Transcutaneous electrical acupoint stimulation for children with attention-deficit/hyperactivity disorder: a randomized clinical trial

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) has a worldwide prevalence of ~5% [1, 2]. ADHD is involved in highly heterogeneous impairments in cognitive and social functions and may lead to lifelong adverse outcomes such as serious mental illness and academic failure [1, 3]. Psychostimulant and nonpsychostimulant medications are effective for reducing the main symptoms of ADHD. However, not all children respond to pharmacological treatment, and some medications have significant adverse effects [4, 5]. Hence, other alternative approaches are urgently needed.

Acupuncture or electroacupuncture is being increasingly used to manage ADHD in some countries [6–8], especially for medication-refractory patients or patients presenting intolerable adverse events with medications [9]. Transcutaneous electrical acupoint stimulation (TEAS), a noninvasive treatment, was shown to produce stimulation on acupoints similar to that of electric acupuncture [10, 11]. Consequently, TEAS is an easily accepted alternative option that has been used for children with psychiatric disorders such as autism [12, 13]. However, little is known about its efficacy on patients with ADHD.

Several studies involving neuroimaging techniques, including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have been used to investigate the cerebral mechanism of acupuncture [14, 15]. Neuroimaging studies using PET or fMRI coupled with interventions in children with ADHD are scarce due to logistic issues, including head motion, which is a frequent problem for children with ADHD. Due to its unrestrictiveness and accessibility, functional near-infrared spectroscopy (fNIRS) has been increasingly used to assess the brain response in therapeutic protocols for children with ADHD [16, 17]. Therefore, the present clinical trial aims (1) to assess the effect of TEAS compared with that of sham TEAS in improving ADHD symptoms and (2) to explore the cerebral response to both TEAS and sham TEAS using fNIRS.

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METHODS

Study design and participants
This was a randomized, 4-week trial comparing TEAS and sham TEAS treatment for ADHD. The clinical trial was approved by the Ethics Committee of the First Affiliated Hospital of Xi’an Jiaotong University. The detailed trial protocol is provided in Supplement 1. Study enrollment started on July 1, 2019, and continued to December 1, 2019, with data collection completion on January 17, 2020. The participants and their parents provided written informed consent, respectively.

Seventy-eight children with ADHD from Xi’an Children’s Hospital were recruited and randomized for the present study. All participants fulfilled the clinical diagnostic criteria of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V). The formal ADHD diagnosis was performed by two experienced child psychiatrists using clinical data and rating scales from parents, teachers, and investigators, including the Conners’ Parent Rating Scales-Reduced: Short Form (CPRS-R: S), Conners’ Teacher Rating Scales-Reduced: Short Form (CTRS-R: S), and Clinical Global Impression-Severity of Illness (CGI-S). The IQ of each child was evaluated by the Chinese version of the Wechsler Intelligence Scale for Children-Revised [18].

The inclusion criteria were (a) formal clinical diagnosis of ADHD and (b) age between 6 and 12 years. The exclusion criteria were (a) the presence of any other mental or neurodevelopmental disorder (e.g., comorbidities such as Autism Spectrum Disorder, Tic Disorder, Anxiety Disorder, Major Depressive Disorder, Conduct Disorder, and Oppositional Defiant Disorder) or epilepsy according to the DSM-V by clinical assessments, (b) IQ score below 75, (c) any previous acupuncture-associated treatment experiences, (d) use of any ADHD medication within 1 month prior to TEAS treatment, and (e) left-handedness.

Randomization and blinding
Eligible participants were randomly assigned in an equal ratio to undergo either TEAS or sham TEAS treatment according to a computer-generated randomization sequence. Allocation of participants was performed by a clinical researcher who was not involved in outcome assessment. Participants in the true and sham TEAS groups were treated in separate rooms and blinded to the intervention. The investigators who manipulated the true or sham TEAS could not be blinded to the group allocations. The psychiatrists, parents, teachers, data collectors, and statisticians were blinded to treatment assignments.

