Check for updates

*Research article*

Journal of Alzheimer's Disease
1–9
© The Author(s) 2026
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/13872877261492561
journals.sagepub.com/home/alz

# High-intensity transcranial alternating current stimulation improves sleep quality in patients with mild Alzheimer's disease: Findings from the TRANSFORM-AD study

**Yuchen Qiao[1], Hong Chen[1], Kaiting Fan[1], Xuan Yang[1], Yueyi Yu[2], Rui Wang[1], Yi Xing[2,*] and Yi Tang[2,*]**

## Abstract

**Background:** High-intensity transcranial alternating current stimulation (Hi-tACS) has shown beneficial effects on cognitive function in Alzheimer's disease (AD). However, data on the effects of hi-tACS on sleep quality and emotional state in patients with AD are still limited.

**Objective:** This study aimed to investigate the influences of hi-tACS on sleep quality and emotional state in AD.

**Methods:** The TRANSFORM-AD study was a double-blind, randomized-controlled trial that enrolled individuals with mild AD. Participants were randomized to receive hi-tACS group or sham stimulation group, and underwent 30 one-hour sessions of either 40 Hz tACS or sham stimulation over consecutive 15 consecutive days. Pittsburgh sleep quality index (PSQI), Hamilton anxiety Rating Scale (HAMA), Hamilton depression Rating Scale (HAMD) and Quality of life in Alzheimer's Disease scale (QOL-AD) were evaluated at baseline, and the end of the intervention.

**Results:** Among 43 participants with complete baseline and post-intervention assessments, Hi-tACS reduced post-intervention PSQI scores compared with sham after adjustment for baseline PSQI (adjusted mean difference, −2.34 points; 95% CI, −3.63 to −1.05; $p < 0.001$). Baseline-adjusted effects for HAMA (−1.43; 95% CI, −2.89 to 0.02), HAMD (0.44; 95% CI, −1.28 to 2.15), and QOL-AD (2.07; 95% CI, −1.57 to 5.70) were imprecise and included the null.

**Conclusion:** Hi-tACS improved subjective sleep quality in patients with mild AD. The present secondary analysis did not provide conclusive evidence of effects on anxiety, depression, or quality of life; these exploratory outcomes require confirmation in larger, adequately powered trials.

**Trial registration:** ClinicalTrials.gov, NCT 03920826.

## Keywords

Alzheimer's disease, anxiety, depression, sleep disorder, transcranial alternating current stimulation

Received: 5 May 2026; accepted: 18 August 2026

[1]Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China
[2]Department of Neurology & Innovation Center for Neurological Disorders, Xuanwu Hospital, National Center for Neurological Disorders, Capital Medical University, Beijing, China

*These authors contributed equally to this work.

**Corresponding authors:**
Yi Xing, Department of Neurology & Innovation Center for Neurological Disorders, Xuanwu Hospital, National Center for Neurological Disorders, Capital Medical University, Beijing China.
Email: xingyi_211@163.com
Yi Tang, Department of Neurology & Innovation Center for Neurological Disorders, Xuanwu Hospital, National Center for Neurological Disorders, Capital Medical University, Beijing China.
Email: tangyi@xwhosp.org

## Introduction

Alzheimer's disease (AD), the most prevalent form of dementia, is an irreversible and progressive neurodegenerative disorder. According to the World Health Organization (WHO) 2021 report, AD ranks as the seventh leading cause of death globally.[1] Furthermore, global dementia prevalence is predicted to triple, increasing from 57.4 million cases in 2019 to 152.8 million by 2050,[2] which will impose a substantial socioeconomic and healthcare burden.

Sleep disorders are commonly reported non-cognitive symptoms in patients with AD. Approximately 45% of individuals with AD experience sleep-related issues, such as insomnia, sleep fragmentation, and excessive daytime sleepiness.[3] Accumulating evidence supports a bidirectional relationship between sleep disorders and AD pathology.[4–6] Neuropsychiatric symptoms such as anxiety and depression are commonly observed during the clinical course of the illness. In AD, the prevalence of anxiety ranges from 9.4% (preclinical phase) to 39% (from mild to severe decline) and the prevalence of depression in mild-to-moderate AD varies from 14.8% to 40%.[7] Notably, anxiety and depression have been identified as critical mediators in the association between poor sleep quality and elevated risk of cognitive impairment.[8] Therefore, interventions that improve sleep quality and psychological well-being may play a crucial role in improving the overall quality of life and delaying disease progression in patients with AD.

In AD, disruption of neural oscillations leads to impaired gamma oscillations-dominated activity and following memory and cognitive deficits.[9] Gamma oscillations are also implicated in the regulation of sleep-wake cycles as well as in the modulation of mood states such as anxiety and depression.[10,11] Re-synchronization of these disturbed oscillations may represent a putative therapeutic mechanism for ameliorating sleep disorders and anxiety/depression in AD patients.[12] Transcranial alternating current stimulation (tACS), a non-invasive neuromodulatory technique, achieves frequency-dependent synchronization of endogenous neural oscillations via phase-resonant interactions with cortical networks.[13] In recent years, 40 Hz gamma stimulation has garnered significant attention within the field of AD research. It has been demonstrated to enhance cognitive functions, particularly memory capabilities, in patients with AD.[14,15] In addition to frequency, current intensity is also a critical determinant of clinical outcomes. The conventional tACS current range is 1–4 mA (peak-to-peak), while "high-intensity" typically refers to >7 mA.[13] The brain-wide activation induced by high-intensity tACS can effectively reach deep brain structures, rendering it a promising potential approach for the treatment of neuropsychiatric disorders.[16] Previous studies have demonstrated that 77.5 Hz hi-tACS not only improves sleep quality in patients with chronic insomnia but also alleviates depressive symptoms in patients with major depressive disorder, which validates the safety and efficacy of hi-tACS.[17,18]

The TRANSFORM-AD study is a randomized double-blind controlled trial investigating the effects of 40 Hz hi-tACS on AD.[19] Our preliminary results have already demonstrated improvements in AD cognitive function and enhanced theta-gamma coupling strength in the hippocampal region.[20] However, the potential relationship between 40 Hz stimulation and sleep or mood in AD patients is not yet clear. Consequently, this research analysis aims to investigate the potential role of 40 Hz hi-tACS in modulating sleep, anxiety and depression symptoms, utilizing data from the TRANSFORM-AD study.

