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Research paper

The role of 15 mA and 77.5 Hz transcranial alternating current stimulation in blood pressure regulation: A post hoc analysis of a randomized controlled trial

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ABSTRACT

Background: Transcranial alternating current stimulation (tACS) at 77.5 Hz and 15 mA, targeting the forehead and mastoid areas, has proven efficacious in patients with major depressive disorder (MDD) by simultaneously stimulating multiple brain nuclei and regions, many of which are critical for blood pressure regulation. This post hoc analysis aimed to assess the potential blood pressure-lowering effects of 77.5 Hz, 15 mA tACS in first-episode drug-naive MDD patients with normotension.

Methods: Data from a previous randomized controlled trial (RCT) involving first-episode drug-naive MDD patients were analyzed. Participants underwent 20 sessions of either active tACS or sham stimulation. Vital signs, including systolic blood pressure (SBP) and diastolic blood pressure (DBP), were measured at baseline, after treatment (Week 4), and at follow-up (Week 8). Multivariate linear regression and Generalized Estimating Equations (GEE) models were used to evaluate the effects of the treatment on blood pressure.

Results: Totally 68 participants were analysis (33 in the sham group and 35 in the active group). By Week 4, the active tACS group exhibited a significant reduction in both SBP and DBP compared to the sham group (coefficient − 2.04, 95 % CI -3.01 to −1.07, $p < 0.001$ on SBP, and coefficient − 1.92, 95 % CI -2.69 to −1.18, $p < 0.001$ on DBP).

Conclusions: tACS at 77.5 Hz and 15 mA can effectively reduce SBP and DBP in first-episode drug-naive depressive individuals with normotension, with greater reductions observed in those with higher baseline levels.

1. Introduction

Transcranial alternating current stimulation (tACS) is a form of transcranial electrical stimulation that delivers varying electrical currents to the scalp to modulate cortical excitability and spontaneous brain activity (Bikson et al., 2019; Louviot et al., 2022). In our previous randomized controlled trials (RCTs) and case series study, we demonstrated that transcranial alternating current stimulation (tACS) with a frequency of 77.5 Hz and current level of 15 mA, targeting the forehead and both mastoid areas, has potential as an effective and safe intervention (Wang et al., 2022; Wang et al., 2020; Zhao et al., 2023). Specifically, it was beneficial for chronic insomnia (Wang et al., 2020) and first-episode drug-naive patients with major depressive disorder (MDD) (Wang et al., 2022) over four consecutive weeks (20 sessions in total) and for

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treatment-resistant depression (TRD) with twice-daily sessions over four consecutive weeks (40 sessions in total) (Zhao et al., 2023). Compared to other interventions using tACS currents <4 mA (Alexander et al., 2019; Antal et al., 2017; Frohlich and Riddle, 2021; Shekelle et al., 2018; Zaghi et al., 2010), high-intensity tACS (Liu and Wang, 2024) at 15 mA appears to have more consistent and definitive therapeutic effects (Liu and Wang, 2024; Wang et al., 2022; Wang et al., 2020).

The ability of 15 mA high-intensity tACS to rapidly alleviate symptoms of depression and insomnia may be attributed to its simultaneous stimulation of multiple nuclei, widespread brain regions, and brain networks (Liu and Wang, 2024). This brain-wide activation effectively reaches deep brain structures (Shan et al., 2023; Wang et al., 2024). Using magnetic resonance imaging (MRI) of eight outpatient volunteers with drug-naïve, first-episode MDD, we constructed actual human head models, and the electric field distributions in the sagittal, coronal, and axial planes demonstrated that 15 mA tACS resulted in whole-brain activation involving the cortex, subcortical structures (including the hypothalamus, thalamus, amygdala, among others), cerebellum, and brainstem (Wang et al., 2024).

The brainstem, subcortical structures, and cerebral cortex are crucial for controlling blood pressure as the central hub of the nervous system (Cheng et al., 2020; Kobuch et al., 2019; Tavares et al., 2004). Accumulated evidence indicates that it contains the essential circuits needed for maintaining and regulating this function (Barman et al., 2005; Seyedabadi et al., 2006; VanNess et al., 1999; Waki et al., 2006). Although no adverse events related to blood pressure deviations from normal values were observed throughout our RCT study on MDD (Wang et al., 2022), our experimental records indicated a trend toward reduced blood pressure in the active stimulation group. Therefore, we hypothesize that 15 mA tACS can lower blood pressure. The aim of this post hoc analysis of the RCT on tACS for treating first-episode drug-naive MDD (Wang et al., 2022) is to determine whether tACS reduces systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the end of the treatment period.

2. Methods

2.1. Participants

The inclusion criterion required participants to have been enrolled in a previous on MDD (ChiCTR1800016479) (Wang et al., 2022). The exclusion criterion was the presence of incomplete or unqualified data. Qualified data required measurements at least three time points: baseline, the end of treatment (Week 4), and the follow-up visit (Week 8). The data covered Blood Pressure (BP), Body Temperature (BT), Heart Rate (HR), and Body Mass Index (BMI). Participants assigned to the active tACS treatment were classified as the active group, while those assigned to the sham tACS treatment were classified as the sham group in this investigation.

