ARTICLE

Efficacy and safety of transcranial alternating current stimulation in adults with attention deficit hyperactivity disorder: a double-blind randomized sham-controlled trial

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The transcranial alternating current stimulation (tACS) has been reported to improve attention-related neurophysiological measures in individuals with attention deficit hyperactivity disorder (ADHD); however, robust clinical evidence remains limited. This randomized, double-blind, sham-controlled trial aimed to explore the clinical efficacy, safety, and underlying neural mechanisms of tACS in adults with ADHD. A total of 56 adults with ADHD were randomly assigned in a 1:1 ratio to receive either active tACS or sham stimulation across 20 sessions over four consecutive weeks, with follow-up assessments conducted at week 8 and week 16. Clinical symptoms and resting-state magnetoencephalography (MEG) data were collected before and after the intervention. The tACS group showed significantly greater improvement in inattention symptoms compared to the sham group at week 4, as measured by the Adult ADHD Self-Report Scale – inattention subscale (ASRS-IA) (-10.1 vs. -5.5, $p < 0.001$, Cohen's $d = 1.02$). This improvement was sustained at week 8 but attenuated at week 16. Safety profiles were comparable between the two groups. Furthermore, the reduction in ASRS-IA scores was positively correlated with decreased gamma-band connectivity between the orbitofrontal cortex and the precuneus, indicating a desynchronization of neural activity in these brain regions. These findings suggest that tACS may serve as a promising neuromodulation intervention for adult ADHD, demonstrating both clinical benefits and specific neurophysiological mechanisms. TRIAL REGISTRATION: ChiCTR Identifier: ChiCTR2400081121.

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders, and often persists into adulthood [1, 2], with a prevalence of 2.5% in adulthood [3]. Adults with ADHD experience functional impairments across various life domains, including unemployment, low academic achievement, and high traffic accident rates [4], with up to 80% also having at least one coexisting psychiatric disorder [5, 6]. While stimulants are the most effective treatment [7, 8], they are not efficacious for all patients [9]. Additionally, challenges such as poor medication adherence [10] and long-term adverse events, including cardiovascular events [11], further limit the effectiveness of pharmacological treatment. Therefore, the development of new non-pharmacological intervention techniques for adults with ADHD is both promising and urgently needed.

Over the past few decades, noninvasive brain stimulation (NIBS) techniques have been found to be effective for improving core symptoms and cognitive functioning in patients with various mental disorders [12, 13]. Transcranial alternating current stimulation (tACS) has emerged as a promising NIBS approach for mental disorders and cognitive function [14, 15]. A pilot study involving children with ADHD revealed that 1 mA tACS, which uses a stimulation frequency determined by time–frequency decomposition of the P300 wave, could increase the amplitude of P300 [16], which is considered as a potential biomarker for ADHD [17]. However, this conclusion was not supported by a subsequent crossover-designed study [18]. Another RCT in which tACS was applied for 15 min across 10 sessions reported improvements in selective attention and working memory in athletes with ADHD [19]. Although existing evidence for the application of tACS in treating ADHD is relatively limited with a small stimulation electric current and varying frequencies used, it still offers intriguing possibilities for tACS in the treatment of adults with ADHD. Therefore, further efficacy and safety data are essential for tACS to be recognized as a viable and practical treatment option in clinical practice.

The mechanism of tACS involves generating oscillating electric fields in the brain, influencing cognitive performance by modulating underlying brain oscillation, facilitating local or distal synchronization, and affecting metabolic activity [14, 20, 21]. Gamma oscillation, in particular, plays crucial roles in attention, memory, neuronal communication and synaptic plasticity, underpinning neuronal processing in both local and distributed cortical networks engaged in complex cognitive functions [22, 23].

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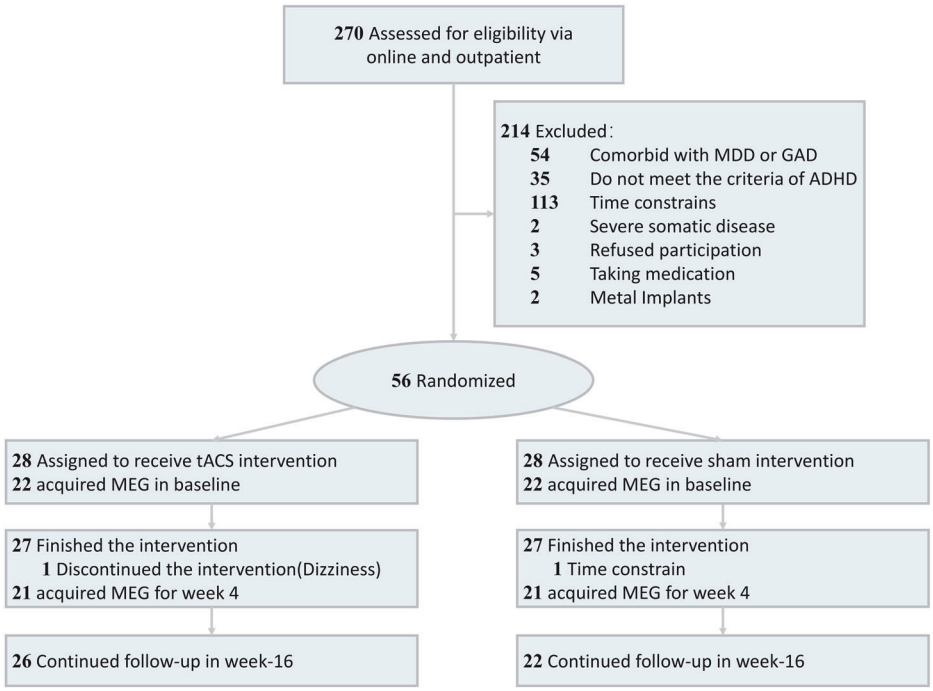

Fig. 1 CONSORT diagram. ADHD attention deficit/hyperactivity disorder, MDD major depression disorder, GAD general anxiety disorder, MEG magnetoencephalogram, tACS transcranial alternating current stimulation.