## Methods

### *Study design and participants*

We used data from the TRANSFORM-AD study (ClinicalTrials.gov identifier NCT 03920826), which recruited 46 patients with probable AD dementia who met NIA-AA core clinical criteria. In this study, a total of 43 patients were included in this analysis. The detailed trial design and primary results have been previously published.[19,20] This study adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines and its extension for non-pharmacological interventions (CONSORT-NPT).

### *Trial protocol*

Participants were randomly allocated (1:1) to receive either hi-tACS or sham stimulation. An independent statistician blinded to the intervention performed the random allocation of patients using the random number table method in SAS software.

Research nurses opened opaque sealed envelopes to obtain the group allocation code for each participant prior to the first intervention. This process did not unblind the study; participants, caregivers, outcomes assessors and research nurses remained blinded to group assignments throughout the trial.

Research nurses administered stimulation using the NEXALIN ADI transcranial alternating current stimulator or sham stimulator, with electrodes placed on the participants' forehead and bilateral mastoid regions. In the hi-tACS group, participants received 30 one-hour stimulation sessions at a frequency of 40 Hz with a peak-to-peak amplitude of 15 mA across consecutive 15 days (twice a day, intervals of at least 4 h). The sham stimulation group followed the same procedural protocol but received stimulation with zero current output. The hi-tACS and sham stimulation were indistinguishable based on stimulators' appearance or patients' feelings. The details are shown in the published protocol.[19] The flowchart of the study is shown in Figure 1.

Adverse effects will be evaluated after every five sessions via a participant self-report questionnaire. The

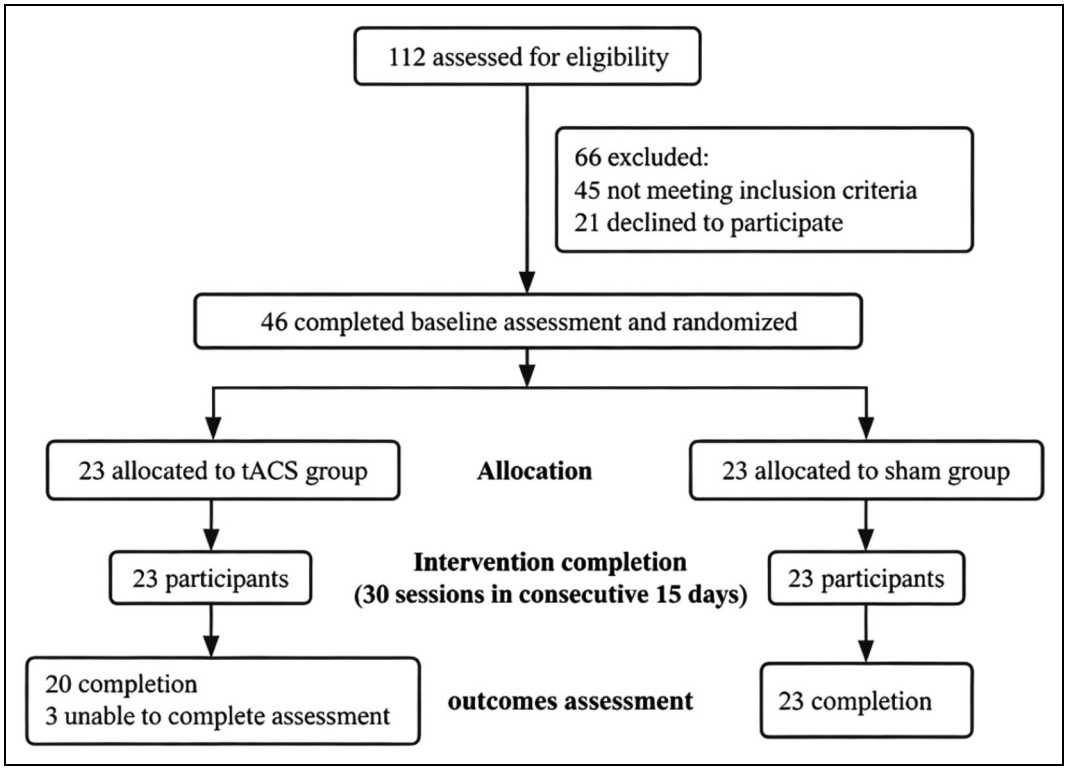


**Figure 1.** The flowchart of our study.

questionnaire covers headache, neck pain, scalp pain, tingling, pruritus, tinnitus/buzzing, burning sensation, erythema, drowsiness, impaired concentration, acute mood fluctuations, dizziness, phosphenes, and other adverse symptoms. Participants score each symptom from 0 to 3 based on occurrence and severity (0 = absent; 1 = mild; 2 = moderate; 3 = severe), and rate the likelihood of symptom association with tACS (0 = no association; 1 = possible; 2 = probable; 3 = definite).