2.2. Intervention and comparison

All participants underwent 20 treatment sessions, with the active group receiving stimulation at 77.5 Hz and 15 mA, while the sham group received no active stimulation, as detailed in the previously published study (Wang et al., 2022) (Fig. 1).

2.3. Measurements

BP: Blood pressure was measured with the pulse rate recorded under standardized conditions with the participant seated quietly, ensuring the back was supported and the arm was positioned at heart level. To minimize environmental influences, conversation was avoided (Holland and Lewis, 2014). A validated upper arm cuff device (Yuwell, Jiangsu Diving Medical Equipment Co., Ltd., China), compliant with international standards and regularly calibrated, was used for accurate measurement (Imai et al., 2003). Three repeated measurements were taken and averaged to improve accuracy and minimize the potential "white coat effect" (Myers, 2012).

HR: After completing the blood pressure and pulse rate measurement, the heart rate was assessed under the same environmental conditions and patient positioning, with the stethoscope (MDF747E, MDF Instruments Medifriend Inc., China) components checked beforehand to

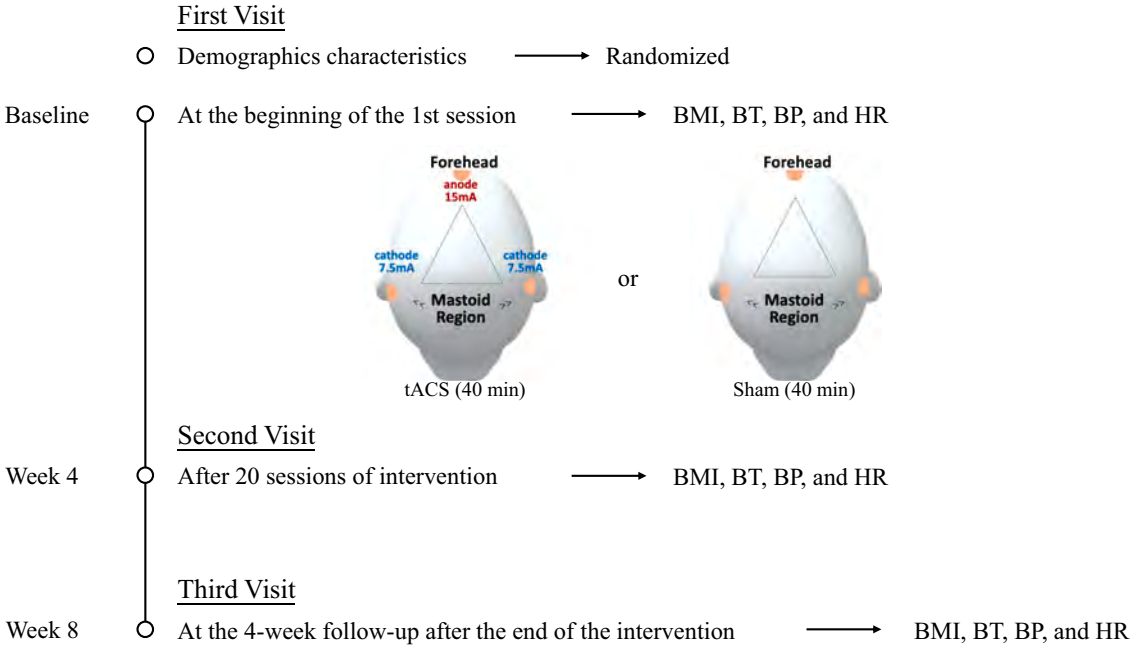

Fig. 1. Experimental design.
BMI, Body Mass Index; BT, Body Temperature; BP, Blood Pressure; HR, Heart Rate; tACS, transcranial alternating current stimulation.

ensure proper function and cleanliness (Vogel et al., 2004). The fifth intercostal space on the left side, just below the midclavicular line, served as the optimal site for auscultating heart sounds (Nagueh et al., 2017). Heart rate was measured over 60 s following the blood pressure measurements, with each measurement repeated three times to obtain an average for accuracy.

BT: A mercury thermometer (Meifang, Anhui Fangda Medical Equipment Co., Ltd., China) was selected for measuring axillary temperature (Khorshid et al., 2005). Before use, the thermometer was gently shaken to ensure the mercury column was below 35 °C. After cleaning the measuring end with a disinfectant wipe, the thermometer was placed in the center of the axilla, with the arm held tightly against the body. After 8 min, the thermometer was removed, and the temperature was carefully read from the position of the mercury column.

BMI: When measuring weight and height, a calibrated scale was used (Suhong, Jiangsu Suhong Medical Device Co., Ltd., China), ensuring it was placed on a flat and solid surface. Participants were weighed in light clothing, without shoes or additional items, standing upright and relaxed at the center of the scale with weight evenly distributed. Weight was recorded to the nearest decimal place. Participants were also asked to remove their shoes and head accessories and to stand with their heels together, toes slightly apart, and back against the wall for height measurement. The head was aligned straight, with eyes forward to ensure the Frankfurt plane was level. The stadiometer bar was gently lowered to touch the head, pressing down if needed, and height was recorded to the nearest millimeter. Weight was measured in kilograms (kg) and height in meters (m). BMI was calculated using the formula: BMI = weight (kg) / height (m^2) (Greenwood et al., 2011).