Interventions
Following randomization, participants had an appointment with the TEAS operator, who manipulated the true or sham TEAS treatment at the same acupuncture points and held a membership with a national professional association in China. The Baihui (GV 20), bilateral Taichong (LR 3) and bilateral Taichong (LR 3) acupuncture points were selected according to previous acupuncture research and were not involved in outcome assessment. Participants in the true and sham TEAS groups were treated in separate rooms and blinded to the intervention. The investigators who manipulated the true or sham TEAS could not be blinded to the group allocations. The psychiatrists, parents, teachers, data collectors, and statisticians were blinded to treatment assignments.

Secondary outcomes included the CGI-S score, CPRS-R: S score, CTRS-R: S score, go/no-go performance, and HbO concentration at channel 37 (CH 37) within the frontal lobe cortex at week 4 and its changes from baseline to week 4. The CGI-S is a clinical psychiatrist-rated scale that includes seven levels for scoring: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse [19]. The clinical manifestation of the patients at week 4 was considered to be moderate (1 ≤ very much improved ≤ 3) or very severe (5 ≤ very much worse ≤ 7), which is defined as a clinically meaningful response. We obtained CGI-S ratings at week 4 after complete treatment or at the time of dropout for participants who withdrew from the trial.

Secondary outcome differences between the two groups are described by the mean (SD). The primary outcome difference between the randomized groups was analyzed by using the chi-square test for intergroup and intragroup differences before and after treatment between the TEAS and sham TEAS groups to verify the treatment effect while controlling for potential confounding factors. The mean accuracy (ACC) of go/no-go trials and reaction time (RT) of go trials were separately calculated [16]. A significant increase in HbO concentration in the specific channel from baseline to week 4 was considered an enhancement of the regional cerebral blood flow [22]. CH 37, located in the prefrontal cortex, was a priori defined as a sensitive region for discriminating children with ADHD from those with typical development [23].

Statistical analysis
There were no studies available concerning the effect of TEAS on ADHD, to provide information about an optimal sample size. In this trial, the sample size was calculated according to the results of a pilot study (n = 40) that found that the CGI-S scale rated a global improvement of 45% and 5% in TEAS and sham TEAS groups, respectively. A sample size of 36 participants (18 per group) was estimated according to a priori computation using the program G*Power (version 3.1.9.2, University of Dusseldorf) with a power of at least 80% to detect a 2-sided significance level of 5%. Here, 78 participants were included to account for potential missing samples.

Statistical analyses were based on both the intention-to-treat (ITT) and planned per-protocol (PP) principles and were performed with IBM SPSS Statistics 19. The baseline characteristics of the TEAS and sham TEAS groups are described by the mean (SD). The primary outcome difference between the randomized groups was analyzed by using the chi-square test to assess the CGI-I scores for dichotomy, comparing “very much improved” and “much improved” (defined as improved) with all other ratings (defined as not improved). Secondary outcome differences between the two groups were analyzed by calculating the mean (95% CI). The group-by-time interaction of the mixed model for repeated measures (MOMM) was used to analyze differences in the secondary outcomes, with groups (TEAS vs. sham TEAS) and time (baseline vs. week 4) as individual fixed effects. The cluster-robust variance estimator was used to adjust for potential clustering in the data.
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33.41 (95% CI, 28.56–38.25) at week 4 in the sham TEAS group. No difference was found between the two groups in the mean CTRS-R:S scores after true or sham TEAS treatment.

