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Clinical efficacy and safety of rTMS combined with bright light therapy for sleep disorders in patients with Alzheimer's disease: study protocol for a randomized controlled study

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Study protocol

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Abstract

Background

Sleep disorders are highly prevalent in Alzheimer's disease (AD) and significantly contribute to cognitive decline and reduced quality of life. While current pharmacotherapies offer limited efficacy and pose significant risks, there remains an urgent need for safe and effective non-pharmacological alternatives. Although both repetitive transcranial magnetic stimulation (rTMS) and bright light therapy (BLT) have shown promise as monotherapies, their combined therapeutic effects remain insufficiently explored. This study therefore aims to evaluate the efficacy and safety of combined rTMS-BLT intervention for AD-related sleep disturbances and to investigate the underlying neurobiological mechanisms.

Methods

This prospective, randomized, open-label, controlled, single-center trial will enroll 80 AD patients with sleep disorders. Participants will be randomly assigned to one of four groups: combined rTMS-BLT, single-rTMS, single-BLT, or control intervention, receiving treatment for 4 weeks (5 sessions / week). Assessments will be conducted at baseline, immediately post-intervention (week 4), and at follow-up (week 8). The primary outcome is the change in the Pittsburgh Sleep Quality Index (ΔPSQI). Secondary outcomes include sleep parameters assessed by polysomnography and actigraphy parameters, serum melatonin and reactive oxygen species levels, excitatory/inhibitory neurotransmitter levels measured via encephalofluctuography, and adverse events. Data will be analyzed using a 2×2 factorial design to examine main and interaction effects.

Discussion

By assessing the clinical utility of combined rTMS-BLT and exploring its potential mechanisms, this trial may offer a promising non-pharmacological strategy for managing sleep disturbances in AD.

Trial registration:

Chinese Clinical Trial Registry, ChiCTR2500105104. Registered on 30 June 2025. https://www.chictr.org.cn/showproj.html?proj=278328

Background

Alzheimer’s disease (AD) is a leading neurodegenerative disorder affecting 9.83 million elderly individuals in China [1]. Its core pathological hallmarks-including amyloid-beta (Aβ) plaques and tau tangles disrupt synaptic function, trigger neuronal loss [2], and perturb the excitatory/inhibitory (E/I) neurotransmitter balance [3], while also impairing melatonin secretion by damaging the suprachiasmatic

nucleus [4]. Additionally, Aβ pathology promotes excessive generation of reactive oxygen species (ROS), thereby aggravating oxidative stress-induced neuronal damage [5]. Collectively, these complex pathophysiological mechanisms are implicated in the emergence and progression of sleep disorders in patients with AD (Fig. 1). In turn, sleep disorders in AD accelerate cognitive decline, exacerbate neuropsychiatric symptoms, and increase caregiver burden [6], underscoring the clinical importance of effective management strategies for such comorbidities.

However, the management of sleep disorders in AD remains particularly challenging, owing to incompletely elucidated pathophysiology, multifactorial etiology, and frequent polypharmacy [7]. Both pharmacological and non-pharmacological interventions currently yield only limited therapeutic efficacy [7]. While pharmacotherapies may offer symptomatic relief, they confer considerable risks in elderly patients, including falls, cognitive decline, and other adverse events [8]. Non-pharmacological approaches are widely recommended as first-line treatments given their favorable safety profiles, but their beneficial effects as monotherapy remain modest [7]. Therefore, novel therapeutic strategies are urgently required to either alleviate sleep-related symptoms or enhance the efficacy of existing interventions.

Bright light therapy (BLT) is a non-invasive intervention that modulates melatonin secretion and recalibrates disrupted circadian rhythms in AD patients [9]. Specifically, morning administration of BLT improves sleep-wake cycles by suppressing daytime melatonin secretion and is considered most effective in patients with mild to moderate AD [10]. Additionally, BLT may reduce ROS production and mitigate Aβ-related damage to the suprachiasmatic nucleus and pineal gland along the visual pathway, thereby ameliorating sleep and circadian disturbances [11]. Current research on BLT in AD primarily focuses on circadian-regulating mechanisms and key parameters (i.e., intensity, duration, and wavelength). Nevertheless, evidence regarding its synergistic potential when combined with other physical therapies remains scarce.

Repetitive transcranial magnetic stimulation (rTMS) is another non-invasive technique increasingly recognized for managing AD-related sleep disturbances. By delivering repeated magnetic pulses to specific cortical regions, rTMS modulates neuronal excitability and inhibition, thereby influencing neural circuit activity [12]. This modulation may be associated with AD-related sleep disturbances, particularly through its effects on fronto-parietal network [13]. rTMS may help restore normal sleep architecture by modulating activity within these circuits and enhancing synaptic plasticity [14], potentially improving both cognitive and sleep outcomes. In addition, rTMS influences the release and metabolism of key sleep-regulating neurotransmitters (i.e., acetylcholine, dopamine, and serotonin) [15], which may contribute to improved sleep quality in patients with AD [15]. The dorsolateral prefrontal cortex (DLPFC), a common rTMS target, plays a critical role in sleep regulation, and its stimulation may indirectly enhance sleep quality [16]. Notably, low-frequency (≤ 1 Hz) rTMS has demonstrated particular promise in improving sleep quality among patients with AD [17].