All four measurements were collected at three time points. The baseline measurement was conducted prior to randomization (baseline). The second measurement was taken after the end of the 20th session of either active or sham tACS (week 4). The third measurement occurred during the follow-up visit at week 8 (week 8). To minimize the impact of daily variability on vital signs, all measurements were conducted at either 9 a.m. or 3 p.m., depending on the participant's finalized treatment schedule. Participants were consistently measured at a fixed daytime interval for both the baseline and week 8 assessments. For the week 4 assessment, measurements were taken 20 min after the final treatment session. The sequence of measurements was as follows: BMI, BT, BP, and HR (Fig. 1).

2.4. Outcomes

The primary outcomes of this study were the differences in SBP and DBP changes between the two groups, assessed at week 4 relative to baseline. The secondary outcomes included the differences in SBP and DBP changes at week 8, as well as the changes in BT, HR, and BMI at weeks 4 and 8, all compared to baseline.

2.5. Statistical analysis

The analysis presented continuous variables as the mean with standard deviation (SD) for normally distributed data, or as the median with interquartile range (Q1-Q3) for non-normally distributed data. The Student *t*-test was applied for normally distributed data, while the Mann-Whitney test was employed for data with non-normal distributions. Categorical variables were represented as counts and percentages. The statistical significance of categorical variables was assessed using Pearson's chi-square test or Fisher's exact test. Multivariate linear regression was performed to assess the primary outcomes, and results were reported as coefficients (coef.) with 95 % confidence intervals (CI). Generalized Estimating Equations (GEE) models were used as a sensitivity analysis for the primary outcomes, accounting for repeated BP measurements, and evaluating the treatment efficacy on changes in BP using both exchangeable and independent models.

The sample size was calculated based on the two primary outcomes. To control the false discovery rate (FDR) under 0.05, a Bonferroni adjustment was applied, setting the type I error (α) at 0.025 for each primary outcome and the type II error (β) at 0.2. We assumed a change in SBP of 2.5 (1) in the active group and 1.5 (1) in the sham group, requiring data from 21 participants in each group. Similarly, for the change in DBP, we assumed 1.5 (1) in the active group and 0.5 (1) in the sham group, also requiring data from 21 participants in each group.

Two-tailed *p*-values below 0.025 were considered to indicate significant differences in the primary outcome tests. *P*-values for the secondary outcomes are presented as nominal values.

Stata SE 13 (Serial number 401306302851), R software (version 3.6.1, http://cran.r-project.org/) and EmpowerStat 2.0 (www.empowerstats.com) were applied for the data analysis.

3. Results

3.1. Demographic characteristics of participants

Data from 68 participants were analyzed, with 33 from the sham group and 35 from the active group. Fig. 2 shows the flow diagram of the enrollment of the analyzed data. Sex (male) distribution was 26.47 % in the entire cohort, with 30.30 % in the sham group and 22.86 % in the active group, showing no significant difference ($p = 0.487$). Educational status was distributed as follows: 1.47 % illiterate, 2.94 % primary school, 22.06 % middle school, 38.24 % high school, 5.88 % associate's degree, 27.94 % bachelor's degree, and 1.47 % master degree and above. There were no significant differences between the groups ($p = 0.737$). Working activities included 1.47 % government officials/employees, 1.47 % service staff, 39.71 % professional and technical staff, 4.41 % administrative staff, 48.53 % retired personnel, and 4.41 % property management staff. There were no significant differences between the groups ($p = 0.341$). Both smoking and alcohol consumption were reported as 0 % in all groups (Table 1).

3.2. Primary outcome

3.2.1. Descriptive analysis of SBP

At baseline, the mean SBP was 118.40 (7.30) mmHg overall, 118.15 (7.99) mmHg in the sham group, and 118.63 (6.69) mmHg in the active group, with no significant difference between the groups ($p = 0.790$). At week 4, the mean SBP was 116.63 (7.1) mmHg overall, 117.45 (8.12) mmHg in the sham group, and 115.86 (6.00) mmHg in the active group, with no significant difference ($p = 0.358$). At week 8, the mean SBP was 117.81 (7.33) mmHg overall, with 118.03 (7.84) mmHg in the sham group and 117.60 (6.92) mmHg in the active group, showing no significant difference ($p = 0.811$). For the change in SBP from baseline to

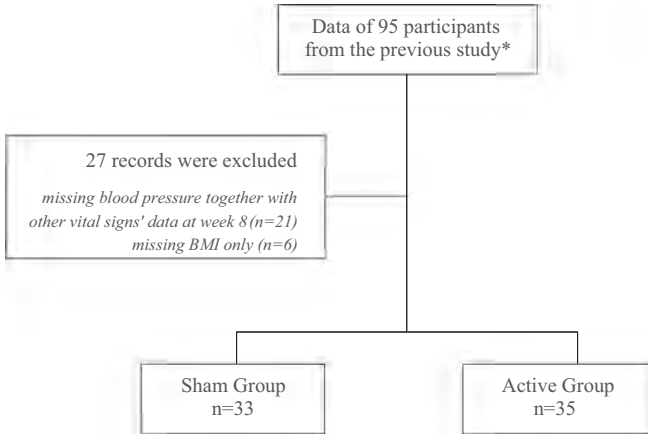

Fig. 2. Flow diagram of the enrollment of the analyzed data.
* ref.: https://doi.org/10.1093/brain/awab252.

