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Efficacy of transcranial alternating current stimulation in treating chronic insomnia and the impact of age on its effectiveness: A multisite randomized, double-blind, parallel-group, placebo-controlled study

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ABSTRACT

Objective: Insomnia is a significant health issue associated with various systemic diseases. Transcranial alternating current stimulation (tACS) has been proposed as a potential intervention for insomnia. However, the efficacy and mechanisms of tACS in chronic insomnia remain unclear. Accordingly, this study aimed to investigate the efficacy of tACS in treating chronic insomnia in adults and assess the impact of age on its effectiveness using a large sample from two centers.

Methods: A total of 120 participants with chronic insomnia underwent 20 daily sessions of tACS (duration: 40 min, frequency: 77.5 Hz, and intensity: 15 mA) or sham tACS targeting the forehead and both mastoid areas over 4 weeks. Assessments were conducted at baseline, post-treatment, and 4-week follow-up. Primary outcomes included sleep quality and efficiency, onset latency, total sleep time, and daily disturbances. Secondary outcomes included depression, anxiety, and clinical impression.

Results: Compared with the control group, the tACS group demonstrated improved sleep quality and efficiency, increased total sleep time, and reduced daily disturbance (all $ps < 0.01$). Moreover, tACS had a significant effect on clinical impression ($p < 0.001$), but not depression and anxiety scores. Subgroup analyses revealed that older participants experienced significant benefits from tACS in sleep quality, efficiency, and overall insomnia reduction at post-treatment and follow-up ($p < 0.001$). Notably, improved insomnia correlated with attenuated depressive and anxiety symptoms.

Conclusions: These findings suggest that tACS may be an effective intervention for chronic insomnia within an eight-week timeframe, and age affects the response to tACS in terms of insomnia improvement.

1. Introduction

Chronic insomnia is characterized by difficulty in initiating or maintaining sleep, and early morning awakening, occurring at least three nights per week for at least 3 months, accompanied by daytime consequences such as fatigue, attention deficits, and emotional instability (Riemann et al., 2015). As one of the most common sleep disorders (Wong et al., 2017), Chronic insomnia has a high prevalence and incidence, with approximately 6%–10% of adults experiencing this condition (Buysse, 2013; Morin and Benca, 2012). It can manifest independently or as a result of other underlying diseases and is more commonly observed in women and older adults (Siengsukon et al., 2020; Xu et al., 2011). Chronic insomnia is associated with various adverse health outcomes, neurocognitive disorders, and a severely reduced quality of life (Kyle et al., 2010; Medalie and Cifu, 2017; Riemann et al., 2015), making it a significant public health concern worldwide. Currently, medication is the mainstay treatment option for chronic insomnia, along with cognitive behavioral therapy for insomnia (CBT-I) (Riemann et al., 2017). The approved hypnotic drugs have demonstrated effectiveness only in the short term and are often accompanied by numerous side effects and potential risks of dependence and misuse (Huedo-Medina et al., 2012; Riemann et al., 2017). In addition, CBT-I is

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recommended as the first-line non-drug treatment for insomnia, it is a treatment package including behavioral techniques, relaxation, and cognitive therapy (Qaseem et al., 2016; Trauer et al., 2015). With CBT-I, insomnia symptoms can be significantly reduced in the short and long-term (Trauer et al., 2015). However, CBT-I does have some limitations, including a lack of qualified therapists and the significant personnel, time, and space costs required for face-to-face therapy. Due to these reasons, the application of face-to-face individual or group CBT-I in clinical setting is still limited (Thomas et al., 2016; van Straten and Cuijpers, 2009). Moreover, not all patients respond positively to the above approaches (Morin and Benca, 2012). Therefore, the development of effective treatments for insomnia is urgently needed.

A potentially novel treatment modality for insomnia is transcranial alternating current stimulation (tACS), a noninvasive electrical stimulation technique that modulates brain activity by applying low-intensity electrical currents to the scalp. Prior studies have shown that tACS can enhance the consolidation of sports memory (Lustenberger et al., 2016), improve psychophysiological states (Lebedev et al., 2002), modulate the default mode network connectivity, and regulate neuroplasticity (Feusner et al., 2012). Moreover, tACS can alter the level of serotonin in the hypothalamus, which is involved in the neurobiological mechanisms underlying chronic insomnia (Morin and Benca, 2012; Riemann et al., 2015). However, previous studies have reported conflicting results regarding the effectiveness of tACS in improving sleep efficiency, probably due to variations in study designs, such as differences in electrode positioning, patient management procedures, or tACS stimulation current frequencies (Annarumma et al., 2018; Antal et al., 2017; Antonenko et al., 2013; D'Atri et al., 2016; Lande and Gragnani, 2013; Matsumoto and Ugawa, 2017; Shekelle P and Miake-Lye IM, 2018). In addition, large-scale studies evaluating the efficacy of tACS in treating chronic insomnia are lacking. Accordingly, to address these gaps in knowledge, we performed a two-center, large-sample, randomized controlled trial to explore the effect of tACS on chronic insomnia and identify potential factors that mediate treatment benefits in adults.

2. Material and methods

2.1. Design

This study was an 8-week, randomized, double-blind, parallel-group, placebo-controlled trial. All eligible participants who consented and fulfilled the inclusion criteria were randomly allocated to either the tACS or sham tACS (control) group. Primary outcome measures, including the Pittsburgh Sleep Quality Index (PSQI) total score, sleep onset latency (SOL), total sleep time (TST), sleep efficiency, sleep quality, and daily disturbances, were assessed at baseline (week 0), post-treatment (week 4), and follow-up (week 8). Secondary outcomes, including Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), and Clinical Global Impression (CGI), were also evaluated at the same time points. The study was approved by the local ethics committee and registered at the Chinese Clinical Trial Registry (ChiCTR1800016480). All participants provided their written informed consent.

2.2. Participants

Participants with chronic insomnia were recruited from October 17, 2017, to March 5, 2018, at Xuanwu Hospital of Capital Medical University in Beijing and Beijing Anding Hospital. During the screening process, potential participants who met the inclusion criteria underwent further assessment using the Chinese version of the Mini-International Neuropsychiatric Interview (M.I.N.I.) to exclude those with mental disorders. The M.I.N.I. is a commonly used short, structured diagnostic interview that enables the diagnosis of psychiatric disorders based on the Diagnostic and Statistical Manual of Mental Disorders 4th edition (text revision) (DSM-IV-TR) and International Classification of Diseases-10 (ICD-10) (American Psychiatric Association, 2010; Sheehan et al., 1998).

Inclusion criteria were as follows: age between 18 and 65 years, a diagnosis of chronic primary insomnia according to the DSM-IV-TR (American Psychiatric Association, 2010) or ICD-10 (Sheehan et al., 1998), difficulties in falling asleep and maintaining sleep or early morning awakening for more than three times per week over a period of three or more consecutive months (Riemann et al., 2015), significant impairment of daytime functioning, a baseline PSQI total score >8, not taking hypnotics or insomnia drugs for at least four weeks before the baseline visit, agreement to use birth control (for female patients aged 18–50 years) during the study period, and willingness not to undergo drug therapy or other non-drug therapy throughout the trial.