## Outcome measures

Four outcome measures were assessed in this secondary analysis, including the Pittsburgh Sleep Quality Index (PSQI), Hamilton Anxiety Rating Scale (HAMA), Hamilton Depression Rating Scale (HAMD), and Quality of Life–Alzheimer's Disease (QOL-AD). We predefined the PSQI as the primary outcome given its core clinical relevance to the research question, while HAMA, HAMD and QOL-AD were designated as exploratory secondary outcomes. All outcomes were measured at baseline and post-intervention under standardized conditions by blinded assessors.

*Sleep quality evaluation.* Sleep quality was quantified using the validated PSQI, a 19-item multidimensional instrument assessing seven clinical domains: 1) sleep quality, 2) sleep latency, 3) sleep duration, 4) sleep medication, 5) sleep disturbances, 6) daytime dysfunction, and 7) habitual sleep efficiency. A 4-point scale was employed (0 = no difficulty; 3 = severe difficulty), yielding a global score range of 0–21. Higher composite scores reflect greater sleep impairment.[21]

*Anxiety assessment.* Anxiety was measured through the HAMA, comprising 14-item clinician-rated items across psychic subscale (Items 1–6, 14, cognitive and affective components, e.g., anxious mood, tension, fears, difficulty concentrating) and somatic subscale (Items 7–13, autonomic/physiological manifestations, such as autonomic arousal, respiratory, gastrointestinal and cardiovascular symptoms). Each item employs a 5-point Likert scale (0 = absent; 4 = disabling), with total scores categorizing anxiety severity (≥29: severe anxiety, 21–28: marked anxiety, 14–20: moderate anxiety, 8–13: mild anxiety, ≤7: non-clinical range). The total anxiety score ranges from 0 to 56.[22]

## Depression assessment

Depression was evaluated using the 24-item HAMD, a clinician-administered instrument assessing affective, cognitive and somatic symptoms. Each item is scored on a Likert scale, with response options of 0–4 (absent, mild, moderate, to severe) or 0–2 (absent, slight or trivial, to clearly present). Total scores were interpreted as follows:

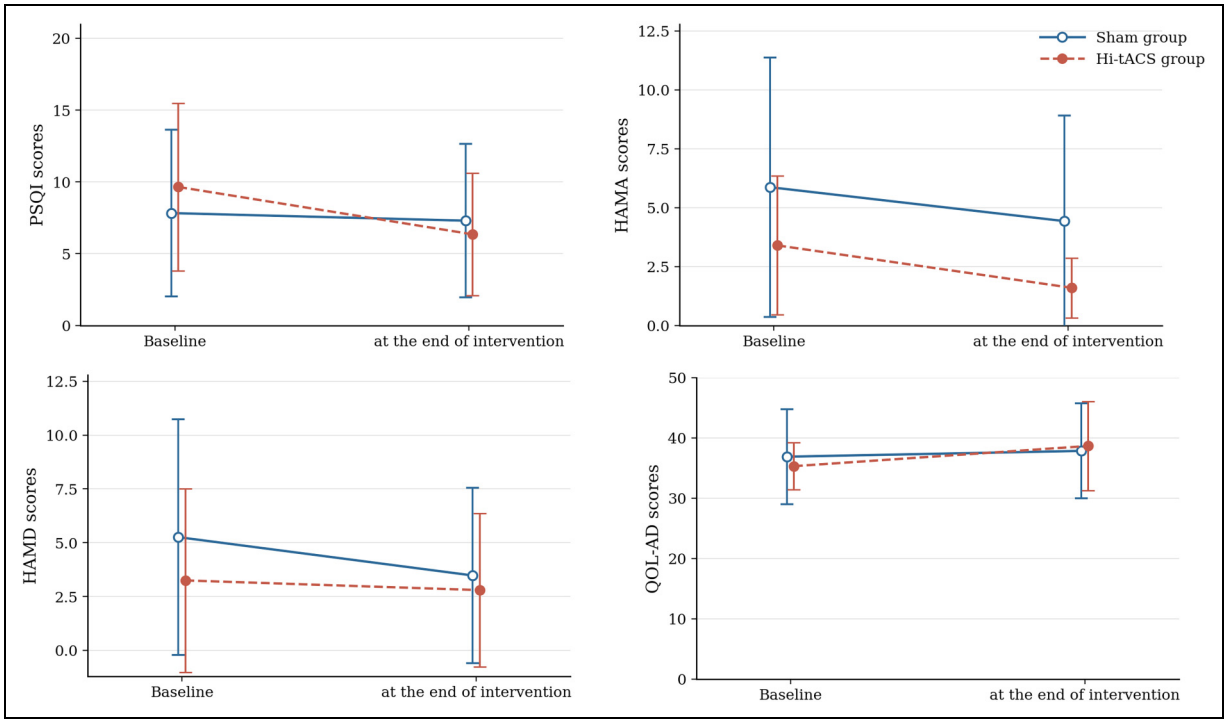


**Figure 2.** Change in outcome assessment over intervention period.

≥35 indicated severe depression,20–34 suggested mild or moderate depression, and scores ≤7 were considered within the normal range.[23]

## *Quality of life assessment*

QoL was assessed using the 13-item QOL-AD, with total scores ranging from 13 to 52 (higher scores indicating better QoL). This scale evaluates a variety of domains (physical health, mood, relationships, activities, and ability to complete tasks) on a 4-point ordinal scale (1 = poor to 4 = excellent). Both patients' self-reports and caregivers' proxy-assessment were obtained. A composite weighted total score was calculated as follows: Weighted QOL-AD score = (patient-assessed score × 2 + caregiver-assessed score)/3.[24]

## *Statistical analysis*

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). The analysis population comprised participants with both baseline and post-intervention outcome assessments (complete-case population). Continuous variables are summarized as mean ± standard deviation (SD), and categorical variables as number and percentage. Baseline characteristics were described using standardized mean differences (SMDs), without relying on baseline significance tests to establish comparability. The PSQI was prespecified as the primary outcome; HAMA, HAMD, and QOL-AD were exploratory secondary outcomes.

