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Effect of Transcranial Alternating Current Stimulation for the Treatment of Chronic Insomnia: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Clinical Trial

Hong-Xing Wang[a–c] Li Wang[a] Wen-Rui Zhang[a] Qing Xue[a] Mao Peng[a] Zhi-Chao Sun[a] Li-Ping Li[a] Kun Wang[d] Xiao-Tong Yang[a] Yu Jia[a] Qi-Lin Zhou[a] Zhe-Xue Xu[a] Ning Li[a] Kai Dong[a] Qian Zhang[a] Hai-Qing Song[a] Shu-Qin Zhan[a] Bao-Quan Min[a] Chun-Qiu Fan[a] Ai-Hong Zhou[a] Xiu-Hua Guo[e, f] Hai-Bin Li[e, f] Li-Rong Liang[g] Lu Yin[h] Tian-Mei Si[i] Jing Huang[j] Tian-Yi Yan[k] Fiammetta Cosci[l] Atsushi Kamiya[m] Jie Lu[j] Yu-Ping Wang[a–c]

[a]Division of Neuropsychiatry and Psychosomatics, Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China; [b]Beijing Key Laboratory of Neuromodulation, Beijing, China; [c]Center of Epilepsy, Beijing Institute for Brain Disorders, Capital Medical University, Beijing, China; [d]Department of Neurology, Beijing Puren Hospital, Beijing, China; [e]Department of Epidemiology and Health Statistics, School of Public Health, Capital Medical University, Beijing, China; [f]Beijing Municipal Key Laboratory of Clinical Epidemiology, Capital Medical University, Beijing, China; [g]Department of Epidemiology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China; [h]Medical Research and Biometrics Center, National Center for Cardiovascular Diseases, Beijing, China; [i]Peking University Sixth Hospital, Beijing, China; [j]Department of Radiology, Xuanwu Hospital, Capital Medical University, Beijing, China; [k]School of Life Science, Beijing Institute of Technology, Beijing, China; [l]Department of Health Sciences, University of Florence, Florence, Italy; [m]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Keywords
Transcranial alternating current stimulation · Insomnia · Efficacy · Randomized controlled trial

Abstract
Background: Not all adults with chronic insomnia respond to the recommended therapeutic options of cognitive behavioral therapy and approved hypnotic drugs. Transcranial alternating current stimulation (tACS) may offer a novel potential treatment modality for insomnia. ***Objectives:*** This study aimed to examine the efficacy and safety of tACS for treating adult patients with chronic insomnia. ***Methods:*** Sixty-two participants with chronic primary insomnia received 20 daily 40-min, 77.5-Hz, 15-mA sessions of active or sham tACS targeting the forehead and both mastoid areas in the laboratory on weekdays for 4 consecutive weeks, followed by a 4-week follow-up period. The primary outcome was response rate measured by the Pittsburgh Sleep Quality Index (PSQI) at week 8. Secondary outcomes were remission rate, insomnia severity, sleep onset latency (SOL), total sleep time

First author: Dr. Hong-Xing Wang; E-Mail: wanghongxing@xwh.ccmu.edu.cn.

E-Mail karger@karger.com
www.karger.com/pps

Hong-Xing Wang or Yu-Ping Wang
Department of Neurology, Xuanwu Hospital, Capital Medical University
No. 45, Changchun Street, Xicheng District
Beijing 100053 (China)
E-Mail wanghongxing@xwh.ccmu.edu.cn or wangyuping01@sina.cn

(TST), sleep efficiency, sleep quality, daily disturbances, and adverse events at the end of the 4-week intervention and at the 4-week follow-up. ***Results:*** Of 62 randomized patients, 60 completed the trial. During the 4-week intervention, 1 subject per group withdrew due to loss of interest and time restriction, respectively. Based on PSQI, at 4-week follow-up, the active group had a higher response rate compared to the sham group (53.4% [16/30] vs. 16.7% [5/30], $p = 0.009$), but remission rates were not different between groups. At the end of the 4-week intervention, the active group had higher response and remission rates than the sham group ($p < 0.001$ and $p = 0.026$, respectively). During the trial, compared with the sham group, the active group showed a statistically significant decrease in PSQI total score, a shortened SOL, an increased TST, improved sleep efficiency, and improved sleep quality ($p < 0.05$ or $p < 0.001$). Post hoc analysis revealed that, in comparison with the sham group, the active group had improved symptoms, except for daily disturbances, at the end of the 4-week intervention, and significant improvements in all symptoms at the 4-week follow-up. No adverse events or serious adverse responses occurred during the study. ***Conclusion:*** The findings show that the tACS applied in the present study has potential as an effective and safe intervention for chronic insomnia within 8 weeks.