Electroencephalography (EEG) and magnetoencephalography (MEG) have revealed that atypical resting-state high gamma activity and connectivity in individuals with ADHD [24–27]. Gamma-band tACS was shown to have positive effects on memory and attention in individuals with Alzheimer's disease and mild cognitive impairment [28, 29]. The tACS frequency of 77.5 Hz has been proven to elicit the highest level of β-endorphins [30], thus promoting the release of dopamine [31], which might improve the clinical symptoms of ADHD [3]. Furthermore, tACS exhibited dose-dependent effects on the brain [32], with previous clinical RCTs demonstrating its clinical efficacy in treating major depression disorder [33, 34] and insomnia [35]. On the basis of these findings, we hypothesized that gamma-band tACS may improve inattention symptoms in adults with ADHD by modulating the connectivity of gamma oscillations.

In this study, we conducted a double-blind sham-stimulation controlled RCT of tACS, utilizing a large gamma-frequency current over twenty sessions across 4 consecutive weeks, to assess its efficacy in reducing inattention symptoms in adults with ADHD, as well as the safety of the intervention. In addition, we used MEG to measure changes in gamma connectivity strength, providing insights into the neural mechanisms underlying tACS efficacy.

METHODS AND MATERIALS

The study is a parallel group, double-blind, randomized, sham-controlled clinical trial investigating the efficacy and safety of tACS versus sham stimulation in adults with ADHD, and exploring its underlying mechanism. The study was conducted from January 2023 to August 2024 at Peking University Sixth Hospital. This study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Participants

A total of 56 participants were recruited from the outpatient department or through online advertisements (as shown in Fig. 1). The inclusion criteria were as follows: 1) aged 18 to 39 years; 2) diagnosed with ADHD (according to the DSM-5); 3) baseline Adult ADHD Self-report Scale - inattention (ASRS-IA) scores of at least 21; 4) no pharmacological treatment or systematic non-pharmacological intervention for ADHD in the 4 weeks prior to the baseline assessment. The exclusion criteria included the following: 1) diagnosis of bipolar disorder, schizophrenia or another psychotic disorder, or autism spectrum disorder; 2) current diagnosis of other mental disorders; 3) current suicidal thoughts or plans; 4) current severe physical illness; 5) history of seizure or head injury with loss of consciousness; 6) pregnancy or intention to become pregnant within the next three months; 7) receiving other brain stimulation interventions in the past three months; 8) presence of metal implants, including cochlear implants and cardiac pacemakers, or metal implants in the head or brain; 9) hyperalgesia, damage, or inflammation in the stimulated area; 10) inability to undergo tACS for any reason.

Sample Size

The sample size calculation was based on measures from a previously published study assessing the efficacy of transcranial direct current stimulation (tDCS) in adults with ADHD [36]. After 4 consecutive week of intervention, the clinical-based ASRS score of the tDCS group was 18.88 ± 5.79, the score of the sham group was 23.63 ± 3.97, $\alpha = 0.05$, $\beta = 0.1$, $1\text{-}\beta = 0.9$, the rate of loss to follow up was 20%, and the ratio of the numbers of two groups (k) was 1:1. Finally, the sample size was 28 participants for each group, with 56 participants in total.

Procedures

The entire procedure included three phases: screening and baseline assessment, intervention phase, and follow-up phase.

After the online screening of basic information, a trained and certificated psychiatrist conducted a diagnostic interview with the participant via the Conner's Adult ADHD Diagnostic Interview (CAADID), which is based on DSM criteria [37], to confirm the diagnosis of ADHD. The Mini International Neuropsychiatric Interview (MINI) based on the DSM-IV [38, 39] was used to exclude potential comorbidities. If the participants met the criteria of this study, a baseline assessment (T0) was performed. All participants were required to complete baseline questionnaires and underwent MEG and T1-weighted magnetic resonance imaging(T1-MRI) scans. The participants were subsequently randomly assigned to the tACS group or the sham group.

During the intervention phase, participants were randomly assigned to the tACS group, or the sham group. The participants received 20 forty-minute sessions of tACS or sham tACS across 4 consecutive weeks (once a day, five weekdays a week). After 10 sessions in 2 consecutive weeks, they underwent a midterm assessment (T1, week-2), and after completing

20 sessions over 4 consecutive weeks, they received a posttreatment assessment (T2, week-4). Throughout the intervention period, participants could not take any psychiatric pharmacology.

The follow-up period was a naturalistic observation period. Participants underwent a follow-up assessment at 4 weeks (T3, week-8) and 12 weeks (T4, week-16) after the end of the intervention, and they can take medication or received other non-pharmacological intervention as they want, under the suggestions of clinicians.

Randomization, Blinding

The participants were randomly divided into group A and group B, which anonymously represented the tACS group and the sham group, respectively. The random sequence was generated via computer software and stratified randomly according to age (18-29 years or 30-39 years) and sex(male/female). The allocation protocol was concealed for both the investigator and the participants. Two machines were used in the experiment, one for true stimulation and the other for the sham stimulation. The appearances, usage and feelings of stimulation between the two machines were exactly the same. The two machines were distinguished only by letters A and B, and the participants did not know their own allocations. The operators performed the intervention according to the determined grouping plan and carried out exactly same operation process and steps for the two groups of participants. The operators did not participate in the assessment of the subjects. Bang's Blinding Index [40, 41] was used to evaluate the success of blinding, and was calculated per treatment arm, yielding a continuous value ranging from -1 to 1, with a score of 0 indicating successful blinding. A positive Bang's Blinding Index indicates that participants guessed their treatments correctly beyond chance.

Intervention

Participants received FDA-approved tACS treatment (Nexalin Technology, Inc, U.S.A), which has been utilized in previous studies. The machine was registered with the U.S. Food and Drug Administration (FDA), (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm?lid=574524&lpcd=QJQ#), and was also registered with the National Medical Products Administration in China (NMPA, https://www.nmpa.gov.cn/datasearch/search-info.html?nmpa=aWQ9NjMzOTImaXRlbUlkPWZmODA4MDgxODMwYjEwMzUwMTgzOGQ0ODcxYjUzNTQz) before the trial started. During stimulation, the participants were seated in a comfortable chair, and were advised to remain relaxed or even sleep. The stimulation procedures were carried out by trained physical therapy technicians. One 4.45*9.53 cm tACS electrode was positioned on the forehead, corresponding to the Fpz, Fp1 and Fp2 locations according to the 10/20 international placement system. Additionally, two smaller electrodes, each measuring 3.18 * 3.81 cm, were placed on the mastoid region on both sides of the head. The current density is 3.54 A/m^2 in the forehead and 6.19 A/m^2 in each mastoid, which are under the threshold of "potential brain injury at current densities of 6.3-13 A/m^2 [42, 43]. The tACS stimulation waveform included ramp-up and ramp-down periods of 180 and 12 s, respectively (as shown in Supplementary Fig. 1). The alternating current with a square waveform has a mean square current intensity of 15 mA within one current period, and its frequency was 77.5 Hz. The waveforms were square waves and were distributed equally from the frontal region to the mastoid areas. For the sham group, there was no electric current output from the machine.

