



## Analgesia induced by anodal tDCS and high-frequency tRNS over the motor cortex: Immediate and sustained effects on pain perception

Junjie Yao <sup>a,1</sup>, Xiaoyun Li <sup>a,1</sup>, Wenyun Zhang <sup>a</sup>, Xinxin Lin <sup>a</sup>, Xiaohan Lyu <sup>a</sup>, Wutao Lou <sup>b</sup>, Weiwei Peng <sup>a,\*</sup>

<sup>a</sup> School of Psychology, Shenzhen University, Shenzhen, Guangdong, China

<sup>b</sup> Department of Biomedical Engineering, The Chinese University of Hong Kong, Hong Kong SAR, China

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### ABSTRACT

**Background:** Many studies have shown effects of anodal transcranial direct current stimulation (a-tDCS) and high-frequency transcranial random noise stimulation (tRNS) on elevating cortical excitability. Moreover, tRNS with a direct current (DC)-offset is more likely to lead to increases in cortical excitability than solely tRNS. While a-tDCS over primary motor cortex (M1) has been shown to attenuate pain perception, tRNS + DC-offset may prove as an effective means for pain relief.

**Objective:** This study aimed to examine effects of a-tDCS and high-frequency tRNS + DC-offset over M1 on pain expectation and perception, and assess whether these effects could be influenced by the certainty of pain expectation.

**Methods:** Using a double-blinded and sham-controlled design, 150 healthy participants were recruited to receive a single-session a-tDCS, high-frequency tRNS + DC-offset, or sham stimulation over M1. The expectation and perception of electrical stimulation in certain and uncertain contexts were assessed at baseline, immediately after, and 30 min after stimulation.

**Results:** Compared with sham stimulation, a-tDCS induced immediate analgesic effects that were greater when the stimulation outcome was expected with uncertainty; tRNS induced immediate and sustained analgesic effects that were mediated by decreasing pain expectation. Nevertheless, we found no strong evidence for tRNS being more effective for attenuating pain than a-tDCS.

**Conclusions:** The analgesic effects of a-tDCS and tRNS showed different temporal courses, which could be related to the more sustained effectiveness of high-frequency tRNS + DC-offset in elevating cortical excitability. Moreover, expectations of pain intensity should be taken into consideration to maximize the benefits of neuromodulation.

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### Introduction

Transcranial direct current stimulation (tDCS), as the most commonly used type of transcranial electrical stimulation (tES), delivers a weak direct current to the surface of the head and non-invasively manipulates neuronal excitability via membrane polarization [1,2]. Generally, anodal stimulation (applying an anode over the target area) is thought to increase cortical excitability by depolarizing membrane potential and cathodal stimulation

(applying a cathode over the target area) is thought to inhibit cortical excitability by hyperpolarizing the membrane potential [3,4]. The induced after-effects on cortical excitability depend on factors such as the intensity and duration of the stimulation [5,6]. Due to its neuromodulatory effects, tDCS has been considered as a promising approach for pain management [7–10]. Particularly, applying tDCS over the primary motor cortex (M1) has been shown to attenuate pain perception in both healthy participants and clinical pain patients [9–11], manifested as increased pain thresholds and decreased levels of pain perception. One of the potential mechanisms underlying this phenomenon is the activation of subcortical structures of endogenous pain inhibitory pathway including thalamus, cingulate gyrus, midbrain periaqueductal gray, and subnucleus reticularis dorsalis [11–13].

\* Corresponding author. School of Psychology, Shenzhen University, Nanhai Ave 3688, Shenzhen, Guangdong, 518060, China.

E-mail address: [ww.peng0923@gmail.com](mailto:ww.peng0923@gmail.com) (W. Peng).

<sup>1</sup> These authors contributed equally.

Unlike tDCS that uses constant direct currents, transcranial random noise stimulation (tRNS) uses random levels of alternating currents within a broad spectrum. Studies have shown that weak tRNS over M1 led to enhanced motor cortical excitability where high-frequency subdivision of the whole tRNS spectrum between 100 and 640 Hz was functionally responsible for inducing excitability enhancement [2,14,15]. For instance, 10 min of tRNS stimulation was reported to induce a consistent excitability increase lasting at least 60 min after stimulation [15]. This effect could be attributed to the repeated opening of sodium channels or to the increased sensitivity of neuronal networks to field modulation [2,15,16]. Although some studies have shown effects of anodal-tDCS (a-tDCS) and tRNS on enhancing motor cortical excitability [3,4,14,15], the latter effect appears to be more sustained and stable [17–19]. Moreover, Ho et al. [20] suggest that tRNS with a direct current (DC)-offset (tRNS + DC-offset) may be more likely to lead to increases in cortical excitability than solely tRNS. In addition to the neuromodulatory effects, there are some studies showing the promising effects of tRNS + DC-offset on the improvement of cognitive functions [21] and on the treatment of psychiatric disorders [22,23]. These evidences raise the possibility that tRNS + DC-offset may prove as an effective and reliable means to relieve pain perception, while a-tDCS effects on pain-relief have been reported by previous studies [10,24–26].

Human pain perception involves complex interactions between bottom-up nociceptive inputs and top-down cognitive processes, with subjective pain perception greatly shaped by expectations [27,28]. Electroencephalographic (EEG) studies have shown cortical alpha-band rhythm states are associated with the cortical processes of pain expectation [29,30], and that a-tDCS can alter spontaneous cortical oscillatory activity in the alpha frequency band [31,32]. Thus, a-tDCS and/or tRNS likely affect pain perception by exerting top-down influence on pain expectation. In addition, the level of expectation certainty is associated with different emotional, physiological, and behavioral consequences [33]: while certain expectation of upcoming pain has been associated with the emotional state of fear that leads to decreased pain sensitivity [34], being uncertain has been associated with emotional state of anxiety that leads to increased pain sensitivity [35]. The impact that brain stimulation has on perception and cognition greatly depends upon the particular psychophysiological state of the participant [36–38]. Thus, effects of a-tDCS and/or tRNS on pain are likely to be modulated by how certain we are that pain will be forthcoming.

