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Closed-loop phase-locked auditory stimulation system at home enhance slow wave sleep for patients with chronic insomnia: A randomized, placebo-controlled trial

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Abstract

Background

Neuromodulation is a promising therapeutic alternative for insomnia. We aimed to explore the efficacy and safety of closed-loop phase-locked auditory stimulation (PLAS) system at home in patients with chronic insomnia.

Methods

A sham-controlled, double-blinded, randomized study applying a closed-loop PLAS system was conducted in patients with chronic insomnia. Recruitment of eligible patients will be on a 1:1:1 basis of randomizing into randomized into an experimental group (EG, a pink noise when the slow wave of sleep reaches its peak), a sham group (SG, a powdered noise that was played at any time in the slow sleep cycles), or a control group (CG, not exposed to the noise). A 5-day intervention was performed after baseline data collection. Participants were required to wear the device every night before bed and remove from the head upon waking up the next morning. The primary outcome measures are sleep quality, and secondary outcome points were mainly assessed by the questionnaires scale that sleep, mental, and cognitive-related assessment. MNE package and custom Python scripts were utilized for pre-processing and analysis of the EEG data and SPSS was used for statistical analysis.

Results

Thirty-seven patients were recruited for this study, of whom 36 completed the experiment after being randomized. Twelve patients were randomly allocated to each of the EG, SG, and CG. Significant enhancements in the slow wave and theta bands were observed in the stimulation group compared to both the SG and CG ($p < 0.05$). The stimulating group experienced significantly longer NREM3/4 and REM times compared to the SG or CG ($p < 0.05$). For the Clinical Global Impression, the score of global improvement is 2.31±1.38 and efficacy index is 2.35±1.01 in STIM group, which indicates that the treatment is effective and safe. Additionally, we analyzed changes in the Montreal Cognitive Assessment, Symbol Digit Modalities Test, Hamilton Depression Scale, and Hamilton Anxiety Scale before and after the intervention. No significant differences were found in cognitive and mental scores among the groups.

Conclusion

Our results indicate that PLAS has the capacity to enhance slow wave sleep in patients with chronic insomnia, which suggest new possibilities for using PLAS as a low-cost, home-based intervention to improve sleep for insomnia patients, without cognitive and emotional side effects.

Introduction

Sleep is crucial for maintaining physical and mental health, including learning and memory[1], emotion[2], brain metabolic clearance[3,4], and peripheral health[5], as evidenced by epidemiological and experimental studies. Recently, about 6% of the adult population in developed countries had chronic sleep disorders, and a third have experienced insomnia symptoms at any given time[6]. Insomnia has been linked to a wide range of physical, psychiatric, and neurodegenerative diseases, including obesity, hypertension, diabetes, cerebrovascular accidents, cognitive deficits, and depression[7-9]. Furthermore, sleep disturbances can lead to additional health problems and a higher mortality rate[10]. The economic burden of untreated insomnia, attributed to work absences and reduced productivity related to insomnia, is much higher than the cost of treating it[11]. Current treatments for insomnia primarily include cognitive behavioral therapy (CBT) and pharmacological treatment. The cost of CBT therapy is well-known to be high. Pharmacological treatment is often limited by issues such as drug resistance, addiction, and other side effects. Long-term use of benzodiazepines or benzodiazepine receptor agonists is not recommended for chronic insomnia in Europe. Approximately 40% of patients with chronic insomnia do not achieve sustained remission with current treatments[6,12].

During the entire night's sleep, slow-wave sleep (SWS) is closely linked to essential functions like memory consolidation, energy restoration, endocrine regulation, and immune system renewal[13,14]. Low-frequency brain oscillations (0.5-4 Hz), known as slow-wave activity (SWA), are widely recognized as the hallmark of SWS.[15] A decrease in SWA has been identified as a cross-diagnostic issue across various neuropsychiatric disorders[16,17]. Noninvasive physical stimulation has emerged as a promising technology for treating impaired sleep in recent years. This technology offers the advantages of low cost, minimal side effects, and direct impacts on specific brain regions. Attempts to enhance SWA have included transcranial electrical stimulation[18], transcranial magnetic stimulation[19], and phase-locked auditory stimulation (PLAS)[15,20]. Slow waves induced by low-frequency physical stimulation share the same forms and functions as those generated spontaneously in the brain[21]. When exogenous stimulation coincided with the peak of endogenous slow waves (EEG phase coupling), the enhancement effect on slow waves amplitude was robust[20]. Among these technologies, PLAS has shown the most potential as a household method due to its robust effects and minimal device requirements. However, these studies were normally conducted under strict laboratory conditions[15,20,22-24], and the reliability and feasibility in a home setting remains unknown. Moreover, the devices claimed to enable closed-loop control were conducted in healthy subjects, however, their efficacy and safety in patients with chronic insomnia have never been investigated.

In this study, we used a newly developed wearable device comprising two Bluetooth-connected components (an EEG recorder and a receiver) to deliver closed-loop stimulation. We aimed to conduct a randomized controlled trial (RCT) applying a closed-loop PLAS system to patients with chronic insomnia, evaluating benefits in sleep disorders, memory deficits, and emotional disturbances. This approach may offer a new potential therapeutic strategy for many patients with chronic insomnia.