Outcomes

The primary efficacy endpoint was the change in ASRS-IA scores from baseline to week 4 (with 20 treatment sessions completed). The secondary outcomes included the ASRS-hyperactivity/impulsivity (ASRS-HI) scores, and the ASRS-total (ASRS-TO) scores at T0-T4; the Behavior Rating Inventory of Executive Functions-Adult (BRIEF-A), the Weiss Functional Impairment Rating Scale – Self (WFIRS-S), Pittsburgh Sleep Quality Index (PSQ-I), Hamilton Depression Scale-17 (HAMD-17), the Hamilton Anxiety Scale (HAMA), which is rated at T0, and T2-T4; and the Clinical Global Impression-Improvement (CGI-I), which is rated by clinicians at T1-T4.

Safety assessments

We assessed adverse events at 2 time points (week 2/week 4), with a questionnaire reporting common adverse events in transcranial electric stimulation (tES) trials [36]. The participants were also asked to report other adverse events that were not presented on the questionnaire.

MEG and MRI data acquisition and connectivity analysis

Forty-two participants ($N_{tACS} = 21$, $N_{sham} = 21$) completed two MEG and MRI sessions, at baseline and the day after the end of intervention, respectively. MEG data were recorded for six minutes (3 min eyes open [EO], 3 min eyes closed [EC]). Subsequently, a T1-weighted anatomical MRI scan was acquired after MEG recording for MRI/MEG co-registration. Preprocessing and analyses were conducted in MATLAB using the FieldTrip toolbox [44]. MEG data were downsampled, band-pass filtered, and segmented into epochs. Artifacts were removed using independent component analysis (ICA). Source-level activity was reconstructed and estimated for six canonical frequency bands: (delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), low gamma (40-60 Hz), and high gamma (60-90 Hz)). Functional connectivity was computed between 90 regions of interest defined by the Automated Anatomical Labeling (AAL90) atlas [45], yielding a 90*90 connectivity matrix for each frequency band (as shown in Supplementary Table 6 & Supplementary Fig. 2). Additional methodological details are provided in the Supplementary Methods.

Statistical analysis of demographics and clinical outcomes

To compare the demographic and clinical measurements between the tACS group and the sham group, the independent two sample t-test was applied for the continuous variables, whereas the Chi-square test was used for categorical variables.

For each continuous clinical outcome variable, a single general linear mixed effect model was established, with treatment group (tACS vs. sham), time (T0/T1/T2/T3/T4), and group-by-time interaction as fixed effect and the participant-level intercept as a random effect. For CGI-I, Chi-square tests were performed at week-2 and week-4. Statistical significance was defined as two-sided P value < 0.05. All analyses were conducted via R 4.4.1 and SAS version 9.4 (SAS Institute Inc). For sensitivity analysis, we also established the single LMM for clinical symptoms (ASRS-IA/HI/TO) after excluding the participants who received stimulant treatment during the follow-up period at week 8 and week 16. Effect size differences between the tACS and sham groups were estimated via Cohen's d and the number needed to treat (NNT). The NNT calculation was based on the change rate of ASRS-IA from baseline to the end of treatment. The response was defined as change in the ASRS-IA score of 30%. Cohen's d was categorized into small (≥0.2), medium (≥0.5), and large (≥0.8) effects. The NNT cutoff values for small, medium, and large effects were defined as 9, 4, and 2, respectively.

Statistical analysis of the MEG data

We investigated whether changes in low and high gamma connectivity strength differed between the tACS and sham groups before and after treatment. Exploratory analyses were conducted in other frequency bands. Using the Network-Based Statistic (NBS) toolbox [46], we conducted a repeated-measures analysis of variance (RM-ANOVA), of groups (tACS and sham) by time (baseline and post-treatment), via the general linear model (GLM). A primary threshold (T-value = 2.5) was applied to the test statistic matrix to identify supra-threshold connections (edges). These edges were then grouped into connected components (clusters) via spatial adjacency, which is defined in the NBS toolbox as edges that share at least one node in common. In other words, if two supra-threshold connections shared a node (i.e., brain region), they were considered part of the same topological cluster. This process allows the detection of spatially connected subnetworks rather than isolated individual connections. Statistical significance of each cluster was evaluated via permutation testing (5000 permutations), with significance set at $p < 0.05$ (family-wise error rate corrected). For clusters showing a significant group*time interaction effect, simple effect analyses were performed to explore which edge strengths changed between pre- and post- sessions in each group [47]. Edges with significant changes in connectivity strength in the tACS group were defined as edges of interest (EOIs). Pearson's correlation coefficients were calculated to examine the relationships between changes in connectivity strength in the EOIs and ASRS-IA or ASRS-TO changes (post-treatment vs. baseline). False discovery rate (FDR) correction was applied to control the false positive rate. All the statistical tests were two-tailed, with $p < 0.05$ indicating statistical significance. The demographic and main outcomes of participants in the MEG subgroup were also reanalyzed as the full set process progressed.

Table 1. Baseline characteristics of participants.