To overcome the limitations of monotherapy, this randomized controlled trial will evaluate the efficacy and safety of rTMS combined with BLT (rTMS-BLT) compared with single-rTMS, single-BLT, and control for treating AD-related sleep disorders. In addition to neuropsychological assessments, we will investigate potential mechanisms by measuring serum melatonin, ROS, and E/I neurotransmitter levels via encephalofluctuography (EFG). These outcomes will be assessed at baseline, immediately post-intervention, and at an 8-week follow-up. We hypothesize that the combined intervention will yield superior improvement in sleep quality compared to monotherapy or sham conditions, potentially through regulation of melatonin secretion, restoration of cortical E/I balance, and reduction of oxidative stress.

Methods

Participants, interventions and outcomes

Study setting

This prospective, randomized, open-label, controlled, single-center trial will enroll 80 AD patients with sleep disorders from Center for Cognitive Disorders, Beijing Geriatric Hospital, Beijing, China. Recruitment commenced on July 15, 2025, and all eligible patients will be enrolled continuously until the process is complete. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist is provided as Additional file 1 [18].

Eligibility criteria

During the screening phase, participants will be assessed for eligibility based on the predefined inclusion and exclusion criteria (Table 1). Participants may withdraw from the study at any time in accordance with the termination criteria (also listed in Table 1). Table 2 presents the baseline characteristics of eligible patients.

Table 1
Inclusion / exclusion / termination criteria

Inclusion criteria	Exclusion criteria	Termination criteria
(1) Right-handed; aged ≥ 60 years, any restriction; (2) Able to cooperate with rTMS and BLT; (3) Diagnosed with probable or possible AD (MoCA > 15, CDR < 2); (4) ≥ 2 sleep problems occurring several times / week, assessed by PSQI; (5) At least third-grade primary school education.	(1) History of other neurological or psychiatric disorders, or severe diseases affecting other organ systems (e.g., cardiac, hepatic, pulmonary, renal); (2) Presence of implanted metallic devices (e.g., pacemakers, coronary stents, aneurysm clips) or ferromagnetic implants (e.g., cochlear implants); (3) Severe aphasia, agnosia, or any other condition precluding completion of neuropsychological assessments and interventions; (4) Severe visual impairment or medical contraindications to bright light exposure.	(1) Failure to comply with the predetermined study protocol; (2) Occurrence of local anesthetic adverse reactions, puncture needle entering into the pleural cavity, or other complications during the puncture procedure; (3) Changes in the patient's condition; (4) Patient's unwillingness to continue participating in the study.

MoCA: Montreal Cognitive Assessment; CDR: Clinical Dementia Rating; PSQI: Pittsburgh Sleep Quality Index

Table 2
Baseline characteristics of participants across the four groups.

Characteristics	rTMS-tDCS	Single-rTMS	Single-BLT	Control
Gender, N				
Male				
Female				
Age, years				
Education, years				
BMI, kg/m^2				
Duration, years				
Severity, N				
Mild				
Moderate				
Drug usage, N				
Yes				
No				

BMI: Body Mass Index; N: Number

Recruitment and informed consent

Figure 2 outlines the timeline of main research activities for each study visit. Individuals meeting preliminary diagnostic criteria will be approached by neurology outpatient experts and invited to participate the study. Those expressing interest will then undergo a comprehensive screening process, including detailed assessments to confirm eligibility based on the inclusion and exclusion criteria. Once eligibility is confirmed, participants will receive comprehensive study details. Informed consent will be obtained from the participant or their legally authorized representative. Participants retain the right to withdraw consent at any time during the trial.

Randomisation and Blinding

Randomisation. All 80 participants will be equally randomized (1:1:1:1) to four groups (Fig. 3): rTMS-BLT, single-rTMS, single-BLT, or control. A computer-generated randomization sequence (SPSS Statistics, version 26.0) will be created using a block randomization design with a fixed block size to ensure balanced group allocation throughout the trial. Allocation concealment will be achieved using

sequentially numbered, opaque, sealed envelopes, which will be opened only after completion of the baseline assessment and informed consent.

Blinding. Given the physical nature of the non-invasive brain stimulation and light therapy, this study will be conducted under open-label conditions. Therefore, participants and operators administering the interventions will not be blinded to treatment assignment. However, to minimize risk of bias, outcome assessors and the statistician will be blinded to group allocation throughout the trial. The dataset provided for statistical analysis will contain only non-identifiable group codes (e.g., 1, 2, 3, 4) for each participant, without labels indicating the actual intervention. The master key linking these codes to the specific treatment arms will be securely maintained by the principal investigator and will not be disclosed to the blinded personnel until the final statistical analysis is complete and the database is locked.