Exclusion criteria included current medical diseases, a history of seizures, comorbid psychiatric disorders, active suicidal intent or plan, prior exposure to other electrical stimulation therapies, presence of a cochlear implant, a cardiac pacemaker, an implanted device (such as deep brain stimulation), metal in the brain, pregnant or breastfeeding, night work, presence of other sleep disorders (such as sleep apnea, periodic limb movements, parasomnias, and hypersomnia), and concurrent participation in other clinical trials.

2.3. Sample size calculation

In our pilot study, the response rates at the 4-week follow-up were 67% (10/15) in the tACS group and 7% (1/15) in the control group. Assuming a response rate of 50% in the tACS group and 10% in the control group at a 4-week follow-up, a sample size of 20 per group was calculated to achieve an 80% power with a two-tailed alpha level of 5%. Considering a 20% attrition rate and a block size of 4, the target enrolment was set at 62 participants.

2.4. Randomization of treatment and blinding

The CONSORT flow diagram in Fig. 1 illustrates the randomization of 124 participants. Sixty-two patients from Xuanwu Hospital of Capital Medical University (China) and 62 patients from Beijing Anding Hospital were randomly assigned to either the tACS intervention or control group in a 1:1 ratio (Fig. 1) based on computer-generated random numbers. Randomization was independently conducted by a statistician who was not involved in the enrolment or assessment of the participants. The randomization sequence was computed in permuted blocks of four. A random number table, which was provided in sealed envelopes, was used to generate randomization. To evaluate the integrity of the trial-group blinding, participants were asked to guess the intervention they had received. Emergency unblinding was possible if necessary. Both study staff and participants were blinded to the assignment of the intervention group.

2.5. Outcome measures

Primary outcomes: The sleep quality of the patients was assessed using the PSQI, a widely used 19-item self-report questionnaire (Buysse et al., 1989; Riemann et al., 2017). The Chinese version of the PSQI has a three-factor scoring model that includes sleep efficiency, sleep quality, and daily disturbances. It has demonstrated a high correlation with the insomnia severity index (Lu T et al., 2014). The primary outcome measures included the PSQI total score, SOL, TST, sleep efficiency, sleep quality, and daily disturbances.

Secondary outcomes: Anxiety and depression symptoms were assessed using the HAMD and HAMA. Functional outcomes were evaluated using CGI.

Others: At the end of the 4-week intervention, adverse events were assessed by asking participants the following question: "Did you experience any discomfort, seizures, or abnormal sensations during the study period?"

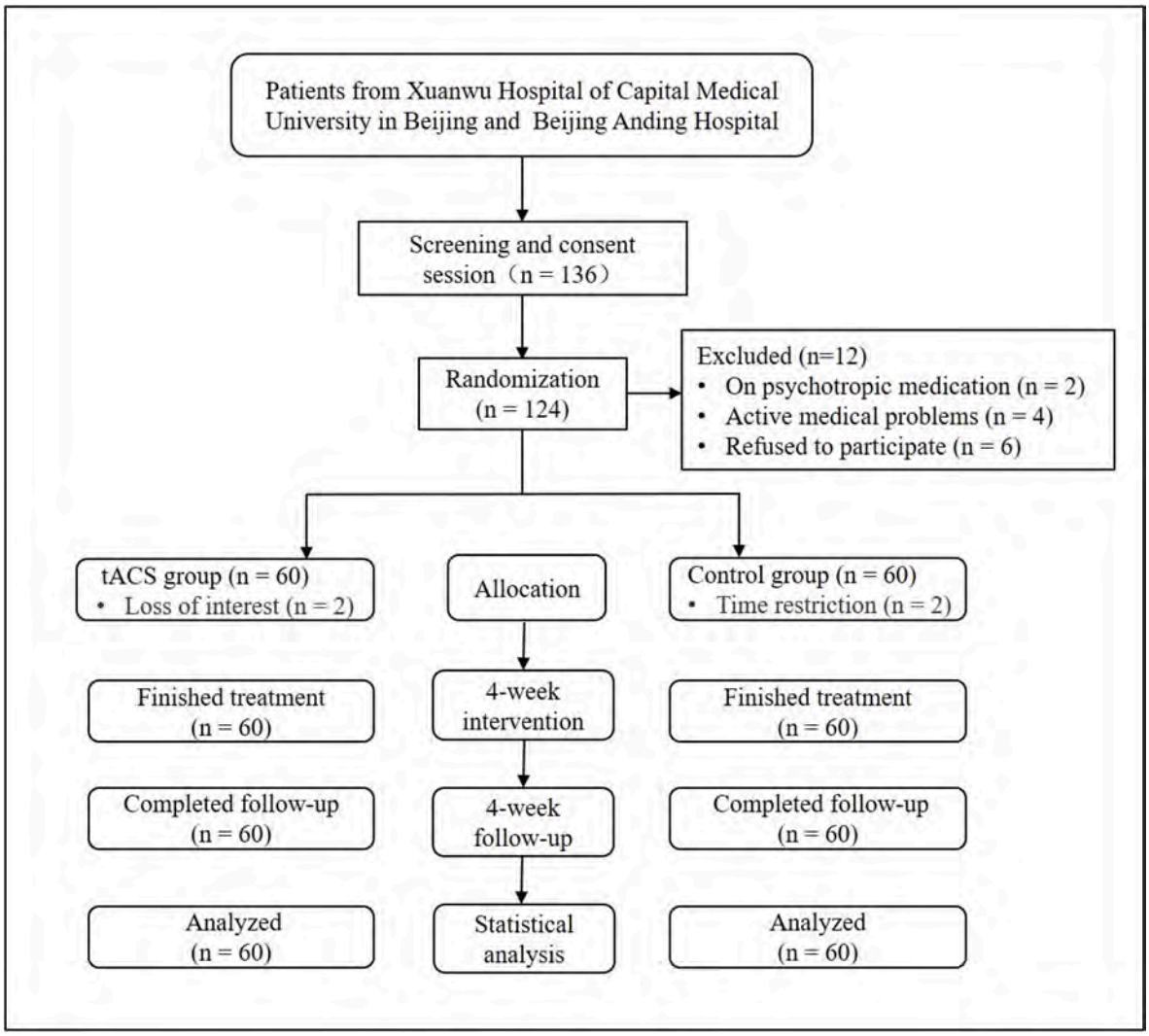

Fig. 1. Study flowchart.

2.6. Therapies

Each patient underwent 20 sessions of tACS intervention administered by two trained nurses over a four-week period, from Monday to Friday, once a day. Each session lasted 40 min. On tACS intervention days, participants were instructed to sit in a comfortable reclined chair and turn off their smartphones and were encouraged to drink water, relax, and fall asleep. Communication with the nurses was limited during the sessions. The tACS intervention involved the stimulation of the scalp with three Nexalin electrodes (Nexalin Technology, Inc., Houston, TX, USA). The electrode placements followed the international 10/20 system for electroencephalogram recording; one 4.45 × 9.53 cm electrode was positioned over the forehead (Fpz, Fp1, and Fp2), and two 3.18 × 3.81 cm electrodes were placed over the mastoid areas. A current level of 15 mA with a patented frequency of 77.5 Hz was applied to the tACS group, whereas no stimulation was applied to the control group.