Table 1
Demographic characteristics for all participants.

	All (n = 68)	Sham (n = 33)	Active (n = 35)	Statistics	p-value
Sex (male)	18 (26.47 %)	10 (30.30 %)	8 (22.86 %)	χ^2 = 0.4838	0.487
Educational status					0.737*
Illiterate	1 (1.47 %)	1 (3.03 %)	0 (0.00 %)		
Primary school	2 (2.94 %)	2 (6.06 %)	0 (0.00 %)		
Middle school	15 (22.06 %)	6 (18.18 %)	9 (25.71 %)		
High school	26 (38.24 %)	13 (39.39 %)	13 (37.14 %)		
Associate's degree	4 (5.88 %)	2 (6.06 %)	2 (5.71 %)		
Bachelor degree	19 (27.94 %)	9 (27.27 %)	10 (28.57 %)		
Master degree and above	1 (1.47 %)	0 (0.00 %)	1 (2.86 %)		
Working activity					0.341*
Government officials/employees	1 (1.47 %)	1 (3.03 %)	0 (0.00 %)		
Service staff	1 (1.47 %)	0 (0.00 %)	1 (2.86 %)		
Professional and technical staff	27 (39.71 %)	15 (45.45 %)	12 (34.29 %)		
Administrative staff	3 (4.41 %)	0 (0.00 %)	3 (8.57 %)		
Retired	33 (48.53 %)	15 (45.45 %)	18 (51.43 %)		
Property management staff	3 (4.41 %)	2 (6.06 %)	1 (2.86 %)		

* Fisher test.

week 4, the median (q1 ~ q3) were − 1.00 (−1.00 to 0.00) in the sham group and − 2.00 (−3.50 to −1.00) in the active group, with a significant difference ($p < 0.001$) (Table 2, Fig. 3A).

3.2.2. Treatment efficacy on SBP at week 4 analyzed by multivariate linear regression

The treatment group (vs. sham) showed a significant difference in the change of SBP with a Coef. of −2.04 (95 % CI: −3.01 to −1.07, $p < 0.001$). The Coef. of baseline SBP for changes in SBP was −0.07 (95 % CI, −0.14 to −0.00, $p = 0.048$). In contrast, age, sex, and BMI did not show significant differences in the changes of SBP, with Coef. values of 0.01 (95 % CI: −0.05 to 0.06, $p = 0.774$), 0.19 (95 % CI: −0.99 to 1.30, $p = 0.742$), and 0.03 (95 % CI: −0.14 to 0.20, $p = 0.712$), respectively (Table 3).

3.2.3. Treatment efficacy on the changes of SBP at week 4 analyzed by GEE

In the exchangeable model, age had a Coef. of −0.00 (95 % CI: −0.03 to 0.02) with a p-value of 0.883. Sex (female vs. male) had a Coef. of 0.30 (95 % CI: −0.20 to 0.81, $p = 0.238$). The baseline SBP had a Coef. of 0.03 (95 % CI: −0.01 to 0.06, $p = 0.118$). BMI had a Coef. of −0.01 (95 % CI: −0.09 to 0.07, $p = 0.822$). The treatment group (vs. sham) had a significant negative effect on the changes of SBP with a Coef. of −1.01 (95 % CI: −1.44 to −0.57, $p < 0.001$). In the independent model, age had a Coef. of −0.00 (95 % CI: −0.03 to 0.02, $p = 0.864$). Sex (female vs. male) had a Coef. of 0.31 (95 % CI: −0.20 to 0.82, $p = 0.238$). The baseline SBP had a Coef. of 0.03 (95 % CI: −0.01 to 0.06, $p = 0.099$). BMI had a Coef. of −0.01 (95 % CI: −0.09 to 0.07, $p = 0.828$). Coincidence with the above model, the treatment group (vs. sham) had a significant negative effect with a Coef. of −1.01 (95 % CI: −1.45 to −0.57, $p < 0.001$) (Table 4).

3.2.4. Descriptive analysis of DBP

At baseline, the mean DBP was 74.41 (6.06) mmHg overall, with 74.27 (6.57) mmHg in the sham group and 74.54 (5.62) mmHg in the active group ($p = 0.856$). At week 4, the mean DBP was 73.34 (5.79) mmHg overall, with 74.18 (6.51) mmHg in the sham group and 72.54 (4.99) mmHg in the active group ($p = 0.247$). At week 8, the mean DBP was 74.01 (5.93) mmHg overall, with 74.27 (6.37) mmHg in the sham group and 73.77 (5.56) mmHg in the active group ($p = 0.730$). However, the change in DBP from baseline to week 4 was significantly different between groups, with a median (q1 ~ q3) of 0.00 (0.00 to 0.00) mmHg in the sham group versus −2.00 (−3.00 to −0.50) mmHg in the active group ($z = 5.183$, $p < 0.001$) (Table 2, Fig. 3A).

