

Cerebellar High Frequency Transcranial Pulsed Current Stimulation Increases Total Sleep Time in Chronic Insomnia: A Pilot Study

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Abstract

Chronic insomnia is characterized by reduced sleep duration and is associated with substantial physical and psychological morbidity. Existing treatments are limited by accessibility, tolerability, and persistent residual symptoms. Given emerging evidence implicating the cerebellum in sleep–wake regulation, we evaluated the safety and efficacy of cerebellar high-frequency transcranial pulsed current stimulation (tPCS) in individuals with chronic insomnia. In this double-blind, randomized, sham-controlled pilot trial, thirty adults on stable pharmacotherapy were assigned 1:1 to receive 12 sessions of bilateral cerebellar active tPCS (400 Hz, 0.6 mA average current, 30 minutes/session) or sham stimulation over two weeks. The primary outcome was actigraphy-derived total sleep time (TST). Between-group comparisons were performed using rank analysis of covariance adjusting for baseline values. Compared with sham stimulation, active tPCS significantly increased TST (adjusted mean difference, 34.25 minutes; 95% CI, 1.60–66.89; $P = 0.022$; partial $\eta^2 = 0.180$) and improved Pittsburgh Sleep Quality Index (PSQI) global score, including subjective sleep quality and sleep duration. Exploratory analyses demonstrated greater reductions in anxiety and depressive symptoms. No serious adverse events occurred. These findings suggest that cerebellar high-frequency tPCS may improve objective sleep duration and subjective sleep quality in insomnia and warrant confirmation in larger randomized controlled trials.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2300072403, Date of registration: Jun 12, 2023; (URL: <https://www.chictr.org.cn/showproj.html?proj=199226>)

Introduction

Insomnia is the most prevalent sleep disorder in the general population, affecting up to 30% of adults worldwide¹. Insomnia is generally defined as difficulty initiating or maintaining sleep, or waking earlier than desired, despite adequate opportunity for sleep, and associated with excessive daytime impairment². If symptoms persist for more than 3 months, insomnia is considered chronic, and it is associated with a wide range of adverse health outcomes, including an increased risk of cardiovascular disease, neuropsychiatric disorders, and an elevated all-cause mortality^{3–5}.

The clinical diagnosis of insomnia is primarily based on the patient's subjective experience of persistent sleep difficulties and associated daytime impairment, rather than on objectively measured sleep duration. Thus, a patient may meet diagnostic criteria for insomnia disorder despite having a normal sleep duration on objective measures such as actigraphy. However, it is commonly assumed that there is a presence of relation between subjective perceptions of sleep and objectively measured sleep duration.

Therapeutic approaches target different predisposing, precipitating, and perpetuating factors thought to contribute to chronic insomnia. Predisposing factors include genetic susceptibility, heightened stress reactivity, and personality traits. Precipitating factors can be an illness, pain, acute stress, or a major life event. Perpetuating factors include poor sleep hygiene, maladaptive sleep behaviors, anxiety with excessive worry and monitoring of sleep, etc. Cognitive behavioral therapy (CBT-I), which targets the behavioral, cognitive, and physiological processes that maintain the disorder, is the recommended first-line therapy, and involves stimulus control, sleep restriction, relaxation training, cognitive restructuring, and sleep hygiene education. CBT-I exhibits robust efficacy in improving sleep quality, but its widespread implementation is limited by a shortage of trained providers and logistical barriers⁶. Pharmacological therapies, including melatonin, hypnotics, and sedating antidepressants, are commonly prescribed for the management of insomnia and co-occurring depression. Although most clinical guidelines recommend these agents for short-term use only (typically ≤ 4 weeks), many patients remain on medication for substantially longer because of the limited availability of effective long-term alternatives. Prolonged use is associated with tolerance, drug dependence, cognitive and psychiatric adverse effects, and disruption of normal sleep architecture⁷. Consequently, many patients continue to report dissatisfaction with their sleep⁸, underscoring the need for safe, effective, and accessible non-pharmacological treatment options.

Transcranial electrical stimulation (tES) is increasingly being investigated for sleep modulation across both healthy and clinical populations due to its portability, favorable safety profile and ability to directly target sleep-related neural circuits and oscillations. tES is a form of non-invasive brain stimulation technique that can deliver low-intensity electrical currents (e.g. 1 to 2 mA) via scalp electrodes to modulate neuronal excitability changes in targeted cortical regions⁹. Three different forms of tES, transcranial direct current stimulation (tDCS)^{10–12}, slow-oscillatory (so)-tDCS (~ 0.5 –1 Hz)^{13–15}, and transcranial alternating current stimulation (tACS)^{16–19}, have been investigated for sleep promotion in both healthy and clinical populations. Across studies, tES most commonly targeted frontal cortical regions (EEG sites: Fp1, Fp2, F3, F4) aiming to entrain slow-wave activity during non-rapid eye movement (NREM) deep sleep, grounded in the hypothesis that frontal lobe neurons exert “top-down” control over cortico-thalamic feedback loops that are essential for sleep–wake regulation¹¹. Several studies have reported increases in deep sleep duration, improvements in subjective sleep quality, and reductions in comorbid mood symptoms^{12,16,18,19}. However, findings remain heterogeneous. For example, bifrontal tDCS was reported to reduce total sleep time¹¹, whereas so-tDCS altered sleep-stage architecture without improving overall sleep duration¹⁴ and was associated with reduced slow-wave sleep accompanied by impaired visuospatial memory consolidation¹⁵. Similarly, one study demonstrated very low-frequency (0.75 and 1.0 Hz) sinusoidal tACS failed to entrain endogenous sleep oscillations²⁰ and another reported that neither 0.5 Hz nor 100 Hz tACS improved sleep quality over sham stimulation²¹.

In recent years, transcranial pulsed current stimulation (tPCS) has emerged as a novel form of tES. tPCS delivers low intensity pulsed currents (typically ≤ 2 mA average; 1–500 Hz) to modulate neuronal activity in targeted brain regions^{22–24}. Relative to tDCS, tPCS produces stronger neurophysiological effects and may recruit a broader range of sensory, motor, and nociceptive fibers at intensities as low as 0.3 mA²². Compared to tACS, tPCS has a rapid onset of each pulse that creates a larger instantaneous change in the transmembrane electric field (dE/dt), which may be more effective at altering neuronal firing probability than the slowly varying sinusoidal waveform of tACS. Rather than aiming to entrain an endogenous rhythm, tPCS appears to act as a series of brief perturbations that may perturb network activity, making it less dependent on precise phase alignment with ongoing oscillations. Computational head-modeling indicates that tPCS applied currents can reach deep subcortical structures, including the thalamus, hypothalamus, and brainstem²⁵, regions central to sleep–wake regulation. Mechanistically, tPCS may produce polarity-dependent modulation of cortical and corticospinal excitability²³. Preclinical

studies show that high-frequency (100-500Hz) pulsed electrical stimulation enhances GABAergic signaling through reduced GABA reuptake²⁶ and interneuron activation²⁷ while it suppresses neuronal firing, potentially through partial axonal conduction block^{28,29}.