Methods

Study design

This study was a randomized, double-blind, parallel controlled, and single-center clinical study and will be conducted at Zhongshan Hospital, Fudan University. The purpose of this study is to assess the effects of closed-loop EEG coupled physical stimulation on sleep quality, cognitive function, and emotional symptoms in patients with insomnia. The patients who met inclusion criteria will be randomized into the experimental group (EG), sham group (SG) or control group (CG). Then subjects will enter into five stages: diagnosis period, evaluation period, and discharge following-up period. The data about sleep quality, cognitive function, and emotional symptoms in patients with insomnia were collected and analyzed. If the subjects feel unwell during the physical intervention, the experiment will be stopped immediately, and their treatment of other diseases will not be affected. All adverse events that occurred from enrollment to completion or termination of the trial will be summarized. This study was approved by the ethics committee of Zhongshan Hospital, Fudan University (Approval No.: SK2020-005).

Participants

The present study will included participants who were diagnosed with chronic insomnia[25]. We plan to recruit participants in multiple ways, and the recruitment location will be restricted to Zhongshan Hospital of Fudan university. Our hospital is a comprehensive tertiary hospital with scientific research, clinical treatment, and teaching practice. The main source of the subjects will be the outpatients who meet our criteria (Detail are presented in Table 1). Moreover, we will also recruit participants through social media, newspapers, and advertising. The inclusion criteria are as follows: (1) Diagnosed as chronic insomnia according to American Academy of Sleep Medicine. (2) Between 18 and 60 years of age. (3) Agree to sign the informed consent, comply with research procedures and cooperate with the implementation of wholes research. (4) Existing self-care ability and non-drug abuse

The exclusion criteria are as follows: (1) Pregnant women, heart, lung, liver, kidney and other important organs function decline or failure, or vital signs are not stable. (2) Serious organic lesions in the brain or other body parts. (3) Hearing impairment, tinnitus or visual impairment. (4) Irregular living routine. (5) Taking drugs that affect the nervous system. (6) Having a history of drug addiction. (7) Any condition (medical, psychological, social, or geographic) that may endanger the patient's safety or prevent the patient from successfully participating in the study.

Randomization and blinding

Each included subject has a the screening number and the screening number consists of the three letters DSD plus the three subject numbers (e.g. DSD001). Randomization will occur after recruitment of eligible patients and will be on a 1:1:1 basis of randomizing into EG, SG, or CG to ensure balance in the treatment allocation. A randomization sequence has been computer generated by an blinded investigator who will not have any contact with participants or will not otherwise be involved in the trial. The sequence will be stored in a password-protected online secure system. No study personnel, except

the trial statistician, has access to the randomization list until completion of the trial. Even trial operator and data collector were unaccessible to the randomization sequence.

Procedure

All patients who met the inclusion criteria were randomly divided into 3 groups. Each group will receive three types of stimulation as follow: In the EG, subjects will receive a pink noise when the slow wave of sleep reaches its peak. In the SG, subjects were subjected to a powdered noise that was played at any time in the slow sleep cycles. The CG was a blank control group, and the subjects were not exposed to the noise (Figure 1).

Each patient will complete the entire experiment in the following four stages:

1. Screening period: When subject signed the informed consent, the subjects were recruited according to the inclusion and exclusion criteria. The demographic data of the subjects were recorded, and the subjects were randomly divided into groups.
2. Evaluation period (0th day): the basic information of the subjects was checked, and the physiological parameters, psychological scale, cognitive function and image data of the subjects were collected according to the case report form. The traditional polysomnography (PSG) equipment and portable sleep instrument were used to record the sleep EEG of the subjects for the first time to evaluate the sleep condition of the subjects.
3. Discharge follow-up period (1-5th days): This period was subdivided into two stages. The first stage was the introduction stage (day 1 to 2). In this stage, subjects used a portable sleep apparatus to record sleep EEG, received different forms of powder noise stimulation, and completed the sleep diary. However, This introduction period was only for patients to adapt to the portable sleep apparatus and was not recorded as formal data analysis. The second stage was the formal trial period (day 3 to 5). The subjects also used a portable sleep instrument to record the sleep EEG, received different forms of powder noise stimulation during the sleep period, and completed the sleep diary, which was used as the formal data for analysis.
4. Evaluation period (6-7th day): The portable sleepometer was returned and the sleep, psychological, and cognitive functions were assessed again.

Outcome

Baseline assessments included gender, age, disease duration, and medication history. Sleep quality analysis was used as the primary outcome measure, and questionnaires scale was used as secondary outcome points. For sleep quality, besides analyzing slow waves, event-related potentials (ERPs), and vent-related spectral perturbations after stimulation, we also analyze various nighttime sleep-related variables. These variables encompass total sleep time (TST), wake after sleep onset (WASO), sleep latency (SL), sleep efficiency (SE), total wake time (TWT), total red time (TST), length of N1/2 stage, length of N3 stage, and length of rapid eye movement (REM) stage. Among questionnaires, the sleep-

related assessment scale stands out, comprehensively incorporating the Insomnia Scale (ISI)[26], the Pittsburgh Sleep Quality Index (PSQI)[27,28], the Epworth Sleepiness Scale (ESS)[29], and the Clinical Global Impression Scale (CGI)[30]. Moreover, participants will also undergo mental and cognitive evaluation through a series of questionnaires including the Montreal Cognitive Assessment (MoCA)[31], Symbol digit modalities test (SDMT)[32], Hamilton Depression Scale (HAMD)[33,34], and Hamilton Anxiety Scale (HAMA)[35]. Adverse events will be recorded daily. Physicians' notes and online medical records will be used to identify potential adverse events. An adverse event is defined as any undesirable experience that occurs in patients in association with the use of medical product.