3.2.5. Treatment Efficacy on DBP at week 4 analyzed by multivariate linear regression

The treatment group (vs. sham) showed a significant difference in the change of DBP with a Coef. of −1.92 (95 % CI: −2.69 to −1.18, $p < 0.001$). Baseline DBP also showed a significant difference with a Coef. of −0.09 (95 % CI: −0.15 to −0.02, $p = 0.011$). In contrast, age, sex, and BMI did not show significant differences in the changes of DBP, with Coef. values of −0.02 (95 % CI: −0.06 to 0.03, $p = 0.446$), 0.06 (95 % CI: −0.85 to 0.97, $p = 0.891$), and − 0.04 (95 % CI: −0.18 to 0.09, $p = 0.523$), respectively (Table 3).

3.2.6. Treatment efficacy on the changes of DBP at week 4 analyzed by GEE

In the exchangeable model, age had a Coef. of −0.02 (95 % CI: −0.04 to 0.01, $p = 0.269$). Sex (female vs. male) had a Coef. of 0.36 (95 % CI: −0.25 to 0.96, $p = 0.245$). Baseline DBP had a significant effect with a Coef. of 0.05 (95 % CI: 0.01 to 0.10, $p = 0.024$). BMI had a Coef. of 0.02 (95 % CI: −0.07 to 0.10, $p = 0.742$). The treatment group (vs. sham) had a significant negative effect on the changes of DBP at week 4 with a Coef. of −0.93 (95 % CI: −1.42 to −0.43, $p < 0.001$) (Table 4). In the independent model, age had a Coef. of −0.02 (95 % CI: −0.04 to 0.01, $p = 0.159$). Sex (female vs. male) had a Coef. of 0.17 (95 % CI: −0.32 to

Table 2
Descriptive analysis of SBP/DBP.

		All (n = 68)	Sham (n = 33)	Active (n = 35)	Statistics	p-value
SBP at baseline	*mean (sd)*	118.40 (7.30)	118.15 (7.99)	118.63 (6.69)	$t = -0.2675$	0.790
SBP at week 4	*mean (sd)*	116.63 (7.10)	117.45 (8.12)	115.86 (6.00)	$t = 0.93$	0.358
SBP at week 8	*mean (sd)*	117.81 (7.33)	118.03 (7.84)	117.60 (6.92)	$t = 0.2402$	0.811
SBP change at week 4	*mean (sd)*	−1.76 (2.22)	−0.70 (0.85)	−2.77 (2.62)		
	median(q1 ~ q3)	−1.00 (−2.25–0.00)	−1.00 (−1.00–0.00)	−2.00 (−3.50 ~ −1.00)	z = 4.665	<0.001
DBP at baseline	*mean (sd)*	74.41 (6.06)	74.27 (6.57)	74.54 (5.62)	$t = -0.1825$	0.856
DBP at week 4	*mean (sd)*	73.34 (5.79)	74.18 (6.51)	72.54 (4.99)	$t = 1.17$	0.247
DBP at week 8	*mean (sd)*	74.01 (5.93)	74.27 (6.37)	73.77 (5.56)	$t = 0.3462$	0.730
DBP change at week 4	*mean (sd)*	−1.07 (1.83)	−0.09 (0.38)	−2.00 (2.16)		
	median(q1-q3)	0.00 (−2.00–0.00)	0.00 (0.00–0.00)	−2.00 (−3.00 - -0.50)	z = 5.183	<0.001

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; sd, standard deviation.