2.7. Statistical analysis

All data were analyzed using IBM SPSS software (version 20.0; IBM Corp., Armonk, NY, USA). Differences between the two groups were assessed using t-tests for continuous variables, while $\chi 2$ test and Fisher's exact test were used to analyze categorical variables.

Intention-to-treat analyses were performed to examine the effects of tACS on all outcome variables. General linear mixed models (GLM) with model parameters estimated by maximum likelihood based on normality were used for efficacy analysis and exploration of secondary outcomes. The models included fixed effects for the experimental factors (i.e., main effect of group [control or tACS group] and time [post-treatment and follow-up] and group × time interaction), and baseline values of the outcome measure were included as covariates. A significant group × time interaction indicated a differential effect of treatment at post-treatment and follow-up, and further simple effect analyses were conducted with Bonferroni correction for multiple comparisons for the significant group × time interaction. If the interaction effect was not significant, the model was refitted excluding the interaction term to assess the overall group effect. The main effect of the group was interpreted as an overall effect of tACS across both post-treatment and follow-up. In addition, random effects for participants and study sites were also included in the models.

To explore the influence of age on treatment benefits, we divided the participants into two age groups (younger group: <50 years; older group: ≥50 years) (Luca et al., 2015; Madrid-Valero et al., 2017). GLM analyses were also used, but these models included additional fixed effects for the age group and two-way or three-way interactions for moderator analyses. The model was adjusted by excluding the interaction term if it was not significant. Furthermore, a simple effect analysis of the significant group × age group interaction was conducted.

To investigate the putative effects of clinical symptom improvement on insomnia improvement, we performed a Pearson or partial

correlation analysis, controlling for age, sex, and years of education in the tACS and control groups. Insomnia improvement was defined as a reduction in the PSQI total score from baseline to post-treatment. Improvements in clinical symptoms were assessed by changes in HAMD (baseline to post-treatment) and HAMA (baseline to post-treatment). The statistical *P*-values were corrected using Bonferroni correction across all 5 subfield tests of PSQI ($P < 0.05/5 = 0.01$).

3. Results

A total of 136 subjects were screened. Among them, 12 were excluded (2 were on psychotropic medication, 4 had other active medical conditions, 6 declined). Therefore, 124 patients were included and randomized into the control group or the tACS group. During the process of collecting information, four participants withdrew from the experiment due to time and interest reasons. 120 patients completed the trial with a retention rate of 96.8% (120/124), as shown in Fig. 1. Table 1 presents the baseline characteristics of the two groups. There were no significant differences in demographics between the two groups. The mean baseline scores for insomnia severity, clinical symptoms, and functional outcomes were similar across both groups (Table 2).

3.1. Treatment effects of tACS on primary and secondary outcomes

The GLM analysis revealed longitudinal changes in insomnia severity, as assessed by the PSQI total score, in both groups over 8 weeks. Table 3 shows the results of the formal analyses of the main and secondary outcomes. For more detailed analysis, please refer to Supplement Table 1 and Table 2. There were significant group effects on PSQI total score, TST, sleep efficiency, sleep quality and daily disturbances. The tACS group demonstrated a statistically significant decrease in insomnia severity compared with the control group (95% CI: 1.47 to 3.75, $p < 0.001$). Similarly, statistically significant patterns of change were found for TST (95% CI: −1.06 to −0.24, $p = 0.002$), sleep efficiency (95% CI: 0.48 to 1.62, $p < 0.001$), sleep quality (95% CI: 0.29 to 1.34, $p = 0.003$), and daily disturbances (95% CI: 0.58 to 1.25, $p < 0.001$) (Table 3).

Regarding the secondary outcomes, tACS exhibited significant effects on CGI-SI (95% CI: 0.38 to 1.30, $p < 0.001$), CGI-GI (95% CI: 0.42 to 1.06, $p < 0.001$), and CGI-EI (95% CI: −1.02 to −0.39, $p < 0.001$), but not on the total scores of HAMD and HAMA.

Table 1
Demographic, clinical and functional outcomes of the two groups.

Characteristics	Control group (n = 60)	tACS group (n = 60)	t/χ^2	*P* value
Sex (male/female)	23:37	19:41	0.59	0.444[b]
Mean age (SD), year	52.25 ± 10.38	48.93 ± 12.78	1.56	0.121[a]
Mean education years (SD), year	12.33 ± 3.41	12.78 ± 2.81	−0.79	0.432[a]
Duration of illness (SD), year	4.39 ± 5.43	4.48 ± 5.70	−0.10	0.923[a]
Mean onset age (SD), year	47.87 ± 10.84	44.45 ± 12.39	1.61	0.111[a]
PSQI total score	13.77 ± 2.00	13.85 ± 1.75	−0.24	0.809[a]
HAMD score	6.57 ± 3.33	7.13 ± 3.60	−0.90	0.372[a]
HAMA score	6.63 ± 5.92	7.25 ± 6.84	−0.53	0.599[a]
CGI-SI	4.15 ± 1.01	4.05 ± 0.93	0.57	0.572[a]
Advent Events (yes/no)	3:57	4:56	–	0.500[c]
Epileptiform discharges (yes/no)	1:59	1:59	–	0.752[c]

PSQI, Pittsburgh Sleep Quality Index; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; CGI-SI, Clinical Global Impression Scale severity of illness.
[a] Independent samples *t*-test.
[b] chi-square tests.
[c] Fisher's exact test.

While most outcomes did not show significant interactions, two significant interactions were observed for the sleep quality score of the PSQI ($F_{1,118} = 6.21$, $p = 0.014$) and the HAMD total score ($F_{1,118} = 4.58$, $p = 0.034$). The sleep quality score in the control group showed an estimated increase of 0.37 points from post-treatment to follow-up (95% CI 0.03 to 0.70, $p = 0.033$). The HAMD total score in the tACS group demonstrated an estimated decrease of 0.80 points from post-treatment to follow-up (95% CI: −1.41 to −0.19, $p = 0.012$).

3.2. Effect of age on treatment efficacy

In the exploratory subgroup analysis, there was no group-by-age interaction observed for age, education, duration of illness, and onset age at baseline within the four age subgroups, and no group-by-age interactions were found for the primary and secondary outcomes (see Online Supplementary Table S3). However, when additional fixed effects for age group were included in the GLM analyses, after the removal of the non-significant interactions, we observed group-by-age interactions for the PSQI total score ($F_{1,115} = 4.51$, $p = 0.036$), sleep efficiency ($F_{1,115} = 5.81$, $p = 0.018$), sleep quality ($F_{1,115} = 6.04$, $p = 0.015$), CGI-SI ($F_{1,115} = 5.02$, $p = 0.027$), CGI-GI ($F_{1,116} = 8.11$, $p = 0.005$), and CGI-EI ($F_{1,115} = 7.31$, $p = 0.008$), with relevant baseline scores as covariates (except for CGI-GI and CGI-EI) (see Online Supplementary Table S4).