Therefore, the present study aimed to examine the effects of single-session a-tDCS and high-frequency tRNS + DC-offset on pain expectation and perception, and assess whether these effects are moderated by the certainty of pain expectation. Given the evidence for the effectiveness of a-tDCS and tRNS in increasing cortical excitability which effects may be more stable for tRNS, we hypothesized that both a-tDCS and tRNS over M1 would induce analgesic effects and tRNS would induce more sustained effects. Second, the analgesic effects of both stimulation methods would be partially explained by their effects on decreasing pain expectation, since subjective pain perception is greatly shaped by our expectations of pain. Third, as expectation certainty affects mental states that would affect the response to brain stimulation, the level of certainty regarding the pain stimulation will influence the analgesic effects of a-tDCS and tRNS.

## Materials and methods

### Participants

*A priori* power analysis using G\*Power software [39] was conducted using the average of effect sizes from previous studies that

compared the effects of a-tDCS and sham stimulation on experimental pain perception among healthy participants (Cohen's  $d$  ranging from 0.49 to 0.64 [40–43]) to calculate the needed sample size. It yielded a sample size of  $n = 49$  per group to detect a medium effect size of  $d = 0.58$  at a standard error probability of  $\alpha = 0.05$  with a power of  $1 - \beta = 0.8$ . Therefore, a total of 150 participants (age: mean  $\pm$  standard error of mean [SEM] =  $19.82 \pm 0.13$  years; 73 females) were recruited for this study. All participants were right-handed, had normal or corrected-to-normal vision, and were free from any contraindications for tES application. No participant reported any medical condition associated with acute or chronic pain, cardiovascular or neurological diseases, psychiatric disorders, or current use of any medication. The participants were randomly allocated to the a-tDCS, tRNS, or sham group, and were blinded to the applied tES intervention. Each group comprised 50 participants. Due to equipment failure, one participant in the sham group failed to complete the experiment. Thus, we analyzed data from 149 participants (a-tDCS group:  $n = 50$ ; tRNS group:  $n = 50$ ; sham group:  $n = 49$ ). All participants gave their written informed consent before the experiments according to Declaration of Helsinki. All experimental procedures were approved by the local research ethics committee.

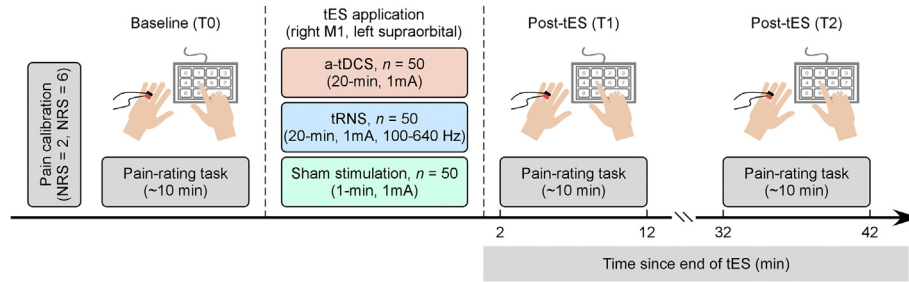
### General experimental procedure

Two researchers participated in the experiment: one as an assessor and the other as the tES administrator. The assessor was responsible for data collection and analysis, and was blinded to the stimulation condition (a-tDCS, tRNS, or sham). The tES administrator was responsible for delivering the tES interventions, and was not involved in any data collection or analysis. In addition, the tES administrator used computer-generated random stimulation conditions and allocated the participants to one of the three experimental groups (a-tDCS, tRNS, or sham) according to their order of entry. Before the experiment, all participants were instructed to complete pain-related questionnaires that measured their pain-sensitivity profiles, including pain sensitivity questionnaire, fear of pain questionnaire, pain catastrophizing scale, and pain vigilance and awareness questionnaire.

As shown in Fig. 1, a single-session tES procedure lasted 20 min. Before tES application (T0, baseline), immediately after tES application (T1), and 30 min after the end of tES application (T2), participants were instructed to complete a pain-rating task. During the task, either painful or nonpainful electrical stimuli preceded by certain or uncertain cues were delivered to the left hand of the participants. After each stimulation, participants reported the perceived pain intensity and unpleasantness by pressing keys on the keyboard using their right hand. Prior to the first pain-rating task, a pain calibration procedure was conducted to determine the physical intensity of electrical stimulation to be used for each individual participant.

### Calibration of stimulation intensity

Painful and nonpainful stimuli were electrical pulses (duration: 50 ms) that were applied to the left fourth finger through a pair of ring electrodes. Electrical pulses were generated by a multichannel electrical stimulator (SXC-4A, Sanxia Technique Inc., China). A series of electrical stimuli were delivered to the participants, with intensity started at 300  $\mu$ A and gradually increased in steps of 200  $\mu$ A. After each stimulation, participants were instructed to rate the intensity of pain they had experienced on a 0–10 numerical rating scale (NRS), in which 0 indicated no sensation, 4 indicated starting to be painful, and 10 indicated unbearable pain. Painful and nonpainful electrical stimuli to be used in the pain-rating task were



**Fig. 1.** Schematic illustration of the experimental procedure

A total of 150 participants were randomly allocated to receive a single-session a-tDCS (1 mA, 20 min), tRNS (1 mA, 20 min, 100–640 Hz), or sham stimulation (1 mA, 1 min). The montage of M1 and contralateral supraorbital was used, with the anodal electrode placed on the right M1 (C4 electrode on the 10–20 system) and the cathodal electrode placed on the left supraorbital. Before (T0), immediately after (T1), and 30 min after (T2) tES application, participants completed a pain-rating task that lasted about 10 min. During the pain-rating task, either nonpainful or painful electrical stimuli were delivered to the left fourth finger through a pair of ring electrodes. Participants rated expected pain and perceived pain by pressing keys on the keyboard with their right hand. Electrical stimulations in the task were calibrated individually to include a nonpainful but detectable stimulation level (level 2 on the 0–10 scale) and a painful but tolerable stimulation level (level 6).

determined: the first for eliciting a nonpainful but detectable sensation (NRS = 2) and the second for a painful but tolerable sensation (NRS = 6). The calibrated current intensities for painful and nonpainful stimuli were comparable among a-tDCS, tRNS and sham groups (Table 1). For all participants, the painful stimuli were reported to evoke prickling or tingling sensations.