Characteristics	tACS group (N = 28)	Sham Group (N = 28)	t/χ^2	*p*
Age (years, mean (SD))	26. 07 (4.41)	27.39 (5.49)	−0.99	0.325
Gender (n (%))			0.08	0.771
Male	9 (32.1%)	8 (28.6%)		
Female	19 (67.9%)	20 (71.4%)		
Ethnic (n (%))			1.19	0.275
Han	22 (78.6%)	25 (89.3%)		
Other Ethnic Minorities	6 (21.4%)	3 (10.7%)		
Educational years (years, mean (SD)	16.46 (2.63)	16.39 (1.40)	0.13	0.900
IQ level (n (%))			1.95	0.377
Level I (≥ 95%)	21 (75%)	17 (60.7%)		
Level II (75% - 95%)	7 (25%)	10 (35.7%)		
Level III (50% - 75%)	0 (0%)	1 (3.6%)		
Marital status (n (%))			0.22	0.639
Unmarried	25 (89.3%)	26 (92.9%)		
Married	3 (10.7%)	2 (7.1%)		
Working status (n (%))			5.01	0.082
Studying	9 (32.1%)	10 (35.7%)		
Employed	16 (57.1%)	9 (32.1%)		
Unemployed	3 (10.7%)	9 (32.1%)		
Family history (n (%))			0.13	0.716
With	24 (85.7%)	23 (82.1%)		
Without	4 (14.3%)	5 (17.9%)		
ADHD diagnosis (n (%))			0.38	0.537
ADHD-I	22 (78.6%)	20 (71.4%)		
ADHD-C	6 (21.4%)	8 (28.6%)		
Lifetime affective diagnosis (n (%))			0.08	0.771
With	20 (71.4%)	19 (67.9%)		
Without	8 (28.6%)	9 (32.1%)		
Lifetime ADHD diagnosis (n (%))			0.07	0.789
With	14 (50%)	15 (53.6%)		
Without	14 (50%)	13 (46.4%)		
Previous use stimulant (n (%))			0.69	0.408
Ever	12 (42.9%)	9 (32.1%)		
Never	16 (57.1%)	19 (67.9%)		
Baseline ASRS score (mean (SD))				
Inattention	28.79 (3.83)	27.21 (3.36)	1.63	0.109
Hyperactivity/ Impulsivity	17.54 (7.56)	18.00 (6.71)	−0.24	0.809
Total	46.32 (9.94)	45.21 (8.05)	0.46	0.649

tACS transcranial alternating current stimulation, *ASRS* adult ADHD self-report Scale.

RESULTS

Demographics

In total, 270 participants were screened through online advertisements and at the outpatient department, as illustrated in Fig. 1. Ultimately, 56 participants were included in this study, with 28 in each group (tACS group and sham group). Table 1 presents the baseline demographics and clinical characteristics of the participants, which were well matched between the two groups. Among all participants, two underwent a one-month washout period of stimulants before the initiation of the intervention. Two participants (1 in the tACS group and 1 in the sham group) did not finish all 20 session stimulations. The adherence rate was 96.43% for both groups. At the end of week-16, 26 participants in the tACS group and 22 in the sham group were followed up.

Primary outcomes

For the primary endpoint at week 4, the mean change in the ASRS-IA score was -10.1 (95% CI, -12.1 to -8.1) in the tACS group and -5.5 (95% CI, -7.5 to -3.6) in the sham group compared with the baseline score. Compared with the sham group, the tACS group presented significantly greater reductions in the ASRS-IA score (mean difference, 4.6 [95% CI, 1.8 to 7.4]; $P_{time*group} < 0.001$; Cohen's d: 1.02) (Table 2). Among participants receiving active tACS, a statistically significant improvement in the ASRS-IA score compared with the sham group was presented at week 2 (mean difference, 4.6[95% CI, 2.3 to 6.8], $P_{time*group} < 0.001$; Cohen's d, 1.04) and could be maintained through the follow-up period at week 8 (mean difference, 3.9 [95% CI, 0.6 to 7.2]; $P_{time*group} = 0.005$; Cohen's d, 0.85) and week 16 (mean difference, 4.7, [95% CI, 1.3 to 8.0], $P_{time*group} < 0.001$; Cohen's d, 0.93). However, the mean change from baseline attenuated at week 16 (-9.5 [95% CI, -11.8 to -7.2], as shown in Fig. 2A, Table 2). The response rate in tACS group was 57.1% in the tACS group, and 32.1% in the sham group, and NNT was 4.0. During the follow-up period, 6 participants in the tACS group and 3 in sham group reported receiving stimulant treatment for ADHD at week 16. After excluding these participants at week 8 and week 16, the conclusion was consistent with the full-set results (Supplementary Table 1).

Secondary outcomes

The CGI-I showed statistical significance at week 4 ($\chi^2 = 14.75$, $p = 0.002$) between the tACS group and the sham group. Specifically, 16 (57.1%) participants in tACS group improved, whereas only 3 (10.7%) in the sham group improved (details in Supplementary Fig. 3). For the ASRS-TO score at week 4, the tACS group presented significantly greater reductions than the sham group did (mean difference, 4.9 [95% CI, 0.5 to 9.3]; $P_{time*group} = 0.03$; Cohen's d: 0.54), and presented a similar pattern of mean change from baseline to week-16 as the changes in ASRS-IA scores (as shown in Fig. 2C, Table 2). However, the mean change from baseline to each time point in ASRS-HI score between the two groups did not significantly differ (as shown in Fig. 2B, Table 2).

For the other secondary outcomes, no statistically significant treatment-by-time interaction effect was observed, but all the time effects except for the PSQ-I and HAMD-17 scores were significant (details in Supplementary Table 2).

Safety

The adverse events recorded during the intervention phase are presented in Table 3. Most of these events were mild. No severe or serious adverse events were observed. The most common adverse event was drowsiness in both the tACS group and the sham group (all *P* values > 0.05). Only one participant in the tACS group withdrew from the trial due to dizziness and insomnia-early, after 14 sessions. After the withdrawal from the trial, the adverse events disappeared within a few days.

Blinding integrity

The Bang's Blinding Index was 0.19 (95% CI, -0.11 to 0.48) in the tACS group, and 0.11 (95% CI, -0.21 to 0.43) in the sham group, indicating the success of a pattern consistent with a random distribution of responses in both the tACS group and the sham group (details in Supplementary Table 3).

Table 2. Mean change of ASRS scores from baseline to each time points.