Interventions

All participants will receive one of four interventions. The rTMS-BLT group will receive 1-Hz rTMS targeting to the right DLPFC combined with active BLT (10,000 lux); the single-rTMS group will receive 1-Hz rTMS plus sham BLT; the single-BLT group will receive active BLT plus sham rTMS; and the control group will receive both sham interventions. All participants will complete a four-week intervention consisting of five consecutive sessions (one session per day) each week, followed by a two-day rest period. Each session will comprise 30 minutes of BLT, immediately followed by 30 minutes of rTMS. All interventions will be delivered by trained independent operators aware of group allocation.

BLT application. BLT will be administered using a light box (Uplift Technologies, DL930) positioned at the patient's eye level, 0.5 meters away, and within a 45º visual field. The active BLT group will receive 10,000 lux of full-spectrum white light, while the sham BLT group will receive 300 lux (simulating typical indoor natural light). Patients will undergo daily 30-minute sessions between 7:00 and 11:00 a.m. under caregiver supervision. To facilitate engagement during sessions, therapists will assist caregivers in selecting appropriate activities (e.g., reading, conversation). Additionally, caregivers and therapists will collaborate to develop an individualized sleep hygiene plan for each patient, focusing on establishing consistent sleep-wake schedules, minimizing daytime napping, and identifying potential triggers for nighttime awakenings.

rTMS application. rTMS will be delivered using a Magstim Super Rapid^2 (Magstim Company Ltd., United Kingdom) with an air-cooled figure-eight coil. Figure 4 shows the rTMS stimulation pattern of this trial: 1-Hz frequency, 10-second stimulation followed by 2-second interval, and a total of 1,500 pulses per session at an intensity set to 100% of the resting motor threshold (rMT). The rMT will be measured before the first treatment and defined as the minimum stimulus intensity that elicits at least 5 motor evoked potentials with an amplitude > 50 μV in 10 consecutive trials. The right DLPFC will be selected as the stimulation target, given its demonstrated therapeutic efficacy in previous studies [19] and localized according to 10–20 International EEG system at FC4 site (coil diameter: 70-mm; peak magnetic field: 2.0

T). This location will be marked with a permanent marker to ensure consistent coil placement throughout the 4-week treatment period. For sham stimulation, an identical-appearing 70-mm double air diaphragm sham coil will be used, which replicates the acoustic artifacts of active stimulation but only produces superficial scalp sensation without inducing intracranial currents. Participants will wear earplugs and recline in a comfortable chair with slightly flexed elbows during stimulation. Operators will monitor participants closely to minimize head movement and will document protocol adherence by signing a post-stimulation report for each participant.

Participants will be instructed to avoid other sleep improvement programs during the study period. The use of short-acting sleeping pills and standard medical treatment for comorbid conditions (e.g., hypertension, diabetes mellitus) will be permitted when necessary. Allocated interventions may be discontinued or adjusted in response to serious adverse events, participant withdrawal, or clinical deterioration. All such modifications will be documented and reported to the ethics committee for review.

Outcome Measures

Outcome assessments will be conducted at baseline (T_{W0}), immediately post-intervention (T_{W4}), and 4-week post-intervention (T_{W8}) by assessors blinded to group allocation.

The primary outcome is the change of PSQI total score (ΔPSQI) from baseline to T_{w4} and T_{w8}.

- The secondary outcomes include sleep parameters (total sleep time, sleep efficiency, sleep latency, wake after sleep onset, and sleep architecture) assessed by actigraphy and polysomnography (PSG); neurotransmitter levels, specifically excitatory and inhibitory neurotransmitters, measured via encephalofluctuogram; serum biomarker levels, including melatonin and ROS; as well as adverse events, encompassing their frequency, severity, type and duration.

Sample size

The sample size was determined a priori using PASS software (version 2021), employing a 2×2 factorial design with two independent interventions (rTMS and BLT), each at two levels (active or sham), yielding four experimental conditions. The primary objective was to test the main effects of each intervention and their interaction on ΔPSQI from baseline to week 4. The calculation assumed a two-sided Type I error rate (α) of 0.05 and statistical power (1-β) of 0.90.

The effect size, specified as Cohen's f, was derived from a pilot study involving 20 participants (n = 5 per group). The pilot data provided the following group means and standard deviations (SDs) for ΔPSQI: rTMS-BLT (mean = 5.00, SD = 1.00); single-rTMS (mean = 2.39, SD = 1.40); single-BLT (mean = 4.47, SD = 1.04); and control (mean = 0.20, SD = 0.76). Analysis of these data indicated that the interaction effect between rTMS and BLT corresponded to a Cohen's f of 0.424. For the main sample size calculation, this value was conservatively approximated to f = 0.40.