The ability of higher frequency tPCS to enhance inhibitory control and suppress excessive excitatory activity may be particularly relevant for the treatment of insomnia, a disorder increasingly recognized as being driven by disrupted excitatory–inhibitory (E/I) balance and persistent hyperactivity in key arousal networks³⁰. In particular, wake-promoting neuronal populations within the ascending reticular activating system (ARAS), the principal brainstem arousal network, are thought to remain pathologically overactive because of insufficient GABAergic inhibition from the ventrolateral preoptic area (VLPO), which normally suppresses ARAS activity during sleep initiation and maintenance³¹. Although these core sleep–wake nuclei are anatomically inaccessible to tES, the cerebellum represents an attractive target due to its superficial location and extensive reciprocal connections with the thalamus, hypothalamus, brainstem reticular formation and cerebral cortex involved in sleep regulation^{32,33}. Additionally, electrophysiological and neuroimaging studies demonstrate state-dependent modulation of cerebellar neuronal activity across the sleep–wake cycle³², while functional neuroimaging shows region-specific activation across cerebellar lobules during both NREM and REM sleep³⁴. Consistent with these observations, sleep fragmentation and REM sleep abnormalities are common in patients with cerebellar lesions or degenerative cerebellar ataxias, supporting a causal role for the cerebellum in sleep regulation³⁵.

Accordingly, we hypothesized that adjunctive bilateral cerebellar 400-Hz tPCS would increase objective actigraphy-derived total sleep time (TST), compared with sham tPCS in individuals with chronic insomnia. Actigraphy-derived TST was selected as the primary endpoint as objective sleep duration is more likely to capture the direct physiological effects of a brain stimulation intervention, such as cerebellar tPCS, on sleep regulation. We further hypothesized and prespecified as the key secondary endpoint that - relative to sham stimulation - adjunctive cerebellar 400-Hz tPCS would improve the overall patient-reported sleep quality, assessed using the Pittsburgh Sleep Quality Index (PSQI) global score.

Results

A total of 59 individuals were screened for inclusion criteria eligibility and 21 were excluded. Participant flow is illustrated in the CONSORT diagram (Fig. 1). The remaining 38 participants were randomized to receive either active-tPCS or sham tPCS. During the trial, 6 participants (4 from active-tPCS and 2 from sham-tPCS group) withdrew (see Fig. 1). Consequently, 30 participants (9 males, 21 females; mean age 43 ± 12 years, range 24–70 years) completed the study, yielding a retention rate of 93.8% (30/32). Participant flow is illustrated in the CONSORT diagram (Fig. 1).

Estimation of induced electric-field by 400Hz tPCS

Figure 2 shows current flow (colored by local current density distribution) together with cerebellar and brain surface maps of the normal electric field component, the principal exposure metric governing Purkinje cell firing modulation. Peak electric field magnitudes are shown at the temporal maximum of the stimulation pulse. Despite the highly folded cerebellar anatomy, distinct anodal and cathodal electric field distributions were observed beneath the respective electrodes. The highest induced cerebellar electric field magnitude occurred within the cerebellar cortex immediately beneath the electrodes and was estimated to alter the spontaneous firing rate of Purkinje cells by up to ± 5 Hz from a baseline rate of 69 Hz seen from the Purkinje cell model, depending on field orientation.

Safety of tPCS

No serious adverse events occurred in either the active-tPCS or sham group during the study. The most reported adverse events were mild skin symptoms and mild headache. Their incidence did not differ significantly between groups (26.7% vs. 6.7%; RD = 20.0%, 95% CI – 5.7% to 45.7%; $P = 0.330$). Table 1 presents the between-group comparisons of SAEs. eTable 2a and eTable 2b in Supplement 3 presents the complete list of safety adverse event across all participants.

Baseline comparison of demographic and clinical characteristics

Baseline demographic and clinical characteristics are presented in Table 2. Compared with the sham group, participants randomized to active tPCS were older (48.6 ± 10.7 vs. 37.7 ± 11.6 years; SMD = -1.02; 95% CI: -1.78, -0.25). No significant between-group differences were observed in sex, body mass index, educational attainment, or concomitant medication use. Relative to the sham group, the active-tPCS group exhibited shorter actigraphy-derived TST, shorter total time in bed, fewer nocturnal awakenings, and less WASO (SMDs, 1.21 to 1.45). The active-tPCS group also had poorer perceived sleep quality and sleep efficiency (PSQI subjective sleep quality, SMD = 0.86; PSQI habitual sleep efficiency, SMD = 1.98), but lower self-rated anxiety and depression (SAS, SMD = 1.69; SDS, SMD = 2.01) scores.

Effect of tPCS on Primary and Secondary Efficacy Outcomes

Post-treatment, between-group comparisons were performed using rank ANCOVA with corresponding baseline values as covariates because of the small sample size, non-normal data distribution, and baseline imbalances. Actigraphy-derived TST, the prespecified primary outcome, increased by 81.63 minutes (28.1%) in the active-tPCS group compared with 6.25 minutes (1.7%) in the sham group. Rank ANCOVA showed a significantly greater increase in TST with active tPCS after adjusting for baseline differences (adjusted mean difference = 34.25 minutes; 95% CI, 1.60–66.89; $P = 0.022$; partial $\eta^2 = 0.180$). No other actigraphy-derived secondary sleep outcomes remained statistically significant after Bonferroni correction.

Mean PSQI global score, the pre-specified key secondary outcome, decreased by 4.87 points (28.0%) in the active-tPCS group compared with 0.13 points (0.8%) in the sham group. Rank ANCOVA revealed a significantly greater improvement in the active-tPCS group (adjusted mean difference = - 4.39; 95% CI, - 6.47 to - 2.30; $P < 0.001$; partial $\eta^2 = 0.451$). After Bonferroni correction, significant improvements remained for the PSQI subjective sleep quality and PSQI sleep duration subscales (adjusted mean differences = - 1.54 and - 1.49, respectively; both $P < 0.001$), favoring the active-tPCS group. No other PSQI component scores remained statistically significant after Bonferroni correction.

Figure 3 illustrates individual and mean trajectories for actigraphy-derived TST and PSQI global score. From baseline to post-treatment, the active-tPCS group demonstrated an upward shift in mean TST and a downward shift in mean PSQI global score, indicating longer sleep duration and improved overall sleep quality, respectively. In contrast, the sham group exhibited minimal change in either outcome, with relatively flat mean trajectories over time. Despite inter-individual variability, most participants in the active-tPCS group showed improvements consistent with the overall treatment effect.

Exploratory psychological outcomes were assessed using the SAS and SDS. Compared with the sham group, the active-tPCS group demonstrated greater reductions in both anxiety and depressive symptoms. Mean SAS scores decreased by 7.42 points (15.5%) in the active-tPCS group versus 0.67 points (1.0%) in the sham group. Rank ANCOVA revealed a significantly greater reduction in the active-tPCS after adjusting for baseline differences (adjusted mean difference = - 11.85; 95% CI, - 17.58 to - 6.12; $P < 0.001$; partial $\eta^2 = 0.409$). Similarly, mean SDS scores decreased by 7.2 points (15.0%) in the active-tPCS group compared with 2.1 points (3.1%) in the sham group. Rank ANCOVA revealed a significantly greater reduction in the active-tPCS after adjusting for baseline differences (adjusted mean difference = - 12.13; 95% CI, - 17.24 to - 7.03; $P < 0.001$; partial $\eta^2 = 0.408$). Post-treatment results for all outcomes are presented in Table 3.

Sensitivity Analysis of Additional Baseline Covariates

Given the baseline imbalances between groups generated by the 1:1 randomization in the small sample size, an exploratory post hoc sensitivity analysis evaluated the impact of additional baseline variables as covariates in the rank ANCOVA models. Partial F-tests showed that none of the candidate variables explained significant additional variance in post-treatment TST or PSQI global score beyond treatment group and the corresponding baseline outcome (See Table 4).