Participants will independently complete a series of sleep-related questionnaires within a private conference room setting. Follow-up rates will be evaluated and reasons for participants' absences will be thoroughly investigated. Outcome assessors will receive specialized training to ensure the collection of high-quality data. All data will be systematically uploaded, securely stored, and regularly maintained. The research team will shoulder the responsibility for all data entry tasks and quality control activities, ensuring the integrity and reliability of the study results. The study database will remain blinded until the scientific review process is fully completed.

EEG recording and preprocessing

Each participant received a LANMAO device (QuanLan Technology Co., LTD, CHINA), as shown in Figure 2A. The device was preset with uniform phase-locked algorithm parameters. After receiving face-to-face instructions, participants were required to wear the device every night before bed, selecting the paradigm of closed-loop phase-locked auditory stimulation. Upon waking up the next morning, the recorder was removed from the head.

The LANMAO device recorded whole-night EEG signals near Fp1, using the reference electrode at the right mastoid (M2). Ag-AgCl hydrogel electrodes were utilized to maintain impedances below 20 kΩ. EEG signals were sampled at 500 Hz and filtered between 0.1 and 100 Hz. Sleep stages were automatically classified using the algorithm embedded in the LANMAO device[36]. Following sleep stage classification, N3 stage sleep slow waves were identified using a previously established method. The algorithm ran on the edge computing platform, the LANMAO receiver. Before detecting slow oscillations, EEG was pre-processed using a Chebyshev second-order bandpass filter with cutoff frequencies between 0.5 and 35 Hz.

Each acoustic tone was delivered approximately 45 degrees ahead of the wave's ascending phase, equivalent to about 150 ms during a 0.85-Hz slow oscillation[37]. This approach compensated for hardware delays, ensuring precise peak audio delivery at the anticipated peak of each SWA up-phase(Figure 2B). Detailed preprocessing descriptions of EEG data were showed in supplementary data material one.

Statistics analysis

Based on the data characteristics, the specific statistical description and inference of data are carried out. Categorical parameters will be compared using Pearson $\chi 2$ test or Fisher's exact test as applicable. Qantitative parameters will be compared by paired or unpaired t-test. The evaluation of sleep quality mainly includes traditional sleep parameters, sleep scale scores, and analysis of high-frequency sleep electroencephalogram rhythms. The secondary analyses include changes in cognitive function and emotional symptoms before and after the intervention. Finally, all adverse events (AE) that occurred from the enrollment to the completion will be summarized using incidence rate and the denominator is the number of subjects who provided informed consent. Two-tailed $p<0.05$ was considered to be statistically significant. SPSS will be used for statistical analysis.

Results

General characteristics

According to the trial design, the last patient to complete the intervention and following-up represents the recruitment ending. Thirty-seven patients were recruited in this study, of which 36 were randomized completed the experiment. 12, 12, 12 randomly allocated to the EG, SG and CG. The mean age was 84 years, and 68% were female. One adverse event was reported, which was mild electrode allergy (Details showed in Table 1).

Table 1 The clinical characteristics of each group

Variables	EG	SG	CG
Age	41.3±12.3	34.3±7.4	37.6±12.9
Gender (male/female)	4/8	6/6	3/9
Total sleep time (min)	427.5±100.2	397.4±92.3	467.2±68.4
Sleep efficiency (%)	71.3±24.5	62.5±29.7	74.8±19.2
Length of N1/2 stage (min)	282.4±67.5	299.8±72.3	273.4±84.1
Length of N3 stage (min)	62.3±33.2	70.5±47.8	59.9±38.4
Length of REM stage (min)	70.2±29.6	58.3±25.2	83.7±34.6
Proportion of N1/N2 (min)	66.0±19.7	75.1±15.4	58.5±19.3
Proportion of N3 (min)	14.5±5.8	17.6±7.2	13.9±6.7
Proportion of REM (min)	15.5±5.2	14.5±6.9	16.4±7.2

The variation of low-frequency EEG power, ERPs and ERSP among three groups.

We examined whether the sleep EEG activity can be changed by the phase-locked tone stimulations. ERP analysis revealed that closed-loop acoustic stimulation induced two new slow waves contrasted with CG

and the wave crest is near 1000ms and 2200ms respectively (Figure 3A). Compared to the ineffective stimulus control group, the closed-loop acoustic stimulus also induced two slow waves, while the randomly applied stimulus did not produce any slow waves (Figure 3B). ERSP analysis were performed between ES and CS, ES and SG. The energy in the frequency band below 2.5Hz increased significantly near 500-1500ms and 1500-2500ms after stimulation contrast with CG, indicating slow wave enhancement moreover, at 600ms, 1600ms and 2200ms after stimulation, the theta and slow spindle bands were significantly enhanced (Figure 3C). It revealed similar result when compared with SG, the energy in the frequency band below 2.5Hz increased significantly near 500-1500ms and 1500-2500ms after stimulation, and the theta and slow spindle bands were significantly enhanced at 600ms, 1600ms and 2200ms after stimulation (Figure 3D). Last, spectrum analysis were also performed and it showed significantly enhancement of slow wave band and theta band in the stimulation group, whether compared with the SG or the CG (Figure 4E-H, $p<0.05$). In conclusion, phase-locked tone stimulation significantly enhances slow-wave oscillations in patients with chronic insomnia.