Based on these parameters (α = 0.05, power = 0.90, f = 0.40), a total of 64 participants will be required to detect a significant effect. To account for an anticipated 20% dropout rate, the recruitment target was set at 80 participants, with 20 individuals randomly allocated to each of the four groups.

Data management

Data Collection and Quality Control

Baseline and outcome data will be collected by trained assessors following standardized procedures to ensure data quality. All patient data generated in this clinical study will be documented and archived in the corresponding Case Report Form (CRF). Independent outcome assessors will record outcome measures using paper-based forms. A trained research assistant independent of the trial team will manually enter data into encrypted electronic spreadsheets stored in a secure folder with restricted access. A second independent assistant will verify data quality using range checks and identification of missing mandatory entries. All paper records, including signed informed consent forms, will be stored in a locked cabinet. To enhance data reliability, key outcome measures will be collected in duplicate, and data entry will employ an electronic system with built-in logic checks. Data collection forms and operational manuals are available from the corresponding author upon request.

Peripheral venous blood samples will be collected by nurse practitioners following standardized procedures for sample collection, handling, and storage to ensure biological data consistency.

The Data Monitoring Committee (DMC) is an independent expert body responsible for safeguarding participant safety, ensuring data validity and integrity, and maintaining the scientific rigor of this clinical study, operating under the oversight of the Beijing Haidian District Health Commission. An interim analysis will be conducted when approximately 50% of the target sample size has completed the primary outcome assessment, focusing on efficacy and safety endpoints to determine whether early termination is warranted due to overwhelming efficacy, futility, or safety concerns. The DMC will conduct periodic reviews at key stages (e.g., trial initiation, interim analysis, conclusion), and all recommendations and decisions will be documented and submitted to the Beijing Haidian District Health Commission.

Statistical Analysis

All data will be analyzed using SPSS Statistics (version 26.0; IBM Corp.). A two-sided p-value < 0.05 will be considered statistically significant. The primary analysis will follow the intention-to-treat (ITT) principle, including all randomized participants in the groups to which they have been originally assigned. Descriptive statistics will be used to summarize demographic and baseline characteristics, with continuous variables presented as mean ± SD and categorical variables as frequencies and percentages.

To evaluate the effects of the interventions over time, a repeated-measures analysis of variance (ANOVA) will be employed for the primary and secondary continuous outcome measures (e.g., PSQI, MoCA scores). This model will feature a 2 (rTMS: active vs. sham) x 2 (BLT: active vs. sham) between-subjects factorial design and a within-subjects factor of Time with three points (T_{W0}, T_{w4}, and T_{W8}). The

model will test the main effects of the two interventions (rTMS, BLT), the main effect of Time, and all potential interaction effects (rTMS x BLT, rTMS x Time, BLT x Time, and the three-way rTMS x BLT x Time interaction). If a significant interaction involving Time is found, simple effects analyses will be conducted to interpret the nature of the interaction. The Greenhouse-Geisser correction will be applied if the sphericity assumption is violated. Effect sizes for significant findings will be reported as partial eta-squared (ηp^2) with 95% confidence intervals.

Categorical outcomes will be compared between groups at week-4 and week-8 using Chi-square or Fisher's exact tests, as appropriate. Adverse events will be summarized descriptively by treatment group, reporting frequencies.

Prior to the main analysis, the pattern of missing data will be examined. If data are judged to be missing at random (MAR), multiple imputation will be employed to handle missing values in the primary outcome for the ITT analysis. To assess the robustness of the primary findings, a sensitivity analysis will be conducted on a per-protocol basis, including only participants who completed the intervention as prescribed.

Adverse event monitoring and reporting

This trial will systematically monitor adverse events (AEs) associated with rTMS and / or BLT. AEs will be categorized into three domains: neurological (e.g., headaches, auditory/visual disturbances), dermatological (e.g., skin pain, erythema during light exposure), and device-related (e.g., rTMS coil / light box malfunctions, software errors, or improper calibration / application). A serious adverse event (SAE) is defined as any event that is life-threatening, requires inpatient hospitalization or prolonging existing hospitalization, or results in persistent or significant disability / incapacity.

Continuous monitoring will be conducted throughout the trial to ensure participant safety and data quality. For rTMS, the device will be equipped with automatical alert system to flag parameter deviations, while trained operators will continuously observe participants' physiological responses throughout stimulation sessions. For BLT, periodic assessments of visual acuity and subjective comfort will be conducted. All rTMS and BLT devices will undergo pre-trial calibration and regular performance verification to ensure output accuracy and minimize risks associated with parameter drift. The severity of all AEs will be graded as mild, moderate, or severe, and the investigator will assess the causal relationship to the study interventions as unrelated, unlikely, possible, probable, or definite.