Discussion

Chronic insomnia is associated with substantial morbidity and increases long-term health risks³⁻⁵. This single-centre, double-blind, sham-controlled randomized pilot trial evaluated the safety and efficacy of adjunctive high-frequency (400 Hz) cerebellar tPCS in individuals with chronic insomnia receiving stable pharmacotherapy.

Throughout the study, no serious adverse events occurred in either group, indicating that high-frequency cerebellar tPCS was well tolerated. Mild adverse events, including transient skin erythema and headache, were more frequent in the active tPCS group (4/15 vs 1/15; RD: 20.0% [- 5.7%, 45.7%]; $P = 0.330$), but overall adverse event incidence did not differ significantly between groups. These findings support the safety of cerebellar tPCS in adults with chronic insomnia.

Post-treatment, in the between-group rank ANCOVA adjusted for baseline actigraphy-derived TST to account for baseline between-group differences, the active-tPCS group demonstrated a significantly greater increase in TST compared to the sham group, which corresponded to an adjusted mean rank difference of 34.25 minutes. No other actigraphy-derived sleep parameter remained significant after Bonferroni correction. These findings suggest that 400 Hz cerebellar tPCS, when added to stable pharmacotherapy, may increase objective sleep duration in individuals with chronic insomnia.

The active-tPCS group also exhibited greater improvement in the pre-specified key secondary endpoint of overall subjective sleep quality compared to the sham group, with the between-group baseline-adjusted rank ANCOVA demonstrating significant between-group difference in PSQI global score at post treatment. This effect was mainly attributable to significant changes in the PSQI subcomponent scores of subjective sleep quality ($P < 0.001$, ES = 0.510) and sleep duration ($P < 0.001$, ES = 0.589), aligning with results of actigraphy. In addition, participants receiving active tPCS experienced significantly greater reductions in self-reported anxiety (SAS: $P < 0.001$, ES = 0.409) and depressive symptoms (SDS: $P < 0.001$, ES = 0.408) compared with those receiving sham stimulation.

Our results on the tPCS-induced improvement in subjective sleep measures are consistent with previous tES studies in individuals with sleep disturbances^{12,17,18}. However, the previous tES studies that primarily stimulated the frontal cortex generally reported limited or no effects on objective sleep measures^{10,14}. In contrast, cerebellar 400-Hz tPCS produced a significant increase in objective total sleep time alongside marked improvement in participants' subjective perception of overall sleep quality. These results suggest that high-frequency cerebellar tPCS engages sleep-wake regulatory circuitry distinct from those modulated by frontal tES approaches, potentially reflecting differences in the target being the cerebellum, tPCS-specific stimulation characteristics and mechanisms of action. In any case, the concordance between objective and subjective sleep outcomes observed in the present study is clinically meaningful as these two dimensions of sleep are typically only weakly correlated³⁶ and their dissociation may contribute to sleep-state misperception, a characteristic feature of chronic insomnia associated with adverse health outcomes³⁷.

Although the mechanisms by which high-frequency tPCS increased sleep duration remain incompletely understood, our electric-field modelling demonstrates substantial effects on Purkinje cells, which respond robustly to high-frequency stimulation³⁸. As the sole output neurons of the cerebellar cortex, Purkinje cells exert powerful inhibitory control over the deep cerebellar nuclei (DCN), the principal output structures of the cerebellum. The DCN project extensively to

thalamic and brainstem regions, including components of the ARAS involved in sleep–wake regulation^{32,33}. Consequently, cerebellar 400-Hz tPCS may have influenced large-scale sleep–wake networks by modulating Purkinje cell activity and, in turn, cerebellar output to these downstream pathways.

Supporting this hypothesis, spontaneous Purkinje cell firing decreases during non-REM sleep in freely behaving cats³⁹, whereas experimentally increasing Purkinje cell activity suppresses DCN output and promotes arousal during transitions from non-REM sleep to wakefulness in mice⁴⁰. Together, these findings suggest that 400-Hz tPCS may have prolonged total sleep time by transiently suppressing Purkinje cell activity^{28,29}, thereby disinhibiting the DCN and enhancing downstream thalamic and brainstem pathways involved in sleep–wake regulation. Future studies incorporating polysomnography and neurophysiological measures will be required to delineate the specific circuit-level mechanisms underlying these effects.

Although exploratory, the observed reductions in anxiety and depressive symptoms following cerebellar 400-Hz tPCS are noteworthy given the high prevalence of comorbid affective symptoms among individuals with chronic insomnia⁴¹. Extensive anatomical, neurophysiological, and imaging evidence reveals that activity in cerebellar hemispheres, particularly the posterior lobules and dentate nuclei, causally modulate contralateral prefrontal cortical activity⁴². Additionally, lateralized prefrontal cortical activity has been linked to mood regulation, with increased left prefrontal activity associated with antidepressant effects⁴³. Accordingly, polarity-dependent modulation of Purkinje cell activity may have altered dentate output and, in turn, contralateral prefrontal cortical excitability, contributing to the mood improvements observed in this study. Nevertheless, whether lateralized cerebello–prefrontal network modulation contributes to the mood effects remains uncertain.

This study has several limitations. First, despite randomization, baseline imbalances were observed between groups in age, several actigraphy-derived sleep parameters, PSQI components, and anxiety and depression scores, with the active-tPCS group generally exhibiting greater baseline severity. To minimize potential confounding, between-group comparisons were performed using rank ANCOVA with adjustment for baseline values, and sensitivity analyses confirmed that the treatment effect on the primary outcome (total sleep time) and the key secondary outcome (PSQI global score) remained robust after accounting for potential confounding covariates. The robustness of our findings is supported by sensitivity analyses, which showed that none of the candidate baseline covariates significantly influenced the between-group differences in the primary outcome of actigraphy-derived TST or they key secondary outcome of PSQI global score (See Table 4), suggesting that observed effects were unlikely attributable to the baseline imbalances.

Second, participants remained on stable pharmacotherapy throughout the study because of the exploratory nature of high frequency tPCS and the need to maintain clinical stability in individuals who relied on these medications for daily functioning. Although concomitant sedative medications may have influenced objective sleep measures and introduced confounders, medication use was comparable between groups at baseline, reducing the likelihood that the observed treatment effects were attributable to differences in pharmacotherapy.

Third, although participant blinding was not formally assessed using a blinding questionnaire, the risk of unblinding was low because stimulation was delivered at low intensity, adverse events were mild, expected, and comparable between groups, and participants had no opportunity to interact during the study. In addition, stimulation technicians and all study personnel interacting with participants remained blinded to group allocation.

Fourth, owing to recruitment constraints, this pilot trial enrolled a relatively small sample, limiting statistical power and generalizability. Accordingly, these findings should be considered preliminary and require confirmation in larger, adequately powered randomized controlled trials.

Finally, polysomnography was not performed due to resource constraints, precluding assessment of sleep architecture and preventing determination of whether the observed increase in total sleep time was attributable to specific sleep stages, such as slow-wave sleep.

In conclusion, this pilot double-blind, randomized, sham-controlled trial demonstrated that adjunct cerebellar 400-Hz tPCS was safe and significantly improved both objective actigraphy-derived total sleep time and subjective sleep quality in individuals with chronic insomnia as compared with sham stimulation. Improvements seem clinically meaningful, as objective and subjective sleep measures often correlate only weakly, and their discordance contributes to sleep misperception in individuals with insomnia. Exploratory analyses further suggested potential benefits for comorbid anxiety and depressive symptoms. Collectively, these findings identify the cerebellum as a promising therapeutic target for chronic insomnia and support further evaluation of high-frequency cerebellar tPCS as a non-pharmacological adjunct to standard care in larger, adequately powered trials incorporating longer follow-up, and assessment of potential medication-sparing effects.