Further analyses revealed that in the older group, tACS treatment resulted in a significant benefit in sleep quality ($F_{1,72} = 14.399$, $p < 0.001$; an estimated decrease of 1.263 points; 95% CI: 0.599 to 1.926), sleep efficiency ($F_{1,72} = 16.908$, $p < 0.001$; an estimated decrease of 1.542 points; 95% CI: 0.795 to 2.290), PSQI total score ($F_{1,72} = 26.183$, $p < 0.001$; an estimated decrease of 3.552 points; 95% CI: 2.168 to 4.936), CGI-SI ($F_{1,72} = 16.020$, $p < 0.001$; an estimated decrease of 1.233 points; 95% CI: 0.619 to 1.848), CGI-GI ($F_{1,73} = 31.244$, $p < 0.001$; an estimated decrease of 1.083 points; 95% CI: 0.697 to 1.470), and CGI-EI ($F_{1,73} = 28.759$, $p < 0.001$; an estimated increase of 1.025 points; 95% CI: −1.406 to −0.644) at both post-treatment and follow-up. However, these benefits were not observed in the younger group (Figs. 2 and 3). In addition, age had no effect on clinical symptoms after tACS treatment (Online Supplementary Table S2).

3.3. Correlation between clinical symptoms and insomnia improvement

Regarding post-treatment outcomes, HAMD improvement was positively correlated with PSQI improvement in both groups (tACS: r = 0.485, $p < 0.001$; control: r = 0.448, $p < 0.001$). Similarly, a positive correlation was found between HAMA and PSQI improvements in both groups (tACS: r = 0.359, $p = 0.005$; control: r = 0.333, $p = 0.009$). For the clinical impression, CGI-SI improvement was positively correlated with PSQI improvement in both groups (tACS: r = 0.641, $p < 0.001$; control: r = 0.751, $p < 0.001$). After controlling for age, sex, and educational level, these correlations remained significant (all $Ps < 0.01$).

4. Discussion

This double-center, large-sample study explored the effects of tACS on chronic insomnia. The results showed that patients who underwent a 4-week active tACS intervention at a frequency of 77.5 Hz and a current of 15 mA exhibited reduced insomnia severity, increased TST, improved sleep efficiency, and enhanced sleep quality. Additionally, daily disturbances were alleviated. These results align with other studies and meta-analyses and further suggest that tACS is effective and well-tolerated in treating chronic insomnia (Motamedi et al., 2022; Zheng et al., 2023). A possible mechanism underlying the efficacy of tACS treatment in chronic insomnia may be frequency-specific entrainment, i.e., the phase alignment of endogenous brain oscillations with oscillating tACS currents (Motamedi et al., 2022). Neurobiological research has found that insomnia patients have neuroendocrine disorders (Riemann

Table 2
Linear model for mean (S.D.) scores on PSQI, Clinical symptom and functional outcome by group (tACS and Control) for baseline, post-treatment and the follow-up.

	Control group (n = 60/60/60)			tACS group (n = 60/60/60)		
	Baseline	Post-treatment	Follow-up	Baseline	Post-treatment	Follow-up
PSQI						
PSQI total score	13.77 ± 2.00	8.58 ± 3.22	9.40 ± 3.30	13.85 ± 1.75	6.12 ± 3.24	6.40 ± 3.98
SOL (min)	79.67 ± 53.50	48.67 ± 41.80	50.33 ± 46.21	93.25 ± 60.68	42.18 ± 37.69	41.27 ± 38.00
TST (hour)	4.01 ± 1.10	5.43 ± 1.17	5.29 ± 1.34	3.84 ± 1.11	6.02 ± 1.42	5.84 ± 1.35
Sleep efficiency	5.07 ± 1.15	3.17 ± 1.73	3.32 ± 1.83	5.25 ± 0.91	2.15 ± 1.75	2.43 ± 1.82
Sleep quality	5.20 ± 0.88	3.18 ± 1.55	3.55 ± 1.53	5.23 ± 0.79	2.67 ± 1.54	2.45 ± 1.78
Daily disturbances	3.50 ± 1.13	2.23 ± 1.43	2.53 ± 1.26	3.37 ± 1.31	1.30 ± 0.83	1.52 ± 1.08
Clinical Symptoms						
HAMD score	6.57 ± 3.33	2.45 ± 2.32	2.60 ± 2.76	7.13 ± 3.60	3.22 ± 2.91	2.42 ± 2.69
HAMA score	6.63 ± 5.92	3.22 ± 4.29	3.07 ± 3.34	7.25 ± 6.84	3.58 ± 4.14	3.12 ± 3.97
Functional Outcome						
CGI-SI	4.15 ± 1.01	2.97 ± 1.19	3.15 ± 1.46	4.05 ± 0.93	2.17 ± 1.46	2.12 ± 1.55
CGI-GI	–	2.63 ± 0.92	3.08 ± 1.01	–	1.90 ± 1.00	2.33 ± 1.28
CGI-EI	–	2.38 ± 0.92	2.00 ± 0.92	–	3.08 ± 0.96	2.72 ± 1.17

PSQI, Pittsburgh Sleep Quality Index; SOL, sleep onset latency; TST, total sleep time; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; CGI-SI, Clinical Global Impression Scale severity of illness; CGI-GI, Clinical Global Impression Scale global improvement; CGI-EI, Clinical Global Impression Scale efficacy index.

Table 3
Results of the mixed models analyses.

Cognitive Outcome	Interaction test	Group effect (excluding non-significant interaction)	Estimated advantage to tACS (no. of points on the scale)/ 95% Confidence Interval	Effect Size (95% Confidence Interval)
PSQI				
PSQI total score	F (1,118) = 1.54; P = 0.217	F (1,117) = 20.63; P < 0.001	2.61(1.47–3.75)	0.76(0.43–1.09)
SOL (min)	F (1,118) = 0.13; P = 0.722	F (1,117) = 3.44; P = 0.066	11.15(-0.76 to 23.06)	0.29(-0.02 to 0.60)
TST (hour)	F (1,118) = 0.07; P = 0.797	F (1,117) = 10.04; P = 0.002	−0.65(-1.06 to −0.24)	−0.54(-0.88 to −0.20)
Sleep efficiency	F (1,118) = 0.31; P = 0.580	F (1,117) = 13.27; P < 0.001	1.05(0.48–1.62)	0.62(0.28–0.95)
Sleep quality	F (1,118) = 6.21; P = 0.014	F (1,117) = 9.46; P = 0.003	0.82(0.29–1.34)	0.51(0.18–0.84)
Daily disturbances	F (1,118) = 0.18; P = 0.672	F (1,117) = 29.78; P < 0.001	0.91(0.58–1.25)	0.86(0.55–1.17)
Clinical Symptoms				
HAMD score	F (1,118) = 4.58; P = 0.034	F (1,117) = 0.22; P = 0.643	−0.20(-1.04 to 0.65)	−0.08(-0.40 to 0.25)
HAMA score	F (1,118) = 0.21; P = 0.652	F (1,117) = 0.00; P = 0.964	−0.02(-1.12 to 1.07)	−0.01(-0.31 to 0.30)
Functional Outcome				
CGI-SI	F (1,118) = 1.66; P = 0.200	F (1,117) = 13.22; P < 0.001	0.84(0.38–1.30)	0.61(0.28–0.95)
CGI-GI	F (1,118) = 0.01; P = 0.933	F (1,118) = 20.44; P < 0.001	0.74(0.42–1.06)	0.70(0.39–1.00)
CGI-EI	F (1,118) = 0.01; P = 0.925	F (1,118) = 19.97; P < 0.001	−0.71(-1.02 to −0.39)	−0.71(-1.02 to −0.39)