Introduction

Chronic insomnia, one of the most common sleep disorders [1], is a critical public health concern due to its high prevalence and increasing incidence [1–3]. Chronic insomnia can contribute to existing neurocognitive impairment, medical illness, reduced quality of life, increased risk of disabilities, and even fatal injuries or death [2, 3]. Multiple physiological, psychological, and environmental factors can cause chronic insomnia [1, 2]. The recommended therapeutic options for chronic insomnia are limited to cognitive behavioral therapy and approved hypnotic drugs [4], but not all patients respond to them [5]. Also, approved hypnotic drugs for chronic insomnia have been shown to be effective in the short term only and often result in multiple side effects and risk of misuse [4, 6]. The treatment efficacy of cognitive behavioral therapy in chronic insomnia relies on the patient's willingness to accept treatment recommendations [5] and may be overestimated because of the lack of blinding of therapists in clinical trials [4]. Therefore, additional treatments for chronic insomnia are needed.

Transcranial alternating current stimulation (tACS) is a noninvasive cranial electrical stimulation consisting of a low-intensity electrical current applied to the scalp to modulate brain activity [7–10]. It was shown to enhance motor memory consolidation [11], improve human psycho-physiological status [12], alter connectivity in the default mode network [13], and modulate neuroplasticity [14–16]. For the effect of tACS on insomnia, previous randomized controlled trials only provided restricted information due to limited design related to blinding and randomization [17, 18]. Additionally, studies reported conflicting results on the efficiency of tACS in improving sleep [18–21], which may be related to different positioning of electrodes, different patient management procedures, or different tACS stimulation current frequencies and/or densities [18–24]. Moreover, tACS with a frequency of 77.5 Hz delivered via electrodes placed on the forehead and the mastoid areas has reportedly an analgesic effect by altering beta-endorphin levels and neurotransmitters, including serotonin, in the cerebrospinal fluid, brainstem, hypothalamus, and cortex [12, 18, 25]. While it is known that hypothalamus and serotonin are involved in the neurobiological mechanisms of chronic insomnia [2, 5], the effect of tACS in adults with chronic insomnia remains poorly understood. Furthermore, in comparison with another transcranial electrical stimulation, transcranial direct current stimulation, tACS appears to be advantageous as it involves less sensory experience [26] and has fewer known adverse effects [23]. Thus, we hypothesized that tACS delivered at 77.5 Hz targeting the forehead and both mastoid areas could be effective in mitigating chronic insomnia.

In this framework, we performed a double-blind, randomized, parallel-group, placebo-controlled trial to examine the efficacy and safety of tACS in adults with chronic insomnia by assessing response and remission rates, insomnia severity, sleep onset latency (SOL), total sleep time (TST), sleep efficiency, sleep quality, daily disturbances, and adverse events.

Methods

An 8-week randomized, double-blind, parallel-group, placebo-controlled trial was run, two groups being examined: an active tACS group and a sham tACS group. The outcome measures were assessed at baseline, at the end of the 4-week intervention, and at the 4-week follow-up. This study was performed in the Laboratory of Neuromodulation, Department of Neurology, Xuanwu Hospital of Capital Medical University, Beijing, China. There was a financial compensation offered to participants who completed the trial. All data are available from the first author upon request.

Study Participants

Subjects with chronic insomnia were recruited from Xuanwu Hospital of Capital Medical University in Beijing by our investigators, physicians' referral, and flyers posted in the common areas. They were prescreened via a brief interview and those who met the inclusion criteria were further screened on site by trained, licensed psychiatrists via the use of the Mini-International Neuropsychiatric Interview (M.I.N.I.) [27] to verify the presence of comorbid mental disorders, listed as exclusion criteria in the study.

Inclusion criteria were (1) age 18–65 years, (2) male or female, (3) diagnosis of chronic primary insomnia according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (text revision) (DSM-IV-TR) [28] or the International Classification of Diseases-10 (ICD-10) [29], (4) having had at least 3 nights per week of difficulties in falling asleep/maintaining sleep/early morning awakening for more than 3 months [2], (5) having had a significant impairment of daytime functioning (i.e., ≥2 on component 7 [Daytime dysfunction] of the Chinese version of the Pittsburgh Sleep Quality Index [PSQI]) [30], (6) having a baseline total score >8 on the PSQI [31], (7) not taking hypnotics or medications for insomnia for at least 4 weeks before the baseline visit, (8) agreeing to birth control (for female patients aged 18–50 years) during the study period, and (9) agreeing not to take pharmacological or other nonpharmacological treatment during the whole trial.