Mandatory reporting protocols require immediate documentation of any AE, detailing its onset time, duration, severity, and all remedial actions taken. For AEs judged as "severe" and / or with at least "possible" relationship to the interventions, the principal investigator and the ethics committee must be notified within 24 hours. This initial report must be followed by a comprehensive root-cause analysis report within 72 hours, evaluating potential contributing factors such as device performance, operator compliance, and participant-specific risk factors.

All safety-related data, including raw physiological traces, AE assessment logs, device performance logs, and detailed SAE reports, will be archived in a secure, password-protected electronic system. This system will maintain a complete trail for retrospective analysis and regulatory audits, ensuring data integrity and traceability in accordance with institutional archiving policies. The ethics committee will periodically review the accumulated safety data and provide independent oversight of the trial's risk-benefit profile.

Discussion

As non-invasive neuromodulation techniques, both rTMS [19] and BLT [20] have demonstrated potential in managing sleep disorders in patients with AD. However, the efficacy and safety of their combined application in treating AD-related sleep disorders remain unestablished in clinical research.

The present study exhibits several notable strengths. First, it employs a randomized controlled trial (RCT) design with a 2×2 factorial structure, which minimizes selection bias and ensures balanced baseline characteristics across groups, thereby enhancing internal validity. Second, this trial provides much-needed clinical evidence on the therapeutic synergy between BLT and rTMS. While BLT modulates the sleep-wake cycle through circadian entrainment [20], low-frequency rTMS is known to dampen cortical hyperexcitability [16]; their integration is thus hypothesized to produce a more comprehensive therapeutic effect than either monotherapy alone. Third, the study utilizes a multi-dimensional assessment strategy that integrates subjective sleep scales (PSQI) with objective measures, including PSG, actigraphy, and encephalofluctuography, alongside biomarker analyses (melatonin [21] and ROS [22] levels). This comprehensive evaluation framework facilitates a systematic assessment of clinical efficacy while simultaneously elucidating potential underlying mechanisms.

The study further explores underlying pathophysiological mechanisms through three specific aims: first, it investigates the melatoninergic pathway by comparing pre- and post-intervention serum melatonin levels and rhythmic characteristics to examine whether rTMS and / or BLT exert therapeutic effects via modulation of the melatonin system [23]. Given that melatonin is a critical regulator of the sleep-wake cycle and its secretion abnormal in AD patients [23], restoring melatonin rhythms is hypothesized to be a key therapeutic target. Second, the study examines the role of oxidative stress mechanisms. A bidirectional relationship exists between AD pathology and sleep disturbances [24], with ROS-mediated oxidative stress serving as a central mechanism perpetuating this deleterious cycle [22]. In this study, longitudinal analysis of ROS concentration changes will further clarify whether the interventions disrupt this pathological cycle via antioxidant pathways [22]. Third, the study assesses cortical excitatory-inhibitory (E / I) balance. Characterized by elevated excitatory and reduced inhibitory neurotransmitter levels, E / I imbalance is a core pathological feature of AD with comorbid sleep disturbances [25], potentially leading to excessive cortical activation and impaired sleep regulation. By quantifying E/I neurotransmitter fluctuations via EFG before and after treatment, this aim verifies whether the combined intervention alleviates sleep disturbances through the restoration of cortical homeostasis [26]. Furthermore, the mechanistic insights gained from these specific aims are anticipated to inform the development of personalized treatment protocols. By identifying which patients are most likely to

respond to rTMS, BLT, or their combination based on their individual pathophysiological profile (e.g., degree of melatonin rhythm disruption, oxidative stress levels, or E/I imbalance), this study lays the groundwork for a more stratified and precision medicine approach to managing sleep disorders in AD.

Finally, systematic safety monitoring and rigorous data quality control enhance the clinical applicability and reliability of our findings. Blinded outcome assessment minimizes detection bias, while the comprehensive data collection protocol- encompassing subjective and objective sleep assessments, serum biomarker analyses, and E / I neurotransmitters evaluations enables a thorough evaluation of treatment effects across multiple domains of patient well-being. The periodic, independent review of accumulated safety data by the Institutional Ethics Committee provides an additional layer of oversight, ensuring that the study's risk-benefit profile remains acceptable throughout its duration.

Abbreviations

AD
Alzheimer's Disease
rTMS
Repetitive Transcranial Magnetic Stimulation
BLT
Bright Light Therapy
PSQI
Pittsburgh Sleep Quality Index
PSG
Polysomnography
ROS
Reactive Oxygen Species
E/I
Excitatory/Inhibitory
EFG
Encephalofuctuograph
DLPFC
Dorsolateral Prefrontal Cortex
PASS
Power Analysis and Sample Size
SD
Standard Deviations
MoCA
Montreal Cognitive Assessment
CDR
Clinical Dementia Rating
rMT

resting Motor Threshold
EEG
Electroencephalogram
SPIRIT
Standard Protocol Items:Recommendations for Interventional Trials
ITT
Intention-to-treat
ANOVA
Analysis Of Variance
MAR
Missing At Random
AE
Adverse Events
SAE
Serious Adverse Events
RCT
Randomized Controlled Trial

Declarations

Trial Status

The protocol version used for this study is Version 2.0, dated May 28, 2025.

