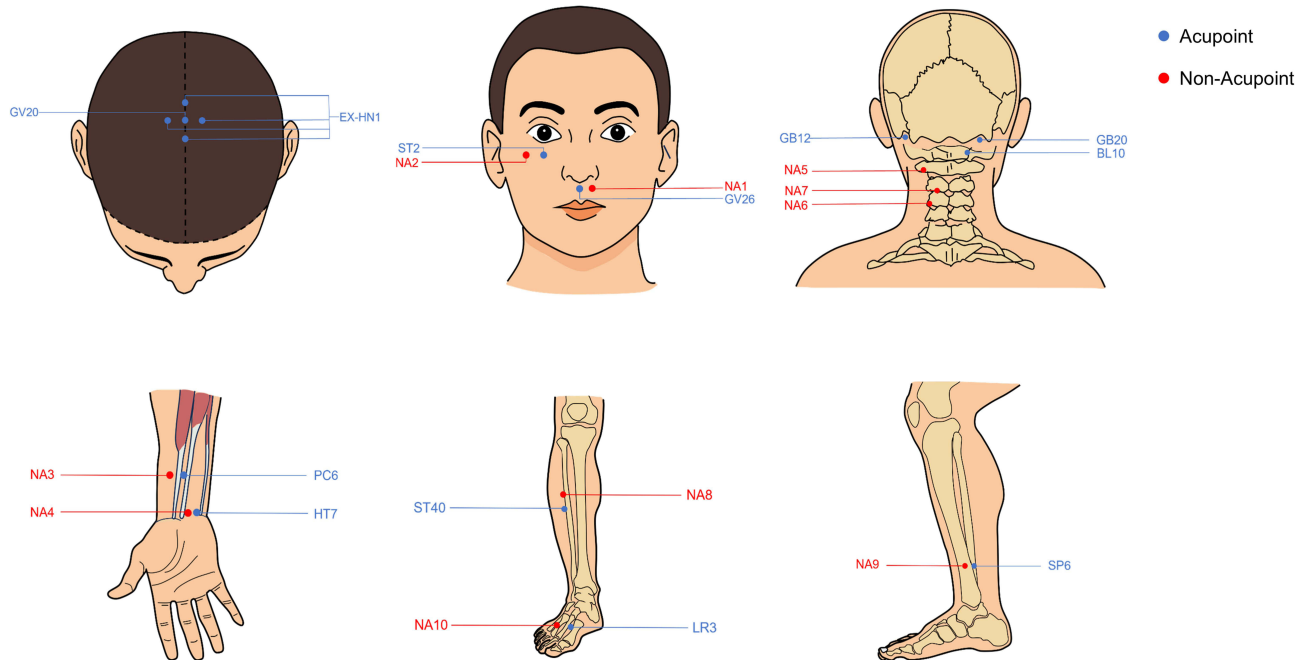


Figure 2 Location of the acupoints and non-acupoints. Blue dots represent acupoints, including Neiguan (PC6), Renzhong (GV26), Baihui (GV20), Sishencong (EX-HN1), Fengchi (GB20), Vangu (GB12), Tianzhu (BL10), Sibai (ST2), Shenmen (HT7), Fenglong (ST40), Sanyinjiao (SP6), and Taichong (LR3). Red dots represent non-acupoints (NA1–NA10).

Primary Outcome

MoCA

The MoCA will be used to evaluate cognitive function. It is a screening tool that has been shown to outperform the MMSE in identifying MCI.²⁶ It tests multiple cognitive domains including memory, executive function, attention, language, abstraction, naming, delayed recall, and orientation.²⁷ The MoCA is particularly sensitive to executive dysfunction.²⁸ A score of 26 or below indicates cognitive impairment, with lower scores reflecting poorer cognitive performance.²⁷

Secondary Outcomes

MMSE

We will also administer the MMSE. Its high specificity complements the MoCA, providing a more balanced and comprehensive cognitive evaluation.²⁹ The MMSE assesses orientation, memory, attention, language, and visuospatial ability.³⁰ It contains 30 items. Scores decline as cognitive function worsens.