Exclusion criteria were (1) presence of a current medical disease, (2) history of seizures, (3) presence of a comorbid psychiatric disorder according to the M.I.N.I., (4) active current suicidal intent or plan according to the M.I.N.I., (5) prior exposure to electroconvulsive therapy, transcranial magnetic stimulation, or transcranial direct current stimulation, (6) having a cochlear implant, a cardiac pacemaker, an implanted device (i.e., deep brain stimulation), or metal in the brain, (7) being pregnant or lactating, (8) doing night shift work, (9) presence of other sleep disorders including sleep apnea, periodic limb movements, parasomnias, hypersomnia, and (10) participation in concurrent clinical trials.

Criteria for the study termination were (1) occurrence of severe adverse events, (2) pregnancy, (3) diseases for which treatment may interfere with the assessment of tACS results, (4) missed two consecutive sessions, (5) could not receive on-site assessment and examination at the end of the 4-week intervention and at the 4-week follow-up, and (6) withdrawal of consent.

Response rates at the 4-week follow-up were 67% (10/15) in the active group and 7% (1/15) in the sham group in our pilot study. We conservatively assumed a 50% response rate at the 4-week follow-up in the active group and a 10% response rate in the sham group, thus a sample size of 20 per group was needed to have a power of 80% and a two-tailed alpha level of 5%. Considering the 20% attrition rate and a block size of 4, we set our enrolment target at 62 subjects.

Randomization to Treatment and Blinding

Study participants were randomized to either active or sham tACS intervention in a 1:1 ratio (Fig. 1) based on computer-generated random numbers made by an independent statistician (L.-R. Liang) who was neither involved in the enrolment nor in the assessment of the participants. The randomization sequence was computed in permuted blocks of 4. Each participant was assigned a number by nurses before the first intervention via opening a sealed, opaque envelope to determine the instrument choice. A total of 12 tACS devices were used in this trial, including 6 sham and 6 active ones, all of which had the same size, color, appearance, weight, and odor. Two of them (1 sham and 1 active) were intended to be used as a backup in case any one of the other 10 devices did not work. To maintain double blinding, all devices were coded by a statistician (L.-R. Liang). Each participant was assigned to the same instrument during the entire intervention. The integrity of the trial-group blinding was evaluated by asking patients to guess which intervention they had received. Blinding could be broken in case of an emergency. All study staff and participants were blinded to the intervention group assignment.

Procedure

At screening, all subjects were assessed by the Chinese version of the M.I.N.I. to exclude a mental disorder. The M.I.N.I. is a commonly used short structured diagnostic interview which allows to diagnose psychiatric disorders according to the DSM-IV-TR and ICD-10 [28, 29]. The reliability and validity of the Chinese version 5.0 are consistent with those of the English version [27, 29].

At baseline, demographic data such as age, sex, marital status, education, and occupation were collected as well as clinical data such as body mass index, pregnancy status, personal history of surgery, family and personal history of insomnia, alcohol abuse, and substance abuse. In the event of one of the previous diseases, the duration of the illness was collected.

At baseline, at the end of the 4-week intervention, and at the 4-week follow-up, the PSQI total score was assessed. The PSQI is a 19-item self-report questionnaire widely used to measure overall sleep quality [4, 32]. The Chinese version showed a three-factor scoring model which includes sleep efficiency, sleep quality, and daily disturbances. It showed high correlations with the Insomnia Severity Index [30].

Following the request of the local ethics committee, electroencephalogram (EEG) was also recorded. All participants underwent EEG recordings lasting >30 min [33] according to the electrode locations of the international 10/20 system for EEG recording (see online supplement 2; for all online suppl. material, see www.karger.com/doi/10.1159/000504609). The epileptiform discharges were determined by two qualified and experienced EEG professional technicians (Z.-C. Sun and L.-P. Li). The EEG results were classified into two groups: nonepileptiform and emerged epileptiform discharges. Then, the principal investigators (H.-X. Wang and Y.-P. Wang) reviewed the original EEG recordings combining the clinical manifestations of epileptic seizures to examine whether the participant had had an epileptic seizure.

At the end of the 4-week intervention and at the 4-week follow-up, adverse events were also assessed based on the single question "Did you have any discomfort or epileptic seizures or abnormal feelings during the study?" which was proposed to the participants.