Time points	tACS group (N = 28)	Sham group (N = 28)	β_{int}	T_{int}	P_{int}	Cohen's d (95% CI)	β_{time}	T_{time}	P_{time}
ASRS-Inattention									
Week 2	−8.2 (4.9)	−3.6 (3.6)	−4.6 (−6.8 to −2.3)	−3.6	**<0.001**	1.04 (0.42 to 1.66)	−3.6 (−5.3 to −1.9)	−4.0	**<0.001**
Week 4	−10.1 (4.6)	−5.5 (5.4)	−4.6 (−7.4 to −1.8)	−3.6	**<0.001**	1.02 (0.40 to 1.64)	−5.5 (−7.3 to −3.8)	−6.2	**<0.001**
Week 8	−10.7 (5.0)	−6.8 (4.3)	−3.9 (−7.2 to −0.6)	−2.8	**0.005**	0.85 (0.26 to 1.44)	−7.1 (−8.9 to −5.2)	−7.4	**<0.001**
Week 16	−9.3 (5.1)	−4.6 (4.3)	−4.7 (−8.0 to −1.3)	−3.5	**<0.001**	0.93 (0.33 to 1.54)	−4.8 (−6.7 to −2.9)	−5.0	**<0.001**
ASRS-Hyperactivity/Impulsivity									
Week 2	−5.7 (5.9)	−4.9 (5.1)	−0.8 (−3.5 to 1.9)	−0.6	0.571	0.11 (−0.42 to 0.65)	−4.9 (−6.8 to −3.0)	−5.0	**<0.001**
Week 4	−6.6 (4.8)	−6.3 (6.6)	−0.4 (−3.0 to 2.3)	−0.3	0.797	0.05 (−0.48 to 0.59)	−6.3 (−8.1 to −4.4)	−6.4	**<0.001**
Week 8	−7.8 (6.6)	−7.1 (4.3)	−0.3 (−3.1 to 2.5)	−0.2	0.837	0.01 (−0.52 to 0.55)	−7.5 (−9.5 to −5.4)	−7.2	**<0.001**
Week 16	−7.7 (5.8)	−5.2 (4.0)	−2.5 (−5.3 to 0.3)	−1.7	0.087	0.31 (−0.23 to 0.85)	−5.4 (−7.4 to −3.4)	−5.1	**<0.001**
ASRS-Total Score									
Week 2	−13.9 (8.7)	−8.5 (7.6)	−5.4 (−9.7 to −1.0)	−2.4	**0.019**	0.60 (0.05 to 1.14)	−8.5 (−11.6 to −5.4)	−5.3	**<0.001**
Week 4	−16.7 (7.2)	−11.8 (10.7)	−4.9 (−9.3 to −0.5)	−2.2	**0.031**	0.54 (0.01 to 1.09)	−11.7 (−14.9 to −8.7)	−7.3	**<0.001**
Week 8	−18.5 (10.2)	−14.0 (7.3)	−4.0 (−8.6 to 0.5)	−1.7	0.089	0.38 (−0.17 to 0.92)	−14.6 (−17.8 to −11.2)	−8.5	**<0.001**
Week 16	−17.0 (8.9)	−9.8 (7.1)	−7.2 (−11.9 to −2.6)	−3.0	**0.003**	0.65 (0.08 to 1.22)	−10.2 (−13.5 to −6.9)	−5.9	**<0.001**

The mean change score of ASRS score from baseline to each time point were presented as mean (SD).
tACS transcranial alternating current stimulation, *ASRS* adult ADHD self-report scale, *CI* confidential interval.
β_{int}, T_{int}, and P_{int}, the estimated coefficients, the T statistic value, and the P value of time*group interaction in the linear mixed effect model; β_{time}, T_{time}, and P_{time}, the estimated coefficients, the T statistic value, and the P value of time effect in the linear mixed effect model.

MEG Results

Connectivity analyses in gamma- frequency bands. The demographics and main outcomes of the participants in the MEG subgroup were similar to those of the participants in the full cohort (details in Supplementary Table 4-5). For the eye-open (EO) resting state, one cluster in the low gamma band ($p = 0.029$, 88 edges) and one cluster in the high gamma band ($p = 0.043$, 93 edges) demonstrated significant group-by-time interactions (see Supplementary Fig. 4). No edges exhibited a time effect, whereas a significant group effect was observed in the low gamma band ($p = 0.028$, 105 edges, tACS > sham) and the high gamma band ($p = 0.047$, 104 edges, tACS > sham). For the eye-closed (EC) resting state, one cluster showed a marginally significant interaction effect in the high gamma band ($p = 0.070$, 82 edges), whereas no edges showed significant time and group effects in the high gamma band. Additionally, a cluster in the low gamma band exhibited a significant main effect of group ($p = 0.039$, 83 edges, tACS > sham). No edges showed significant group-by-time interactions across other bands or for the EO/EC recordings (as shown in Supplementary Fig. 5).

Simple effect analyses revealed significant reductions in connectivity following the tACS intervention in both the low and high gamma bands for the EO recordings (as shown in Fig. 3, Supplementary Table 7 & 8). We defined these edges as edges of interest (EOIs) for subsequent correlation analyses. No significant correlation was observed between changes in EOI strength and ASRS-IA or ASRS-TO changes in the high gamma band (Supplementary Table 8). However, the change in low gamma connection strength between the left orbitofrontal cortex and the left precuneus was positively correlated with ASRS-IA and ASRS-overall score changes (ASRS-IA: r = 0.69, FDR-corrected $p = 0.033$; ASRS-TO: r = 0.78, FDR-corrected $p = 0.004$). We also found that the changes in low gamma connection strength between the right anterior cingulum (ACC) and the right middle temporal gyrus (MTG) were negatively correlated with changes in the ASRS-IA score (r = -0.66, FDR-corrected $p = 0.042$), whereas no significant correlation was observed with changes in the ASRS-TO score (r = -0.45, FDR-corrected $p = 0.748$) (details in Supplementary Table 7 & 8).

Connectivity analyses in other frequency bands. In addition to low and high gamma frequency bands, we conducted exploratory analyses in frequency bands. NBS analyses revealed no significant group × time interaction or group effect in any frequency band. However, connections exhibiting a main effect of time were observed in the theta band ($p = 0.026$, 66 edges, post-treatment > pre-treatment) during the eye-open recording, and in the delta band ($p = 0.044$, 48 edges, post-treatment > pre-treatment) during the eye-closed recording (Supplementary Fig. 5).