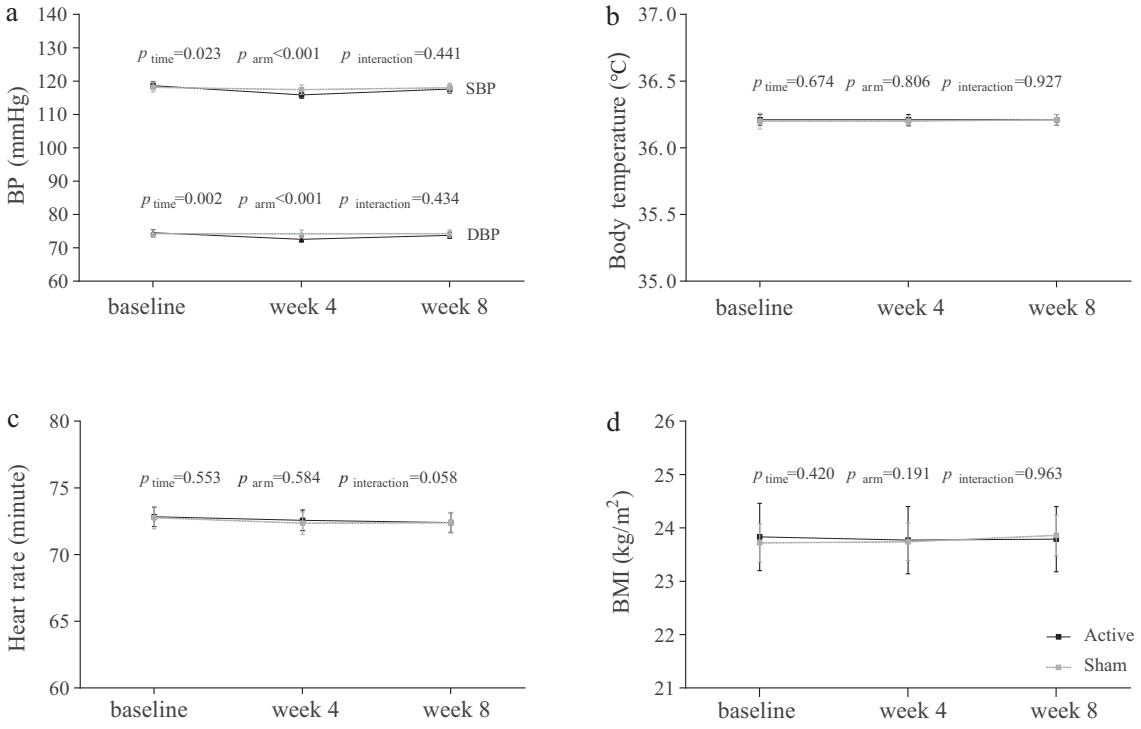

Fig. 3. Changes in physiological parameters over time.
The dark solid lines represent the results of the active group. The gray dashed lines represent the results of the sham group. (A). SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; (B). BT, Body Temperature; (C). HR, Heart Rate; (D). BMI, Body Mass Index.

Table 3
Treatment efficacy on SBP/DBP change at week 4 analyzed by multivariate linear regression.

	SBP at Week 4					DBP at Week 4				
	Coef.	95 % CI	SE	t	*p*-value	Coef.	95 % CI	SE	t	*p*-value
Age	0.01	−0.05–0.06	0.028	0.29	0.774	−0.02	−0.06–0.03	0.021	−0.77	0.446
Sex (female vs. male)	0.19	−0.93–1.32	0.559	0.33	0.742	0.06	−0.85–0.97	0.454	0.14	0.891
Baseline BP	−0.07	−0.14 ~ −0.00	0.034	−2.01	0.048	−0.09	−0.154 ~ −0.02	0.033	−2.62	0.011
BMI	0.03	−0.14–0.20	0.085	0.37	0.712	−0.04	−0.18–0.09	0.067	−0.64	0.523
Treatment group (active vs. sham)	−2.04	−3.01 ~ −1.07	0.484	−4.21	<0.001	−1.92	−2.69 ~ −1.18	0.372	−5.17	<0.001

Coef., Coefficient; SE, Standard Error; CI, Confidence Interval; BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.

Table 4
Treatment efficacy on SBP/DBP change at week 4 analyzed by generalized estimating equations.

SBP	Exchangeable model					Independent model				
	Coef.	95 % CI	SE	z	*p*-value	Coef.	95 % CI	SE	z	*p*-value
Age	−0.00	−0.03–0.02	0.013	−0.15	0.883	−0.00	−0.03–0.02	0.013	−0.17	0.864
Sex (female vs. male)	0.30	−0.20–0.81	0.257	1.18	0.238	0.31	−0.20–0.82	0.262	1.18	0.238
Baseline SBP	0.03	−0.01–0.06	0.016	1.56	0.119	0.03	−0.01–0.06	0.016	1.65	0.099
BMI	−0.01	−0.09–0.07	0.039	−0.23	0.822	−0.01	−0.09–0.07	0.040	−0.22	0.828
Treatment group (active vs. sham)	−1.01	−1.44 ~ −0.57	0.222	−4.54	<0.001	−1.01	−1.45 ~ −0.57	0.226	−4.46	<0.001

DBP	Exchangeable model					Independent model				
	Coef.	95 % CI	SE	z	*p*-value	Coef.	95 % CI	SE	z	*p*-value
Age	−0.02	−0.04–0.01	0.014	−1.10	0.269	−0.02	−0.04–0.01	0.011	−1.41	0.159
Sex (female vs. male)	0.36	−0.25–0.96	0.308	1.16	0.245	0.17	−0.32–0.65	0.249	0.66	0.507
Baseline DBP	0.05	0.01–0.10	0.023	2.26	0.024	0.01	−0.02–0.05	0.019	0.65	0.515
BMI	0.02	−0.07–0.10	0.046	0.33	0.742	−0.00	−0.08–0.07	0.037	−0.10	0.922
Treatment group (active vs. sham)	−0.93	−1.42 ~ −0.43	0.252	−3.67	<0.001	−0.94	−1.33 ~ −0.54	0.203	−4.62	<0.001

Coef., Coefficient; SE, Standard Error; CI, Confidence Interval; BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.

0.65, $p = 0.507$). Baseline DBP had a Coef. of 0.01 (95 % CI: −0.02 to 0.05, $p = 0.515$). BMI had a Coef. of −0.00 (95 % CI: −0.08 to 0.07, $p = 0.922$). The treatment group (vs. sham) had a significant negative effect with a Coef. of −0.94 (95 % CI: −1.33 to −0.54, $p < 0.001$) (Table 4).