PLAS effect on sleep-related variables at the night

In addition to focusing on the effect of auditory stimulation on the intensity of SWA, we also investigated the effect on the duration of different sleep stage at the night. We found that stimulating group had significantly longer NREM3/4 time than the SG, however, no significant difference existed between the EG and the CG (Figure 4A). It had also revealed a significantly longer REM time in the EG than that in the SG, and significantly higher trend than the CG, the statistical difference was not significant (Figure 4B). With respect to other sleep-related variables, there were no significant differences in length of N1/2 stage, TRT, TST, TWT, SE, SL, REML and WASO among the three groups (Figure 4C-J $p> 0.05$).

PLAS effect on sleep scales, cognitive and mental assessment

Apart from the analysis of some objective sleep variables, we also conducted subjective sleep scale analysis. For the CGI, the score of global improvement is 2.31±1.38 and efficacy index is 2.35±1.01 in STIM group, which indicates that the treatment is effective and safe (Figure 5A, $p<0.05$). With PSQI, ISI and ESS as the assessing indicators, there was no significant sleep improvement after the intervention in the three groups (Figure 5B-D, $p> 0.05$). Moreover, we also analyzed the variation of MoCA, SDMT, HAMD, and HAMA between before and after the intervention, no significant difference in cognitive and mental scores in each group (Figure 5E-I, $p> 0.05$).

Discussion

In this study, we found that phase-locked tone with SWA peak significantly enhanced slow wave brain oscillations for health subjects and patients with chronic insomnia. Although the duration of slow wave sleep did not increase significantly after acoustic stimulation treatment, the overall impression of sleep in patients with chronic insomnia was improved to some extent. Moreover, the device was safe and did not cause adverse effects on patients' cognition and mood. Notably, the enhancement effect can be repeated for all participants by phase-locked auditory stimulation system in home settings.

Better sleep quality is expected to enhance physical and mental health, and may also decrease the risk of sleep-related diseases. Thus, better sleep can reinforce quality of life and prevent premature death. Insomnia also impairs carers' daytime work performance. The main treatment strategy CBT and pharmacologic treatment both have drawbacks for insomnia. It is important to find an innovative and economically intervention for sleep disorder. The slow waves in NREM sleep period was involved in sleep quality, memory function and depression symptoms. SWA-enhancing technologies provide an exciting opportunity to improve sleep quality when some studies have found that slowly oscillating potential stimulation induced an immediate increase in slow wave sleep[19, 38]. Acoustic stimulation technique has several advantages including non-invasive, safe, feasible and easily apply in family environment. The presence of a shared pathway through the reticular formation between the hypothalamus and the thalamus may explain increased SWA after acoustic stimulation, which ultimately result in synchronization of the thalamo-cortical networks[39]. This synchronization may lead to enhanced slow oscillation that further potentiate memory either through repeated reactivations, synaptic homeostasis, and synchronizations of the hippocampal-thalamic-cortical activity, or both[40].

The precise timing of stimulation is crucial in acoustic stimulation. Out-of-phase stimulation, where pulses are emitted at the falling edge instead of the rising edge of the slow wave activity had no enhancing effects. A recent study demonstrated that stimulation applied at a random phase of the SWA resulted in an increase in SWA but a decrease in slow and fast spindle power, failing to improve overnight retention of word pairs[41]. Our results indicate that phase-locked tone pulses, even when employed in a wireless transmission system with a about 100 ms transmission delay, effectively enhance the slow oscillation. This finding is consistent with previous studies[15, 20, 42]. These stimuli are precisely synchronized with the up-phase of SWA, leading to an increase in SWA and spindles, which are closely associated with memory consolidation.

Sound stimulation can be regulated and closed loop[43], and moreover it is important to highlight that the closed-loop device utilized in this study is designed for convenient home use. While our primary focus in this study was to enhance SWA and spindles through acoustic stimulation, we unexpectedly observed concurrent increases in theta, and beta activity in patients with chronic insomnia. These findings are slightly different with previous studies that primarily reported significant increases in SWA and spindle power[15, 20, 23]. It may be that previous studies have paid less attention to other frequency band changes except SWA. In addition, we hypothesize that it may be attributed to the micro-arousals induced by PLAS, based on the following cues: beta activity typically increases during quiet wakefulness[44]. However, the exact mechanism remains to be further explored. These findings suggest that the volume of 55 dB may disrupt the sleep process and require optimization, despite its widespread use in previous studies[15, 20, 23]. In totally, our study suggest that the acoustic stimulation enhanced SWA sleep intensity in insomnia participants, and the increase in SWA power may supports the notion that memory consolidation of participants is enhanced. We found that stimulating group not only enhanced slow-wave intensity, but also increased NREM3/4 time and REM time than the SG or CG in the RCT section. However, for some objective sleep variables, with PSQI, ISI and ESS as the assessing indicators, there was no significant sleep improvement after the intervention in the three groups. The

possible reason may be that the intervention time for these with long-term chronic insomnia is only five days, and the treatment effect has not been shown. However, the clinical global impression was significantly improved after PLAS intervention. In addition, the cognitive and emotional scores of the stimulating group were not significantly different from those of the control group. First, the cognitive and depressive scores of patients in baseline were not significantly decreased or even normal, so the effects of sleep improvement on cognition and emotion were not significant. Second, the treatment and observation time were short, resulting in insufficient effects on cognition and emotion, these are chronic diseases, after all. At least the device has been shown to have no adverse effects on cognition and mood.