Table 1 The Timeline for Assessment

Time Point	Baseline	Treatment Phase		Follow-Up Phase
	Week 0	Week 1	Week 8	Week 16
Enrollment				
Eligibility screen	√	×	×	×
Informed consent	√	×	×	×
Randomization	√	×	×	×
Interventions				
Acupuncture group	×	24 sessions treatment		√
Sham acupuncture group	×	24 sessions treatment		√

(Continued)

Table 1 (Continued).

Time Point	Baseline	Treatment Phase		Follow-Up Phase
	Week 0	Week 1	Week 8	Week 16
Waiting-list group	×	No treatment		√
Assessment				
MoCA	√	×	√	√
MMSE	√	×	√	√
UPDRS-III	√	×	√	√
ADL	√	×	√	√
TCCD	√	×	√	×
sNfL	√	×	√	×
DTI scan	√	×	√	×

Abbreviations: MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; UPDRS-III, Part III of the Unified Parkinson's Disease Rating Scale; ADL, Activities of Daily Living; TCCD, Transcranial Color-Coded Doppler; sNfL, serum neurofilament light chain; DTI, diffusion tensor imaging.

Part III of the Unified Parkinson's Disease Rating Scale (UPDRS-III)

UPDRS-III will be used to rate the severity of motor symptoms, which has been revised by the Movement Disorder Society.³¹ UPDRS-III is a commonly used tool for motor impairment in patients having parkinsonian syndromes. An increase in scores shows a greater level of motor impairment.³²

Activities of Daily Living (ADL)

Functional independence in everyday life will be measured with the help of the ADL. The version that we used is based on Lawton and Brody.³³ This tool has two components, namely the Physical Self-Maintenance Scale (PSMS) and Instrumental Activities of Daily Living (IADL). A score higher than 14 indicates ADL impairment, with higher scores reflecting greater limitations in daily living activities and poorer quality of life.

Transcranial Color-Coded Doppler (TCCD)

TCCD will be used to evaluate cerebral hemodynamics. The analysis will enable the establishment of the peak systolic velocity (Vp) and the mean flow velocity (Vm). Such measurements will be made based on bilateral internal carotid arteries (ICA), anterior cerebral arteries (ACA), and middle cerebral arteries (MCA).

Serum Neurofilament Light Chain (sNfL)

Previous studies have shown that sNfL is a biomarker that indicates neuroaxonal damage and cognitive decline.³⁴ Approximately 5 mL of blood will be collected from the antecubital vein into a plain vacuum tube (without anticoagulant) under sterile conditions. The blood collected will be centrifuged at 3000 rotations per minute for 15 minutes. Serum will be aliquoted in the cryovials and stored at -80°C . sNfL levels will be quantified using enzyme-linked immunosorbent assay (ELISA).

DTI Acquisition and Analysis

We plan to investigate the neurological mechanisms by which acupuncture can relieve symptoms of VP-MCI. Twelve participants will be randomly selected from each of the acupuncture and sham acupuncture groups to undergo DTI scanning at weeks 0 and 8. In addition, 12 healthy controls will be recruited to complete DTI scanning.

We will perform all MRI scans with a GE Healthcare Discovery MR750 3.0 T scanner. This machine features an 8-channel head-neck coil. For structural imaging, a 3D-T1 BRAVO sequence will be acquired using the following parameters: repetition time (TR)/echo time (TE) = 8.16/3.18 ms, flip angle (FA) = 12°, slice thickness = 1.0 mm, field of view (FOV) = $256 \times 256 \text{ mm}^2$, matrix = 256×256 , and 188 sagittal slices. DTI will be performed using the following parameters: TR/TE = 6000/61 ms, FA = 90°, slice thickness = 3.0 mm, interslice gap = 0 mm, number of slices = 50, FOV = $256 \times 256 \text{ mm}^2$, matrix = 128×128 , diffusion weighting (b-value) = 1000 s/mm², with diffusion gradients applied in 64 noncollinear directions.