3.3. Secondary outcomes

The SBP change at week 8 had a mean (SD) of −0.59 (1.44) overall, −0.12 (1.27) in the sham group, and − 1.03 (1.46) in the active treatment group. The median (q1-q3) values were 0.00 (−1.00 to 0.00) overall, 0.00 (−1.00 to 0.00) in the sham group, and − 1.00 (−1.00 to 0.00) in the active treatment group ($p = 0.014$). The DBP change at week 8 had a mean (SD) of −0.40 (1.73) overall, 0.00 (0.43) in the sham group, and − 0.77 (2.33) in the active treatment group. The median (q1-q3) values were 0.00 (−1.00 to 0.00) overall, 0.00 (0.00 to 0.00) in the sham group, and − 1.00 (−2.00 to 0.00) in the active treatment group ($p = 0.016$) (Table S1 in the Supplementary tables).

The multivariate linear regression analysis showed that the treatment group (vs. sham) has a coefficient of −0.88 with a 95 % CI of −1.57 to −0.19 ($p = 0.013$). Other variables, including age, sex, baseline SBP, and BMI, did not show a significant association with SBP change (all $p > 0.05$) (Table S2 in the Supplementary tables). The multivariate linear regression analysis indicates that baseline DBP has a coefficient of −0.08 (95 % CI: −0.15 to −0.01, $p = 0.028$), showing a significant association with DBP change. The treatment group (vs. sham) has a coefficient of −0.77 with a 95 % CI of −1.59 to 0.04 ($p = 0.062$), which was not statistically significant. Other variables, including age, sex, and BMI, did not show a significant association with DBP change (all $p > 0.05$) (Table S2 in the Supplementary tables).

For BT, the baseline mean (SD) was 36.20 (0.34)°C in the sham group and 36.21 (0.26)°C in the active group ($p = 0.971$). At week 4, BT was 36.20 (0.22)°C in the sham group and 36.21 (0.22)°C in the active group ($p = 0.747$). By week 8, BT was 36.21 (0.20)°C in the sham group and 36.21 (0.25)°C in the active group ($p = 0.949$). No significant changes in BT were observed from baseline to week 4 ($p = 0.965$) or week 8 ($p = 0.799$) (Table S3 in the Supplementary tables, Fig. 3B).

Initially, the mean HR was 72.76 (4.74) in the sham group and 72.83 (4.27) in the active group ($p = 0.948$). At week 4, HR was 72.36 (4.78) in the sham group and 72.57 (4.60) in the active group ($p = 0.856$). By week 8, HR was 72.39 (4.44) in the sham group and 72.40 (4.31) in the active group ($p = 0.996$). No significant changes in HR were observed from baseline to week 4 ($p = 0.684$) or week 8 ($p = 0.858$) (Table S3 in the Supplementary tables, Fig. 3C).

Baseline BMI was 23.72 (2.05) in the sham group and 23.83 (3.74) in the active group ($p = 0.882$). At week 4, the mean (SD) BMI was 23.74 (2.04) in the sham group and 23.77 (3.72) in the active group ($p = 0.967$). By week 8, BMI was 23.86 (2.17) in the sham group and 23.79 (3.62) in the active group ($p = 0.931$). No significant BMI changes were found from baseline to week 4 or week 8 (Table S3 in the Supplementary tables, Fig. 3D).

4. Discussion

To our knowledge, this is the first study to report the antihypertensive effects of the high-intensity tACS. The findings suggested that 20 sessions of tACS at 77.5 Hz and 15 mA, applied to the forehead and mastoid regions, reduce SBP and DBP at the end of treatment. These results were confirmed by several statistical analysis models, including linear regression, GEE exchangeable model, and independent model. Meanwhile, the high-intensity tACS at 15 mA did not influence BT, HR, or BMI, and its safety profile was excellent (Wang et al., 2022). Interestingly, multivariate linear regression indicated a positive correlation between baseline blood pressure and the extent of reduction after treatment, with higher baseline SBP associated with greater SBP reduction at 4 weeks and a similar pattern observed for DBP. Four weeks after discontinuing the tACS treatment, blood pressure gradually returned to near baseline levels but remained slightly lower compared to baseline. Notably, multivariate linear regression analysis showed a sustained reduction in SBP, indicating a lasting effect of the tACS.

Given that neuromodulation may influence potential pathogenic brain-heart pathways (Gianaros and Sheu, 2009; Manuel et al., 2020; Thayer and Lane, 2009), studies have investigated the effects of TMS and tDCS on blood pressure, heart rate, and heart rate variability. A meta-analysis of non-invasive neuromodulation techniques in normotensive individuals (including those with MDD, healthy participants, and stroke patients, among others) revealed that both transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) can reduce heart rate while increasing heart rate variability (HRV), but they have no significant impact on blood pressure. Moreover, TMS appeared to be more effective than tDCS, particularly when targeting the prefrontal cortex (Makovac et al., 2017). Another study conducted in hypertensive patients demonstrated that tDCS significantly reduced both SBP and DBP over a 24-h period, with a decrease in sympathetic activity and an increase in vagal activity following tDCS sessions (Rodrigues et al., 2021). In patients with resistant hypertension, both acute and short-term tDCS interventions reduced blood pressure, improved autonomic control, and enhanced central blood pressure and pulse wave velocity (Rodrigues et al., 2022). These studies highlight the role of cortical modulation in influencing sympathetic outflow and blood pressure regulation, suggesting a potential therapeutic approach for hypertension through brain stimulation techniques.