Recruitment is scheduled to begin on July 15, 2025, and is expected to be completed by May 31, 2027.

Clinical efficacy and safety of rTMS combined with bright light therapy for sleep disorders in patients with Alzheimer's disease□study protocol for a randomized controlled study

Ethics approval and consent to participate

Written informed consent (including consent for biological sample collection and publication) will be obtained from all participants, as approved by the Ethics Committee of Beijing Geriatric Hospital (No: BJLNYY-2025-007). Revisions to the protocol that impact study conduct, participant safety, or scientific validity must be submitted to the ethics committee for approval, and approved changes will be communicated to investigators and the trial registry. If the amendments affect participant rights, safety, or welfare, an updated informed consent form will be prepared and re-consent obtained as necessary. The protocol provides for ancillary care during the trial, post-trial follow-up care for beneficial effects, and fair compensation for any harm incurred as a result of trial participation.

Competing interests

The authors declare no competing interests.

Dissemination policy

This trial is committed to the timely dissemination of its findings to all relevant stakeholders, including healthcare professionals, the general public, and the scientific community, in accordance with international best practices and ethical guidelines, thereby maximizing the research's impact and reach.

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Author Contribution

Yueqing Hu conceptualized the study and, together with Jihui Lyu and Shouzi Zhang, developed the methodology. Yueqing Hu drafted the manuscript, while Zongjuan Ma, Lin Zhu, and Dongshuang Yang were responsible for reviewing and editing the manuscript. All authors reviewed the final version of the manuscript.

Availability of data and materials

To promote transparency and reproducibility, de-identified data and statistical code will be made available upon reasonable request.