Follow-Up

Following the 8-week therapy duration, all participants will go through another 8-week follow-up phase. The assessors will contact participants by telephone prior to each scheduled follow-up visit. If there is no response after one week of continuous attempts, or if a participant indicates unwillingness to cooperate, the case will be considered lost to follow-up, and subsequent follow-up procedures will be discontinued.

Safety Assessment

Adverse events (AEs) are the vital markers to assess the safety of treatment. Any adverse reaction caused by acupuncture will be noted, such as bleeding, hematoma, pain, or retention of the needle. The AEs will be monitored on CRFs and the information will include the time, the degree, and how it was addressed. In case of any serious adverse event (SAE), it will be reported immediately to the ethics committee. The committee has the authority to suspend the trial temporarily in response to any reported SAE.

Sample Size Estimation

The sample size calculation is based on changes in the MoCA score as the primary outcome. Since the differential effects of acupuncture on VP-MCI have not yet been reported, we estimated the sample size based on a related study, which found that Tiaoshen Yizhi acupuncture improved MoCA scores with a pooled Cohen's *d* of 0.83, compared with the control group.²⁴ Given the exploratory nature of the present trial, this effect size was used as a reference for a conservative sample size calculation, corresponding to a Cohen's *f* of 0.4 for a three-group design.³⁵ A priori power analysis using G*Power 3.1.9.7 ($\alpha = 0.05$, power = 0.90, $f = 0.4$) indicates that 28 participants per group are required. Considering an expected 20% attrition rate, we plan to recruit 35 participants per group, resulting in a total of 105 participants.

Data Collection and Management

The CRFs will be filled on paper by two independent workers before the start of the research. The data will be registered in Microsoft Excel by a specified data manager. Data accuracy will then be verified by another research assistant so as to ensure the accuracy of the data entries. Any records that we keep will be confidential. The data will be monitored and validated on a frequent basis during the study. The original documents will be kept in First Teaching Hospital of Tianjin University of Traditional Chinese Medicine.

Quality Control

Before the start of the study, all research personnel will participate in standardized training sessions covering the study objectives, protocol, and quality control procedures. The acupuncture treatments will be performed by registered acupuncturists with a minimum of five years of clinical experience. Prior to the study, they will receive further training and assessments to make sure that all acupuncture procedures are consistent.

Statistical Analysis

Data will be analyzed with SPSS 26.0 (IBM Corp., Armonk, NY, USA). Baseline characteristics will be summarized with descriptive statistics. The normality of continuous data will be examined using the Kolmogorov–Smirnov test. Normally distributed data will be reported as mean $\pm$ standard deviation, whereas non-normal data as median with interquartile

range. Baseline differences among the three groups will be evaluated using one-way analysis of variance (ANOVA) or Kruskal–Wallis *H*-test for continuous variables, and chi-squared or Fisher's exact tests for categorical variables.

The intention-to-treat principle will be applied. Missing outcome data will be handled using the multiple imputation method. Intervention effects on primary and secondary outcomes will be analyzed using a linear mixed-effects model (LMM). Fixed effects will include group, time, and time-by-group interaction. Baseline values will be incorporated as covariates following the analysis of covariance (ANCOVA) principle. A random intercept will be included for each participant, and a random slope for time will be considered if it significantly improves the model fit, as assessed by likelihood ratio tests. Model estimation will use maximum likelihood, and a first-order autoregressive covariance structure will be applied unless alternative structures show better model fit. A *p*-value < 0.05 will be considered statistically significant. Bonferroni correction will be used for the analyses of primary outcomes, secondary outcomes, and post hoc analyses to prevent inflation of the Type I error.

Structural MRI (3D-T1 BRAVO) images will be preprocessed using the Statistical Parametric Mapping software (SPM8; Wellcome Department of Imaging Neuroscience, London, UK) in MATLAB 2016 (MathWorks, Natick, MA, USA). DTI data will be processed with FSL 5.0.10 (FMRIB Software Library; University of Oxford, UK). In this study, fractional anisotropy will be calculated and analyzed by tract-based spatial statistics. Associations between imaging measures and clinical variables will be examined using Pearson or Spearman correlation tests based on data distribution.