*Pain-rating task*

The pain-rating task was adopted to assess individual pain expectation and perception in certain or uncertain contexts. A schematic illustration of the trial structure is shown in Fig. 2. A visual cue indicating the intensity of the upcoming electrical stimulation (pain-predictability cues). There were three pain-predictability cues: certain-nonpain (a circle; 25 % of trials), certain-pain (a triangle; 25 % of trials) and uncertain (a diamond; 50 % of trials). The pairing of patterning and predictability was counterbalanced among the participants. These pain-predictability cues were completely predictive of the upcoming pain-stimulation intensity, which was explicitly explained to the participants.

The pain-rating task conformed to a 2 (pain-predictability: certain vs uncertain) × 2 (physical stimulation intensity: nonpain vs pain) within-participant design. This resulted in four conditions: certain-nonpain, certain-pain, uncertain-nonpain, and uncertain-pain. The session comprised 40 trials (10 trials per condition), which were presented in a pseudo-randomized order. As illustrated in Fig. 2, each trial began with a 1000-ms fixation, followed by the presentation of one of the three pain-predictability cues (duration = 2000 ms). Then, participants were instructed to use the keyboard with their right hand to rate the pain intensity (on the

predefined 0–10 NRS) that they expected the upcoming electrical stimulation would be. Then, an 800–1200-ms fixation cross was displayed on the screen and either a non-painful or painful electrical stimulation was delivered to the left fourth finger through a pair of ring electrodes. Afterward, participants rated the intensity of perceived pain on the 0–10 NRS, as well as the unpleasantness that they felt (also on the 0–10 NRS, with 0 indicating no unpleasantness and 10 indicating unbearable unpleasantness). The inter-trial-interval was 4000–6000 ms.

*Transcranial electrical stimulation*

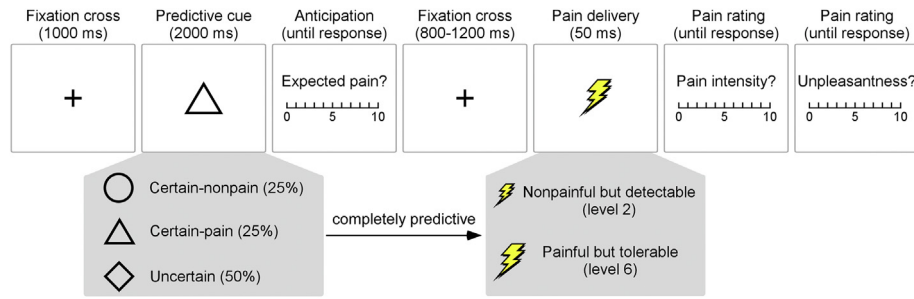
Immediately after the pain-rating task at T0 (baseline), a single-session tES was administered using a Neuroconn DC-STIMULATOR MC (Neuroconn, Ilmenau, Germany). The anodal and cathodal electrodes were two 5 cm × 5 cm rubber electrodes in a motor cortex–contralateral orbit montage. The electrodes were placed in saline-soaked sponges and fixed to the head with elastic rubber bands. For all stimulation conditions, the anode was placed over C4 (using the 10–20 system of electrode placement) which is the approximate location of right M1, and the cathode was placed over the left supraorbital area. Impedances were kept below 5 kΩ.

We delivered a single-session a-tDCS at 1 mA (current density = 0.04 mA/cm<sup>2</sup>) for 20 min (30 s fade-in, 30 s fade-out). High-frequency tRNS (100–640 Hz) was delivered for 20 min (30 s fade-in, 30 s fade-out) at an intensity of 1 mA and a DC-offset of 1 mA. A random level of current was generated for every sample at a rate of 1280 samples/second with a DC-offset of 1 mA. In the frequency spectrum all coefficients had a similar size with a “white noise” characteristic. Here, we chose a frequency spectrum between 100 Hz and 640 Hz because after-effects of tRNS are thought

**Table 1**  
Demographic and psychometrical variables for a-tDCS, tRNS and sham groups.

	a-tDCS (n = 50)	tRNS (n = 50)	Sham (n = 49)	Statistics
Age (years)	19.68 ± 0.23	19.78 ± 0.20	20.04 ± 0.27	F <sub>2, 146</sub> = 0.63
Gender (F/M)	23/27	24/26	25/24	χ <sup>2</sup> (1) = 0.17
PSQ	80.74 ± 2.55	75.74 ± 2.41	81.06 ± 2.56	F <sub>2, 146</sub> = 1.42
FPQ	104.42 ± 2.48	102.58 ± 2.11	101.36 ± 2.53	F <sub>2, 146</sub> = 0.42
PCS	19.92 ± 1.47	21.32 ± 1.28	22.43 ± 1.60	F <sub>2, 146</sub> = 0.74
PVAQ	36.86 ± 1.58	35.78 ± 1.30	39.61 ± 1.45	F <sub>2, 146</sub> = 1.85
Nonpain (mA)	0.91 ± 0.05	0.90 ± 0.07	0.79 ± 0.04	F <sub>2, 146</sub> = 1.40
Pain (mA)	2.02 ± 0.11	1.98 ± 0.12	1.85 ± 0.08	F <sub>2, 146</sub> = 0.68

Notes: Data are expressed using Mean ± SEM. Statistics were obtained by applying one-way ANOVA or Chi-square test with factors of Group (a-tDCS, tRNS, and sham). Abbreviations: F, female; M, male; PSQ, Pain Sensitivity Questionnaire; FPQ, Fear of Pain Questionnaire; PCS, Pain Catastrophizing Scale; PVAQ, Pain Vigilance and Awareness Questionnaire.