Methods

Study Design

A two-week, single-center, parallel-group, double-blind, randomized, sham-controlled clinical trial was conducted at Chongqing Western Hospital, Sichuan Province, China. Eligible participants who met the criteria and provided written informed consent were randomized 1:1 to receive active 400Hz tPCS or sham stimulation. The study was approved by the institutional ethics committee, registered at the Chinese Clinical Trial Registry (ChiCTR2300072403), and conducted in accordance with the Declaration of Helsinki.

Participants

Participants with chronic insomnia were recruited from the outpatient sleep clinic of Chongqing Western Hospital, Chongqing, China, between June 19, 2023, and May 30, 2025. Chronic insomnia was diagnosed according to established clinical criteria² as persistent difficulty initiating or maintaining sleep, or early morning awakening despite adequate opportunity for sleep, occurring ≥ 3 nights per week for ≥ 3 months and associated with clinically significant daytime impairment. Eligible participants underwent three consecutive nights of home wrist actigraphy (ActiGraph wGT3X-BT), and only those with an average whole-

night actigraphy-derived total sleep time (TST) ≤ 480 minutes (≤ 8 hours) were randomized to active or sham tPCS. This TST threshold was selected because participants remained on stable medications, some of which had sedative effects that could reduce movement while awake and cause actigraphy to misclassify periods of quiet wakefulness as sleep, thereby overestimating TST.

Inclusion criteria were age 18–65 years, PSQI score 11–21, stable insomnia medication for ≥ 30 days. Individuals with mild to moderately severe anxiety and depressive symptoms (DSM-5 criteria)⁴⁴ were eligible. Women of childbearing potential required a negative pregnancy test. Exclusion criteria included major psychiatric disorders; history of seizures or craniotomy; implanted electronic or ferromagnetic devices; other primary sleep disorders (e.g., obstructive sleep apnea, periodic limb movement disorder, narcolepsy, parasomnia, or hypersomnia); active suicidal ideation; clinically significant medical or neurological illness; substance dependence; night-shift work; pregnancy or breastfeeding; recent non-invasive brain stimulation (e.g., rTMS or tDCS); concurrent psychological therapy (e.g., CBT-I); or participation in another interventional study.

Sample size calculation

The original sample size was 130 participants (65 per group), calculated to provide 80% power at a two-sided α of 0.05 while allowing for 20% attrition. Recruitment constraints prevented attainment of the planned sample within the approved study period. Consequently, the study was completed as a pilot randomized controlled trial to inform a future fully powered trial, with a target of 30 evaluable participants (15 per group).

Randomization and Blinding

A total of 38 eligible participants were randomized 1:1 to receive either active or sham tPCS using a computer-generated randomization sequence. Sequence generation and allocation were performed by an independent statistician who was not involved in participant enrolment, intervention delivery, or outcome assessment. Allocation concealment was maintained using sequentially numbered, sealed, opaque envelopes opened in order of enrolment. Active and sham devices were identical in appearance and stimulation was administered in separate treatment rooms with comparable layouts located in different areas of the hospital. Participants' visits were scheduled at least two hours apart, and each participant attended all 12 sessions in the same treatment room to minimize contact and reduce the risk of accidental unblinding. All participants were tPCS-naïve and were informed that transient stimulation-related sensations, including mild skin tingling, itching, or headache, could occur during either active or sham stimulation to preserve blinding. Therapists administering the intervention and study personnel responsible for outcome assessments remained blinded to group allocation throughout the trial.

Outcome Measures

The primary outcome was actigraphy-derived total sleep time (TST), calculated as the mean of three consecutive nights of whole-night recordings using wrist actigraphy (ActiGraph wGT3X-BT; ActiGraph LLC, Pensacola, FL, USA) worn on the non-dominant wrist. Actigraphy is a validated method for assessing sleep–wake patterns and demonstrates good agreement with polysomnography for estimating TST, particularly in naturalistic settings⁴⁵. Baseline measurements were obtained during the week preceding the first treatment session, and post-treatment TST was calculated as the mean of the final three nights of the intervention.

The key secondary outcome was the Chinese version of the Pittsburgh Sleep Quality Index (PSQI)⁴⁶ global score. Higher PSQI scores indicate poorer sleep quality (global score range, 0–21; scores > 5 indicate poor sleep quality). Additional secondary outcomes included actigraphy-derived sleep efficiency (SE), sleep latency (SL), total time in bed (TIB), wake after sleep onset (WASO), number of awakenings, average awakening duration, the seven PSQI component scores, and mood symptoms assessed using the Chinese versions of the Zung Self-Rating Depression Scale (SDS)⁴⁷ and Zung Self-Rating Anxiety Scale (SAS)⁴⁸. Higher SDS and SAS scores indicate greater depression and anxiety severity, respectively.

Baseline assessments were performed at Week 0. Post-treatment actigraphy outcomes were derived from the final three intervention days, whereas the PSQI, SDS, and SAS were completed within one week after the final treatment session under the supervision of trained psychologists blinded to treatment allocation.

Intervention

Stimulation was delivered using a transcranial pulsed current stimulator (YQ-D1111; YIQI Biotechnology Ltd., China). Participants underwent 12 daily treatment sessions of 30 minutes each over two consecutive weeks (Monday–Saturday). For each participant, all sessions were applied at a consistent time. 400-Hz tPCS was delivered via two saline-soaked circular silver–fiber cotton electrodes (12.56 cm²) positioned bilaterally over the cerebellar hemispheres (1 cm inferior and 4 cm lateral to theinion), with the cathode over the left and the anode over the right hemisphere. The active group received continuous stimulation at 0.6 mA, whereas the sham group received a 10-s ramp-up followed by a 5-s ramp-down with no subsequent stimulation. Participants were permitted to continue their existing pharmacotherapy. Changes in medications during the study were not permitted.

Computational Exposure Assessment

Electromagnetic field simulations were performed using Sim4Life V8.2 (ZMT, Zurich, Switzerland) and the high-resolution MIDA anatomical model⁴⁹ to estimate cerebellar and whole-brain exposure to tPCS. The clinical electrode montage was reproduced, with tissue conductivities assigned according to the IT'IS Tissue Properties Database v4.2. To estimate neuronal effects, a morphologically and electrophysiologically detailed Purkinje cell model from ModelDB⁵⁰ was coupled to the simulated extracellular electric fields. Changes in spontaneous firing rate (baseline for the Purkinje cell model: 69 Hz) were evaluated as a function of electric field strength and orientation.

Safety monitoring

Adverse events were systematically monitored in both groups. After each session, participants were assessed for treatment-related adverse events, including dizziness, headache, vomiting, seizures, scalp burns, skin redness or itching, scalp or neck pain, and other symptoms. All adverse events were

documented, and any serious adverse events were reported in accordance with institutional procedures using standardized hospital reporting forms.

Statistical Methods

All analyses were performed using IBM SPSS Statistics (version 23.0; IBM Corp., Armonk, NY, USA) and R (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) in the per-protocol population. Baseline balance between groups was assessed using standardized mean differences (SMD), calculated as the difference in means (or proportions) divided by the pooled standard deviation, given the reduced sensitivity of hypothesis testing to imbalance at small sample sizes. Variables with SMD > 0.8 were considered for inclusion as covariates in subsequent adjusted analyses. Normality was assessed using the Shapiro–Wilk and Kolmogorov–Smirnov tests (see Supplement 3, eTable 1). As several variables were non-normally distributed and baseline imbalances were present, post-treatment between-group comparisons were performed using rank analysis of covariance (rank ANCOVA), adjusting for baseline values. All tests were two-sided with a significance level of $P < 0.05$. Bonferroni correction was applied to the six secondary actigraphy-derived sleep parameters and the PSQI global and seven component scores. Actigraphy-derived TST was prespecified as the primary outcome and was not adjusted for multiplicity. Between-group adverse events incidence was compared using chi-square.