Dissemination

The findings from this trial will be submitted for publication in peer-reviewed journals.

Anticipated Results

Our primary hypothesis is that acupuncture will lead to greater improvements in cognitive function, compared with both sham acupuncture and waiting-list controls. As secondary hypotheses, we anticipate improvements in motor performance, activities of daily living, and cerebral hemodynamics. At the mechanistic level, we hypothesize that these clinical effects are accompanied by underlying neural and biological changes rather than reflecting behavioral effects alone. Specifically, we propose that functional improvement will be associated with alterations in the integrity of white matter tracts relevant to cognitive and motor networks, together with changes in sNfL levels, a biomarker of neuroaxonal injury. These anticipated findings are expected to provide preliminary neurovascular and structural insights into the mechanisms underlying the effects of acupuncture in patients with VP-MCI.

Discussion

Non-motor symptoms of VP, particularly cognitive impairment, are increasingly recognized as major determinants of quality of life. Cognitive impairment has thus become a major clinical issue in this population. However, it has not been given due consideration as a distinct research focus and it is often contrasted within the broader category of vascular cognitive impairment. Importantly, cognitive impairment in VP appears to have its own unique pathophysiological mechanisms. A transcranial magnetic stimulation study provided neurophysiological evidence of impaired cortical-subcortical communication, potentially linked to GABAergic system dysfunction, which could result in motor and cognitive symptoms.³⁶ Moreover, sensorimotor integration abnormalities have been reported, which included a decrease in cholinergic activity and impaired glutamatergic synaptic plasticity. These impairments are closely related to deficiencies in executive function, attention, and verbal memory.³⁷ Global cognition assessed using the MoCA and MMSE could provide a clinically relevant measure of treatment response in this trial. With these developments, there are still few effective treatment options for cognitive impairment in VP. This emphasizes the need for novel therapeutic strategies.

Acupuncture has been extensively researched in its neurotrophic and neuroprotective effects. This non-pharmacological therapy presents a promising way of treating VP-MCI. VP-MCI may be categorized as the patterns of “tremor”, “amnesia”, and “dementia” in TCM, which is often attributed to obstruction of cerebral orifices and insufficiency of brain marrow. Accordingly, the Tiaoshen Yizhi acupuncture prescription²⁴ will be used in this study, whereby the selection of acupoints is guided by TCM principles targeting at clearing the orifices, opening the mind,

strengthening the root and balancing the spirit. In line with these traditional concepts, previous studies indicate that needling at acupoints in this protocol like GV20 and GB20 is correlated with increased cerebral blood flow within the anterior and posterior circulation territories.^{38,39} Moreover, stimulation at acupoints including PC6, GV26, SP6, and GV20 is associated with less oxidative stress, inflammation, and iron overload, better cerebral perfusion and motor performance.⁴⁰ Evidence from neuroimaging studies also show that acupuncture could promote neuroplastic changes by increasing the functional connectedness and neural activity of cognitive networks.^{41,42}

Given that previous research suggests potential biological effects of acupuncture, its clinical impact on cognition, motor performance, activities of daily living, and cerebral hemodynamics in patients with VP-MCI has not been adequately studied. Therefore, this study will also evaluate these functionally relevant domains to provide a more comprehensive assessment of clinical response. While behavioral and cognitive scales reflect symptom severity, they provide limited insight into underlying neurobiological changes. To fulfill the exploratory objective of uncovering neural mechanisms, DTI and sNfL will be employed in this trial. Neurofilament light chain is a structural component of myelinated axons and serves as a marker of neuroaxonal injury.⁴³ Elevated sNfL levels have been associated with the severity of WMLs and cognitive decline,⁴⁴ suggesting its potential relevance in VP-MCI. However, how sNfL levels change over time and respond to therapeutic intervention remains unclear. DTI provides a noninvasive approach for assessing white matter microstructural integrity beyond conventional MRI. Previous studies suggest that acupuncture may influence white matter organization and functional network connectivity.^{45–47} We hypothesize that the core pathology of VP-MCI is primarily related to widespread microstructural disruption of white matter networks rather than macroscopic lesions. DTI is therefore anticipated to be an excellent tool for identifying microstructural changes relevant to this hypothesis.