PSQI, Pittsburgh Sleep Quality Index; SOL, sleep onset latency; TST, total sleep time; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; CGI-SI, Clinical Global Impression Scale severity of illness; CGI-GI, Clinical Global Impression Scale global improvement; CGI-EI, Clinical Global Impression Scale efficacy index.
General linear mixed models (GLM) were used for efficacy analysis and exploration of secondary outcomes, and baseline values of the outcome measure were included as covariates. The group effect was interpreted as an overall effect of tACS across both post-treatment and follow-up. A significant interaction (group × time) indicated a differential effect of treatment at post-treatment and follow-up.

et al., 2010). tACS may regulate the abnormal levels of neurotransmitters in insomnia patients, such as serotonin and norepinephrine, to normalize the neuroendocrine levels in the patient's body and achieve corresponding therapeutic effects (Strüber et al., 2015; Gabis et al., 2009).

In addition, tACS demonstrated a significant direct effect on functional outcomes, primarily manifested by the reduction in disease severity assessed using the CGI scale. However, although both groups showed improvement in clinical symptoms, such as anxiety and depression, no significant effect of tACS on these symptoms was observed. This finding is similar to that of a previous study (Motamedi et al., 2022). A potential explanation for the lack of a direct effect of tACS on anxiety and depression could be the relatively low baseline levels of these symptoms in the patients. Due to the floor effect, tACS did not yield clinically significant effects on anxiety and depression.

In terms of age-related differences, we observed the benefits of tACS on sleep quality, sleep efficiency, PSQI total score, CGI-SI, CGI-GI, and CGI-EI among participants aged >50 years, whereas no significant treatment effect was found in younger participants. Similarly, another study found significant improvements in PSQI scores and blood cortisol levels in insomnia patients over 60 years of age who received Low-Frequency Transcutaneous Electric Nerve Stimulation (LF-TENS), but not in the younger group (Lee et al., 2022). This disparity might be attributed to the natural changes in sleep physiology that occur with

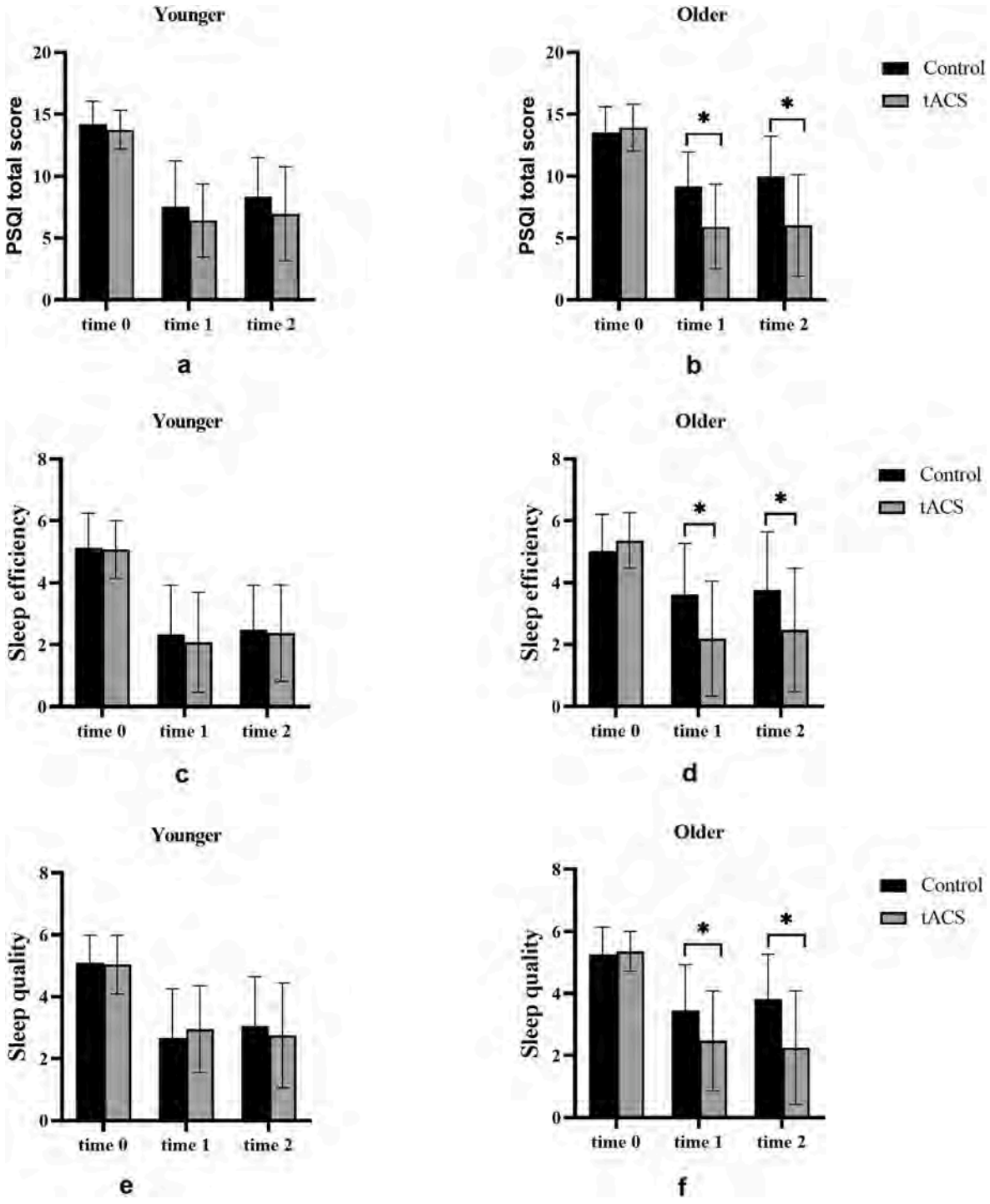

Fig. 2. Effects of tACS on PSQI total score, sleep efficiency, and sleep quality in the older and younger groups.
Note: *$P < 0.001$, compared to the control group. Time 0 = Baseline; time 1 = Post-treatment; time 2 = Follow-up.

aging and the distinct manifestations of insomnia symptoms in older individuals. Sleep quality tends to decrease with age (Ohayon et al., 2004). The natural deterioration of sleep in older adults can lead to anxiety about sleep and the development of dysfunctional sleep habits, resulting in poorer subjective sleep quality and more severe sleep complaints. In our study, the PSQI, used to evaluate sleep quality, was a subjective evaluation scale that could be influenced by patients' subjective feelings. Therefore, the beneficial effects of tACS in older patients with insomnia may be attributed to their elevated levels of sleep-related anxiety and stress responses, which could be potentially higher than those observed in their younger counterparts. Similarly, participants aged >50 years demonstrated the benefits of tACS as indicated by improvements on the CGI scale, which is also a subjective evaluation. In addition, the improvement in insomnia observed in older patients following LF-TENS was suggested to be related to the regulation of hypothalamic-pituitary-adrenal axis activity (Lee et al., 2022). Future research should incorporate various biological indicators to explore the physiological mechanism underlying age-related differences in the therapeutic effect of tACS in patients with insomnia.