For each outcome, the primary treatment effect was estimated using analysis of covariance (ANCOVA), with the post-intervention score as the dependent variable, treatment group (Hi-tACS vs sham) as a between-subjects fixed effect, and the corresponding baseline score as a continuous covariate. The estimand was the baseline-adjusted mean difference at the end of intervention (Hi-tACS minus sham), reported with a two-sided 95% confidence interval (CI) and p value. Model assumptions were evaluated using residual-versus-fitted and normal Q–Q plots, the Shapiro–Wilk test of residual normality, Levene's test of homogeneity of residual variance, and a treatment-by-baseline interaction test for homogeneity of regression slopes. Models allowing separate baseline slopes by treatment group, empirical-sandwich standard errors, and 2000-replicate nonparametric bootstrap percentile CIs with resampling stratified by treatment group were examined as sensitivity analyses when assumptions were questionable.

A mixed model for repeated measures (MMRM) was additionally fitted as a sensitivity analysis. Treatment group was a between-subjects categorical fixed effect, time (baseline and post-intervention) was a within-subjects repeated categorical fixed effect, and the model included treatment, time, treatment-by-time interaction, age, sex, years of education, baseline Mini-Mental State Examination (MMSE), and baseline Montreal Cognitive Assessment (MoCA). Participant was the repeated-

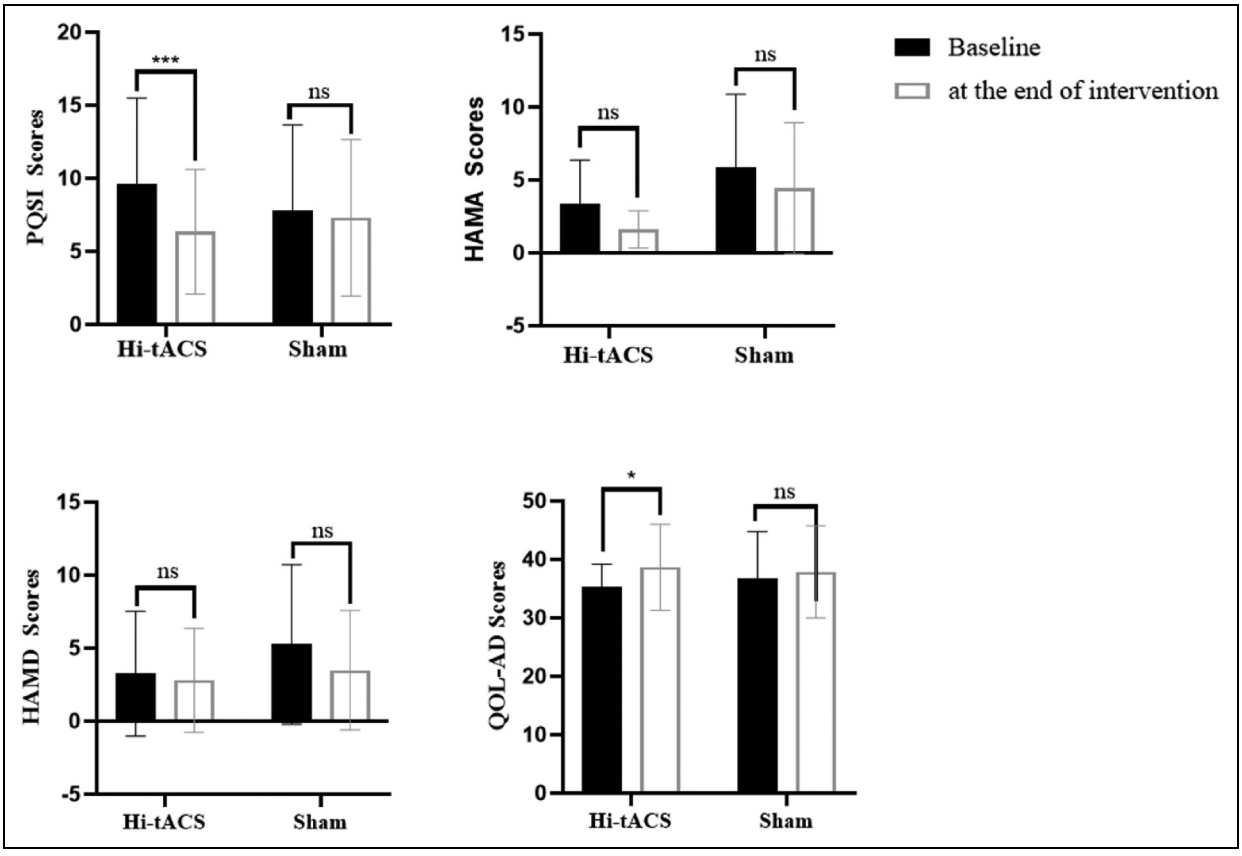


**Figure 3.** Intra-group differences in outcome measures.

measures unit; an unstructured within-participant covariance matrix, restricted maximum likelihood estimation, and Kenward–Roger denominator degrees of freedom were used. No random intercept or random slope was specified. In this model, the treatment-by-time interaction represented the between-group difference in change from baseline.

For descriptive within-group pre–post comparisons, the Wilcoxon signed-rank test was used for paired observations. When change scores were compared nonparametrically between groups, change was first calculated as post-intervention minus baseline and then compared using the Wilcoxon rank-sum (Mann–Whitney U) test. These non-parametric analyses were supplementary and were not used as the primary test of treatment efficacy. All tests were two-sided with $p < 0.05$ denoting statistical significance. Because HAMA, HAMD, and QOL-AD were exploratory, their estimates and 95% CIs were emphasized and no confirmatory claim was based solely on their nominal p values.