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Figures

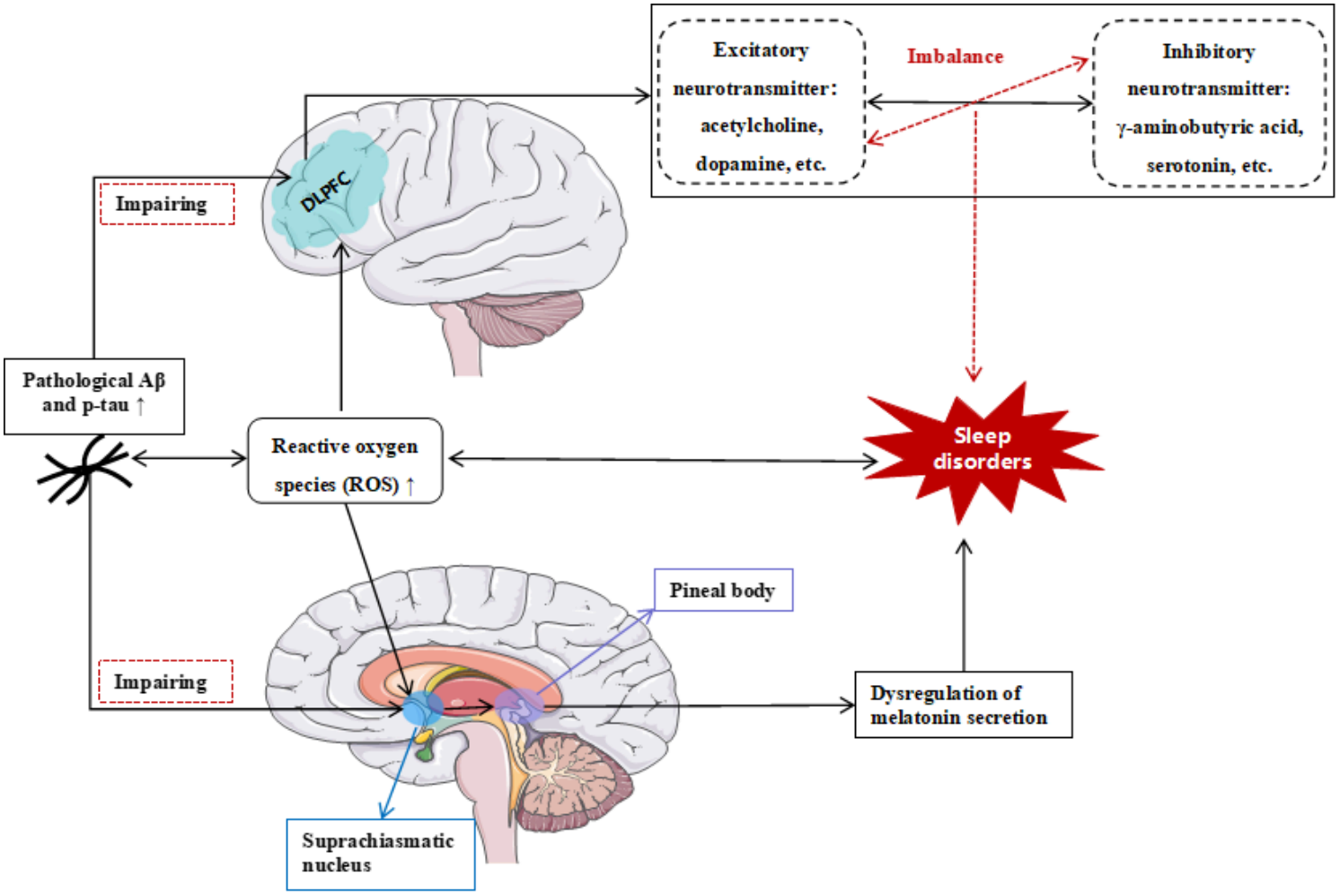


Figure 1

Probable pathogenesis of sleep disorders in AD

Notes: Aβ: amyloid-beta; p-tau: hyperphosphorylated tau; DLPFC: dorsolateral prefrontal cortex

	Trial period			
	Enrolment		Post-randomisation	
Timepoint	**-7 day to 0**	**T_{w0}**	**T_{w4}**	**T_{w8}**
Enrolment				
Eligibility screen	X			
Informed consent	X			
Demographic data	X			
Medical history	X			
Physical examination	X		X	
Randomisation		X		
Intervention or comparator				
rTMS - tDCS group		→	→	
Single- rTMS group		→	→	
Single - tDCS group		→	→	
Control group				
ASSESSMENTS:				
MoCA	X		X	X
CDR	X			
PSQI	X		X	X
Actigraph		X	X	X
PSG		X	X	X
EFG		X	X	X
Melatonin level		X	X	X
ROS level		X	X	X

Figure 2

SPIRIT 2025 diagram of the schedule of enrolment, interventions, and assessments

T_{w0}: baseline; T_{w4}: immediately post-intervention; T_{w8}: follow up at 8 week post-intervention. MoCA: Montreal Cognitive Assessment; CDR: Clinical Dementia Rating; PSQI: Pittsburgh Sleep Quality Index; ROS: Reactive Oxidative Species; EFG: Encephalofuctuograph