On tACS intervention days, patients were asked to sit in a comfortable and reclined chair, to turn off their smartphones, and were encouraged to drink water, relax, and fall asleep. Communication with nurses was limited. Thereafter, each patient received 20 sessions of tACS intervention administered by two trained nurses during 4 consecutive weeks at a fixed day time once daily from Monday through Friday; weekends were off. Each session lasted 40 min. Three Nexalin electrodes (Nexalin Technology, Inc., Houston, TX, USA; https://nexalin.com) were applied to the scalp: one 4.45 × 9.53 cm electrode placed over the forehead (Fpz, Fp1, and Fp2 in the 10/20 international placement system, see online

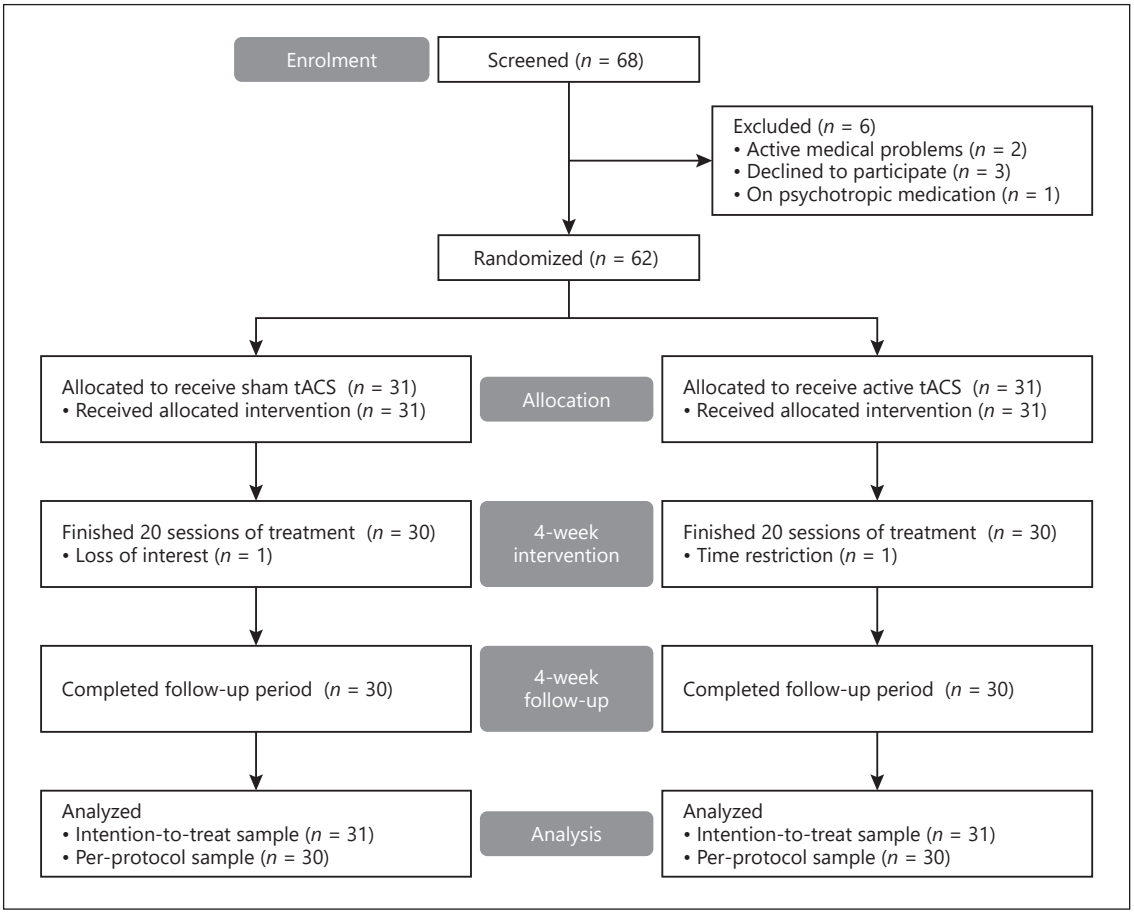

Fig. 1. Journal article reporting standards flowchart. tACS, transcranial alternating current stimulation.

supplement 2) and two 3.18 × 3.81 cm electrodes placed over the mastoid areas (see online supplement 3). A 15-mA current level with a patented frequency of 77.5 Hz was applied in the active group and no stimulation was applied in the sham group.

Statistical Analysis

Between-group comparisons were tested by *t* test for normally distributed continuous variables (i.e., age) and Mann-Whitney U test for non-normally distributed continuous variables (i.e., PSQI total score); χ^2 test or Fisher exact test were used for categorical variables.

The primary outcome measure was the response rate at 4-week follow-up, defined as the percentage of those having at least a 50% reduction in insomnia symptoms from baseline as measured via the PSQI [1]. The secondary outcome measures were (1) changes in other sleep parameters measured via the PSQI, i.e., total score, SOL, TST, sleep efficiency, sleep quality, and daily disturbances [30], (2) clinical remission, defined as a PSQI total score <5 [32], and (3) incidence of adverse events, evaluated by treatment-emergent adverse event and via EEG recordings.