## Results

### *Participants and baseline characteristics*

Of the 46 randomized participants, 43 had both baseline and post-intervention assessments and were included in the complete-case analysis (Hi-tACS, $n = 20$; sham, $n = 23$). Three participants randomized to Hi-tACS lacked post-intervention assessments owing to assessor negligence. Baseline characteristics are presented in Table 1. Although age and years of education were similar between groups, several potentially important baseline imbalances were present. Compared with the sham group, the Hi-tACS group had lower MMSE (SMD=−0.565), MoCA (SMD=−0.413), HAMA (SMD=−0.548), and HAMD (SMD=−0.406) scores, and a higher PSQI score (SMD=0.313). These imbalances motivated baseline-adjusted analyses for all outcomes.

### *Baseline-adjusted clinical outcomes*

After adjustment for baseline PSQI, the post-intervention PSQI score was lower in the Hi-tACS group than in the sham group (adjusted mean difference, −2.34 points; 95% CI, −3.63 to −1.05; $p < 0.001$) (Table 2, Figures 2 and 3). This result was consistent after additional adjustment for age, sex, education, MMSE, and MoCA (−2.56; 95% CI, −3.96 to −1.17; $p < 0.001$) and in the MMRM sensitivity analysis of between-group change (treatment-by-time estimate, −2.78; 95% CI, −4.30 to −1.25; $p < 0.001$).

For HAMA, the baseline-adjusted mean difference was −1.43 points (95% CI, −2.89 to 0.02; $p = 0.054$). The

**Table 1.** Baseline demographic and clinical characteristics.

| Characteristic | Hi-tACS (n = 20) | Sham (n = 23) | SMD |
|---|---|---|---|
| Age, years | 65.50 ± 6.00 | 64.96 ± 5.72 | 0.093 |
| Male sex, n (%) | 4 (20.0) | 9 (39.1) | −0.429 |
| Education, years | 10.20 ± 2.97 | 9.91 ± 2.92 | 0.098 |
| MMSE | 19.75 ± 3.37 | 21.74 ± 3.65 | −0.565 |
| MoCA | 15.20 ± 3.68 | 16.87 ± 4.33 | −0.413 |
| PSQI | 9.65 ± 5.84 | 7.83 ± 5.80 | 0.313 |
| HAMA | 3.40 ± 2.95 | 5.87 ± 5.50 | −0.548 |
| HAMD | 3.25 ± 4.27 | 5.26 ± 5.47 | −0.406 |
| QOL-AD | 35.30 ± 3.88 | 36.87 ± 7.90 | −0.247 |

Values are mean ± SD unless otherwise indicated. SMD is calculated as Hi-tACS minus sham; for binary sex, the pooled-proportion standardization was used. Baseline hypothesis tests are omitted because randomization, rather than a nonsignificant p value, establishes the design basis for comparability. MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; PSQI: Pittsburgh Sleep Quality Index; HAMA: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale; QOL-AD: Quality of Life in Alzheimer's Disease.

corresponding effects for HAMD and QOL-AD were 0.44 points (95% CI, −1.28 to 2.15; p = 0.612) and 2.07 points (95% CI, −1.57 to 5.70; p = 0.257), respectively (Table 2). Thus, the primary ANCOVA did not show clear between-group effects on anxiety, depression, or quality of life. The MMRM treatment-by-time interactions were likewise nonsignificant for HAMA (−0.37; 95% CI, −2.20 to 1.47; p = 0.689), HAMD (1.33; 95% CI, −0.82 to 3.48; p = 0.218), and QOL-AD (2.39; 95% CI, −1.26 to 6.05; p = 0.193).

ANCOVA residuals were compatible with normality for PSQI and QOL-AD, but not for HAMA or HAMD. Residual variance differed by treatment group for HAMA (Levene p = 0.036). Treatment-by-baseline interactions were observed for PSQI (p = 0.011) and HAMA (p = 0.029). A flexible-slope model continued to support the PSQI effect (−2.31; 95% CI, −3.51 to −1.10; p < 0.001); its empirical-sandwich CI (−3.56 to −1.13) and bootstrap percentile CI (−3.58 to −1.04) were also consistent. For HAMA, the empirical-sandwich CI (−2.74 to −0.12; p = 0.032) and bootstrap percentile CI (−2.78 to −0.18) excluded zero, whereas the primary model-based CI and the MMRM CI included zero. Because HAMA was exploratory and affected by low baseline scores, non-normality, heteroscedasticity, and baseline-slope heterogeneity, this model-dependent result was not interpreted as confirmatory evidence of an anxiolytic effect.

### *Adverse events*

During the course of the study, one patient in the tACS group reported a tingling sensation during the first two sessions, while another in the control group reported transient itching at the first session. No serious adverse events were observed in either group.

## Discussion

Our findings demonstrate that 30 one-hour sessions of hi-tACS (15 mA) administered twice daily over 15 consecutive days led to reduction in PSQI scores compared to sham stimulation (p < 0.05). Importantly, this study is the first to investigate the application of hi-tACS for the management of neuropsychiatric comorbidities in patients with AD. Regrettably, no significant improvements in anxiety and depression were observed following tACS intervention in the present study.