**Fig. 2.** Trial structure in the pain-rating task

Each experimental trial started with a 1000-ms fixation, followed by the presentation of the predictability cue (duration: 2000 ms), which predicted the intensity of the upcoming electrical stimulation. There were three types of predictability cues: (1) a circle indicated that the upcoming stimulation would be nonpainful; (2) a triangle indicated that the upcoming stimulation would be painful; (3) a diamond indicated that the upcoming stimulation would be either nonpainful or painful. The probabilities of these predictability cues were 25 %, 25 %, and 50 %, respectively. After seeing the cues, participants rated the expected pain intensity to the upcoming electrical stimulation on the predefined 0–10 NRS through pressing a button on the keyboard using their right hand. After the presentation of 800–1200 ms fixation cross, either a nonpainful but detectable stimulation (level 2 on the 0–10 NRS) or a painful but tolerable stimulation (level 6 on the 0–10 NRS) was deliverable to the left hand. It thus yielded four categories of electrical stimulations, including (1) certain-nonpain, a nonpainful stimulation preceded by a certain-nonpain predictability cue; (2) certain-pain, a painful stimulation preceded by a certain-pain predictability cue; (3) uncertain-nonpain, a nonpainful stimulation preceded by an uncertain predictability cue; (4) uncertain-pain, a painful stimulation preceded by an uncertain predictability cue. After each stimulation, the participant rated the intensity of perceived pain, as well as the unpleasantness that they felt, on two 0–10 NRS.

to be primarily driven by oscillations in the higher frequency range [15]. We added a DC-offset of 1 mA because tRNS with a DC-offset is more likely to lead to increases in cortical excitability than is tRNS alone [20]. In addition, it produces a unidirectional current flow analogous to a-tDCS [21], which fluctuated between +0.5 mA and +1.5 mA at the anode and between –0.5 mA and –1.5 mA at the cathode. Throughout the course of the stimulation session, a-tDCS and tRNS that we used delivered an approximately equivalent net charge (mean charge of +1 mA at the anode and –1 mA at the cathode). Therefore, it was appropriate for directly comparing analgesic effects of a-tDCS and tRNS. Sham stimulation involved delivery of active a-tDCS for 1 min (30 s fade-in, 30 s fade-out). This sham procedure elicited an initial itching sensation under the electrodes, but participants received no current for the remainder of the stimulation period. Following the end of stimulation, participants were asked whether they believed that they had received active tES or not, and were instructed to fill out a questionnaire that evaluated adverse effects caused by tES [24,44].

*Statistical analysis*

Statistical analyses were carried out using the IBM SPSS statistical analysis package (version 22; IBM Corp., Armonk, New York, USA). For each participant and experimental condition, single-participant ratings of expected pain intensity (in response to the pain-predictability cues), as well as ratings of perceived pain intensity and unpleasantness (in response to the electrical stimulation), were calculated by averaging single-trial pain ratings across epochs belonging to the same experimental condition. The immediate effects of tES (the change in ratings between T1 and T0, T1 – T0) and the sustained effects (the change in ratings between T2 and T0, T2 – T0) were analyzed as outcome variables. A negative/positive value indicates decreased/increased pain after tES application.

The immediate and sustained effects of tES on expected pain-intensity ratings were compared using a two-way mixed-design analysis of variance (ANOVA) with factors of Predictability Cue (certain-nonpain, certain-pain, and uncertain) and a between-participant factor of Group (a-tDCS, tRNS, and sham groups). The immediate and sustained effects on perceived pain (intensity and unpleasantness ratings) were separately compared using a three-way mixed-design ANOVA, with two within-participant factors of Predictability (certain and uncertain) and Pain (nonpain and pain), and a between-participant factor of Group (a-tDCS, tRNS, and sham

groups). When a main effect or interaction was significant, we performed post hoc comparisons. We used Bonferroni correction method to correct for multiple comparisons.

If tES modulated both pain expectation and perception ratings, we further tested whether it attenuated pain-perception via the modulation of pain-expectation. A participant-level mediation analysis was performed using the SPSS version of the PROCESS macro [45]. In the mediation models, independent variable (X) was tES type (e.g., 1 for a-tDCS or tRNS; –1 for sham stimulation); tES effects on perceived pain ratings were the dependent variable (Y); tES effects on expected pain ratings were the mediator (M). This analysis determined the indirect effects that tES has on pain-perception via pain-expectation, yielding the 95 % confidence intervals (CIs) of the indirect effects. These effects were considered statistically significant when the 95 % CIs did not include zero.

**Results**

As summarized in Table 1, the age, gender, and pain-sensitivity profiles were well matched among the three groups. None of the participants asked to terminate the stimulation, and the experimental protocol was well tolerated. The effectiveness of tES blinding (whether the participant believed that they had received active tES or not) did not differ among the three groups ( $\chi^2(1) = 1.82, p = 0.18$ , Chi-square test), demonstrating that participants were unaware of their stimulation condition. Reports of tingling, itching, and burning sensations at the stimulated site, as well as those of headaches and sleepiness have been summarized in the supplementary materials (Table S1). These ratings did not differ significantly among the three groups, suggesting that there were no significant adverse effects caused by a-tDCS and tRNS.