Exploratory sensitivity analyses evaluated whether baseline imbalances (age, sleep parameters, PSQI components, SAS, and SDS) had confounding effect on primary outcome of post-treatment TST or key secondary outcome of PSQI global score. Hierarchical rank-based linear regression models were used to test whether any variable showing significant between-group differences at baseline explained additional variance in post-treatment TST (Post-TST) and PSQI global scores beyond treatment group and the corresponding rank-transformed baseline outcome (baseline TST for Post-TST; baseline PSQI global score for Post-PSQI). The incremental contribution was evaluated using the change in explained variance (ΔR^2) and the associated F-change statistic. A significant ΔR^2 ($p < 0.05$) indicated that the covariate accounted for unique variability in post-treatment outcomes; partial eta squared (ηp^2) quantified the magnitude of this unique effect.

Declarations

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Competing Interest Statement:

Dr. Alvaro Pascual-Leone and Sandra Zhong are co-inventors on patents related to the transcranial pulsed current stimulation (tPCS) technology used in this study. These patents have been filed but did not influence the study design, data collection, analysis, interpretation of results, or the decision to submit the manuscript for publication. This interest has been disclosed to the research institution and addressed according to their conflict-of-interest policies. Dr. Alvaro Pascual-Leone is partly supported by grants from the National Institutes of Health (R01AG076708), Jack Satter Foundation, the Eleanor and Herbert Bearak Memory Wellness for Life Program, and BrightFocus Foundation. Dr. Alvaro Pascual-Leone serves as a paid member of the scientific advisory boards for Neuroelectrics, Bitbrain, TetraNeuron, Zeta Surgical, Medical MicroInstruments, and AscenZion Neuromodulation. He is co-founder of TI Solutions AG and co-founder and chief medical officer of Linus Health. Dr. Alvaro Pascual-Leone is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging, and applications of non-invasive brain stimulation in various neurological disorders, as well as digital biomarkers of cognition and digital assessments for early diagnosis of dementia. Dr. Esra Neufeld and Dr. Niels Kuster are co-founders of TI Solutions AG. Dr. Niels Kuster has several pending patents related to TI brain stimulation. All other authors declare no competing interests. Financial Disclosure: none.

Author Contribution

Conception and design: FYH, SZ, RH, NK, EN, APL, XJJ ; Institutional review board approval: FYH, XJJ ; Ran the experiment: FYH, JYL, XYW, XJJ ; Acquisition of data: FYH, JYL, XYW, NK, EN, FK, XJJ ; Analysis and interpretation of data: FYH, SZ, RH, NK, EN, APL, XJJ ; Figure preparation: FYH, SZ, EN, FK; Drafting the manuscript: FYH, SZ, APL, XJJ; Critical revisions: All authors.

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Data Availability

The data underlying this article are available in the Research Manager (ResMan) repository of Clinical Trial Management Public Platform, at <http://www.medresman.org.cn/uc/projectsh/projectedit.aspx?proj=6304>

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Tables

Table 1
Between-group comparison of adverse events

Item	tPCS group [n (%)]	Sham group [n (%)]	RD (95% CI)	P (Fisher)
Week 1 & 2 – Skin symptoms	3 (20.0%)	0 (0.0%)	20.0% (– 0.2%, 40.2%)	0.224
Week 1 & 2 – Mild headache	2 (13.3%)	1 (6.7%)	6.7% (– 14.7%, 28.0%)	1.000
Any skin symptoms	3 (20.0%)	0 (0.0%)	20.0% (– 0.2%, 40.2%)	0.224
Any headache	2 (13.3%)	1 (6.7%)	6.7% (– 14.7%, 28.0%)	1.000
Overall adverse events	4 (26.7%)	1 (6.7%)	20.0% (– 5.7%, 45.7%)	0.330
Note. n = 15 per group. RD = risk difference (tPCS – Sham), reported with 95% Wald confidence interval; P-values from two-tailed Fisher's exact test. * P < 0.05 Participants reporting a given symptom on more than one occasion (e.g., in both Week 1 and Week 2) were counted once (coded as 1) rather than by number of episodes. "Overall adverse events" reflects the number of unique participants reporting at least one adverse event (skin symptoms and/or headache) across the study period.				

Table 2
Baseline demographic and clinical characteristics

	Group			SMD	95% CI
	Overall N = 30	Sham N = 15	Active-tPCS N = 15		
Demographic & Anthropometrics					
Sex, n (%)				0.45	-0.28,1.17
female	21 (70.00%)	12 (80.00%)	9 (60.00%)		
male	9 (30.00%)	3 (20.00%)	6 (40.00%)		
Educational level, n (%)				0.59	-0.14,1.32
Junior high school or below	10 (33.33%)	3 (20.00%)	7 (46.67%)		
Senior high school or above	20 (66.67%)	12 (80.00%)	8 (53.33%)		
Age, Mean ± SD	43.13 ± 12.28	37.67 ± 11.60	48.60 ± 10.68	-1.02	-1.78, -0.25
Height (cm), Mean ± SD	163.27 ± 8.30	161.87 ± 7.37	164.67 ± 9.17	-0.35	-1.07, 0.37
Weight (kg), Mean ± SD	55.84 ± 7.92	55.07 ± 7.45	56.62 ± 8.56	-0.20	-0.92, 0.52
BMI, Mean ± SD	20.93 ± 2.36	21.02 ± 2.53	20.84 ± 2.26	0.08	-0.64, 0.80
Actigraphy					
Actigraphy TST, mean ± SD	328.26 ± 71.28	365.62 ± 62.11	290.90 ± 60.62	1.26	0.48, 2.04
Actigraphy SL, median (Q1, Q3)	5.50 (3.33, 7.33)	4.17 (2.67, 7.67)	6.00 (4.00, 7.33)	0.04	-0.67, 0.76
Actigraphy SE, mean ± SD	86.34 ± 6.39	84.28 ± 7.58	88.40 ± 4.25	-0.69	-1.43, 0.04
Actigraphy TIB, mean ± SD	383.06 ± 92.74	436.55 ± 81.10	329.58 ± 71.48	1.45	0.64, 2.25
Actigraphy WASO, median (Q1, Q3)	33.67 (26.67, 70.33)	64.67 (30.00, 89.00)	27.00 (22.67, 36.00)	1.12	0.35,1.89
Actigraphy No. of awakening, median (Q1, Q3)	16.08 (10.67, 20.60)	19.00 (15.33, 28.14)	11.33 (9.67, 17.67)	1.21	0.43,1.99
Actigraphy Avg. awakening (minutes), median (Q1, Q3)	2.60 (2.11, 3.25)	2.64 (2.15, 3.84)	2.53 (2.10, 3.24)	0.37	-0.35,1.09
PSQI					
PSQI global, median (Q1, Q3)	17.00 (15.00, 18.00)	16.00 (14.00, 18.00)	17.00 (16.00, 18.00)	-0.75	-1.49, -0.01
Subjective sleep quality, n (%)				0.86	0.11,1.61
2 points (fairly bad)	7 (23.3%)	6 (40.0%)	1 (6.7%)		
3 points (very bad)	23 (76.7%)	9 (60.0%)	14 (93.3%)		
Sleep latency, n (%)				0.63	-0.10,1.37
2 points (moderate difficulty)	8 (26.7%)	6 (40.0%)	2 (13.3%)		
3 points (severe difficulty falling asleep)	22 (73.3%)	9 (60.0%)	13 (86.7%)		
Sleep duration, n (%)				0.58	-0.15,1.31
1 point (6–7 hours)	2 (6.7%)	0 (0.0%)	2 (13.3%)		
2 points (5–6 hours)	12 (40.0%)	7 (46.7%)	5 (33.3%)		
3 points (< 5 hours)	16 (53.3%)	8 (53.3%)	8 (53.3%)		
Habitual sleep efficiency, n (%)				1.98	1.11, 2.85
0 points (≥ 85% sleep efficiency)	7 (23.3%)	7 (46.7%)	0 (0.0%)		
1 point (75–84%)	3 (10.0%)	1 (6.7%)	2 (13.3%)		
2 points (65–74%)	7 (23.3%)	5 (33.3%)	2 (13.3%)		
3 points (< 65%)	13 (43.3%)	2 (13.3%)	11 (73.3%)		
Sleep disturbances, n (%)				0.57	-0.16, 1.30
1 point (mild sleep disturbances)	10 (33.3%)	4 (26.7%)	6 (40.0%)		