The primary and the secondary outcomes were examined using modified Poisson regression with robust standard errors and adjusting for baseline PSQI score. Relative risk (RR) and risk difference (RD) were estimated [34]. Longitudinal measures were analyzed as secondary outcomes using intention-to-treat analyses on all 62 randomized participants. Linear mixed-effects models (LMMs) for repeated-measures data were used to examine the effects of intervention over time with a random effect for patients [35]. LMMs can yield precise parameter estimates when the repeated-measures data are assumed to be missing at random. Models were fitted based on three time points (baseline, end of the 4-week intervention, and 4-week follow-up). LMMs included the terms of the intervention group (0 for the sham group and 1 for the active group), continuous time (from baseline to 4-week follow-up), and intervention-week interaction (group × time) as fixed effects and intercept as the only random effect. The coefficient for "group × time" described differences in the slope of the outcomes trajectory for participants between the two groups from baseline to 4-week follow-up. The "time" coefficient was the slope of measure on weeks in the sham group, while the coefficient for "group" was the difference in the two groups at baseline. In a post hoc analysis, the secondary outcomes were also examined using multivariable generalized linear regression adjusting for baseline PSQI score and the intervention group (0 for the sham group and 1 for the active group).

Data were analyzed using Stata 15.0 (College Station, TX, USA). A two-sided significance level of 0.05 was used.

Table 1. Sample characteristics at baseline

	Sham group (n = 31)	Active group (n = 31)	p value
Age at enrolment, years	55.3±8.0	52.5±10.7	0.409
Sex			0.767
Male	8 (25.8%)	7 (22.6%)	
Female	23 (74.2%)	24 (77.4%)	
Marital status: single	0 (0%)	0 (0%)	–
Body mass index	24.2±3.3	23.8±3.9	0.607
Pregnancy screening for 47 females			0.451
Postmenopausal or uterus removed	16 (69.6%)	19 (79.2%)	
Pregnancy negative	7 (30.4%)	5 (20.8%)	
Education			0.948
Junior high school and lower	8 (25.8%)	7 (22.6%)	
Senior high school	12 (38.7%)	13 (41.9%)	
College and above	11 (35.5%)	11 (35.5%)	
Occupation			0.639
Professional	14 (45.2%)	11 (35.5%)	
Retired	14 (45.2%)	15 (48.4%)	
Other	3 (9.7%)	5 (16.1%)	
History of surgery	7 (22.6%)	7 (22.6%)	1.000
History of familial insomnia disorder	0 (0%)	0 (0%)	–
Alcohol abuse	0 (0%)	0 (0%)	–
Smoking	0 (0%)	0 (0%)	–
Drug abuse	0 (0%)	0 (0%)	–
Disease duration, months	51.6±46.3	58.1±80.9	0.553
PSQI total score	13.26±2.08	13.13±1.59	0.725

Data were analyzed using intention-to-treat sample. Figures are presented as mean ± standard deviation or n (%). PSQI, Pittsburgh Sleep Quality Index.

Results

Sixty-eight subjects were screened. Among them, 6 were excluded (1 was on psychotropic medication, 2 had other active medical conditions, 3 declined). Thus, 62 patients were enrolled and randomized into the sham group or the active group. There were no statistically significant differences among patients assigned to the two groups regarding baseline variables (Table 1). Sixty patients completed the trial, and retention rates were 96.8% (60/62) at the end of the 4-week intervention and at 4-week follow-up, with only 1 patient per group stopping the trial during the 4-week intervention due to loss of interest and time restriction, respectively (Fig. 1). When the two groups of 30 subjects were compared for baseline variables, still no statistically significant differences were found (data not shown).

At the end of the 4-week intervention, the response rate was 77.2% (23/30) among subjects in the active group and 19.9% (6/30) among those in the sham group (RD 57.3%, 95% confidence interval [CI] 37.1, 77.5; RR 3.88, 95% CI 1.83, 8.23; $p < 0.001$) (Table 2). The active group had a higher response rate (53.4%; 16/30) compared to the sham group (16.7%; 5/30) at 4-week follow-up (RD 36.7%, 95% CI 14.2, 59.2; RR 3.20, 95% CI 1.33, 7.70; p = 0.009) (Table 2).

LMMs revealed longitudinal changes in insomnia severity, as assessed by PSQI total score, in both groups over 8 weeks. The active group had a statistically significant decrease in insomnia severity compared to the sham group (–0.39/week, 95% CI –0.71, –0.06, p = 0.019). Similarly, statistically significant patterns of change were found for SOL (–7.17 min/week, 95% CI –10.77, –3.58, $p < 0.001$), TST (0.12 h/week, 95% CI 0.02, 0.22, p = 0.020), sleep efficiency (–0.15 points/week, 95% CI –0.29, –0.02, p = 0.025), and sleep quality (–0.18 points/week, 95% CI –0.32, –0.05, p = 0.007), except for daily disturbance (–0.05 points/week, 95% CI –0.14, 0.05, p = 0.335) (Table 3).