The selection of control condition plays an important role in measuring the treatment effects in acupuncture RCTs. The purpose of including sham acupuncture and waiting-list groups is to account for nonspecific influences, such as placebo responses, expectancy effects, and natural disease progression, thereby enabling a more precise understanding of the specific effects of acupuncture.⁴⁸ There are several limitations in this study. First, due to constraints in equipment availability and financial resources, only a subset of participants will undergo DTI scanning. This may have an effect on the generalizability of the findings, even so, it is expected to provide useful preliminary data for exploratory analysis. Second, because of the inherent nature of acupuncture procedures, achieving complete blinding is difficult and may bring about expectation bias. Nevertheless, employing blinded outcome reviewers may reduce this risk. Third, the acupuncture prescription in this trial is based on TCM theory. This approach reflects real-world clinical practice, but it also limits the ability to isolate the specific contribution of individual acupoints. In particular, while participants will be recruited from two hospitals, the external validity of the findings may be limited by the fact that they are located in the same city. Finally, the relatively long treatment duration may increase the risk of participant dropout. To overcome this problem, strict follow-up management and patient education will be implemented to improve adherence.

Conclusion

Taken together, this trial is designed to evaluate the clinical effectiveness of acupuncture for patients with VP-MCI and to explore potential underlying mechanisms. The findings are expected to provide preliminary evidence to support the early management of cognitive decline in this population and to inform future mechanistic and clinical research in VP-MCI.

Abbreviations

PD, Parkinson's disease; VP, vascular parkinsonism; WMLs, white matter lesions; MCI, mild cognitive impairment; RCTs, randomized controlled trials; VP-MCI, vascular parkinsonism with mild cognitive impairment; DTI, diffusion tensor imaging; sNfL, serum neurofilament light chain; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; TCM, Traditional Chinese Medicine; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; CRFs, case report forms; UPDRS-III, Part III of the Unified Parkinson's Disease Rating Scale; ADL, Activities of Daily Living; PSMS, Physical Self-Maintenance Scale; IADL, Instrumental Activities of Daily Living; TCCD, Transcranial Color-Coded Doppler; ICA, internal carotid arteries; ACA, anterior cerebral

arteries; MCA, middle cerebral arteries; ELISA, enzyme-linked immunosorbent assay; TR, repetition time; TE, echo time; FA, flip angle; FOV, field of view; AEs, adverse events; SAE, serious adverse event; ANOVA, analysis of variance; LMM, linear mixed-effects model; ANCOVA, analysis of covariance.

Acknowledgments

We would like to thank all the patients and their families for their participation and cooperation, as well as the clinical and research teams for their invaluable contributions to this study.