Our study contributes to the translation of auditory slow-wave enhancement techniques from the lab to the home setting. This protocol also first provided the powering definitive RCT to investigate the effects of closed-loop auditory stimulating system on modifiable sleep quality in patients with chronic insomnia as well as on memory deficits and depression symptoms. In addition to the sleep quality, memory and depression were evaluated as the second outcomes. This study has several strengths including its novelty and the blinded and randomized design. Some limitations should also be considered. First, the total number of participants was relatively small and this RCT was a single center study. Second, the stimulation duration and observational period of treatment outcome are relatively short, which may affects the final actual conclusion. Thus, future studies with large samples, multi-center and long-term follow-up are needed before generalizing the present findings.

Conclusion

In conclusion, our study demonstrates that PLAS can also be feasible in home-based settings, without the need for professional assistance. Closed-loop acoustic stimulation therapy significantly enhanced slow-wave sleep without side effects of cognitive and emotional impairment. These findings open up new possibilities for the use of PLAS as a low-cost home-based intervention tool for improving sleep for patients with chronic insomnia.

Abbreviations

PLAS Phase-locked auditory stimulation

EG Experimental group

SG Sham group

CG Control group

CBT Cognitive behavioral therapy

SWS Slow-wave sleep

SWA Slow-wave activity

RCT Randomized controlled trial

PSG Polysomnography

TST Sleep time

SE Sleep efficiency

WASO Wake after sleep onset

SL Sleep latency

TST Total red time

TWT Total wake time

REM Rapid eye movement

PSQI Pittsburgh Sleep Scale

ISI Insomnia Scale

ESS Epworth Sleep Scale

CGI Clinical Global Impression

MoCA Montreal Cognitive Assessment

SDMT Symbol digit modalities test

HAMD Hamilton Depression Scale

HAMA Hamilton Anxiety Scale

AE Adverse events

SAE Serious adverse events

Declarations

Conflicts of interest

The authors declare that there is no financial or personal conflict of interests. All authors agree with the submission of the manuscript and approved the final version.

Supplementary Material

Supplementary material is available at online.

Acknowledgment

None

Authors' contribution

D.J. and W.X. supervised and managed the work. D.J. and J.J designed the work. D.J.

provided funding support. Z.QQ. and X.GN. prepared all the figures. Z.QQ., L.MS., X.GN., Z.X., G.AC. and H.SY. acquired the data. Z.QQ., J.J. and X.GN. interpreted the data. Z.QQ., J.J. and X.GN. analyzed the data. L.MS. drafted the manuscript. L.MS., D.J. and J.J substantively revised the work.

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Data availability

The dataset analyzed in the present study as well as scripting and plotting code are available from the corresponding authors via email on reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Zhongshan Hospital, Fudan University (Approval No.: SK2020-005). Informed consent to participate was obtained from all of the participants, or their legal guardian in the specific case such as adults with cognitive decline who may be incapable of providing informed consent.

Consent for publication

Informed consent was obtained from all patients' legal surrogates.

Competing interests

The authors declare no competing interests. All authors agree with the submission of the manuscript and approved the final version.

Registration details

This trial has been registered on the website of Chinese Clinical Trial Registry in August 24, 2020 (Registry number: ChiCTR2000036731, http://www.chictr.org. cn).

Consort

The authors declare that this study adhered to CONSORT guidelines for reporting clinical trials.