In addition, the mean ACC for go/no-go trials was 83.96% (95% CI, 79.71–88.21) at baseline and 84.97% (95% CI, 82.36–87.58) at week 4 in the TEAS group and 84.14% (95% CI, 84.84–89.45) at week 4 in the sham TEAS group. The mean RT for go/no-go trials was 304.2 ms (95% CI, 274.1–334.4) at baseline and 365.0 ms (95% CI, 324.8–405.1) at week 4 in the TEAS group and 318.1 ms (95% CI, 286.9–349.2) at baseline and 332.9 ms (95% CI, 279.2–386.5) at week 4 in the sham TEAS group. Despite increased mean ACC and RT in the TEAS group at week 4 compared with those at baseline (P < 0.001 and P = 0.016), there was no significant difference between the TEAS and sham TEAS groups at week 4 (P = 0.084 and P = 0.252).

fNIRS was used to assess the cerebral blood flow response to TEAS by monitoring HbO concentrations. CH 37, located in the frontal lobe cortex (Fig. 3A), was previously identified as an effective fNIRS channel involved in the go/no-go task and showed a significantly higher HbO concentration in children with typical development than in children with ADHD [23]. The mean baseline HbO concentrations for CH 37 were 0.021 mM mm (95% CI, 0.007–0.049) and 0.024 mM mm (95% CI, 0.009–0.040) in the TEAS group and the sham TEAS group, respectively (P = 0.881). We found a higher mean HbO signal in the ADHD subjects who received TEAS (0.120 mM mm; 95% CI, 0.078–0.162) than in the ADHD individuals in the sham TEAS group (0.029 mM mm; 95% CI, 0.005–0.062) at week 4 (P < 0.001; Table 2 and Fig. 3B). However, no changes were found in the sham TEAS group after 4 weeks of treatment (P = 0.812). We simultaneously analyzed the other 51 channels and did not find significant differences in the

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**Fig. 2** Study design. A Flowchart showing the study design of the TEAS intervention and response evaluation. B Illustration of acupoint locations for TEAS and sham TEAS. The rose-red triangle is the Baihui acupoint in the left panel, and the rose-red circles are the Taichong and Taixi acupoints in the middle and right panels, respectively. C Schematic diagram of the go/no-go task. HbO was measured by fNIRS in the TEAS and sham TEAS groups performing the go/no-go task.
concentration of HbO in these channels between the TEAS and sham TEAS groups after the Bonferroni correction (Supplement 3 and Supplement 4).

MMRM analyses in the PP population (Supplementary Table 2 and Supplementary Table 4) showed differences similar to those in the ITT population.

Adverse events

The guardians of the patients were interviewed about the potential adverse effects of every treatment. Three participants (2 in the TEAS group and 1 in the sham TEAS group) reported adverse events during the treatment period. One patient from the TEAS group complained of skin itching at the right ankle where electrodes were attached. The other patient in the TEAS group had a sleep disorder that mainly manifested as difficulty initiating sleep. The patient in the sham TEAS group described a mood disturbance. None of the three individuals required additional medical interventions for these adverse events and did not withdraw from the entire trial.

DISCUSSION

To our knowledge, this is the first randomized clinical trial of TEAS in patients with ADHD. The primary outcomes from both ITT and PP analyses showed a marked difference between the TEAS and sham TEAS groups. The secondary outcome from the ITT population showed significant differences in the mean CGI-S score, ACC for go/no-go trials, and HbO concentration for CH 37 of fNIRS but not in the mean CPRS-R: S score, CTRS-R: S score, or RT for go trials between the TEAS and sham TEAS groups. Among children with ADHD, treatment with TEAS compared with sham TEAS resulted in a significant investigator-rated clinical improvement in the ADHD-related symptoms at week 4. In addition, patients who under TEAS showed a greater brain response monitored by fNIRS in the prefrontal cortex than individuals under sham TEAS. Very mild adverse effects were found after the intervention.

Here, patients received TEAS or sham TEAS at the Baihui, Taichong, and Taixi acupoints. Stimulation at these points is expected to harmonize the mind and body, and these points have been frequently stimulated alone or in combination with other acupoints in ADHD treatment [6, 7, 24, 25]. Acupuncture at the Baihui acupoint can increase hippocampal and cortical dopamine levels, which might partly mimic the mechanism of medications [26]. Taichong has been practiced to calm excessive Yang [27], and Taixi has been practiced to rectify insufficient Yin [7, 27]. Previous acupuncture or electroacupuncture studies showed improvement in ADHD behaviors [7, 27] or increases in learning/memory abilities [25]. However, most of these acupoint-associated trials were not strict randomized controlled trials.