Hypertension is a widespread condition with a high prevalence, affecting a significant number of patients worldwide (Collaboration, N. C.D.R.F, 2021). Insomnia and mood disorders are significantly associated with an increased risk of developing hypertension (Evans et al., 2005; Li et al., 2021). The cumulative impact of environmental stressors—ranging from everyday events to major challenges—along with the physiological consequences of related harmful behaviors, such as poor sleep, can ultimately contribute to the onset of medical disorders or the worsening of existing conditions like hypertension (Fava et al., 2023; Guidi et al., 2021). The relationship between blood pressure and depression remains complex, even in research involving large sample sizes. Studies have demonstrated that the relationship between blood pressure and the prevalence of depression or depressive symptoms can vary, with findings indicating negative associations (Lenoir et al., 2008; Ng et al., 2010), positive associations (Park et al., 2018; Scalco et al., 2005), or bidirectional relationships (Jeon et al., 2020). Under such circumstances, a consensus on this topic remains elusive, and further studies are expected. Unlike the neural circuit basis in the studies mentioned above, our non-invasive protocol employs a “triangular” high-intensity tACS configuration at 77.5 Hz and 15 mA, with electrode placement on the forehead and bilateral mastoids, allowing for modulation of a broader range of brain regions (Shan et al., 2023; Wang et al., 2024). These extensive brain regions encompass not only key circuits involved in emotion (Etkin et al., 2015) and sleep regulation (Qiu et al., 2016; Xu et al., 2022) but may also include pathways related to blood pressure regulation (Kobuch et al., 2019; Sheng et al., 2022).

Our study has several limitations as a post hoc analysis. First, due to some participants’ data being unavailable, only 71.6 % of the participants enrolled in the previous RCT were analyzed. This means that randomization was compromised, leading to an imbalance in baseline data. To address this potential bias, we utilized multivariate linear regression and GEE models to evaluate the effect of interventional treatment on the primary endpoint. All analytical models consistently demonstrated that active treatment significantly reduced both SBP and DBP. Additionally, we ensured the baseline characteristics of the two groups were well-matched, with all p-values for baseline comparisons exceeding 0.34, thereby minimizing the likelihood of confounding factors affecting the results. Second, since our study was conducted among participants with normotension, the efficacy in hypertensive individuals remains unknown. Additionally, given that the observed blood pressure reduction occurred in depressed patients, it is unclear whether this is

related to the improvement in depressive symptoms. Further research on hypertensive individuals is needed to address this uncertainty. Third, our measurements of vital signs and the selected time points were limited. In future investigations, we should evaluate the effects of tACS across different intervention durations, including single (acute) sessions and multiple sessions (10 to 20 as short-term), with follow-ups every 2 to 4 weeks to assess long-term outcomes. These assessments should encompass not only blood pressure and heart rate but also SBP variability, heart rate variability, hemodynamics, 24-h ambulatory BP monitoring, neurotransmitters, and cytokines levels. Considering the limitations of this study and the findings demonstrating the blood pressure-lowering effects of tACS, conducting RCTs with a long-term follow up in individuals with comorbid depression and primary hypertension is both warranted and anticipated in the future.

In conclusion, the high-intensity tACS treatment at 77.5 Hz and 15 mA, targeting the forehead and both mastoid areas, effectively reduced SBP and DBP in depressive individuals with normotension, with greater reductions observed in those with higher baseline levels, and all safety criteria were satisfied. Based on the findings of this study, it is worth exploring the potential blood pressure-lowering effects of this 77.5 Hz / 15 mA tACS in patients with hypertension comorbid with mood disorders or insomnia. Additionally, for patients with primary or resistant hypertension, this specific tACS protocol could be investigated for its efficacy and safety, either as a standalone treatment or in combination with pharmacotherapy.

CRediT authorship contribution statement

Xiaolei Liu: Writing – original draft, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Kun Wang:** Writing – review & editing, Data curation. **Tianmei Si:** Writing – review & editing, Data curation. **Xiangyang Zhang:** Writing – review & editing, Software. **Fiammetta Cosci:** Writing – review & editing. **Keming Gao:** Writing – review & editing. **Hongxing Wang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Ethics

This study adhered to the ethical and scientific principles outlined in the Helsinki Declaration, as well as the regulations of Chinese law governing Good Clinical Practice for Chinese populations. As a post-hoc analysis, data were retrieved from the published research (ChiCTR1800016479) (Wang et al., 2022) which conducted under a protocol approved by the Ethics Committee of Xuanwu Hospital [Approval No. LXS (2017) 002-Amendment 2]. All participants in the original RCT provided written informed consent.

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Declaration of competing interest

The authors declare that they have no potential competing interest.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2025.01.017.

Data availability

Data used for these analyses are available from the corresponding author upon reasonable request. Code used for these analyses are available from the corresponding author upon reasonable request.

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