*Immediate and sustained effects of single-session tES on pain perception*

The immediate (T1 – T0) and sustained effects (T2 – T0) on pain-perception ratings for each condition and group are summarized in Table 2, and their statistics are summarized in Table 3. In addition, we have provided the original pain ratings and their statistics in the supplementary materials (Figures S1 & S2; Table S2).

Immediate effects on pain perception

Analysis of the immediate tES effects on pain-intensity ratings showed significant main effects of Pain ( $F_{1, 146} = 6.71, p = 0.011, \eta_p^2 = 0.044$ ) and Group ( $F_{2, 146} = 5.45, p = 0.005, \eta_p^2 = 0.07$ ). The analgesic effects were greater for pain-trials than for nonpain-trials ( $p = 0.011$ ) and were greater for a-tDCS and tRNS groups than for the sham group ( $p = 0.011$  and  $p = 0.02$ , respectively). The interaction between Pain and Group was significant ( $F_{2, 146} = 3.61, p = 0.03, \eta_p^2 = 0.047$ ). For the pain-trials, the analgesic effects for a-tDCS and tRNS groups were greater than for sham group ( $p = 0.001$  and  $p = 0.008$ , respectively, Fig. 3A). In contrast, for the nonpain-trials, no significant difference was observed among the groups. The interaction between Predictability and Group was significant ( $F_{2, 146} = 3.14, p = 0.046, \eta_p^2 = 0.041$ ). Regardless of certain-trials or uncertain-trials, the analgesic effects in the a-tDCS and tRNS groups were greater than those for the sham group ( $p < 0.05$  for all comparisons, Fig. 3B). However, a-tDCS induced analgesia for uncertain-trials was greater than that for certain-trials ( $p = 0.05$ ). Similar differences were not observed in the tRNS or sham groups.

Analysis of the immediate tES effects on unpleasantness ratings showed significant main effects of Pain ( $F_{1, 146} = 9.23, p = 0.003, \eta_p^2 = 0.059$ ) and Group ( $F_{2, 146} = 7.42, p = 0.001, \eta_p^2 = 0.092$ ). The analgesic effects were greater for pain-trials than for nonpain-trials ( $p = 0.003$ ) and were greater for a-tDCS and tRNS than for sham stimulation ( $p = 0.001$  and  $p = 0.016$ , respectively). The interaction between Pain and Group was significant ( $F_{2, 146} = 3.57, p = 0.031, \eta_p^2 = 0.047$ ). Regardless of pain-trials or nonpain-trials, the analgesic effects in the a-tDCS and tRNS groups were greater than those for the sham group ( $p < 0.05$  for all comparisons, Fig. 3C). However, while the analgesic effects in the a-tDCS group were greater when stimulation was painful than when it was not ( $p < 0.001$ ), this difference was not significant in the tRNS or sham groups. The interaction between Predictability and Group was not significant ( $F_{2, 146} = 0.66, p = 0.52, \eta_p^2 = 0.009$ ). Regardless of certain-trials or uncertain-trials, the decrease of unpleasantness for a-tDCS and tRNS groups were greater than those for the sham group ( $p < 0.05$  for all comparisons, Fig. 3D). The interaction between Predictability and Pain was significant ( $F_{1, 146} = 6.94, p = 0.009, \eta_p^2 = 0.045$ ). The analgesic effects for pain-trials depended on the certainty (certain < uncertain;  $p = 0.042$ ), while those for nonpain-trials did not.

**Table 2**  
Immediate and sustained effects of tES on pain-perception ratings.

	a-tDCS (n = 50)	tRNS (n = 50)	Sham (n = 49)
<i>Immediate effects on pain-intensity ratings (T1–T0)</i>			
Certain-pain	-0.50 ± 0.15	-0.51 ± 0.15	0.21 ± 0.15
Certain-nonpain	-0.10 ± 0.13	-0.16 ± 0.13	0.07 ± 0.13
Uncertain-pain	-0.66 ± 0.17	-0.39 ± 0.17	0.23 ± 0.17
Uncertain-nonpain	-0.17 ± 0.15	-0.22 ± 0.15	0.22 ± 0.16
<i>Sustained effects on pain-intensity ratings (T2–T0)</i>			
Certain-pain	-0.35 ± 0.17	-0.56 ± 0.17	0.14 ± 0.17
Certain-nonpain	-0.10 ± 0.13	-0.19 ± 0.13	-0.01 ± 0.13
Uncertain-pain	-0.41 ± 0.17	-0.58 ± 0.17	0.004 ± 0.17
Uncertain-nonpain	-0.12 ± 0.14	-0.21 ± 0.14	-0.04 ± 0.14
<i>Immediate effects on unpleasantness ratings (T1–T0)</i>			
Certain-pain	-0.77 ± 0.22	-0.49 ± 0.22	0.38 ± 0.22
Certain-nonpain	-0.29 ± 0.16	-0.26 ± 0.16	0.30 ± 0.16
Uncertain-pain	-1.02 ± 0.24	-0.55 ± 0.24	0.30 ± 0.24
Uncertain-nonpain	-0.25 ± 0.17	-0.20 ± 0.17	0.35 ± 0.17
<i>Sustained effects on unpleasantness ratings (T2–T0)</i>			
Certain-pain	-0.52 ± 0.25	-0.36 ± 0.25	0.07 ± 0.26
Certain-nonpain	-0.21 ± 0.15	-0.20 ± 0.15	0.05 ± 0.15
Uncertain-pain	-0.75 ± 0.25	-0.56 ± 0.25	-0.17 ± 0.25
Uncertain-nonpain	-0.14 ± 0.16	-0.17 ± 0.16	-0.05 ± 0.16

Notes: Data are expressed using Mean ± SEM.