We can obtain specific improvement information from the CGI-I scale as it includes seven options for scoring, and a level of “much” or “very much improved” (score of 1 or 2) is defined as a clinically meaningful response. Therefore, this measure requires the psychiatrist to assess whether children’s behaviors have improved or worsened at the end of TEAS or sham TEAS treatment according to their symptoms at the beginning of treatment. We found that 4 weeks of TEAS significantly relieved the general symptoms of patients compared with sham TEAS. Here, the decrease in CGI-S scores at week 4 from baseline was remarkable in the TEAS group compared with that in the sham TEAS group. However, the changes over 4 weeks in scores on the CPRS-R: S and CTRS-R: S, two rating scales relying on parent and teacher reports, did not show prominent differences between the true and sham TEAS groups, although the mean CPRS-R: S scores in both the TEAS and sham TEAS groups at week 4 were greater than those at baseline. Therefore, there may be moderate placebo effects produced by sham TEAS. We noticed a discrepancy between measurements from clinical psychiatrists and parents/teachers. On one hand, this might suggest that investigators and parents/teachers might have different perspectives on children’s ADHD symptoms. CGI-I and CGI-S scores provide a general impression according to patients’ integrated behaviors, while the CPRS-R: S and CTRS-R: S assessments require more focused evaluation of specific ADHD symptoms. On the other hand, and more importantly, we acknowledge the large numbers of parents and teachers (a fifth to a quarter) who finished the online measurements in a very short time at week 4 after the trial. Thus, it is difficult to guarantee the accuracy and quality of those CPRS-R: S and CTRS-R: S evaluations. We noticed that the MMRM in the ITT population (Table 2) showed a significant difference in the group-by-time interaction effect between the TEAS and sham TEAS groups in the mean ACC for go/no-go trials (p = 0.049), which is very close to 0.05. However, the PP analysis (Supplementary Table 2) showed no significant difference in the group-by-time interaction effect between the TEAS and sham TEAS groups in the mean ACC (p = 0.067).

Acupuncture is known to increase local cerebral blood flow [28, 29], although the mechanisms of its efficacy for ADHD are still largely unknown [30]. fNIRS has been more commonly used to assess brain functioning in infants and children because of its accessibility and its ability to provide valuable results in spite of body movement [31, 32]. Although its detection space is limited to superficial cortical regions of the brain, fNIRS is a viable brain imaging tool for children with ADHD after weighing the pros and cons of the technology [33, 34]. ADHD is associated with dysfunction of the frontostriatal network [35, 36]. In this trial, we used a 3 × 11 probe (52 channels) system to monitor cerebral responses before and after TEAS for patients with ADHD [23, 37]. The neuroimages of children with ADHD, adolescents, and adults showed that right middle frontal activation is distinctly associated with response inhibition dysfunction [38]. CH 37, located in the prefrontal cortex, was a priori defined as a sensitive region for discriminating children with ADHD from children with typical development [23]. Interestingly, 4 weeks of TEAS significantly increased the concentration of HbO in CH 37 in patients during the go/no-go task but not in individuals who underwent sham TEAS. Acupuncture at the Baihui acupoint can increase the dopamine levels in the cerebral cortex, which might partly mimic the mechanism of medications [26]. Therefore, we hypothesized that CH 37 represented not only a sensitive cortex for ADHD diagnosis but also a cortex that is responsive to TEAS in this trial. Moreover, we simultaneously analyzed the other 51 channels and did not find significant differences in the concentration of HbO in these channels between the TEAS and sham TEAS groups.