	Group			SMD	95% CI
	Overall N = 30	Sham N = 15	Active-tPCS N = 15		
Demographic & Anthropometrics					
2 points (moderate sleep disturbances)	15 (50.0%)	7 (46.7%)	8 (53.3%)		
3 points (severe sleep disturbances)	5 (16.7%)	4 (26.7%)	1 (6.7%)		
Use of sleep medication, n (%)				0.40	-0.32, 1.12
2 points (once or twice a week)	4 (13.3%)	3 (20.0%)	1 (6.7%)		
3 points (three or more times a week)	26 (86.7%)	12 (80.0%)	14 (93.3%)		
Daytime dysfunction, n (%)				0.94	0.19,1.70
0 points (no daytime dysfunction)	1 (3.3%)	1 (6.7%)	0 (0.0%)		
1 point (mild daytime dysfunction)	2 (6.7%)	0 (0.0%)	2 (13.3%)		
2 points (moderate daytime dysfunction)	19 (63.3%)	8 (53.3%)	11 (73.3%)		
3 points (severe daytime dysfunction)	8 (26.7%)	6 (40.0%)	2 (13.3%)		
Psychological Outcomes					
SAS, median (Q1, Q3)	53.75 (48.00, 62.50)	60.00 (55.00, 71.25)	48.00 (40.00, 53.75)	1.69	0.86, 2.53
SDS, median (Q1, Q3)	55.63 (47.25, 67.25)	67.25 (57.50, 82.50)	47.25 (41.25, 55.00)	2.01	1.13, 2.89
Concomitant Medications					
Benzodiazepine Use, n (%)	17 (56.7%)	8 (53.3%)	9 (60.0%)	0.13	-0.58, 0.85
Non-benzodiazepine hypnotics (Z-drugs)	8 (26.7%)	2 (13.3%)	6 (40.0%)	0.63	-0.10, 1.37
Sedating SSRIs/SARI/TCA	6 (20.0%)	5 (33.3%)	1(6.7%)	0.71	-0.03, 1.44
Minimally sedating SSRIs/SARI/TCA	6 (20.0%)	5 (33.3%)	1 (6.7%)	0.71	-0.03, 1.44
Sedating antipsychotics	11 (36.7%)	5 (33.3%)	6 (40.0%)	0.14	-0.58, 0.86
Non-sedating antipsychotics	2 (6.7%)	1 (6.7%)	1 (6.7%)	0.00	-0.72, 0.72
Abbreviations: BMI = body mass index; SD = standard deviation; TST = total sleep time; SL= sleep latency; SE = sleep efficiency; TIB = time in bed; WASO = wake after sleep onset; SAS- Zung Self-Rating Anxiety Scale; SDS = Zung Self-Rating Depression Scale; PSQI-Pittsburg Sleep Quality Index. SSRI = selective serotonin reuptake inhibitor; SARI = serotonin antagonist and reuptake inhibitor; TCA = tricyclic antidepressant; CI = Confidence Interval. Threshold: SMD > 0.1 suggests imbalance, > 0.2 small, > 0.5 moderate, > 0.8 large.					

Table 3
Post-treatment Outcomes analyzed using rank ANCOVA

Outcome	Mean ± SD		Adjusted Mean Rank ^a ± SD		Adjusted Mean Rank Diff Btw Grp (95% CI)	P value ^b	Effect Size ^c
	Sham	Active-tPCS	Sham	Active-tPCS			
Actigraphy							
Actigraphy TST, Mean (SD)	372.25 ± 48.60	372.63 ± 42.51	355.32 ± 10.42	389.57 ± 10.42	34.25 (1.60, 66.89)	0.022	0.180
Actigraphy SL, Mean (SD)	4.79 ± 3.48	4.98 ± 1.61	4.78 ± 0.70	4.99 ± 0.70	0.21 (− 1.81, 2.24)	0.995	0.000
Actigraphy SE, Mean (SD)	82.95 ± 6.43	88.29 ± 3.25	84.08 ± 1.03	87.16 ± 1.03	3.08 (0.00, 6.16)	0.030	0.163
Actigraphy TIB, Mean (SD)	449.37 ± 49.25	422.73 ± 50.82	424.85 ± 10.55	447.26 ± 10.55	22.42 (− 11.22, 56.06)	0.432	0.023
Actigraphy WASO, Mean (SD)	72.34 ± 29.31	45.12 ± 16.77	63.54 ± 4.96	53.92 ± 4.96	−9.62 (− 24.97, 5.72)	0.083	0.107
Actigraphy No. of Awakening, Mean (SD)	22.25 ± 6.46	18.42 ± 6.03	20.37 ± 1.53	20.29 ± 1.53	−0.08 (− 4.86, 4.70)	0.520	0.016
Actigraphy Avg. Awakening (min), Mean (SD)	3.26 ± 1.16	2.54 ± 0.63	3.13 ± 0.15	2.67 ± 0.15	−0.46 (− 0.91, − 0.02)	0.017	0.194
PSQI Outcomes							
PSQI Global, Mean (SD)	15.80 ± 2.62	12.53 ± 3.31	16.36 ± 0.70	11.97 ± 0.70	−4.39 (− 6.47, − 2.30)	< 0.001	0.451
Subjective Sleep Quality, Mean (SD)	2.60 ± 0.83	1.27 ± 0.88	2.71 ± 0.23	1.16 ± 0.23	−1.54 (− 2.22, − 0.87)	< 0.001	0.510
Sleep Latency, Mean (SD)	2.60 ± 0.51	2.07 ± 0.88	2.69 ± 0.18	1.97 ± 0.18	−0.72 (− 1.24, −0.20)	0.016	0.195
Sleep Duration, Mean (SD)	2.73 ± 0.46	1.20 ± 0.86	2.71 ± 0.17	1.22 ± 0.17	−1.49 (− 1.99, − 0.99)	< 0.001	0.589
Habitual Sleep Efficiency, Mean (SD)	1.20 ± 1.21	1.53 ± 1.06	1.65 ± 0.29	1.08 ± 0.29	−0.57 (− 1.49, 0.36)	0.216	0.056
Sleep Disturbances, Mean (SD)	2.00 ± 0.85	1.13 ± 0.52	1.90 ± 0.15	1.23 ± 0.15	−0.68 (− 1.13, − 0.22)	0.007	0.244
Use of Sleep Medication, Mean (SD)	2.53 ± 0.83	2.67 ± 0.90	2.58 ± 0.22	2.62 ± 0.22	0.04 (− 0.61, 0.69)	0.422	0.024
PSQI Daytime Dysfunction, Mean (SD)	2.13 ± 0.92	1.33 ± 0.62	2.10 ± 0.20	1.37 ± 0.20	−0.73 (− 1.32, − 0.14)	0.021	0.183
Psychiatric Scales							
SAS, Mean (SD)	62.33 ± 8.97	40.58 ± 7.66	57.38 ± 1.76	45.54 ± 1.76	−11.85 (− 17.58, − 6.12)	< 0.001	0.409
SDS, Mean (SD)	69.08 ± 11.89	40.83 ± 6.38	61.02 ± 1.52	48.89 ± 1.52	−12.13 (− 17.24, − 7.03)	< 0.001	0.408
^a Adjusted mean rank represents the baseline value adjusted average rank of the outcome derived from the Rank ANCOVA model. ^b P-values were obtained using Rank ANCOVA model. ^c Effect sizes represent partial η ² . Partial η ² effect size: Small effect = ~ 0.01; Medium effect = ~ 0.06; Large effect = ≥ 0.14. Multiplicity adjustment (See Supplement 3, eTable 3)							