Differences in correlations between tACS and sham groups. We observed marginally significant differences in the correlation between the edge strength change (Frontal_Sup_Orb_L-Precuneus_L, low gamma band) and ASRS-IA change (sham group: r = 0.33, $p = 0.146$; difference test with active group: Z = -1.50, $p = 0.067$) or ASRS-TO change (sham group: r = 0.48, $p = 0.029$, difference test with active group: Z = -1.57, $p = 0.059$). In contrast, no significant group difference was found in the correlation between the edge strength change (Cingulum_Ant_R-Temporal_Mid_R, low gamma band) and ASRS-IA change (sham group: r = -0.37, $p = 0.104$; difference test with active group: Z = 1.24, $p = 0.108$) or ASRS-TO change (sham group: r = -0.30, $p = 0.189$; difference test with active group: Z = 0.55, $p = 0.292$).

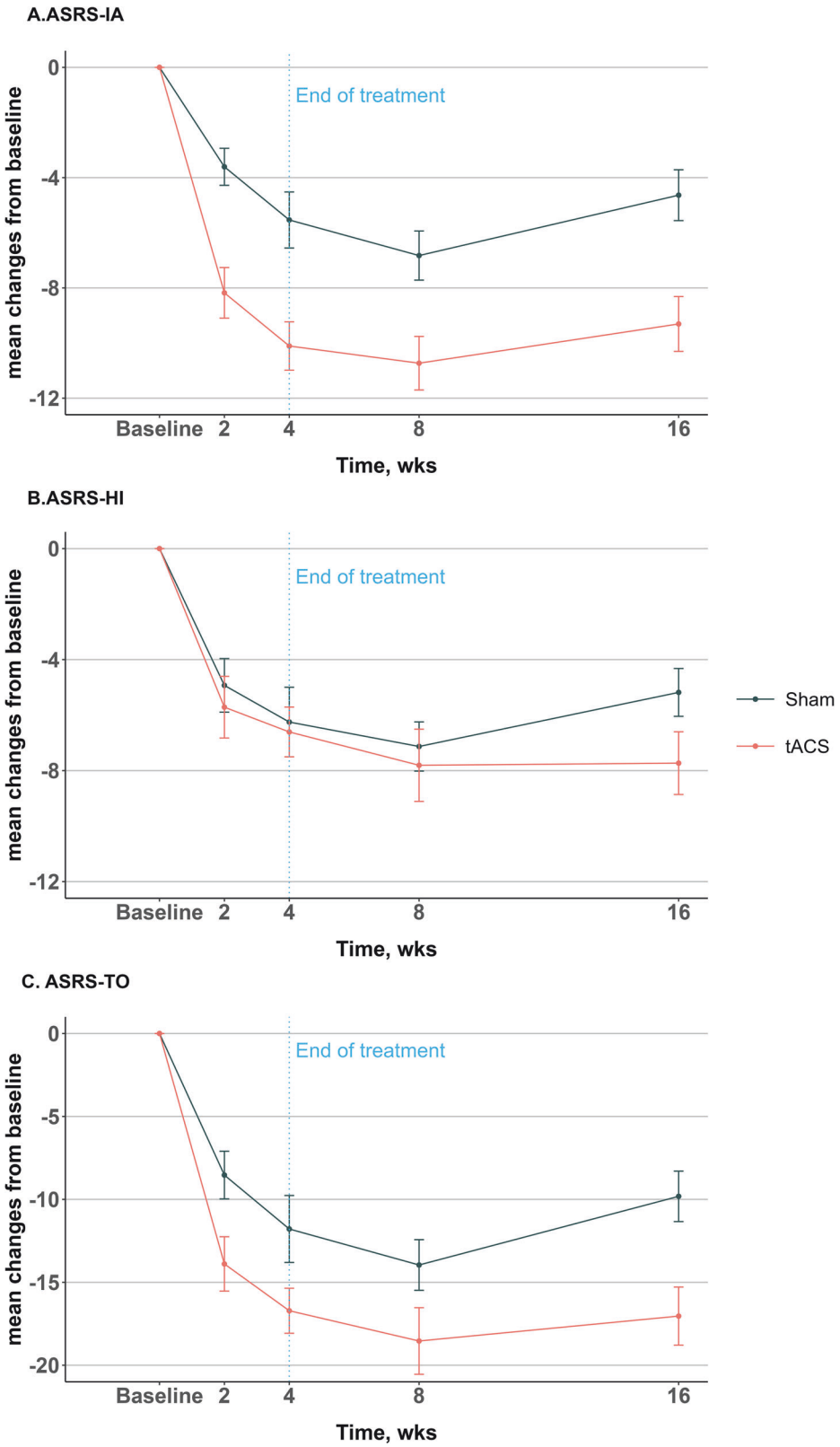

Fig. 2 Comparison of ASRS scores between the tACS and sham-controlled groups during and after the intervention. The point estimates and interval estimates were represented as mean and standard error, respectively. ASRS Adult ADHD Self-report Scale.

Table 3. Adverse effects during intervention period.

	Week 2		χ^2	p	Week 4		χ^2	p
	tACS Group (N = 28)	sham Group (N = 28)			tACS Group (N = 28)	sham Group (N = 28)		
Drowsiness	9 (32.1%)	12 (42.9%)	0.69	0.408	11 (39.3%)	14 (50.0%)	0.65	0.420
Headache	5 (17.9%)	4 (14.3%)	0.13	0.716	2 (7.1%)	5 (17.9%)	1.47	0.225
Skin itch	2 (7.1%)	4 (14.3%)	0.75	0.388	5 (17.9%)	2 (7.1%)	1.47	0.225
Tinnitus	3 (10.7%)	1 (3.6%)	1.08	0.299	2 (7.1%)	2 (7.1%)	0.00	1.000
Neck pain	2 (7.1%)	3 (10.7%)	0.22	0.639	5 (17.9%)	3 (10.7%)	0.58	0.445
Redness of skin on treatment site	2 (7.1%)	2 (7.1%)	0.00	1.000	2 (7.1%)	2 (7.1%)	0.00	1.000
Dizzy	3 (10.7%)	3 (10.7%)	0.00	1.000	2 (7.1%)	4 (14.3%)	0.75	0.388
Stinging skin	1 (3.6%)	1 (3.6%)	0.00	1.000	3 (10.7%)	0 (0%)	3.17	0.075
Scalp pain	0 (0%)	1 (3.6%)	1.02	0.313	1 (3.6%)	1 (3.6%)	0.00	1.000
Loss of appetite	0 (0%)	1 (3.6%)	1.02	0.313	0 (0%)	0 (0%)	0.00	1.000
Allergic rash	0 (0%)	0 (0%)	0.00	1.000	1 (3.6%)	0 (0%)	1.02	0.313
Tingling	1 (3.6%)	0 (0%)	1.02	0.313	1 (3.6%)	0 (0%)	1.02	0.313
Insomnia-early	1 (3.6%)	0 (0%)	1.02	0.313	1 (3.6%)	0 (0%)	1.02	0.313
Burning sensation	0 (0%)	0 (0%)	0.00	1.000	0 (0%)	0 (0%)	0.00	1.000
Visual flickering	1 (3.6%)	0 (0%)	1.02	0.313	1 (3.6%)	0 (0%)	1.02	0.313

All the degree of freedom was 1.