Sustained effects on pain perception

We observed a main effect of Pain ( $F_{1, 146} = 4.16, p = 0.043, \eta_p^2 = 0.028$ ) on sustained tES effects on pain-intensity ratings, such that the analgesic effects were greater for pain-trials than for nonpain-trials. We also observed a marginally significant main effect of Group ( $F_{2, 146} = 2.95, p = 0.055, \eta_p^2 = 0.039$ ) such that the analgesic effect in the tRNS group was greater than it was in the sham group. The interaction between Pain and Group was marginally significant ( $F_{2, 146} = 2.58, p = 0.079, \eta_p^2 = 0.034$ ). For pain-trials, the analgesic effects for the tRNS group were greater than those for the sham group ( $p = 0.014$ , Fig. 4A), whereas no significant difference was observed for nonpain-trials.

We observed main effects of Pain ( $F_{1, 146} = 5.61, p = 0.019, \eta_p^2 = 0.037$ ) and Predictability ( $F_{1, 146} = 4.87, p = 0.029, \eta_p^2 = 0.032$ ) on the sustained tES effects on unpleasantness ratings. The analgesic effects were greater for pain-trials than for nonpain-trials and were greater for uncertain-trials than for certain-trials. The interaction between Pain and Group was not significant ( $F_{2, 146} = 1.16, p = 0.315, \eta_p^2 = 0.016$ , Fig. 4B). The interaction between Predictability and Pain was significant ( $F_{1, 146} = 7.07, p = 0.009, \eta_p^2 = 0.046$ ), such that analgesic effects only depended on outcome certainty for pain-trials (certain < uncertain,  $p = 0.006$ ), but not for nonpain-trials.

Immediate and sustained effects of single-session tES on pain expectation

Immediate and sustained effects on expected-pain ratings are summarized in Table 4. Analysis of the immediate tES effects only revealed a significant main effect of Group ( $F_{2, 146} = 3.06, p = 0.05, \eta_p^2 = 0.04$ ). Post-hoc analysis showed that expected-pain ratings decreased more for the tRNS group than for the sham group, although this effect was only marginally significant ( $p = 0.068$ , Fig. 5A). Analysis of the sustained tES effects revealed a significant main effect of Predictability Cue ( $F_{2, 292} = 4.778, p = 0.01, \eta_p^2 = 0.032$ ), such that the effects for certain-pain cues were greater than those for certain-nonpain cues ( $p = 0.021$ ) or uncertain cues ( $p = 0.045$ ). The main effect of Group or the interaction was not significant (Fig. 5B). These results suggest that compared with sham stimulation, pain expectation for the upcoming electrical stimulation dropped immediately after tRNS application.

Mediation model

Given that tRNS attenuated expectation and perception of pain, we next tested whether tRNS attenuated pain-perception via the modulation of pain-expectation. The bootstrap CIs revealed that the indirect effect of tRNS on immediate analgesic effects via the immediate modulation of expected-pain ratings differed from zero with 95 % confidence ( $a*b = -0.091, SE = 0.041, CI = [-0.18, -0.014]$ , Fig. 6A). This indirect effect accounted for 36.09 % ( $1 - (-0.16)/(-0.25)$ ) of the total effect. Moreover, the indirect effect of tRNS on the sustained analgesic effects via the sustained modulation of expected-pain ratings differed from zero with 95 % confidence ( $a*b = -0.087, SE = 0.045, CI = [-0.18, -0.009]$ , Fig. 6B). This indirect effect accounted for 42.15 % ( $1 - (-0.12)/(-0.21)$ ) of the total effect.

Discussion

Adopting a double-blinded and sham-controlled design, this study examined the analgesic effects of single-session a-tDCS and high-frequency tRNS + DC-offset over M1. Compared with sham stimulation, the decrease in subjective pain perception (including both pain intensity and unpleasantness ratings) was significantly