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Figures

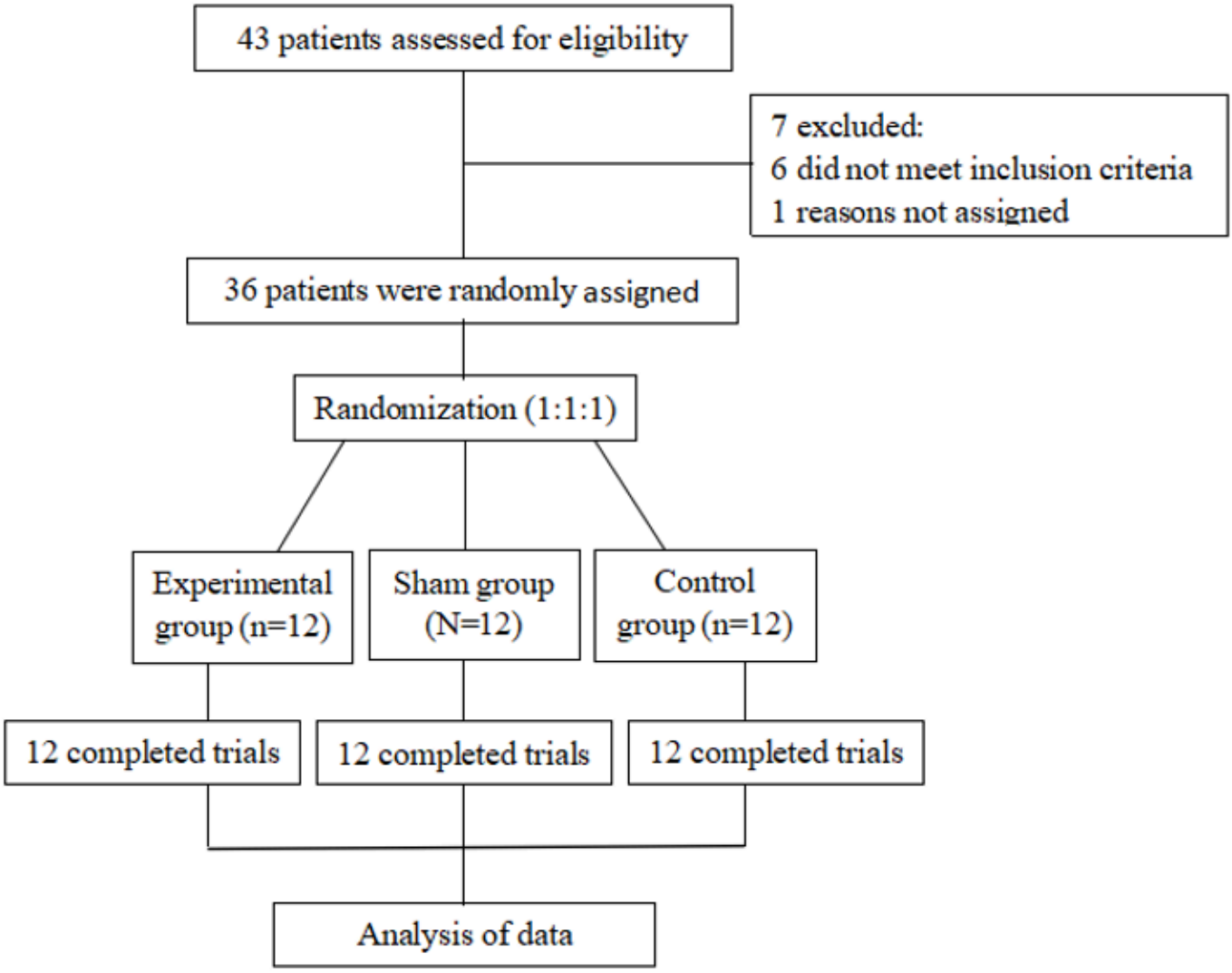

Figure 1

Flowchart for the RCT. This flowchart provides a detailed description of this study, which includes the initial screening, randomization, intervention, following-up, and analysis.

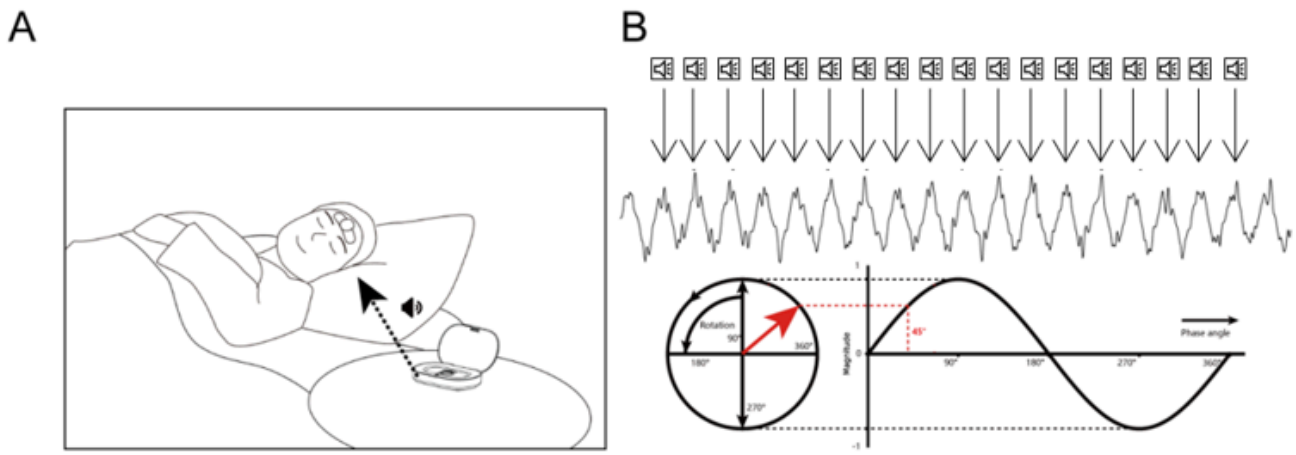

Figure 2

Home setting and the phase-locked stimulation paradigm. (A) The device features two components: an EEG recorder (on head) and a receiver (on desktop). The recorder is attached to the participant's forehead during nighttime sleep, while the receiver received EEG signals, detected slow wave and triggering auditory pulses. The distance between the speaker and the participant's head is approximately 50 cm, with sound level set at 55 dB. The recorder and receiver were connected via Bluetooth. (B) This is the stimulation paradigm shown, when a slow wave is detected, there is an acoustic stimulus at the crest.