DISCUSSION

This randomized, double-blind, sham controlled clinical trial investigated the efficacy and safety of 20 sessions of 15 mA tACS at 77.5 Hz over 4 consecutive weeks for inattention symptoms in adults with ADHD. The results indicated significant improvement in inattention symptoms with no significant side effects. The MEG results further supported tACS-related modulation of gamma-band functional connectivity, which correlated with changes in inattention symptoms. These findings suggest that 4 weeks of 15 mA tACS at 77.5 Hz is a promising treatment for adults with ADHD.

The choice of tACS parameters is crucial for achieving positive clinical outcomes [14, 48]. Compared with prior tACS protocols for ADHD, our study introduced three methodological refinements. First, electrode placement on the forehead (Fpz, Fp1, and Fp2 based on the international 10/20 system) and bilateral mastoid regions was selected on the basis of evidence of widespread brain activation by stimulation, particularly in the bilateral prefrontal cortex, a recognized pathophysiologic mechanism in ADHD [49, 50]. Second, the frequency-dependent synchronization and desynchronization effects of tACS allow the modulation of specific frequency band oscillations, influencing inter-regional communication [51]. We targeted gamma band based on its association with attention and memory functions [22, 52], as well as its dysregulation in ADHD [24–27]. Third, sufficient dosage is essential for the effectiveness of tACS. We pioneered the use of high electric current intensity tACS (15 mA) in adults with ADHD, which was supported by evidence that the modulation of tACS at high frequencies (>20 Hz) requires higher stimulation intensities than at low frequencies [53] and that efficacy increases with intensity in a dose-dependent manner [32, 54]. Previous tES studies on ADHD using lower intensities [18, 36, 55] reported limited efficacy, potentially due to insufficient cortical stimulation [56]. Although there is no consensus regarding the optimal dose for ADHD, our results suggest that 15 mA tACS is effective with minimal adverse events. Regarding the durability of the intervention, we indeed observed attenuated effects at week 16 after the end of treatment, which is consistent with a previous RCT of the effects of tACS on the cognitive function of patients with Alzheimer's disease [57], which used the same stimulation techniques, including electric current intensity and waveform, as in our study. As indicated by our results, the stimulation protocol also needs to be adjusted for clinical translation, such as booster sessions after 2 months, or accelerated sessions (twice daily, 40 sessions in total), to achieve a longer-lasting efficacy.

In the secondary analysis, the tACS group did not exhibit superior improvements compared with the sham group, including clinical measures of hyperactivity/impulsivity symptoms, ecological executive function, social function, emotional symptoms or sleep quality, demonstrating improvements over time in both groups. We speculated that, in addition to placebo effects [58], a regular outpatient treatment schedule fosters a structured daily routine, which is beneficial for organization skills [59], and facilitates the positive outcomes [60, 61]. Additionally, the null findings of time effects on anxiety, depression symptoms and sleep quality might be due to our inclusion and exclusion criteria, which excluded individuals with a diagnosis of depression and anxiety related disorders, leading to a low level of emotional symptoms and sleep disturbance in the participants in this study, and, consequently, minimal improvement in these domains.

Safety is a concern in large current tES applications. Both previous RCTs and this study monitored adverse events during the intervention. No more side effects were observed in the intervention group than in the sham-stimulation group. We also calculated the current density to be 3.54 A/m2 at the forehead and 6.19 A/m2 at each mastoid, which were under the threshold of potential brain injury [42, 43]. As shown in previous reports of visual flickering and somatosensory discomfort [62], in our study, only one participant in the tACS group experienced visual flickering during the stimulation period which disappeared after stimulation. Drowsiness, which is consistent with prior MDD study [34], was the most prevalent. Only one participant withdrew from the tACS group due to transient dizziness, which recovered shortly after cessation.

The MEG results confirmed the neurophysiological effects of tACS in the gamma band, with reductions in low- and high-gamma connectivity following the 4-week intervention. No significant changes were observed in other frequency bands,