Funding

This work is supported by Open Project of National Clinical Research Center for Acupuncture and Moxibustion (NCRCP2024017).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Zhao X, Sun J, Chen F, et al. YOD1 regulates oxidative damage of dopamine neurons in Parkinson's disease by deubiquitinating PKM2. *Clin Transl Med.* **2025**;15(7):e70420. doi:10.1002/ctm2.70420
2. Shen LH, Liao MH, Tseng YC. Recent advances in imaging of dopaminergic neurons for evaluation of neuropsychiatric disorders. *J Biomed Biotechnol.* **2012**;2012:259349. doi:10.1155/2012/259349
3. Sinani O, Dadouli K, Ntellas P, et al. Association between white matter lesions and Parkinson's disease: an impact on postural/gait difficulty phenotype and cognitive performance. *Neurol Res.* **2022**;44(12):1122–1131. doi:10.1080/01616412.2022.2112378
4. Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. *Nat Rev Dis Primers.* **2017**;3(1):17013. doi:10.1038/nrdp.2017.13
5. KKY M, Lin S, Mok VCT. Neuroimaging in Vascular Parkinsonism. *Curr Neurol Neurosci Rep.* **2019**;19(12):102. doi:10.1007/s11910-019-1019-7
6. Wu Y, Feng K. Clinical analysis of senile patients with vascular parkinsonism with different onset forms. *Chin J Geriatr Heart Brain Ves Dis.* **2023**;25(5):501–503. doi:10.3969/j.issn.1009-0126.2023.05.014
7. Rektor I, Bohnen NI, Korczyn AD, et al. An updated diagnostic approach to subtype definition of vascular parkinsonism - recommendations from an expert working group. *Parkinsonism Relat Disord.* **2018**;49:9–16. doi:10.1016/j.parkreldis.2017.12.030
8. Korczyn AD. Vascular parkinsonism--characteristics, pathogenesis and treatment. *Nat Rev Neurol.* **2015**;11(6):319–326. doi:10.1038/nrneurol.2015.61
9. Vale TC, Barbosa MT, Caramelli P, Cardoso F. Vascular Parkinsonism and cognitive impairment: literature review, Brazilian studies and case vignettes. *Dement Neuropsychol.* **2012**;6(3):137–144. doi:10.1590/S1980-57642012DN06030005
10. Al-kuraishy HM, Jabir MS, Al-Gareeb AI, Albuhadily AK. New insight on the possible role of statins in vascular parkinsonism: a need for presumptive therapy. *Ageing Res Rev.* **2024**;95:102209. doi:10.1016/j.arr.2024.102209
11. Tohgi H, Takahashi S, Abe T, Utsugisawa K. Symptomatic characteristics of parkinsonism and the width of substantia nigra pars compacta on MRI according to ischemic changes in the putamen and cerebral white matter: implications for the diagnosis of vascular parkinsonism. *Eur Neurol.* **2001**;46(1):1–10. doi:10.1159/000050748
12. Liu H, Deng B, Xie F, et al. The influence of white matter hyperintensity on cognitive impairment in Parkinson's disease. *Ann Clin Transl Neurol.* **2021**;8(9):1917–1934. doi:10.1002/acn3.51429
13. Farret MS, Cersosimo MG, Ramirez Gomez CC, Micheli F. Clinoradiological comparisons between vascular parkinsonism and Parkinson's disease. *J Neurol Neurosurg Psychiatry.* **2015**;86(9):1049–1050. doi:10.1136/jnnp-2015-311155
14. Vale TC, Caramelli P, Cardoso F. Vascular parkinsonism: a case series of 17 patients. *Arq Neuropsiquiatr.* **2013**;71(10):757–762. doi:10.1590/0004-282X20130117
15. Barbosa MT, Caramelli P, Maia DP, et al. Parkinsonism and Parkinson's disease in the elderly: a community-based survey in Brazil (the Bambui study). *Mov Disord.* **2006**;21(6):800–808. doi:10.1002/mds.20806
16. Levin OS, Chimagomedova A, Iakovleva OV, Skripkina NA, Lyashenko EA. Cognitive impairment and other non-motor symptoms in patients with vascular parkinsonism. *J Alzheimer's Dis Park.* **2017**;7(5). doi:10.4172/2161-0460.1000385
17. Wu J, Teng Y, Xie Y, Xing S, Zhi S. Comparing the efficacy of physical therapy interventions in Alzheimer's disease: a network meta-analysis. *Front Aging Neurosci.* **2025**;17:1541287. doi:10.3389/fnagi.2025.1541287
18. Liu Q, Xiao K, Wan P, Zou Q. Resting-state fMRI reveals the neural correlates of acupuncture in the treatment of vascular cognitive impairment. *Clin Interv Aging.* **2025**;20:1191–1204. doi:10.2147/CIA.S529416
19. Jittiwat J. Baihui point laser acupuncture ameliorates cognitive impairment, motor deficit, and neuronal loss partly via antioxidant and anti-inflammatory effects in an animal model of focal ischemic stroke. *Evid-Based Compl Altern Med ECAM.* **2019**;2019:1204709. doi:10.1155/2019/1204709
20. Lee B, Sur B, Shim J, Hahm DH, Lee H. Acupuncture stimulation improves scopolamine-induced cognitive impairment via activation of cholinergic system and regulation of BDNF and CREB expressions in rats. *BMC Complement Altern Med.* **2014**;14(1):338. doi:10.1186/1472-6882-14-338
21. Dai Y, Wang S, Yang M, et al. Electroacupuncture protective effects after cerebral ischemia are mediated through miR-219a inhibition. *Biol Res.* **2023**;56(1):36. doi:10.1186/s40659-023-00448-z