**Table 3**  
Statistics for the immediate and sustained analgesic effects of tES.

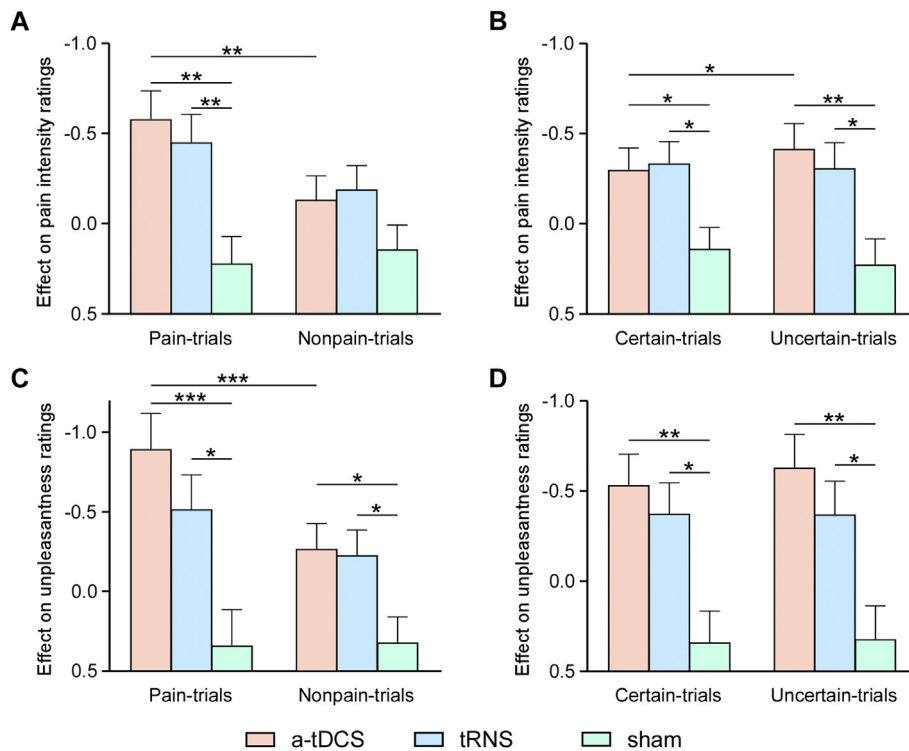
	Immediate analgesic effects (T1-T0)		Sustained analgesic effects (T2-T0)	
	Pain intensity	Unpleasantness	Pain intensity	Unpleasantness
Group	$F_{2, 146} = 5.45^{**}, \eta_p^2 = 0.07$	$F_{2, 146} = 7.42^{**}, \eta_p^2 = 0.092$	$F_{2, 146} = 2.95, \eta_p^2 = 0.039$	$F_{2, 146} = 1.29, \eta_p^2 = 0.017$
Pain	$F_{1, 146} = 6.71^*, \eta_p^2 = 0.044$	$F_{1, 146} = 9.23^{**}, \eta_p^2 = 0.059$	$F_{1, 146} = 4.16^*, \eta_p^2 = 0.028$	$F_{1, 146} = 5.61^*, \eta_p^2 = 0.037$
Predictability	$F_{1, 146} = 0.00, \eta_p^2 = 0.00$	$F_{1, 146} = 0.96, \eta_p^2 = 0.007$	$F_{1, 146} = 1.82, \eta_p^2 = 0.012$	$F_{1, 146} = 4.87^*, \eta_p^2 = 0.032$
Group × Pain	$F_{2, 146} = 3.61^*, \eta_p^2 = 0.041$	$F_{2, 146} = 3.57^*, \eta_p^2 = 0.047$	$F_{2, 146} = 2.58, \eta_p^2 = 0.034$	$F_{2, 146} = 1.16, \eta_p^2 = 0.016$
Group × Predictability	$F_{2, 146} = 3.14^*, \eta_p^2 = 0.047$	$F_{2, 146} = 0.66, \eta_p^2 = 0.009$	$F_{2, 146} = 0.022, \eta_p^2 = 0.003$	$F_{2, 146} = 0.34, \eta_p^2 = 0.005$
Pain × Predictability	$F_{1, 146} = 0.041, \eta_p^2 = 0.00$	$F_{1, 146} = 6.94^*, \eta_p^2 = 0.045$	$F_{1, 146} = 0.60, \eta_p^2 = 0.004$	$F_{1, 146} = 7.07^{**}, \eta_p^2 = 0.046$
Group × Pain × Predictability	$F_{2, 146} = 2.08, \eta_p^2 = 0.028$	$F_{2, 146} = 0.56, \eta_p^2 = 0.008$	$F_{2, 146} = 0.19, \eta_p^2 = 0.003$	$F_{2, 146} = 0.28, \eta_p^2 = 0.004$

Notes: Statistics were obtained by applying a three-way mixed-design ANOVA, with one between-participant factor of Group (a-tDCS, tRNS and sham groups) and two within-participant factors of Pain (nonpain and pain) and Predictability (certain and uncertain) on the immediate (T1 – T0) or sustained (T2 – T0) analgesic effects. \*:  $p < 0.05$ ; \*\*:  $p < 0.01$ .

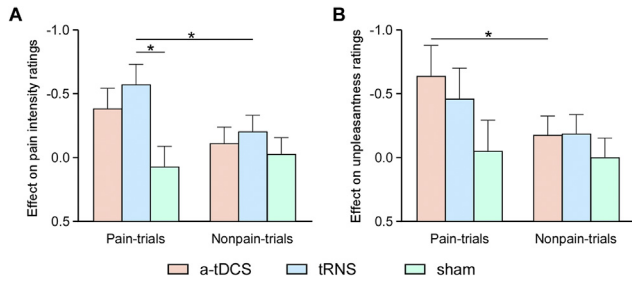
greater after a-tDCS and tRNS, indicating the immediate analgesic effects of a-tDCS and tRNS. About 30 min after tRNS application, the decrease in subjective pain perception remained to be greater than sham stimulation, indicating the sustained analgesic effects of tRNS. However, this difference was not observed for a-tDCS. Therefore, both a-tDCS and tRNS induced immediate analgesia, and only tRNS induced sustained analgesia.

Although this study did not measure the change of cortical excitability after a-tDCS and tRNS, previous studies have explored their neuromodulatory effects using single-pulse transcranial magnetic stimulation (TMS) elicited motor-evoked potentials (MEPs). Both a-tDCS and tRNS significantly increase cortical excitability as indicated by the larger size of MEPs [3,4,15]. However, they seem to affect cortical excitability with different temporal

characteristics: a-tDCS rapidly increased cortical excitability for a few minutes [3], while the after-effects of tRNS were more protracted [19]. In addition, tRNS seems to be a more stable method for cortical excitability enhancement compared with a-tDCS [18]: tRNS induced a significant increase in MEPs compared with sham stimulation at all time-points (0–20 min after stimulation) whereas no significant difference was observed for a-tDCS. Moreover, tRNS with a DC-offset is more likely to induce elevation in cortical excitability than tRNS alone [20], potentially because it combines the characteristics of tRNS (introducing noise into the neural system) with those of a-tDCS (consistent polarization of neuronal membrane potentials). Therefore, the different temporal courses of analgesic effects after a-tDCS and tRNS + DC-offset could be associated with their neuromodulatory after-effects, e.g., the latter



**Fig. 3.** Immediate effects of tES on perceived-pain ratings and unpleasantness ratings. A negative/positive value represents decreased/increased pain perception after tES. The immediate effects for pain-trials and nonpain-trials, as well as for certain-trials and uncertain-trials were compared among a-tDCS, tRNS and sham groups. Compared with the sham group, analgesic effects on perceived pain-intensity and unpleasantness for pain-trials were greater in a-tDCS and tRNS groups (A&C). Regardless of the certainty (certain-trials or uncertain-trials), analgesic effects on perceived pain-intensity and unpleasantness ratings were greater when participants were uncertain about the stimulation outcome (pain or nonpain, B). Data are expressed using Mean ± SEM. \*:  $p < 0.05$ , \*\*:  $p < 0.01$ , \*\*\*:  $p < 0.001$ .