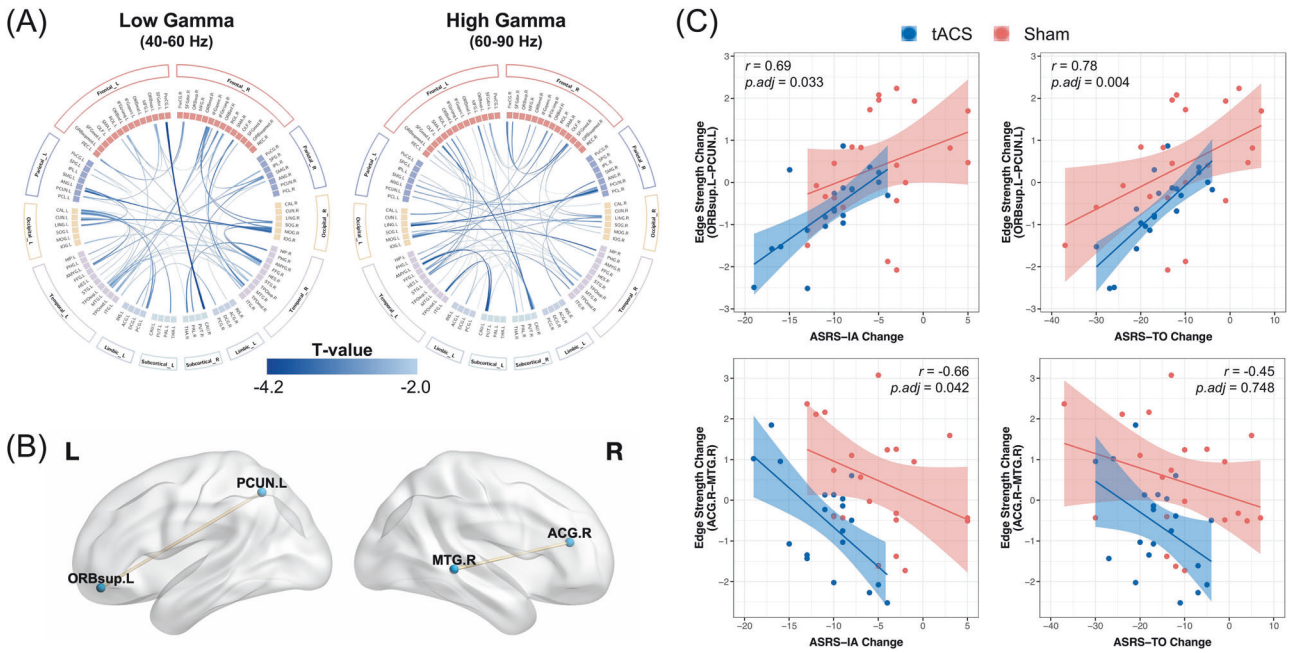

Fig. 3 Gamma functional connectivity changes after 4 weeks of tACS and their correlation with ASRS changes. A Connection plots show edges with significantly reduced strength after 4 weeks of tACS intervention in the low and high gamma bands, based on simple effect analyses. The color intensity of the lines represents different T-values between pre- and post-tACS sessions. **B** Brain connectivity plot displays two low gamma connections where strength changes are significant correlated with ASRS change. Refer to Supplementary Table 9 for the complete names of all brain region abbreviations. ORBsup.L, left superior frontal gyrus (medial orbital); PCUN.L, left precuneus; ACG.R, right anterior cingulate and paracingulate gyri; MTG.R, right middle temporal gyrus. **C** The change in low gamma connection strength between ORBsup.L and PCUN.L is positively correlated with ASRS-IA and ASRS-overall changes in the tACS group. Conversely, a negative correlation is observed between change in low gamma connection strength of ACG.R-MTG.R and ASRS-IA change in the tACS group. p.adj indicates the FDR-corrected p-value.

aligning with the frequency specificity of tACS. Correlation analyses revealed that reduced connection strength between the left orbitofrontal cortex (OFC) and the left precuneus was positively associated with decreased in the ASRS-IA and ASRS-TO scores, suggesting that tACS-induced desynchronization of the OFC-precuneus may be a putative (direct or indirect) mechanism underlying improvements in attention function. A previous meta-analysis indicated that intrinsic functional networks are dysregulated in ADHD individuals, with hyperconnectivity between the default mode network (DMN) and ventral prefrontal regions [63]. The precuneus, a key region of the DMN, plays a crucial role in cognitive attention processes [64, 65]. Our MEG results indicated that the improvement in inattention symptoms with tACS may have occurred through a reduction in the intrusion of DMN-related, internally-focused processing on OFC-related externally oriented processing and task performance, thereby enhancing attentional control [64, 66]. This effect likely reflects normalization of pathological hyperconnectivity in ADHD participants. The homeostatic theory of cognitive systems also provides alternative explanation [14], which proposes that long-range synchronization is crucial for information exchange between distal brain regions, and that hypo- or hyper-synchronization yields suboptimal behavioral performance [14, 67]. Consequently, tACS may optimize connectivity of the OFC-precuneus in gamma bands, improving attention function. Conversely, deviations from optimal connectivity strength may lead to adverse effects. Indeed, we found that decreased gamma connectivity between the right anterior cingulum and the right middle temporal gyrus was negatively correlated with ASRS-IA changes. However, we cannot rule out the possibility that this connectivity change contributes to cognitive functions in other domains. Single-frequency tACS can enhance performance in one domain while possibly interfering with it in another [68]. For example, theta-tACS has been shown to improve reversal learning abilities while simultaneously reducing flexibility [69]. Further studies are necessary to investigate this potential and develop precise tACS protocols for specific cognitive functions.

There are also several limitations in this study. Although 57.1% of the participants in the tACS group improved, approximately 2 out of the 5 participants did not respond effectively. Closed-loop tACS can synchronously record signals and feedback stimulus responses to specific rhythmic activity then adjusting the stimulation waveform in real-time [70]. Future research could benefit from more precise targeting and individualized frequencies or personalized targets [71] to increase the response rate. Furthermore, rigorous RCT studies are warranted to explore the lasting-effects of booster sessions or accelerated protocols. In addition, our sample excluded patients with emotional disorders or current pharmacological treatment for ADHD, limiting generalizability to patients with comorbid depression, anxiety or those taking ADHD medications. We chose the commonly used anatomical parcellation method, the AAL atlas, as our strategy for spatial dimensionality reduction. However, considering the differential sensitivity of MEG across brain regions, future studies should consider the differential sensitivity of MEG across brain regions and develop functionally optimized parcellations to provide more comprehensive insights into the mechanisms of tACS.

In conclusion, our study demonstrated that 20 sessions of 15mA gamma-band tACS targeting the frontal lobe significantly improved inattention symptoms in adults with ADHD. The improvement in inattention symptoms was positively correlated with a reduction in functional connectivity between the OFC and precuneus in the gamma band. In addition, this tACS protocol presented good adherence and safety, indicating that it is a potential alternative therapy for adults with ADHD.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author on reasonable request and with permission of the university administration.

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AUTHOR CONTRIBUTIONS

LY, JD, and ZF conceptualize and designed the study; JT contributed to a portion of study design; LY, JD, ZF, JT, SK, ZQ, QC, and YW were involved in the acquisition, analysis, or interpretation of data; JD generated the random sequence and performed group assignment; LY, JD, ZF, and JT drafted the manuscript; LY, JD, ZF, JT, SK, ZQ, QC, and YW involved in critical revision of the manuscript for important intellectual content; ZF, JT, and ZQ carried out the statistical analysis; LY, JD, ZF, JT, SK, ZQ, QC, and YW involved in administrative, technical, or material support; LY, JD, and QC obtained funding. The study was supervised by LY, JD, QC, and YW.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND REGISTRATION

This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Peking University Sixth Hospital. The study was registered on the Clinical Trial Registry platform (ChiCTR Identifier: ChiCTR2400081121). All the participants provided written informed consent.

ADDITIONAL INFORMATION

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