Existing studies, including our prior report from the TRANSFORM-AD study, have verified that 40 Hz tACS with an intensity of 15 mA exerts beneficial effects on cognitive performance among individuals diagnosed with AD.[20] Non-invasive brain stimulation (NIBS) has been

**Table 2.** Observed outcome scores and baseline-adjusted treatment effects.

| Outcome | Hi-tACS baseline post change | Sham baseline post change | Adjusted mean difference (95% CI) | p |
|---|---|---|---|---|
| PSQI | 9.65 ± 5.84 | 7.83 ± 5.80 | −2.34 (−3.63 to −1.05) | <0.001 |
| | 6.35 ± 4.26 | 7.30 ± 5.36 | | |
| | −3.30 ± 3.23 | −0.52 ± 1.53 | | |
| HAMA | 3.40 ± 2.95 | 5.87 ± 5.50 | −1.43 (−2.89 to 0.02) | 0.054 |
| | 1.60 ± 1.27 | 4.43 ± 4.49 | | |
| | −1.80 ± 2.53 | −1.43 ± 3.30 | | |
| HAMD | 3.25 ± 4.27 | 5.26 ± 5.47 | 0.44 (−1.28 to 2.15) | 0.612 |
| | 2.80 ± 3.56 | 3.48 ± 4.07 | | |
| | −0.45 ± 1.85 | −1.78 ± 4.43 | | |
| QOL-AD | 35.30 ± 3.88 | 36.87 ± 7.90 | 2.07 (−1.57 to 5.70) | 0.257 |
| | 38.65 ± 7.39 | 37.83 ± 7.89 | | |
| | 3.35 ± 7.01 | 0.96 ± 4.78 | | |

Changes are post-intervention minus baseline. The adjusted mean difference is the treatment coefficient from ANCOVA with the post-intervention score as the dependent variable and the corresponding baseline score plus treatment group as predictors. Effects are Hi-tACS minus sham; therefore, negative effects favor Hi-tACS for PSQI, HAMA, and HAMD, whereas positive effects favor Hi-tACS for QOL-AD. Confidence intervals and p values are model-based.

extensively applied in patients with cognitive disorders to investigate its effects on cognitive function and neuropsychiatric symptoms (NPS).[25] Repetitive transcranial magnetic stimulation (rTMS) is the most extensively studied NIBS modality in AD. High-frequency rTMS has demonstrated improvements in global cognition, language, and NPS across multiple RCTs and meta-analyses.[26,27] Intermittent theta-burst stimulation (iTBS) facilitates cognitive function improvement in patients with post-stroke cognitive impairment, but not in those with AD or Parkinson's disease.[28] Transcranial direct current stimulation (tDCS) has been widely investigated in AD meta-analyses report modest improvements in global cognition and memory.[29] Studies using 40 Hz tACS at ≤4 mA have reported improvements in cognitive performance in mild cognitive impairment and AD.[14,15] However, findings regarding the therapeutic effects of low-intensity tACS for insomnia remain inconsistent.[30] Its limitations include restricted current penetration—intensities ≤4 mA predominantly modulate superficial cortical regions—and variable clinical outcomes that may reflect insufficient current delivery to deep structures.

The 15 mA hi-tACS protocol employed in the present study occupies a unique position within this NIBS landscape. Its principal advantage is the capacity to deliver electrical currents directly to deep brain structures. Shan et al. (2023) provided direct electrophysiological evidence using stereoelectroencephalography (SEEG) in awake humans that tACS at 15 mA (77.5 Hz, forehead-bilateral mastoid montage) generates significant local field potential changes in the hippocampus, insula, and amygdala, with currents >7 mA required to produce effects significantly different from sham.[16] Unlike rTMS and conventional tDCS/tACS, hi-tACS can simultaneously modulate cortical and subcortical structures through a single montage, Additionally, hi-tACS is portable and suitable for home-based administration, features not shared with r TMS. However, hi-tACS also has notable limitations. The 15 mA 40 Hz hi-tACS protocol uniquely addresses the depth-of-penetration gap that limits conventional NIBS approaches in AD, but at the cost of spatial focality and mechanistic resolution.

The present study revealed that hi-tACS could significantly improve sleep quality in patients with AD. Hi-tACS induces synchronous activity between the endogenous oscillation frequency and the hi-tACS frequency, thereby modifing endogenous brain oscillations during sleep.[30] Specifically, hi-tACS is capable of enhancing slow oscillatory activity and increasing the occurrence of sleep spindles during non-rapid eye movement sleep, thereby optimizing sleep architecture and prolonging total sleep time in patients.[11] Furthermore, the improvement in subjective sleep induced by hi-tACS may be associated with the stimulation of the reticular formation—a brain structure that plays a central role in regulating sleep and other states of consciousness.[31] It is critical to emphasize that this mechanistic interpretation is proposed exclusively as a prospective research hypothesis, rather than an empirical conclusion drawn from the present study. Similarly, although alterations in cerebral Aβ and tau protein levels were not directly quantified herein, the observed alleviation of sleep disturbances may hypothetically arise from secondary effects related to enhanced glymphatic clearance. Glymphatic clearance, promoted during slow-wave sleep, is considered vital for cerebral Aβ elimination. Whether such clinical gains correlate with enhanced clearance of pathological proteins remains unconfirmed. Prospective investigations integrating hi-tACS with cerebrospinal fluid biomarkers or PET imaging are warranted to test this hypothesis.