22. Leung MCP, Yip KK, Ho YS, Siu FKW, Li WC, Garner B. Mechanisms underlying the effect of acupuncture on cognitive improvement: a systematic review of animal studies. *J Neuroimmune Pharmacol*. 2014;9(4):492–507. doi:10.1007/s11481-014-9550-4
23. Li L, Li J, Dai Y, et al. Electro-acupuncture improve the early pattern separation in Alzheimer's disease mice via basal forebrain-hippocampus cholinergic neural circuit. *Front Aging Neurosci*. 2021;13:770948. doi:10.3389/fnagi.2021.770948
24. Chen X, Zhang L, Mao W, et al. Comparing the effect of acupuncture, sham acupuncture, and waiting-list control on patients with post-stroke cognitive impairment: a randomized clinical trial. *QJM*. 2025; hcafl81. doi:10.1093/qjmed/hcafl81
25. Qi LY, Yang JW, Yan SY, et al. Effect of acupuncture for diarrhea-predominant irritable bowel syndrome: study protocol for a randomized clinical trial. *Trials*. 2022;23(1):711. doi:10.1186/s13063-022-06639-5
26. Pinto TCC, Machado L, Bulgacov TM, et al. Is the Montreal cognitive assessment (MoCA) screening superior to the mini-mental state examination (MMSE) in the detection of mild cognitive impairment (MCI) and Alzheimer's disease (AD) in the elderly? *Int Psychogeriatr*. 2019;31(4):491–504. doi:10.1017/S1041610218001370
27. Nasreddine ZS, Phillips NA, Bédirian V, et al. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695–699. doi:10.1111/j.1532-5415.2005.53221.x
28. Fu C, Jin X, Chen B, et al. Comparison of the mini-mental state examination and montreal cognitive assessment executive subtests in detecting post-stroke cognitive impairment. *Geriatr Gerontol Int*. 2017;17(12):2329–2335. doi:10.1111/ggi.13069
29. Jia X, Wang Z, Huang F, et al. A comparison of the mini-mental state examination (MMSE) with the montreal cognitive assessment (MoCA) for mild cognitive impairment screening in Chinese middle-aged and older population: a cross-sectional study. *BMC Psychiatry*. 2021;21(1):485. doi:10.1186/s12888-021-03495-6
30. Grigore A, Goebel LJ. Frontotemporal dementia and amyotrophic lateral sclerosis: a case report and clinical insights. *Cureus*. 2025;17(3):e80329. doi:10.7759/cureus.80329
31. Goetz CG, Fahn S, Martinez-Martin P, et al. Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): process, format, and clinimetric testing plan. *Mov Disord*. 2007;22(1):41–47. doi:10.1002/mds.21198
32. Goetz CG, Tilley BC, Shaftman SR, et al. Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord*. 2008;23(15):2129–2170. doi:10.1002/mds.22340
33. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969;9(3):179–186. doi:10.1093/geront/9.3_Part_1.179
34. Gu L, Zhang P, Gao R, Shu H, Wang P. Predictive value of serum neurofilament light chain for cognitive impairment in Parkinson's disease. *Front Aging Neurosci*. 2024;16:1465016. doi:10.3389/fnagi.2024.1465016
35. Cohen J. A power primer. *Psychol Bull*. 1992;112(1):155–159. doi:10.1037/0033-2909.112.1.155
36. Agrawal A, Bhattacharya A, Kamble N, Mailankody P, Yadav R, Pal PK. Cortical excitability changes in patients of vascular parkinsonism with cognitive impairment. *Parkinsonism Relat Disord*. 2023;116:105869. doi:10.1016/j.parkreldis.2023.105869