### Table 1. Baseline characteristics of patients in the True TEAS and Sham TEAS groups in the ITT analysis.

| Characteristics | TEAS (n = 39) | Sham TEAS (n = 39) |
|-----------------|---------------|--------------------|
| Male, No. (%)   | 33 (84.6)     | 31 (79.5)          |
| Age, mean (SD), year | 8.05 (1.187) | 8.56 (1.468)       |
| IQ, mean (SD), score | 93.90 (12.333) | 96.72 (11.596)    |
| BMI, mean (SD)  | 17.36 (2.743) | 17.39 (3.419)      |
| Subtype, No. (%)|                |                    |
| ADHD-I          | 17 (43.6)     | 19 (48.7)          |
| ADHD-HI         | 0 (0)         | 0 (0)              |
| ADHD-C          | 22 (56.4)     | 20 (51.3)          |
| Ethnicity, No. (%)|            |                    |
| Han             | 39 (100)      | 38 (97.4)          |
| Others          | 0 (0)         | 1 (2.6)            |

TEAS transcutaneous electrical acupoint stimulation, ITT intention-to-treat, IQ intelligence quotient, BMI body mass index.
The time course measurement was performed 2 h after the last TEAS treatment on the same day. TEAS has a cumulative effect according to the concept of traditional Chinese medicine [13]. Therefore, the influence of acute effects after TEAS needs to be assessed by further follow-up visits. Moreover, to explore the effect of TEAS on the routine development of children, some children with typical development should be recruited to undergo TEAS treatment and detection of the cerebral blood flow using fNIRS and fmRI before and after TEAS in a future study.

Owing to its noninvasive feature, TEAS is an easily acceptable treatment for pediatric patients with ADHD. Parents might be easily taught to administer TEAS to children with ADHD at home. The patients most likely to benefit from TEAS include those who are intolerant or do not respond to psychostimulants. We noticed that a number of qualified patients refused to participate in our trial because their previous medication treatments worked very well. In addition, although inferior to TEAS, sham TEAS still exhibited a slight improvement, and this effect was most likely a result of the placebo effect originating from routine manipulation. Second, the electrodes without electricity may not be completely inert. In the trial, we used an electrode with a small bulge in the middle to match the acupoints (Supplementary Fig. 1).

Of note, this study has several limitations. First, the sample size was moderate since participants were enrolled from a single medical center. Second, only the clinical investigator-rated CGI-I score was used as the primary outcome, and integrated measures for ADHD from psychiatrists and parents/teachers were not included as primary outcomes. Third, it is not known whether all three acupoints contribute to improved behaviors.

Table 2. Primary and secondary outcomes from the ITT Analysis.

|          | TEAS (n = 39) | Sham TEAS (n = 39) | P-value |
|----------|---------------|-------------------|---------|
| Primary outcome |                |                   |         |
| CGI-I Score at wk 4<sup>a</sup> | 4.63 (4.12–4.60) | 4.66 (4.41–4.90) | 0.001   |
|          | 3.49 (3.21–3.76) | 4.38 (4.08–4.67) |         |
| Change at wk 4<sup>b</sup> | −0.87 (−1.12–0.63) | −0.28 (−0.53–0.04) |         |
| Secondary outcomes | Interaction term | TEAS and Sham TEAS | Baseline and Week 4 TEAS |
| CGI-S, mean (95% CI) | Score at baseline | 45.82 (41.96–49.68) | 47.13 (44.29–49.96) | 0.384 |
|          | Score at wk 4 | 38.36 (33.49–43.22) | 41.78 (37.71–45.85) | 0.003 |
| Change at wk 4<sup>c</sup> | −7.46 (−10.87–4.06) | −5.34 (−8.75–1.94) |         |
| CPRS-R: S, mean (95% CI) | Score at baseline | 31.28 (26.37–36.19) | 35.28 (31.17–39.39) | 0.956 |
|          | Score at wk 4 | 29.26 (23.86–34.65) | 33.41 (28.56–38.25) | 0.291 |
| Change at wk 4<sup>d</sup> | −2.03 (−5.82–1.77) | −1.88 (−5.67–1.92) |         |
| CTRS-R: S, mean (95% CI) | Score at baseline | 83.96 (79.71–88.21) | 84.97 (82.36–87.58) | 0.049 |
|          | Score at wk 4 | 90.86 (88.17–93.56) | 87.14 (84.84–89.45) | 0.084 |
| Change at wk 4<sup>e</sup> | 6.90 (3.58–10.22) | 2.18 (−1.14–5.49) |         |
| ACC (%), mean (95% CI) | At baseline | 304.2 (274.1–334.4) | 318.1 (286.9–349.2) | 0.193 |
|          | At wk 4 | 365.0 (324.8–405.1) | 332.9 (279.2–386.5) | 0.551 |
| Change at wk 4<sup>f</sup> | 60.74 (11.5–109.9) | 14.8 (−34.4–64.0) |         |
| RT (ms), mean (95% CI) | At baseline | 0.021 (0.007–0.049) | 0.024 (0.009–0.040) | 0.001 |
|          | At wk 4 | 0.120 (0.078–0.162) | 0.029 (0.005–0.062) | 0.881 |
| Change at wk 4<sup>g</sup> | 0.099 (0.061–0.138) | 0.005 (−0.034–0.043) |         |
| Oxy-HB CH 37 (mM mm), mean (95% CI) | At baseline | 39.39 (36.19–42.59) | 39.39 (36.19–42.59) | 0.001 |
|          | At wk 4 | 45.85 (42.61–49.09) | 45.85 (42.61–49.09) | 0.003 |
| Change at wk 4<sup>h</sup> | 4.46 (1.12–7.77) | 4.46 (1.12–7.77) |         |