Previous studies have shown that insomnia symptoms have a

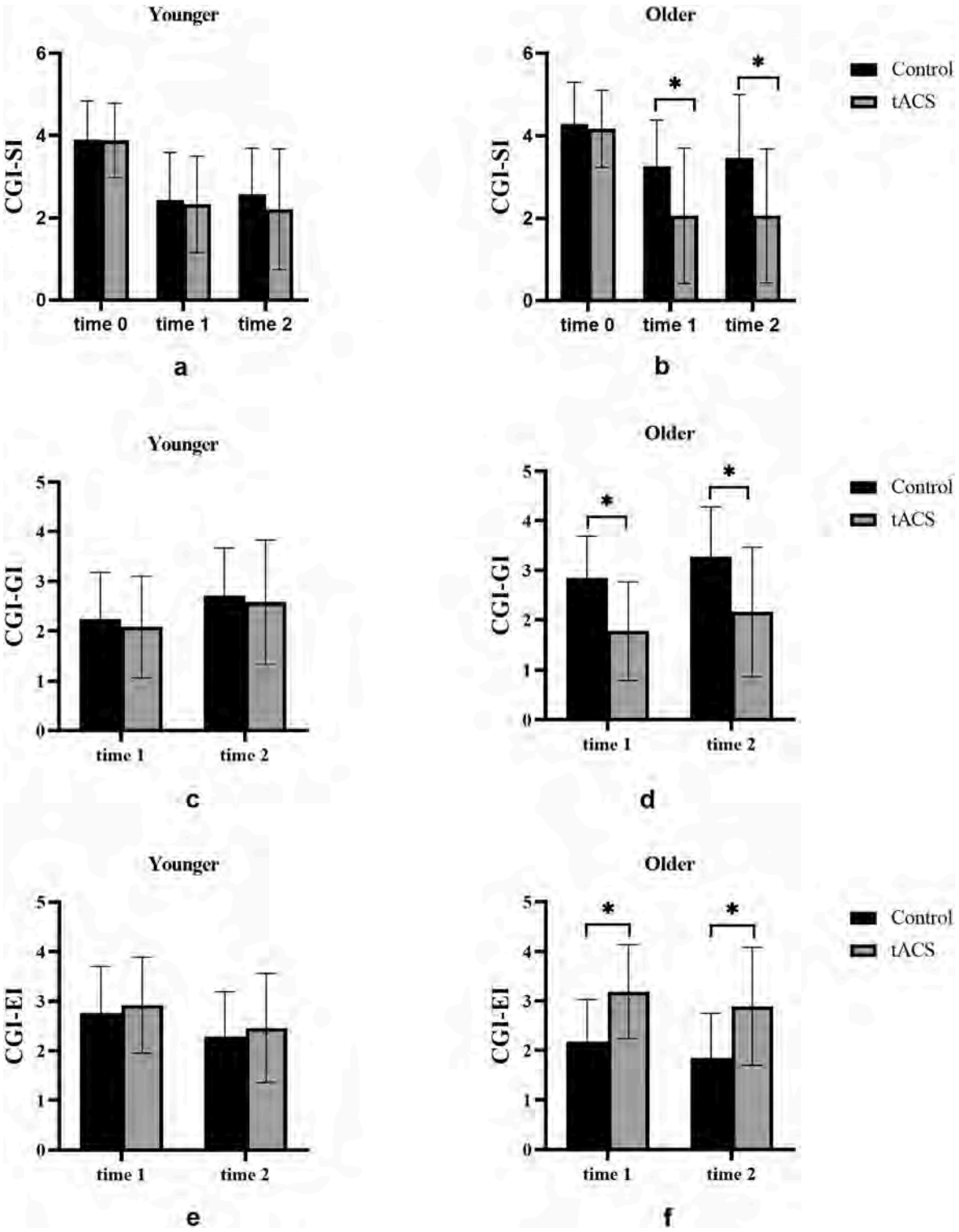

Fig. 3. Effects of tACS on CGI scales in the older and younger groups.
Note: *$P < 0.001$, compared to the control group. Time 0 = Baseline; time 1 = Post-treatment; time 2 = Follow-up.

bidirectional relationship with affective disorders and contribute to the development and maintenance of depressive and anxiety symptoms, and treating insomnia can improve depressive and anxiety symptoms (Hertenstein et al., 2019; Scott et al., 2021). Consistent with these findings, we observed a similar positive correlation between the improvement of depressive and anxiety symptoms and the amelioration of insomnia, regardless of whether participants received tACS. Some studies suggested that insomnia may have similar underlying neural mechanisms to depression and anxiety. Chronic insomnia and depression both exhibit structural abnormalities in brain regions such as the frontal lobe, parietal lobe, thalamus, striatum, and hippocampus, which are closely related to sleep and emotional regulation in physiology (Falgàs et al., 2021; Hong et al., 2021; Bresser et al., 2020). Another study found that insomnia can lead to a decrease or imbalance in circadian rhythms, thereby reducing connectivity between the prefrontal cortex and amygdala, leading to emotional regulation disorders (Gruber and

Cassoff, 2014). An imaging study suggested that the decrease in top-down control of the amygdala is neurobiological evidence for the role of sleep abnormalities in the pathogenesis of anxiety (Pace-Schott et al., 2017). However, there is still much uncertainty regarding the exact neural mechanisms underlying insomnia, anxiety, and depression. Further experiments are warranted.

This study has some limitations. First, the follow-up period was limited to 8 weeks; thus, longer follow-up studies are necessary to explore the sustained effects of tACS on chronic insomnia. Second, the severity of chronic insomnia was determined using PSQI. Future research can enhance the assessment of insomnia severity by incorporating the insomnia severity index, polysomnography, and wrist actigraphy. These objective measures of sleep parameters can provide a more comprehensive evaluation and help determine how tACS improves circadian rhythm sleep-wake disorders, which may underlie the symptoms of chronic insomnia. In this study, the average age of the patients we enrolled was 50.59 years old, ranging from 22 to 65 years old, and we observed the benefits of tACS on insomnia participants aged >50 years. In future research, participants with a wider age range can be enrolled to explore the therapeutic effects of tACS on patients of different age groups.