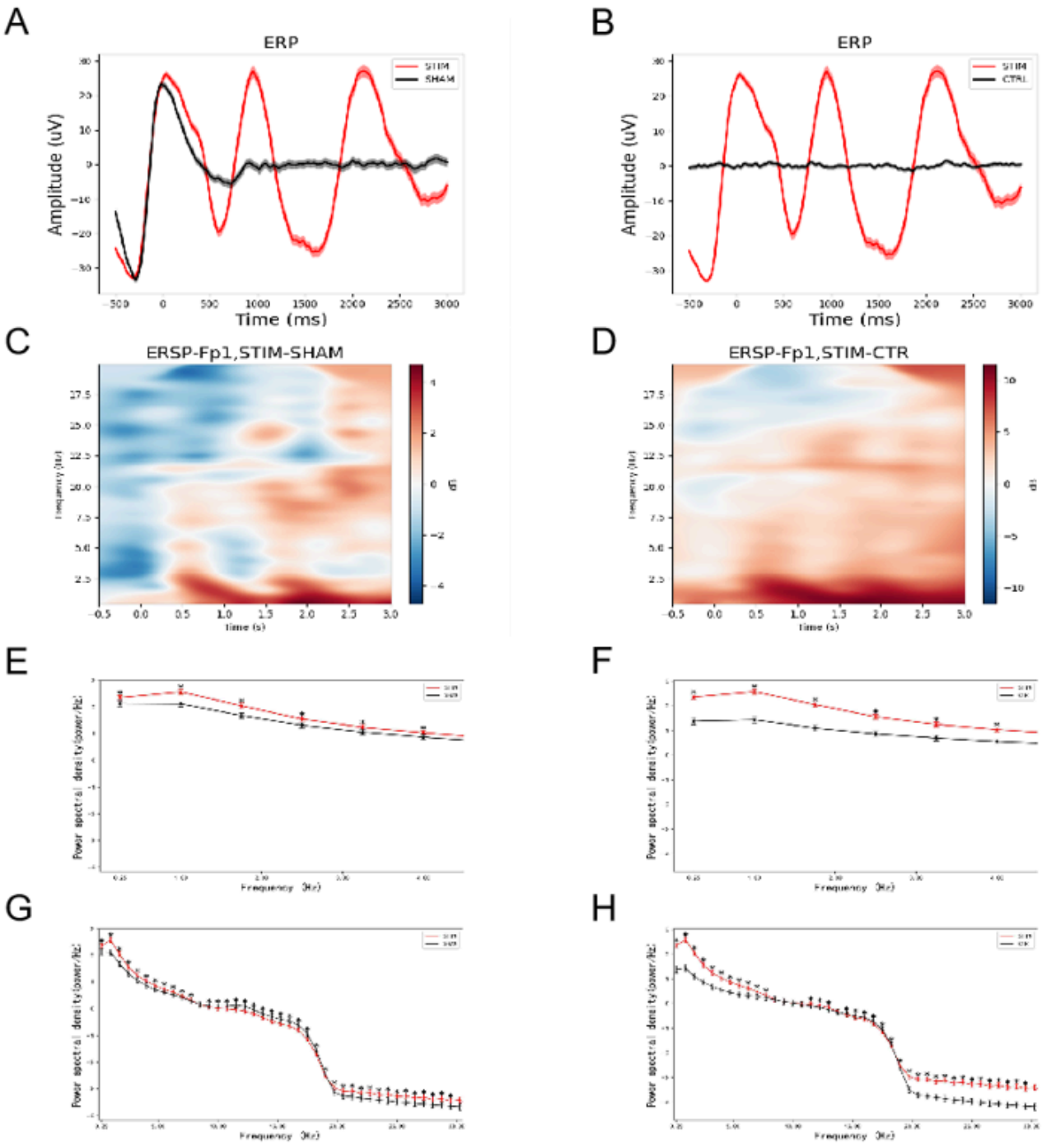

Figure 3

The variation of EEG power, ERPs and ERSP among three groups. (A) Grand ERPs for both the EG and CG conditions. (B) Grand ERPs for both the EG and SG conditions. (C) ERSP for both the EG and CG conditions. (D) ERSP for both the EG and SG conditions. (E) Comparison of mean spectral power between EG and CG blocks for frequencies up to 4 Hz. (F) Comparison of mean spectral power between EG and SG blocks for frequencies up to 4 Hz. (G) Comparison of mean spectral power between EG and CG blocks for frequencies up to 30 Hz. (H) Comparison of mean spectral power between EG and SG blocks for frequencies up to 30 Hz.