Table 2. Adjusted remission and response rates at end of the 4-week intervention and at 4-week follow-up in each group

Analysis by group	Adjusted rate, %	RD (active vs. sham), %	*p* value	RR	*p* value
Response					
End of intervention					
Sham	19.9 (5.4, 34.3)			1 (reference)	
Active	77.2 (63.1, 91.2)	57.3 (37.1, 77.5)	<0.001	3.88 (1.83, 8.23)	<0.001
Follow-up					
Sham	16.7 (3.2, 30.1)			1 (reference)	
Active	53.4 (35.4, 71.4)	36.7 (14.2, 59.2)	0.001	3.20 (1.33, 7.70)	0.009
Remission					
End of intervention					
Sham	20.0 (5.5, 34.5)			1 (reference)	
Active	50.0 (32.3, 67.6)	29.9 (7.1, 52.8)	0.010	2.50 (1.11, 5.59)	0.026
Follow-up					
Sham	13.4 (10.8, 25.5)			1 (reference)	
Active	36.6 (19.3, 53.9)	23.3 (20.3, 44.5)	0.032	2.74 (0.98, 7.71)	0.056

Data on the per-protocol sample were calculated using modified Poisson regression with robust standard errors, adjusted for baseline PSQI score. Response was defined as the percentage of those having at least a 50% reduction in PSQI total score from baseline. Remission was defined as a PSQI total score <5. Figures in parentheses present confidential intervals. PSQI, Pittsburgh Sleep Quality Index; RD, risk difference; RR, relative risk.

The post hoc analysis using multivariable linear regression revealed that at the end of the 4-week intervention, patients in the active group had improved symptoms compared to those in the sham group (all $p < 0.05$), but there was no statistically significant improvement in daily disturbances ($p = 0.565$), while at 4-week follow-up patients in the active group had statistically significant improvements in symptoms as assessed via PSQI total score ($p = 0.006$), SOL ($p < 0.001$), TST ($p = 0.013$), sleep efficiency ($p = 0.012$), sleep quality ($p = 0.006$), and daily disturbances ($p = 0.036$) when compared to those in the sham group (Table 4).

At the end of the 4-week intervention, the remission rate in the active group (50%; 15/30) was higher than that in the sham group (20%; 6/30) based on PSQI score (RD 29.9%, 95% CI 7.1, 52.8; RR 2.50, 95% CI 1.11, 5.59; $p = 0.026$). Marginal significance was observed at 4-week follow-up between the two groups (36.6% [11/30] vs. 13.4% [4/30]; RD 23.3%, 95% CI 20.3, 44.5; RR 2.74, 95% CI 0.98, 7.71; $p = 0.056$) (Table 2).

Adverse Events and Safety

After 20 sessions of intervention 1 subject in each group and at the end of the study 2 subjects in the active group had epileptiform discharges, with no statistically significant differences between the two groups ($p = 0.612$; see online supplement 4). None met the diagnostic criteria for epileptic seizures [36]. No phosphene perception happened, and no somatosensory phenomena under the electrode occurred, such as heat, pinching, itchiness, tickling, tingling, pain, or burning sensation. No common adverse events such as headache, dizziness, or nausea were observed.

Integrity of Blinding

Ten subjects of the sham group and 11 subjects of the active group correctly identified the allocation group ($\chi^2 = 0.073$, $p = 0.787$); no patient complained of unusual sensation after receiving a current of 15 mA. In brief, participants were unable to guess their actual group beyond chance.

Discussion

The present study was run in adult patients with chronic primary insomnia to test the effects of tACS on circadian rhythms [5, 37]. tACS was performed at a frequency of 77.5 Hz and a current of 15 mA. The results showed that, compared with the sham group, the active tACS group had higher response rates based on PSQI score changes from baseline to the end of the 4-week in-

Table 3. Secondary outcomes from intention-to-treat analyses using linear mixed-effects models: main effects of group, time, and group × time interaction