5. Conclusions

This study demonstrated the effectiveness of tACS as an intervention for chronic insomnia and identified the role of age in treatment response using a large sample from two centers. These significant findings contribute substantially to promoting evidence-based practices and facilitating the development of innovative treatment strategies for chronic insomnia.

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6. Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Xiaolin Zhu: Data curation, Writing – original draft, Writing – review & editing. **Yanping Ren:** Data curation, Investigation, Methodology, Conceptualization, Project administration. **Shuping Tan:** Formal analysis, Writing – original draft, Writing – review & editing. **Xin Ma:** Conceptualization, Funding acquisition, Project administration, Resources.

Declaration of competing interest

No competing interests were disclosed for each author.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2023.12.037.

References

American Psychiatric Association, 2010. Diagnostic and Statistical Manual of Mental Disorders, fourth ed. American Psychiatric Association, Washington, DC.

Annarumma, L., D'Atri, A., Alfonsi, V., De Gennaro, L., 2018. The efficacy of transcranial current stimulation techniques to modulate resting-state EEG, to affect Vigilance and to Promote sleepiness. Brain Sci. 8 https://doi.org/10.3390/brainsci8070137.

Antal, A., Alekseichuk, I., Bikson, M., Brockmöller, J., Brunoni, A.R., Chen, R., Cohen, L. G., Dowthwaite, G., Ellrich, J., Flöel, A., Fregni, F., George, M.S., Hamilton, R., Haueisen, J., Herrmann, C.S., Hummel, F.C., Lefaucheur, J.P., Liebetanz, D., Loo, C. K., McCaig, C.D., Miniussi, C., Miranda, P.C., Moliadze, V., Nitsche, M.A., Nowak, R., Padberg, F., Pascual-Leone, A., Poppendieck, W., Priori, A., Rossi, S., Rossini, P.M., Rothwell, J., Rueger, M.A., Ruffini, G., Schellhorn, K., Siebner, H.R., Ugawa, Y., Wexler, A., Ziemann, U., Hallett, M., Paulus, W., 2017. Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. Clin. Neurophysiol.: official journal of the International Federation of Clinical Neurophysiology 128, 1774–1809. https://doi.org/10.1016/j.clinph.2017.06.001.

Antonenko, D., Diekelmann, S., Olsen, C., Born, J., Mölle, M., 2013. Napping to renew learning capacity: enhanced encoding after stimulation of sleep slow oscillations. Eur. J. Neurosci. 37, 1142–1151. https://doi.org/10.1093/sleep/zsaa031.

Bresser, T., Foster-Dingley, J.C., Wassing, R., et al., 2020. Consistent altered internal capsule white matter microstructure in insomnia disorder. Sleep 43 (8). https://doi.org/10.1093/sleep/zsaa031.

Buysse, D.J., 2013. Insomnia. JAMA 309, 706–716. https://doi.org/10.1001/jama.2013.193.

Buysse, D.J., Reynolds 3rd, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatr. Res. 28, 193–213. https://doi.org/10.1016/0165-1781(89)90047-4.

D'Atri, A., De Simoni, E., Gorgoni, M., Ferrara, M., Ferlazzo, F., Rossini, P.M., De Gennaro, L., 2016. Electrical stimulation of the frontal cortex enhances slow-frequency EEG activity and sleepiness. Neuroscience 324, 119–130. https://doi.org/10.1016/j.neuroscience.2016.03.007.

Falgàs, N., Illán-Gala, I., Allen, I.E., et al., 2021. Specific cortical and subcortical grey matter regions are associated with insomnia severity. PLoS One 16 (5), e0252076. https://doi.org/10.1371/journal.pone.0252076.

Feusner, J.D., Madsen, S., Moody, T.D., Bohon, C., Hembacher, E., Bookheimer, S.Y., Bystritsky, A., 2012. Effects of cranial electrotherapy stimulation on resting state brain activity. Brain and behavior 2, 211–220. https://doi.org/10.1002/brb3.45.

Gabis, L., Shklar, B., Baruch, Y.K., Raz, R., Gabis, E., Geva, D., 2009. Pain reduction using transcranial electrostimulation: a double blind "active placebo" controlled trial. J. Rehabil. Med. 41 (4), 256–261. https://doi.org/10.2340/16501977-0315.

Gruber, R., Cassoff, J., 2014. The interplay between sleep and emotion regulation: conceptual framework empirical evidence and future directions. Curr. Psychiatr. Rep. 16 (11), 500. https://doi.org/10.1007/s11920-014-0500-x.

Hertenstein, E., Feige, B., Gmeiner, T., Kienzler, C., Spiegelhalder, K., Johann, A., Jansson-Fröjmark, M., Palagini, L., Rücker, G., Riemann, D., Baglioni, C., 2019. Insomnia as a predictor of mental disorders: a systematic review and meta-analysis. Sleep Med. Rev. 43, 96–105. https://doi.org/10.1016/j.smrv.2018.10.006.

Hong, W., Li, M., Liu, Z., et al., 2021. Heterogeneous alterations in thalamic subfields in major depression disorder. J. Affect. Disord. 295, 1079–1086. https://doi.org/10.1016/j.jad.2021.08.115.

Huedo-Medina, T.B., Kirsch, I., Middlemass, J., Klonizakis, M., Siriwardena, A.N., 2012. Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. BMJ Br. Med. J. (Clin. Res. Ed.) 345, e8343. https://doi.org/10.1016/j.smrv.2009.07.004.

Kyle, S.D., Morgan, K., Espie, C.A., 2010. Insomnia and health-related quality of life. Sleep Med. Rev. 14, 69–82. https://doi.org/10.1016/j.smrv.2009.07.004.

Lande, R.G., Gragnani, C., 2013. Efficacy of cranial electric stimulation for the treatment of insomnia: a randomized pilot study. Compl. Ther. Med. 21, 8–13. https://doi.org/10.1016/j.ctim.2012.11.007.

Lebedev, V.P., Malygin, A.V., Kovalevski, A.V., Rychkova, S.V., Sisoev, V.N., Kropotov, S. P., Krupitski, E.M., Gerasimova, L.I., Glukhov, D.V., Kozlowski, G.P., 2002. Devices for noninvasive transcranial electrostimulation of the brain endorphinergic system: application for improvement of human psycho-physiological status. Artif. Organs 26, 248–251. https://doi.org/10.1046/j.1525-1594.2002.06944.x.

Lee, H.J., Hong, J.K., Choi, H., Chung, S., Yoon, I.Y., 2022. Age-limited effects of low-frequency transcutaneous electric Nerve stimulation on insomnia: a 4-week multi-center, randomized controlled study. Psychiatry investigation 19, 451–461. https://doi.org/10.30773/pi.2021.0374.

Lu T, L.Y., Xia P, Z.G., Wu, D., 2014. Analysis on reliability and validity of the Pittsburgh sleep quality index. Chongqing Med 43, 260–263. https://doi.org/10.3969/j.issn.1671-8348.2014.03.002.