In addition to frequency, current intensity is also a critical determinant of clinical outcomes. While 15 mA hi-tACS demonstrates efficacy in enhancing sleep quality among adult patients with primary insomnia, tACS administered at intensities of less than 4 mA exhibits inconsistent therapeutic effects on insomnia symptoms.[30] Previous studies have demonstrated that alternating current of varying intensities can stimulate brain tissue at different depths. Specifically, when the current intensity reaches 15 mA, it can significantly modulate deep brain structures such as the hippocampus, insula, and amygdala, thereby regulating brain function and providing a therapeutic approach for neuropsychiatric disorders.[16] Building upon this foundation, our research has demonstrated that 40 Hz hi-tACS (15 mA) ameliorates sleep disorders in patients with AD. Given the bidirectional correlational relationship between sleep disturbances and AD pathology, this intervention may be associated with reduced correlates of exacerbated AD progression related to sleep deprivation.[32]

Beyond sleep disorders, tACS has been increasingly implemented in recent years as a therapeutic intervention for various psychiatric conditions, including anxiety and depression. A recent study found that a course of nine consecutive sessions of tACS at gamma frequency (40 Hz) effectively alleviated depressive symptoms in pregnant women, with the therapeutic effects remaining observable at a three-month follow-up.[33] Another study investigated the anxiolytic effects of alpha-frequency tACS. The research revealed that patients reported a reduction in anxiety levels following the treatment.[34] Unfortunately, no effect of hi-tACS on anxiety symptom scores and depression symptom scores were detected. However, patients exhibited a low baseline level of anxiety and depressive symptoms, which might account for the lack of a significant improvement in anxiety and depressive symptom scores.[35] We cannot firmly conclude that hi-t ACS improves emotional states based on the current dataset.

This study has several limitations. First, while the results showed that 30 consecutive hi-ACS sessions produced a treatment effect on sleep disorders in patients with mild AD during the follow-up period, the duration of this

effect remains unclear. Studies with extended follow-up intervals are necessary to cover this gap. Second, the primary outcome relied predominantly on subjective scales. Future investigations should employ objective assessment tools for precise monitoring of patient changes and explore supplementary objective variables, alongside developing novel objective indicators to track clinical outcomes. Cerebrospinal fluid and peripheral blood biomarkers (e.g., plasma p-tau217 and the $A\beta_{42/40}$ ratio) may facilitate participant stratification and help elucidate intervention mechanisms. Moreover, objective speech-based biomarkers can enable more sensitive long-term surveillance of disease progression.[36] The exploration of additional objective variables would further enhance our understanding of the effects of hi-tACS on these conditions. Third, formal blinding integrity assessment was not performed in this study. Although the active and sham stimulation conditions were indistinguishable by appearance and participants' subjective experiences, objective evidence confirming successful blinding is lacking.

In summary, the present study provides evidence that hi-tACS has potential as an effective therapeutic approach for mild AD patients with sleep disorder. The efficacy of hi-tACS is further validated by expanding the sample size in future studies. Simultaneously, the findings encourage additional research focused on elucidating the mechanisms through which hi-tACS influences these clinical indicators.

## Acknowledgements

The authors express their sincere gratitude to the participants for their invaluable support and contributions to this study.

## ORCID iDs

Yuchen Qiao https://orcid.org/0009-0002-5689-865X
Hong Chen https://orcid.org/0009-0001-3456-2103
Xuan Yang https://orcid.org/0000-0003-1818-2634
Rui Wang https://orcid.org/0009-0009-9016-7931
Yi Tang https://orcid.org/0000-0002-8052-065X

## Ethical considerations

This study was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University (2018-077) and was performed in accordance with the Declaration of Helsinki.

## Consent to participate

Prior to the initiation of the study, patients provided written informed consent for themselves.

## Consent for publication

Not applicable

## Author contribution(s)

**Yuchen Qiao:** Conceptualization; Formal analysis; Investigation; Methodology; Writing – original draft.
**Hong Chen:** Data curation; Formal analysis; Writing – original draft.
**Kaiting Fan:** Data curation; Investigation; Methodology; Writing – original draft.
**Xuan Yang:** Data curation; Investigation; Methodology; Writing – original draft.
**Yueyi Yu:** Conceptualization; Methodology; Resources; Writing – original draft.
**Rui Wang:** Data curation; Investigation; Writing – original draft.
**Yi Xing:** Conceptualization; Data curation; Methodology; Project administration; Writing – review & editing.
**Yi Tang:** Conceptualization; Formal analysis; Methodology; Project administration; Writing – review & editing.

## Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by National Key R&D Program of China (2024YFC2510204).

## Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Data availability statement

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

## Supplemental material

Supplemental material for this article is available online.

## References

1. Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet* 2024; 404: 572–628.
2. GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health* 2022; 7: e105–e125.
3. Bubu OM, Brannick M, Mortimer J, et al. Sleep, cognitive impairment, and Alzheimer's disease: a systematic review and meta-analysis. *Sleep* 2017; 40: zsw032.
4. Lacerda RAV, Desio JAF, Kammers CM, et al. Sleep disorders and risk of Alzheimer's disease: a two-way road. *Ageing Res Rev* 2024; 101: 102514.
5. Spira AP, Gamaldo AA, An Y, et al. Self-reported sleep and β-amyloid deposition in community-dwelling older adults. *JAMA Neurol* 2013; 70: 1537–1543.
6. Zhang F, Zhong R, Li S, et al. Alteration in sleep architecture and electroencephalogram as an early sign of Alzheimer's disease preceding the disease pathology and cognitive decline. *Alzheimers Dement* 2019; 15: 590–597.