Outcomes	β	95% CI	*z* value	*p* value
PSQI total score				
Group	−0.40	−1.72, 0.92	−0.59	0.553
Time	−0.42	−0.65, −0.19	−3.59	<0.001
Group × time	−0.39	−0.71, −0.06	−2.34	0.019
SOL, min				
Group	6.01	−18.17, 30.20	0.49	0.626
Time	0.46	−2.08, 3.00	0.35	0.723
Group × time	−7.17	−10.77, −3.58	−3.91	<0.001
TST, h				
Group	−0.06	−0.61, 0.50	−0.21	0.838
Time	0.13	0.06, 0.20	3.51	<0.001
Group × time	0.12	0.02, 0.22	2.33	0.020
Sleep efficiency				
Group	−0.16	−0.75, 0.44	−0.52	0.605
Time	−0.16	−0.26, −0.07	−3.36	0.001
Group × time	−0.15	−0.29, −0.02	−2.23	0.025
Sleep quality				
Group	0.03	−0.55, 0.61	0.11	0.913
Time	−0.14	−0.24, −0.05	−3.00	0.003
Group × time	−0.18	−0.32, −0.05	−2.69	0.007
Daily disturbances				
Group	−0.28	−0.80, 0.25	−1.04	0.300
Time	−0.11	−0.18, −0.04	−3.04	0.002
Group × time	−0.05	−0.14, 0.05	−0.96	0.335

Data were analyzed using the intention-to-treat sample. CI, confidence interval; PSQI, Pittsburgh Sleep Quality Index; SOL, sleep onset latency; TST, total sleep time.

tervention and to the 4-week follow-up, and a higher remission rate at the end of the 4-week intervention. During the 8-week period, the patients who received the active tACS intervention had lower insomnia severity, shortened SOL, elevated TST, improved sleep efficiency, and increased sleep quality. The literature nowadays available on this topic is based on few randomized controlled trials analyzing the effect of tACS in adults with chronic insomnia [20, 38] but producing limited, unsatisfactory, and, above all, inconsistent results [17, 18, 20, 38]. This inconsistency seems to be related to the use of different stimulation sites and to the use of different parameters, which include frequency, current, and duration of the treatment [13, 39, 40]. The present study used a rigorous and replicable methodology to study patients with chronic insomnia and found that the protocol of tACS here applied has a therapeutic effect on treatment of chronic insomnia. This suggests that replication studies are needed to confirm the clinical utility of tACS at a frequency of 77.5 Hz and a current of 15 mA in adult subjects with chronic insomnia.

Although the alternating current of 15 mA applied in the present research was higher than the one applied in previous studies [23, 24], the results did not show unwanted adverse events such as phosphene and stimulation-associated sensation under the electrodes, which may be associated with the stimulation sites [23] and the activating different somatosensory systems by tACS [26]. Overall, 97% (60/62) of the participants completed the trial, which indicates that tACS was well tolerated and safe. Of note, 1 participant per group had epileptiform discharges after 20 sessions of the tACS intervention, and 2 participants in the active group had epileptiform discharges at 4-week follow-up. However, since those participants did not meet the diagnostic criteria for epileptic seizures and epileptiform discharges are not the same as

Table 4. Observed and fitted group mean results for PSQI scores at the end of the 4-week intervention and at 4-week follow-up in each group

Analysis by group	Group mean difference			
	mean (95% CI)		fitted difference (95% CI)	*p* value
	baseline	follow-up	active vs. sham	
PSQI total score				
End of intervention				
Sham	13.23 (12.44, 14.02)	8.43 (6.98, 9.89)		
Active	13.13 (12.53, 13.74)	5.93 (4.47, 7.39)	−2.49 (−4.52, −0.45)	0.017
Follow-up				
Sham	13.23 (12.44, 14.02)	9.93 (8.42, 11.44)		
Active	13.13 (12.53, 13.74)	6.73 (5.05, 8.41)	−3.16 (−5.36, −0.96)	0.006
SOL, min				
End of intervention				
Sham	81.33 (58.66, 104.00)	66.17 (47.41, 84.92)		
Active	91.33 (71.50, 111.16)	31.20 (23.16, 39.24)	−37.39 (−56.28, −18.49)	<0.001
Follow-up				
Sham	81.33 (58.66, 104.00)	84.67 (60.34, 108.99)		
Active	91.33 (71.50, 111.16)	38.50 (30.71, 46.29)	−49.52 (−72.78, −26.27)	<0.001
TST, h				
End of intervention				
Sham	3.87 (3.45, 4.28)	5.23 (4.76, 5.70)		
Active	3.75 (3.41, 4.09)	6.01 (5.41, 6.61)	0.84 (0.13, 1.55)	0.022
Follow-up				
Sham	3.87 (3.45, 4.28)	4.90 (4.30, 5.50)		
Active	3.75 (3.41, 4.09)	5.72 (5.17, 6.27)	0.90 (0.20, 1.61)	0.013
Sleep efficiency				
End of intervention				
Sham	5.30 (4.96, 5.64)	3.67 (3.02, 4.31)		
Active	5.37 (5.03, 5.70)	2.43 (1.68, 3.19)	−1.27 (−2.22, −0.31)	0.010
Follow-up				
Sham	5.30 (4.96, 5.64)	4.00 (3.28, 4.72)		
Active	5.37 (5.03, 5.70)	2.83 (2.11, 3.56)	−1.22 (−2.16, −0.28)	0.012
Sleep quality				
End of intervention				
Sham	4.93 (4.55, 5.31)	3.40 (2.71, 4.09)		
Active	5.13 (4.81, 5.45)	2.37 (1.71, 3.03)	−1.11 (−2.04, −0.18)	0.021
Follow-up				
Sham	4.93 (4.55, 5.31)	3.80 (3.16, 4.44)		
Active	5.13 (4.81, 5.45)	2.53 (1.77, 3.30)	−1.37 (−2.33, −0.41)	0.006
Daily disturbances				
End of intervention				
Sham	3.00 (2.58, 3.42)	1.37 (0.93, 1.80)		
Active	2.63 (2.20, 3.07)	1.13 (0.83, 1.44)	−0.15 (−0.66, 0.36)	0.565
Follow-up				
Sham	3.00 (2.58, 3.42)	2.13 (1.62, 2.65)		
Active	2.63 (2.20, 3.07)	1.37 (0.97, 1.76)	−0.68 (−1.32, −0.05)	0.036