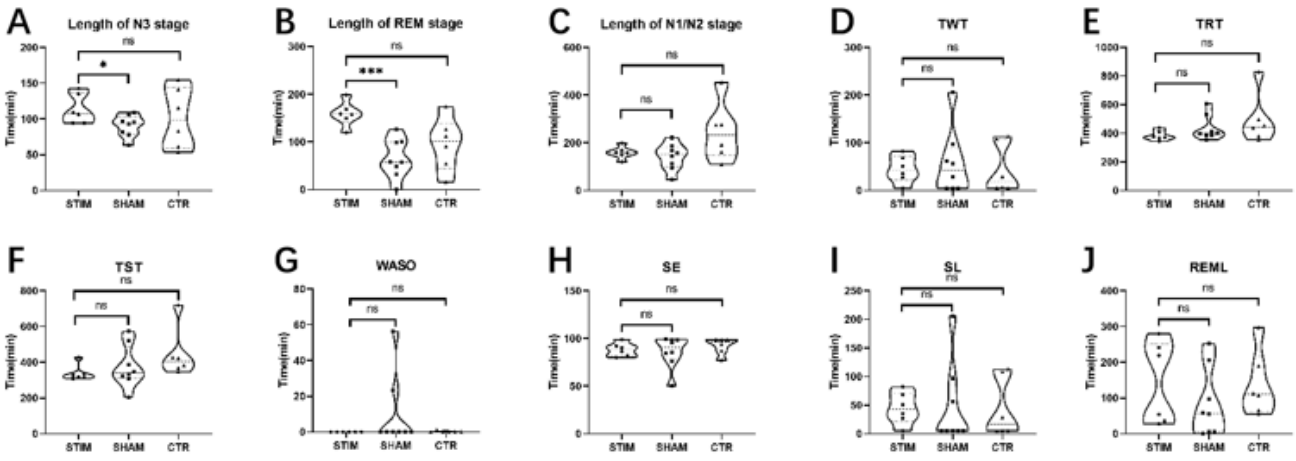

Figure 4

PLAS effect on sleep-related variables at the night. From A-J, it respectively showed the comparison of differences in the length of N3 stage, the length of REM stage, the length of N1/N2 stage, TWT, TRT, TST, WASO, SE, SL, and REML among the three groups. TWT = total wake time, TRT = total red time, TST= total sleep time, SE = sleep efficiency , WASO = wake after sleep onset, SL = sleep latency.

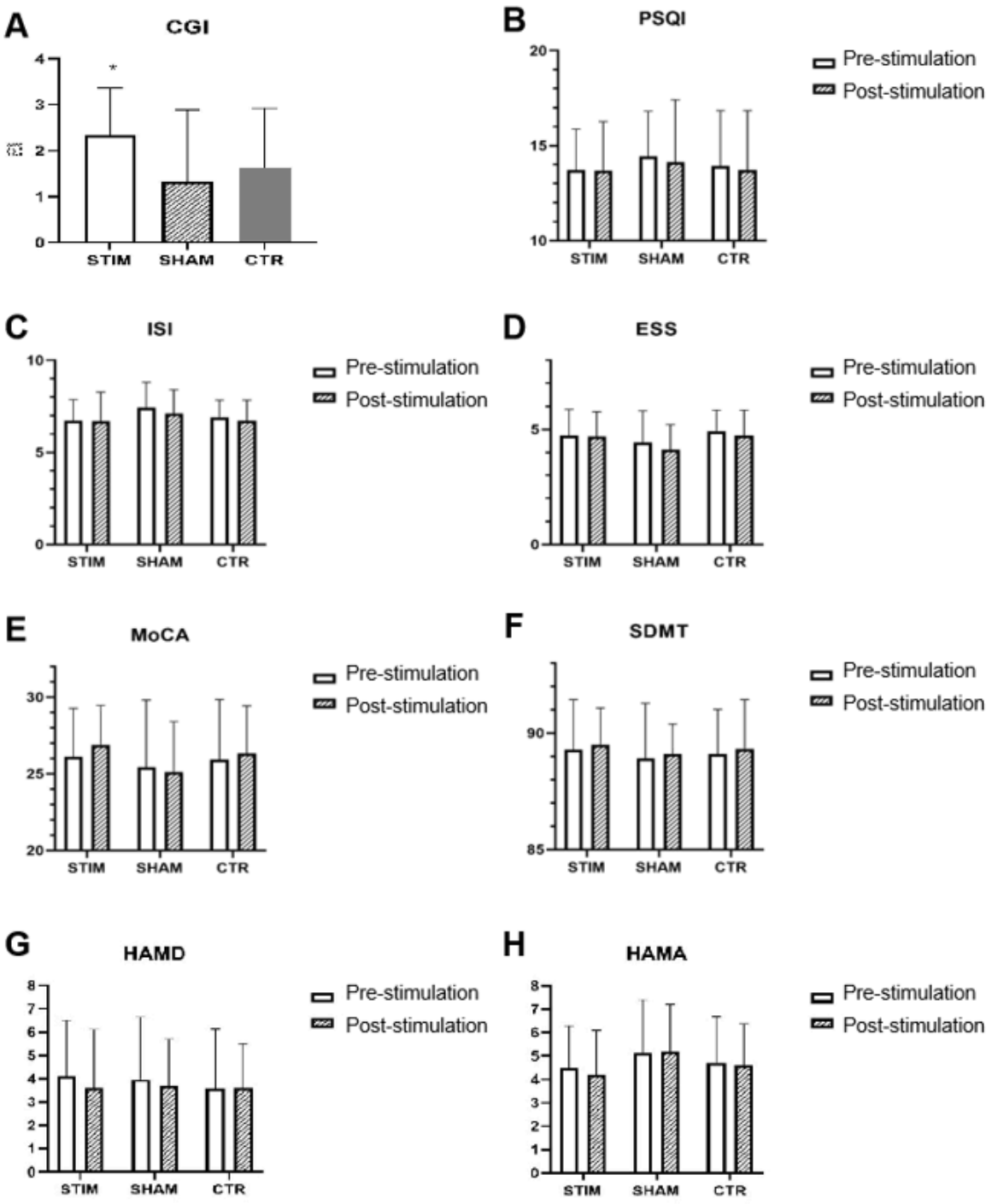

Figure 5

PLAS effect on sleep scales, cognitive and mental assessment. From A-H, it respectively showed the comparison of differences in the PSQI, ISI, ESS, MoCA, SDMT, HAMD, HAMA after the intervention in the three groups. PSQI = Pittsburgh Sleep Scale, ISI = Insomnia Scale, ESS = Epworth Sleep Scale, MoCA = Montreal Cognitive Assessment, SDMT = Symbol digit modalities test, HAMD = Hamilton Depression Scale, HAMA = Hamilton Anxiety Scale.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- LockedphasestimulationSupplementarydata.BMCNeurology.docx