Table 4
Incremental candidate covariates for Post-treatment TST and Post-treatment PSQI global score

Candidate Covariate	F(1,26) (Post-TST)	ΔR^2 (Post-TST)	P-value (Post-TST)	Partial η^2 (Post-TST)	F(1,26) (Post-PSQI Global)	ΔR^2 (Post-PSQI Global)	P-value (Post-PSQI Global)	Partial η^2 (Post-PSQI Global)
AGE	1.204	0.026	0.283	0.044	0.536	0.010	0.471	0.020
Baseline TST (actigraphy)	n.a	n.a.	n.a	n.a.	0.365	0.007	0.551	0.014
Baseline TIB	2.147	0.046	0.155	0.076	0.444	0.008	0.511	0.017
Baseline WASO	0.342	0.008	0.564	0.013	0.475	0.009	0.497	0.018
Baseline No. of Awakenings	0.242	0.006	0.627	0.009	0.035	0.001	0.853	0.001
PSQI Sleep Quality (baseline)	0.083	0.002	0.776	0.003	0.327	0.006	0.572	0.012
PSQI Sleep Efficiency (baseline)	0.411	0.009	0.527	0.016	0.123	0.002	0.729	0.005
Baseline SAS	0.000	0.000	0.983	0.000	0.422	0.008	0.522	0.016
Baseline SDS	0.849	0.019	0.365	0.032	2.161	0.038	0.154	0.077
Each candidate covariate (showing significant between-group differences at baseline) was added separately to the model, and its incremental contribution was evaluated using the change in explained variance (ΔR^2) and the associated F-change statistic. A significant ΔR^2 ($P < 0.05$) indicated that the covariate accounted for unique variability in post-treatment sleep outcomes beyond treatment allocation and baseline severity; partial eta squared (ηp^2) quantified the magnitude of this unique effect.								