37. Benítez-Rivero S, Palomar FJ, Martín-Rodríguez JF, et al. Abnormal sensorimotor integration correlates with cognitive profile in vascular parkinsonism. *J Neurol Sci*. 2017;377:161–166. doi:10.1016/j.jns.2017.03.050
38. Im JW, Moon SK, Jung WS, et al. Effects of acupuncture at GB20 on CO2 reactivity in the basilar and middle cerebral arteries during hypocapnia in healthy participants. *J Altern Complement Med*. 2014;20(10):764–770. doi:10.1089/acm.2013.0240
39. Byeon HS, Moon SK, Park SU, et al. Effects of GV20 acupuncture on cerebral blood flow velocity of middle cerebral artery and anterior cerebral artery territories, and CO2 reactivity during hypocapnia in normal subjects. *J Altern Complement Med*. 2011;17(3):219–224. doi:10.1089/acm.2010.0232
40. Liu Y, Luo K, Yang X, et al. Effectiveness of Xingnao Kaiqiao acupuncture on iron metabolism and efficacy in acute ischemic stroke: a randomized controlled trial. *Chin J Integr Tradit Wes Med*. 2025;45(6):657–665. doi:10.7661/j.cjim.20250326.003
41. Yin Z, Wang Z, Li Y, et al. Neuroimaging studies of acupuncture on Alzheimer's disease: a systematic review. *BMC Complement Med Ther*. 2023;23(1):63. doi:10.1186/s12906-023-03888-y
42. Tan TT, Wang D, Huang JK, et al. Modulatory effects of acupuncture on brain networks in mild cognitive impairment patients. *Neural Regener Res*. 2017;12(2):250–258. doi:10.4103/1673-5374.200808
43. Nwamekang Belinga L, Espourteille J, Wepnyu Njamnshi Y, et al. Circulating biomarkers for Alzheimer's disease: unlocking the diagnostic potential in low- and middle-income countries, focusing on Africa. *Neurodegener Dis*. 2024;24(1):26–40. doi:10.1159/000538623
44. Beydoun MA, Noren Hooten N, Beydoun HA, et al. Plasma neurofilament light and brain volumetric outcomes among middle-aged urban adults. *Neurobiol Aging*. 2023;129:28–40. doi:10.1016/j.neurobiolaging.2023.04.013
45. Cai RL, Shen GM, Wang H, Guan YY. Brain functional connectivity network studies of acupuncture: a systematic review on resting-state fMRI. *J Integr Med*. 2018;16(1):26–33. doi:10.1016/j.joim.2017.12.002
46. Han X, Bai L, Sun C, et al. Acupuncture enhances communication between cortices with damaged white matters in poststroke motor impairment. *Evid-Based Compl Altern Med ECAM*. 2019;2019:4245753. doi:10.1155/2019/4245753
47. Ma SM, Wang L, Su XT, et al. Acupuncture improves white matter perfusion and integrity in rat model of vascular dementia: an MRI-based imaging study. *Front Aging Neurosci*. 2020;12:582904. doi:10.3389/fnagi.2020.582904
48. Shi GX, Yang XM, Liu CZ, Wang LP. Factors contributing to therapeutic effects evaluated in acupuncture clinical trials. *Trials*. 2012;13(1):42. doi:10.1186/1745-6215-13-42

Neuropsychiatric Disease and Treatment**Dovepress**
Taylor & Francis Group**Publish your work in this journal**

Neuropsychiatric Disease and Treatment is an international, peer-reviewed journal of clinical therapeutics and pharmacology focusing on concise rapid reporting of clinical or pre-clinical studies on a range of neuropsychiatric and neurological disorders. This journal is indexed on PubMed Central, the 'PsycINFO' database and CAS, and is the official journal of The International Neuropsychiatric Association (INA). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/neuropsychiatric-disease-and-treatment-journal>