<sup>a</sup>ITT intention-to-treat, TEAS transcutaneous electrical acupoint stimulation, CGI-I Clinical Global Impression Scale-Improvement of Illness, CPRS-R: S Conners’ Parent Rating Scales-Revised: Short Form, CTRS-R: S, Conners’ Teacher Rating Scales-Revised: Short Form, ACC accuracy, RT reaction time, Oxy-Hb oxygenated hemoglobin, SD standard deviation.

<sup>b</sup>Indicates the difference in mean change from baseline to endpoint between the TEAS and sham TEAS groups by MMRM and the Wilcoxon rank-sum test.

<sup>c</sup>Change at wk 4 was used as the primary outcome, and integrated measures for ADHD from psychiatrists and parents/teachers were not included as primary outcomes. Third, it is not known whether all three acupoints contribute to improved behaviors.
Finally, this was only a cross-sectional study at baseline and week 4, without longitudinal assessments.

Overall, TEAS can be safely practiced on children with ADHD. Compared with sham TEAS, TEAS resulted in a larger general symptomatic improvement in patients and greater prefrontal responses within 4 weeks of administration. Further clinical trials are required to understand the long-term benefits of TEAS for children with ADHD, especially for those who are intolerant or have no response to routine psychostimulant therapy.

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Fig. 3  Spatial profiles of fNIRS channels and HBO signals for CH 37. A Map of 52-channel fNIRS used in the present trial. Each yellow square on the standard brain model represents an fNIRS channel, each red dot represents an emitter, and each blue dot represents a detector. Left-, front- and right-side views of the probe arrangements in a 52-channel fNIRS. B Violin plots of HBO signals for CH 37 showed no significant differences at baseline between the TEAS (n = 39) and sham TEAS (n = 39) groups (left panel) but increased brain responses were observed after the 4 weeks of treatment in the TEAS group compared to the sham TEAS group (middle and right panels) (MMRM and Wilcoxon rank-sum test). Hollow circles denote individual data points; solid black lines denote medians, and dashed gray lines denote quartiles. NS not significant. ***p < 0.001.
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AUTHOR CONTRIBUTIONS

LZ, XZ, and YZ contributed equally to this work. Concept and design: YL and JZ. Acquisition, analysis, and interpretation of data: LZ, XZ, YZ, LT, YaZ, XW, XG, CY, and WW. Drafting of the manuscript: YL, JZ, and LAR. Statistical analysis: YZ, BZ, and TZ. Obtained funding: YL. Administrative, technical, or material support: LZ, WG, QW, and JZ.

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