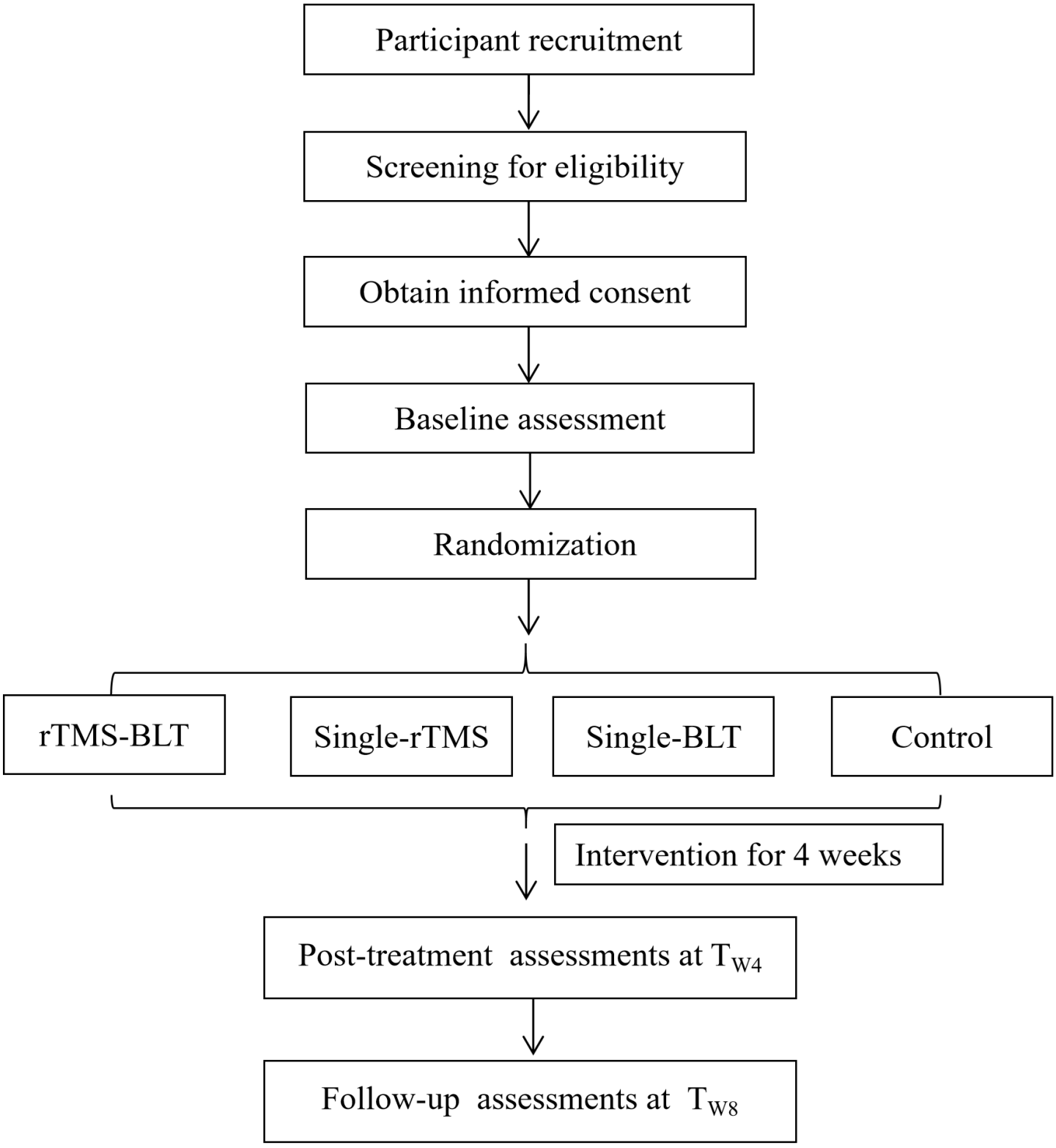


Figure 3

Flow diagram of the study

Notes: Participant recruitment, randomisation, intervention allocation, follow-up, and analysis are shown according to CONSORT guidelines. T_{w4}: immediately post-intervention; T_{w8}: follow up at 4 week post-intervention.

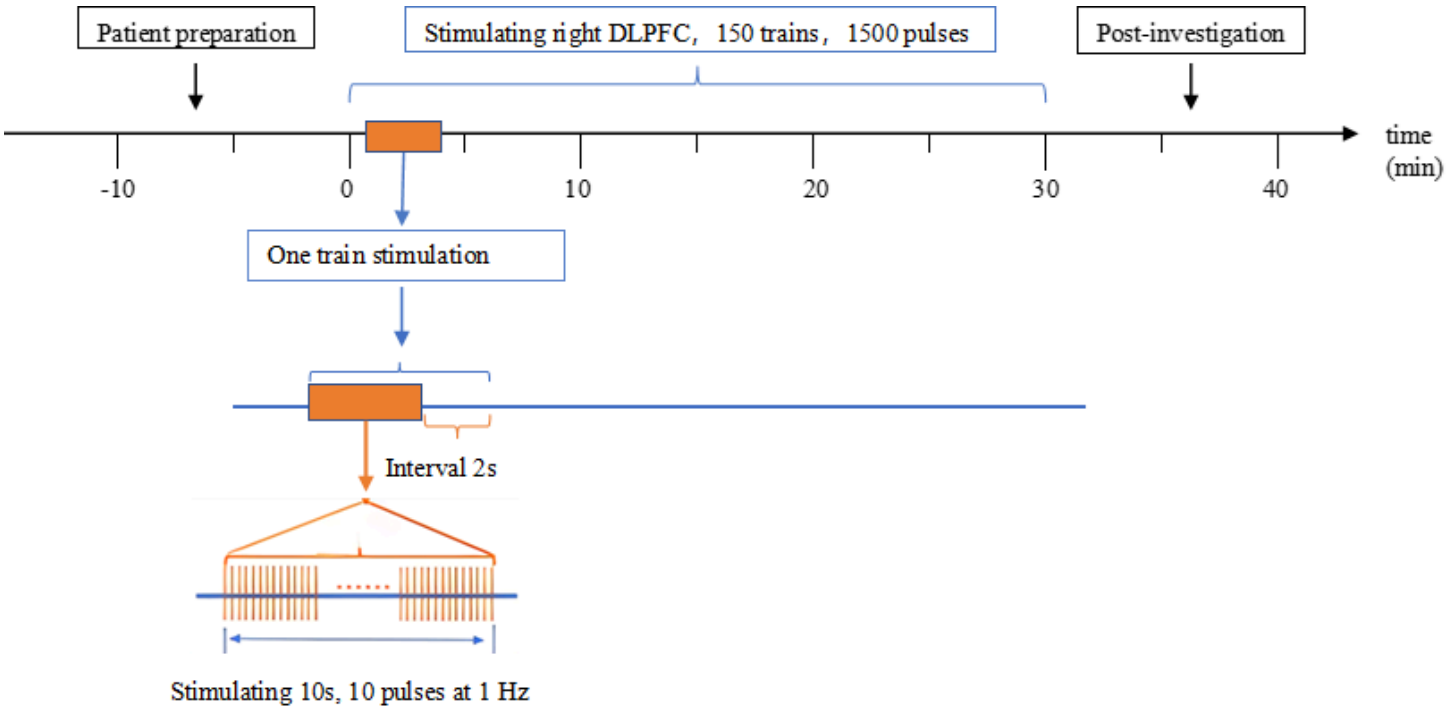


Figure 4

The stimulation pattern of rTMS

Supplementary Files

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- Additionalfile1.doc