7. Botto R, Callai N, Cermelli A, et al. Anxiety and depression in Alzheimer's disease: a systematic review of pathogenetic mechanisms and relation to cognitive decline. *Neurol Sci* 2022; 43: 4107–4124.
8. Sun M, Zhang Q, Han Y, et al. Sleep quality and subjective cognitive decline among older adults: the mediating role of anxiety/depression and worries. *J Aging Res* 2024; 2024: 4946303.
9. Fernández-Ruiz A, Oliva A, Soula M, et al. Gamma rhythm communication between entorhinal cortex and dentate gyrus neuronal assemblies. *Science* 2021; 372: eabf3119.
10. Du X, Wang S, Zhang X, et al. Gamma oscillations of cognitive dysfunction in chronic insomnia patients with anxiety and depression. *Chin J Behav Med Brain Sci* 2020; 29: 523–528.
11. Dondé C, Brunelin J, Micoulaud-Franchi JA, et al. The effects of transcranial electrical stimulation of the brain on sleep: a systematic review. *Front Psychiatry* 2021; 12: 646569.
12. Grover S, Fayzullina R, Bullard BM, et al. A meta-analysis suggests that tACS improves cognition in healthy, aging, and psychiatric populations. *Sci Transl Med* 2023; 15: eabo2044.
13. Liu X and Wang H. Neuromodulations in psychiatric disorders: emerging lines of definition. *Psychother Psychosom* 2025; 94: 31–39.
14. Kim J, Kim H, Jeong H, et al. tACS as a promising therapeutic option for improving cognitive function in mild cognitive impairment: a direct comparison between tACS and tDCS. *J Psychiatr Res* 2021; 141: 248–256.
15. Benussi A, Cantoni V, Cotelli MS, et al. Exposure to gamma tACS in Alzheimer's disease: a randomized, double-blind, sham-controlled, crossover, pilot study. *Brain Stimul* 2021; 14: 531–540.
16. Shan Y, Wang H, Yang Y, et al. Evidence of a large current of transcranial alternating current stimulation directly to deep brain regions. *Mol Psychiatry* 2023; 28: 5402–5410.
17. Wang HX, Wang L, Zhang WR, et al. Effect of transcranial alternating current stimulation for the treatment of chronic insomnia: a randomized, double-blind, parallel-group, placebo-controlled clinical trial. *Psychother Psychosom* 2020; 89: 38–47.
18. Wang H, Wang K, Xue Q, et al. Transcranial alternating current stimulation for treating depression: a randomized controlled trial. *Brain* 2022; 145: 83–91.
19. Xing Y, Wei P, Wang C, et al. TRanscranial AlterNating current Stimulation FOR patients with Mild Alzheimer's Disease (TRANSFORM-AD study): protocol for a randomized controlled clinical trial. *Alzheimers Dement (NY)* 2020; 6: e12005.
20. Tang Y, Xing Y, Sun L, et al. TRanscranial AlterNating current stimulation FOR patients with mild Alzheimer's Disease (TRANSFORM-AD): a randomized controlled clinical trial. *Alzheimers Res Ther* 2024; 16: 203.
21. Osorio CD, Gallinaro AL, Lorenzi-Filho G, et al. Sleep quality in patients with fibromyalgia using the Pittsburgh Sleep Quality Index. *J Rheumatol* 2006; 33: 1863–1865.
22. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959; 32: 50–55.
23. Singh A, Black SE, Herrmann N, et al. Functional and neuroanatomic correlations in poststroke depression: the Sunnybrook Stroke Study. *Stroke* 2000; 31: 637–644.
24. Kahle-Wrobleski K, Ye W, Henley D, et al. Assessing quality of life in Alzheimer's disease: implications for clinical trials. *Alzheimers Dement (Amst)* 2017; 6: 82–90.
25. Wu M, Song W, Wang X, et al. Efficacy of non-invasive brain stimulation interventions on cognitive impairment: an umbrella review of meta-analyses of randomized controlled trials. *J Neuroeng Rehabil* 2025; 22: 22.
26. Jin Y, Li J and Xiao B. Efficacy and safety of neuromodulation for apathy in patients with Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. *J Psychiatr Res* 2024; 171: 17–24.
27. Chou YH, Ton That V and Sundman M. A systematic review and meta-analysis of rTMS effects on cognitive enhancement in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* 2020; 86: 1–10.
28. Zheng B, Chen J, Cao M, et al. The effect of intermittent theta burst stimulation for cognitive dysfunction: a meta-analysis. *Brain Inj* 2024; 38: 675–686.
29. Andrade SM, de Oliveira Marques CC, de Lucena LC, et al. Effect of transcranial direct current stimulation and transcranial magnetic stimulation on the cognitive function of individuals with Alzheimer's disease: a systematic review with meta-analysis and meta-regression. *Neurol Res* 2024; 46: 453–465.
30. Shekelle PG, Cook IA, Miake-Lye IM, et al. Benefits and harms of cranial electrical stimulation for chronic painful conditions, depression, anxiety, and insomnia: a systematic review. *Ann Intern Med* 2018; 168: 414–421.
31. Acler M, Bocci T, Valenti D, et al. Transcranial direct current stimulation (tDCS) for sleep disturbances and fatigue in patients with post-polio syndrome. *Restor Neurol Neurosci* 2013; 31: 661–668.
32. Tabassum S, Misrani A, Tabassum S, et al. Disrupted prefrontal neuronal oscillations and morphology induced by sleep deprivation in young APP/PS1 transgenic AD mice. *Brain Res Bull* 2021; 166: 12–20.
33. Wilkening A, Kurzeck A, Dechantsreiter E, et al. Transcranial alternating current stimulation for the treatment of major depression during pregnancy. *Psychiatry Res* 2019; 279: 399–400.
34. Clancy KJ, Baisley SK, Albizu A, et al. Lasting connectivity increase and anxiety reduction via transcranial alternating current stimulation. *Soc Cogn Affect Neurosci* 2018; 13: 1305–1316.
35. Ren C, Pagali SR, Wang Z, et al. Transcranial electrical stimulation in treatment of depression: a systematic review and meta-analysis. *JAMA Netw Open* 2025; 8: e2516459.
36. Wiechmann D, Kerz E, Albrecht M, et al. Detecting CSF-validated Alzheimer's disease from spontaneous speech in German: an interpretable end-to-end machine-learning framework. *Front Neurol* 2026; 17: 1780783.