Luca, G., Haba Rubio, J., Andries, D., et al., 2015. Age and gender variations of sleep in subjects without sleep disorders. Ann. Med. 47 (6), 482–491. https://doi.org/10.3109/07853890.2015.1074271.

Lustenberger, C., Boyle, M.R., Alagapan, S., Mellin, J.M., Vaughn, B.V., Fröhlich, F., 2016. Feedback-controlled transcranial alternating current stimulation reveals a functional role of sleep spindles in motor memory consolidation. Curr. Biol.: CB 26, 2127–2136. https://doi.org/10.1016/j.cub.2016.06.044.

Madrid-Valero, J.J., Martínez-Selva, J.M., Ribeiro do Couto, B., Sánchez-Romera, J.F., Ordoñana, J.R., 2017. Age and gender effects on the prevalence of poor sleep quality in the adult population. Gac. Sanit. 31 (1), 18–22. https://doi.org/10.1016/j.gaceta.2016.05.013.

Matsumoto, H., Ugawa, Y., 2017. Adverse events of tDCS and tACS: a review. Clinical neurophysiology practice 2, 19–25. https://doi.org/10.1016/j.cnp.2016.12.003.

Medalie, L., Cifu, A.S., 2017. Management of chronic insomnia disorder in adults. JAMA 317, 762–763. https://doi.org/10.1001/jama.2016.19004.
Morin, C.M., Benca, R., 2012. Chronic insomnia. Lancet 379, 1129–1141. https://doi.org/10.1016/S0140-6736(11)60750-2.
Motamedi, G.K., Jeliazkov, P.G., Oyegbile-Chidi, T.O., Song, S.S., Sharma, V.D., Mete, M., Shara, N., Turkeltaub, P.E., Cho, Y.W., Wu, J.Y., 2022. Transcranial alternating current stimulation (tACS) as a treatment for insomnia. Can. J. Neurol. Sci. 1–14, 1-14.10.1017/cjn.2022.33.
Ohayon, M.M., Carskadon, M.A., Guilleminault, C., Vitiello, M.V., 2004. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 27, 1255–1273. https://doi.org/10.1093/sleep/27.7.1255.
Pace-Schott, E.F., Zimmerman, J.P., Bottary, R.M., Lee, E.G., Milad, M.R., Camprodon, J. A., 2017. Resting state functional connectivity in primary insomnia, generalized anxiety disorder and controls. Psychiatry Res. Neuroimaging. 265, 26–34. https://doi.org/10.1016/j.pscychresns.2017.05.003.
Qaseem, A., Kansagara, D., Forciea, M.A., Cooke, M., Denberg, T.D., Clinical Guidelines Committee of the American College of Physicians, 2016. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American college of physicians. Ann. Intern. Med. 165 (2), 125–133. https://doi.org/10.7326/M15-2175.
Riemann, D., Baglioni, C., Bassetti, C., et al., 2017. European guideline for the diagnosis and treatment of insomnia. J. Sleep Res. 26 (6), 675–700. https://doi.org/10.1111/jsr.12594.
Riemann, D., Nissen, C., Palagini, L., Otte, A., Perlis, M.L., Spiegelhalder, K., 2015. The neurobiology, investigation, and treatment of chronic insomnia. Lancet Neurol. 14, 547–558. https://doi.org/10.1016/S1474-4422(15)00021-6.
Riemann, D., Spiegelhalder, K., Feige, B., et al., 2010. The hyperarousal model of insomnia: a review of the concept and its evidence. Sleep Med. Rev. 14 (1), 19–31. https://doi.org/10.1016/j.smrv.2009.04.002.
Scott, A., Webb, T., Martyn-St James, M., Rowse, G., Weich, S., 2021. Does improving sleep lead to better mental health? A meta-analysis of randomised controlled trials. Sleep Med. Rev. https://doi.org/10.1136/bmjopen-2017-016873.
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatr. 59 (Suppl. 20), 22–33 quiz 34-57.
Shekelle P, C.I., Miake-Lye Im, M.S., 2018. VA Evidencebased Synthesis Program Reports; the Effectiveness and Risks of Cranial Electrical Stimulation for the Treatment of Pain, Depression, Anxiety, PTSD, and Insomnia: a Systematic Review. Department of Veterans Affairs, Washington (DC).US.
Siengsukon, C.F., Nelson, E., Williams-Cooke, C., Ludwig, R., Beck Jr., E.S., Vidoni, E.D., Mahnken, J.D., Stevens, S., Drerup, M., Bruce, J., Burns, J.M., 2020. Cognitive behavioral therapy for insomnia to enhance cognitive function and reduce the rate of Aβ deposition in older adults with symptoms of insomnia: a single-site randomized pilot clinical trial protocol. Contemp. Clin. Trials 99, 106190. https://doi.org/10.1016/j.cct.2020.106190.
Strüber, D., Rach, S., Neuling, T., Herrmann, C.S., 2015. On the possible role of stimulation duration for after-effects of transcranial alternating current stimulation. Front. Cell. Neurosci. 9, 311. https://doi.org/10.3389/fncel.2015.00311.
Thomas, A., Grandner, M., Nowakowski, S., Nesom, G., Corbitt, C., Perlis, M.L., 2016. Where are the behavioral sleep medicine providers and where are they needed? A geographic assessment. Behav. Sleep Med. 14 (6), 687–698. https://doi.org/10.1080/15402002.2016.1173551.
Trauer, J.M., Qian, M.Y., Doyle, J.S., Rajaratnam, S.M., Cunnington, D., 2015. Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. Ann. Intern. Med. 163, 191–204. https://doi.org/10.7326/M14-2841.
van Straten, A., Cuijpers, P., 2009. Self-help therapy for insomnia: a meta-analysis. Sleep Med. Rev. 13 (1), 61–71. https://doi.org/10.1016/j.smrv.2008.04.006.
Wong, S.Y., Zhang, D.X., Li, C.C., Yip, B.H., Chan, D.C., Ling, Y.M., Lo, C.S., Woo, D.M., Sun, Y.Y., Ma, H., Mak, W.W., Gao, T., Lee, T.M., Wing, Y.K., 2017. Comparing the effects of mindfulness-based cognitive therapy and sleep psycho-education with exercise on chronic insomnia: a randomised controlled trial. Psychother. Psychosom. 86, 241–253. https://doi.org/10.1159/000470847.
Xu, M., Bélanger, L., Ivers, H., Guay, B., Zhang, J., Morin, C.M., 2011. Comparison of subjective and objective sleep quality in menopausal and non-menopausal women with insomnia. Sleep Med. 12, 65–69. https://doi.org/10.1016/j.sleep.2010.09.003.
Zheng, W., Lan, X.J., Qin, Z.J., Ungvari, G.S., Xiang, Y.T., 2023. Transcranial alternating current stimulation for chronic insomnia: a systematic review. Asian journal of psychiatry 82, 103477. https://doi.org/10.1016/j.ajp.2023.103477.