Figures

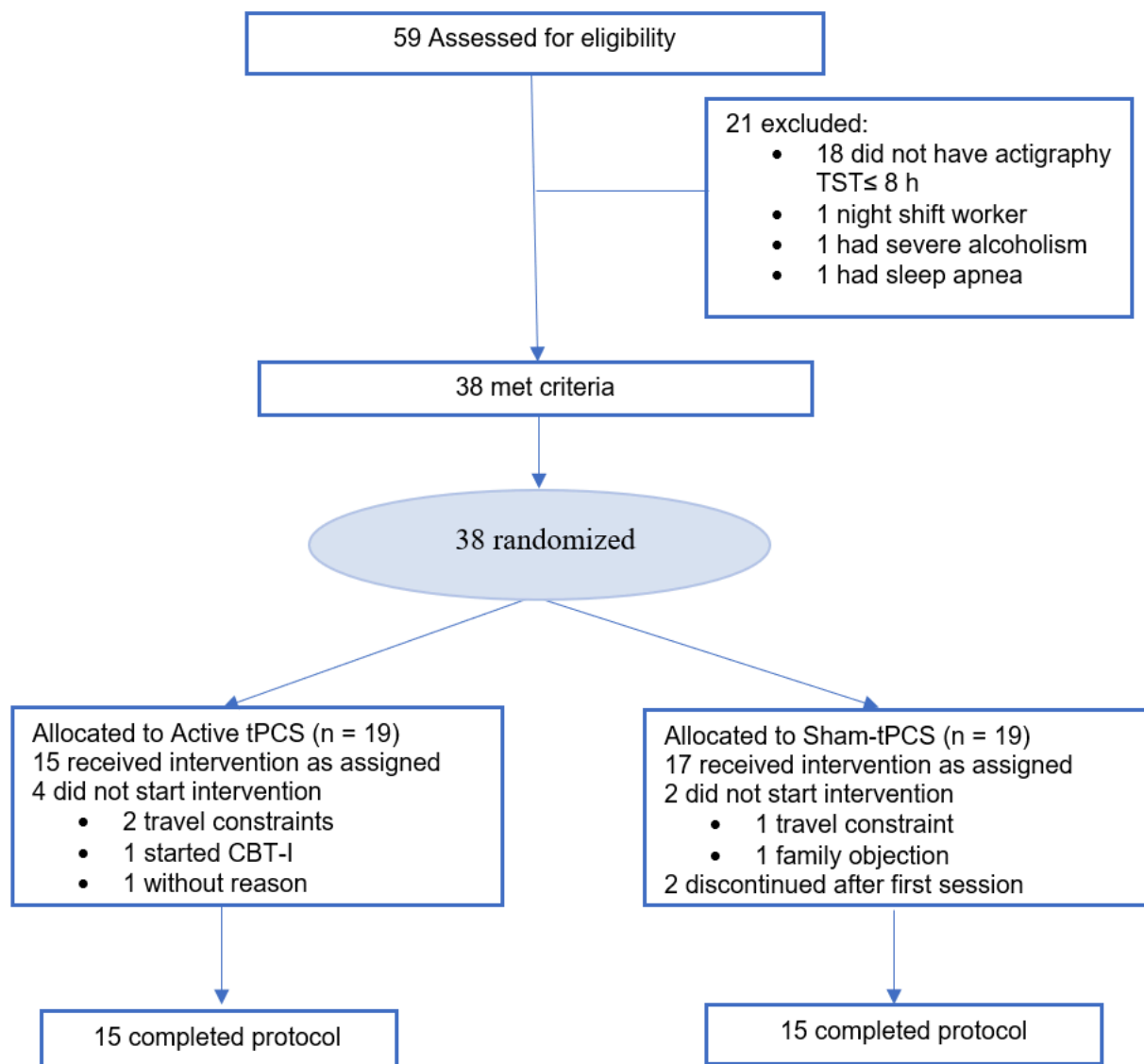


Figure 1

CONSORT flow diagram of the participants in the trial

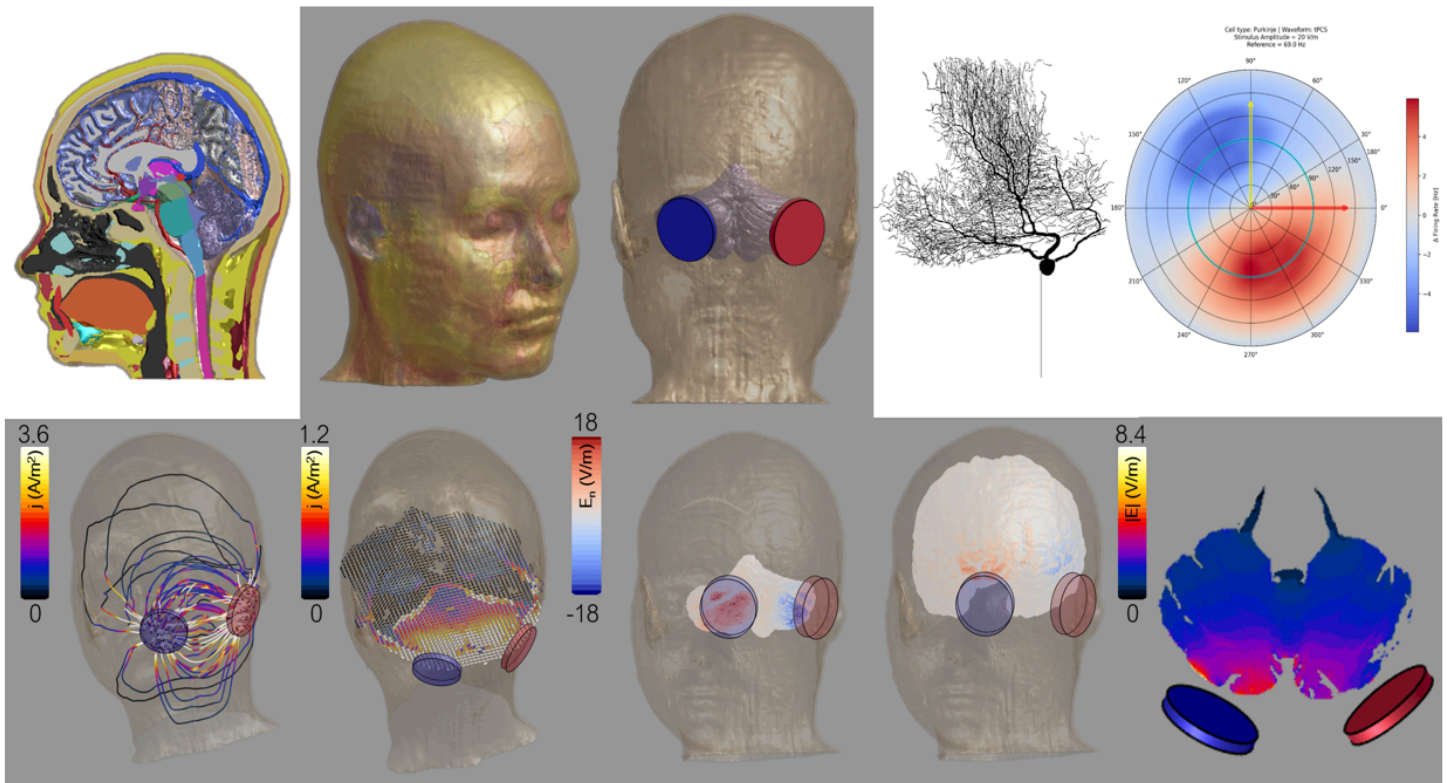


Figure 2

Estimation of induced electric-field by 400Hz tPCS

Computational modeling of tPCS exposure; (top, left to right) cross section and 3D view of the MIDA anatomical head model; electrode placement on the model; morphology of the Purkinje cell model; dependence of modelled Purkinje cell firing rate change on relative field orientation at the predicted cerebellar tPCS exposure conditions; (bottom, left to right) streamline and vector field view of current flow colored by current density at pulse peak; normal E-field component surface view of the cerebellum and cerebrum; E-field magnitude cross-section view through the cerebellum.

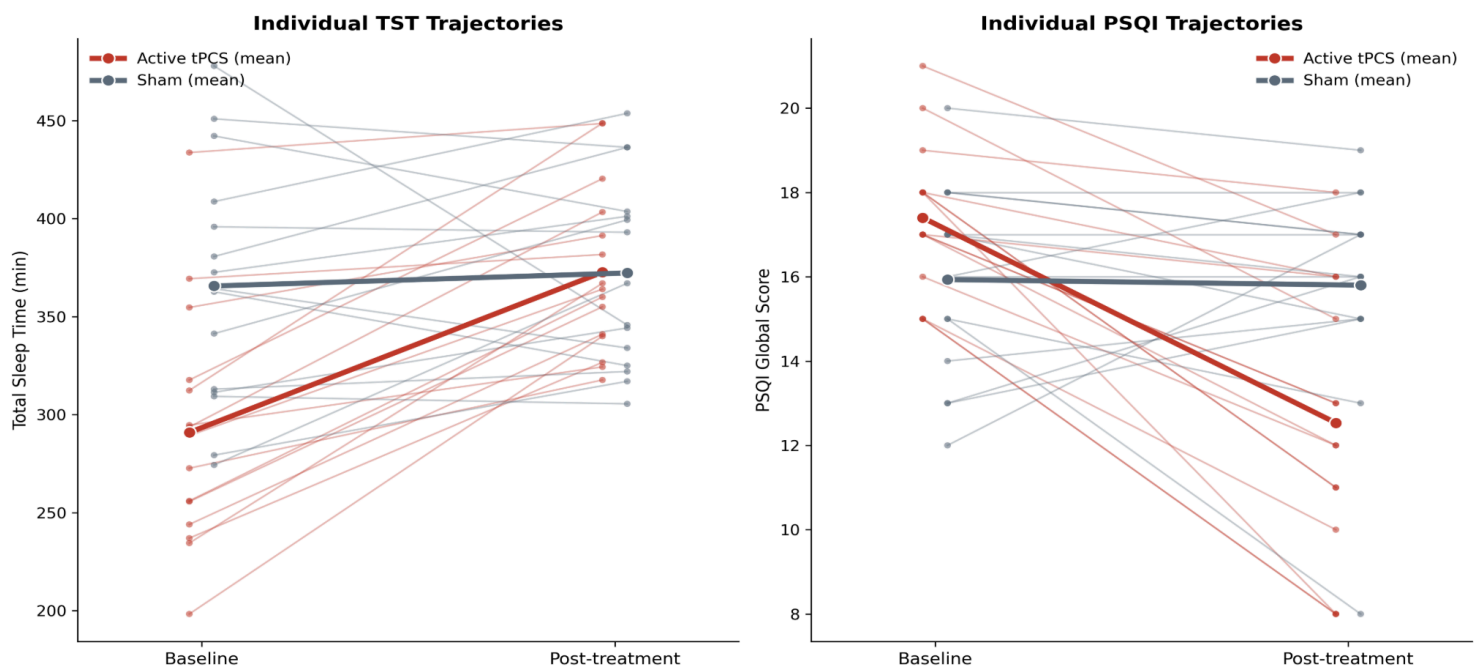


Figure 3

Individual subject trajectories from baseline to post-treatment change in actigraphy-derived TST and PSQI global score

Individual trajectories are shown for actigraphy-derived total sleep time (TST; left) and Pittsburgh Sleep Quality Index (PSQI) global score (right) in the active tPCS and sham groups. Thin lines represent individual participants, and thick lines represent group means.

Supplementary Files

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

- [Supplement1Trialprotocol.pdf](#)
- [Supplement2CONSORT2025checklistCerebellarHighFrequencyTranscranialPulsedCurrentStimulationIncreasesTotalSleepTimeinChronicInsomniaApilots](#)
- [Supplement3eTABLES.pdf](#)