Data for examination of group mean differences by two groups were calculated using multivariable linear regression (adjusting for the baseline score). Data on the per-protocol sample were calculated among patients with follow-up scores. CI, confidence interval; PSQI, Pittsburgh Sleep Quality Index; SOL, sleep onset latency; TST, total sleep time.

epileptic seizures [33], no direct evidence on the causal relationship between the tACS and the appearance of epileptiform discharges can be assumed. Additionally, in a previous study [40] epileptiform discharges were recorded also in the general population [41], which is here confirmed by the fact that also 1 subject under the sham condition had epileptiform discharges. However, the relationship between tACS and epileptiform discharges/epileptic seizure needs further exploration.

This study has some limitations. First, the results showed that 20 consecutive tACS sessions produced a treatment effect on chronic insomnia at follow-up, i.e., 8 weeks since the first intervention, but it is not known how long the effect would last. Studies with longer follow-up periods are needed. Second, the Insomnia Severity Index was not applied since we mainly relied on PSQI to define the level of severity of chronic insomnia. Future studies should use such indexes. Third, no objective assays of sleep parameters, such as wrist actigraphy or polysomnography, were performed. Future research should implement the methods via their use. Fourth, the treatment outcome in the study was the cumulative result of the interaction of tACS and other potential variables [42, 43] such as living conditions, patient characteristics, self-management, illness characteristics, and treatment setting. These additional variables are in need of exploration.

In summary, the present study provides evidence that tACS has potential as an effective and safe therapeutic approach for adult patients with chronic primary insomnia. The results encourage further research aimed at examining how tACS affects sleep with the use also of objective tools, including imaging techniques and biological specimens, taking into account potential additional confounding variables such as living conditions, patient characteristics, self-management, illness characteristics, and treatment setting, and running longer follow-up observations, a 3- and 6-month follow-up duration being desirable.

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Statement of Ethics

The protocol was approved by the local ethics committee, reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (see online supplement 1) and registered at the Chinese Clinical Trial Registry (ChiCTR1800016480). All participants gave their written informed consent.

Disclosure Statement

The authors declare that they have no conflict of interests. They declare that they have had no financial relationships with any organizations that might have an interest in the submitted study in the past 3 years. Milestone (Beijing, China) Medical Appliances Co. Ltd. provided Y.-P. Wang part grant, equipment, and participants' financial compensation.

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Author Contributions

H.-X. Wang and Y.-P. Wang: conception and design. H.-X. Wang, L. Wang, W.-R. Zhang, Q. Xue, M. Peng, K. Wang, X.-T. Yang, Y. Jia, Q.-L. Zhou, Z.-X. Xu, N. Li, K. Dong, Q. Zhang, H.-Q. Song, S.-Q. Zhan, B.-Q. Min, C.-Q. Fan, A.-H. Zhou, and T.-M. Si: conduction. L.-R. Liang: randomization and blinding. H.-X. Wang, X.-H. Guo, H.-B. Li, and L. Yin: statistical analysis. L. Wang, W.-R. Zhang, L.-P. Li, M. Peng, Z.-C. Sun, K. Wang, X.-T. Yang, J. Huang, J. Lu, and T.-Y. Yan: administrative, technical, and material support. H.-X. Wang: drafting of the manuscript. H.-X. Wang, F. Cosci, A. Kamiya, and Y.-P. Wang: critical revision of the manuscript for important intellectual content. All authors read and approved the final paper.

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