**Fig. 4.** Sustained effects of tES on perceived-pain ratings  
Sustained effects of tES on the perceived pain-intensity (A) and unpleasantness (B) ratings. A negative/positive value represents decreased/increased pain perception 30 min after tES. The sustained effects for pain-trials and nonpain-trials, as well as for certain-trials and uncertain-trials were compared among a-tDCS, tRNS and sham groups. The analgesic effects on pain-intensity ratings were greater for the tRNS group than for the sham group (A). The analgesic effects on unpleasantness ratings for the a-tDCS group were greater for pain-trials than for nonpain-trials (B). Data are expressed using Mean ± SEM. \*:  $p < 0.05$ .

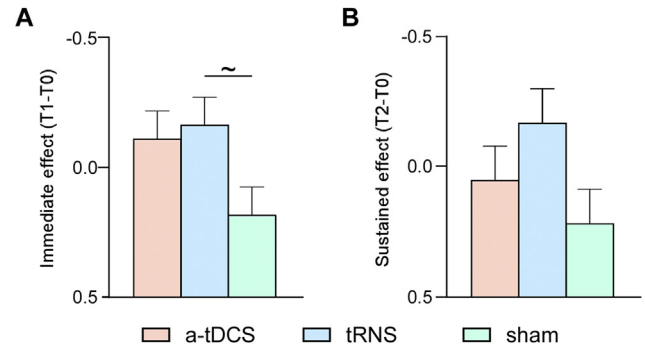
stimulation might induce a more sustained and stable elevation in cortical excitability.

The precise neurophysiological mechanisms underlying the analgesic effects of motor cortex stimulation (e.g., TMS or tES over M1) remain poorly understood. One of the potential mechanisms is that motor cortex stimulation relieves pain through the inhibition of noxious information transmission at the spinal cord level by activating subcortical structures related to the endogenous pain inhibitory pathway such as thalamus, cingulate gyrus, periaqueductal gray and subnucleus reticularis dorsalis [11–13,46–48]. The integrity and function of the endogenous pain inhibitory pathway in humans can be measured by conditioned pain modulation (“pain inhibits pain” phenomenon) that occurs when the response to a painful test stimulus is inhibited by an additional conditioning painful stimulus [49–51]. A recent meta-analysis provided evidence that noninvasive motor cortex stimulation (either tDCS or TMS over M1) not only increased pain threshold but also boosted conditioned pain modulation efficiency [11], supporting the idea that top-down modulation of the endogenous pain inhibitory pathway could be one of the mechanisms underlying the analgesic effects. Beyond the psychophysical measures, neuroimaging studies demonstrated that motor cortex stimulation induced activation of the ventrolateral thalamus via cortico-thalamic projections from motor cortex, initiating a cascade of synaptic events in pain-related structures including the medial thalamus, anterior cingulate and periaqueductal gray that constitutes an important part of the endogenous pain inhibitory pathway [12,13]. Moreover, motor cortex stimulation reverted neuropathic pain phenomena in rats through activating periaqueductal gray [46,52]. These evidences together suggested the observed analgesic effects are likely associated with activations of the endogenous pain

**Table 4**  
Immediate and sustained effects of tES on expected-pain ratings.

	a-tDCS (n = 50)	tRNS (n = 50)	Sham (n = 49)
<i>Immediate effects (T1–T0)</i>			
Certain-pain	0.002 ± 0.13	−0.12 ± 0.13	0.24 ± 0.13
Certain-nonpain	−0.20 ± 0.11	−0.18 ± 0.11	0.13 ± 0.12
Uncertain	−0.14 ± 0.16	−0.21 ± 0.16	0.18 ± 0.16
<i>Sustained effects (T2–T0)</i>			
Certain-pain	0.22 ± 0.16	−0.09 ± 0.16	0.43 ± 0.17
Certain-nonpain	−0.13 ± 0.14	−0.19 ± 0.14	0.09 ± 0.14
Uncertain	0.05 ± 0.17	−0.24 ± 0.17	0.13 ± 0.18

Notes: Data are expressed using Mean ± SEM.



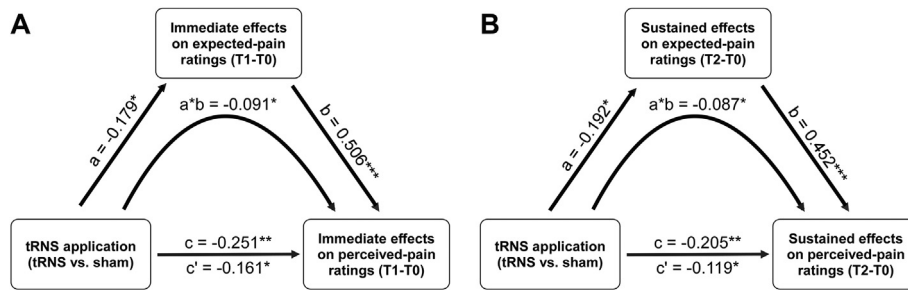
**Fig. 5.** Immediate and sustained effects of tES on expected-pain ratings. Effects of tES on the expected pain-intensity ratings were quantified as the change in ratings after tES application (immediate effect: T1 – T0; sustained effect: T2 – T0). A negative/positive value represents decreased/increased pain expectation after tES application. Compared with sham group, the immediate effect of attenuating expected pain-intensity ratings were marginally greater for the tRNS group ( $p = 0.068$ ). Data are expressed using Mean ± SEM. -:  $p < 0.10$ .

inhibitory pathway by motor cortex stimulation through a-tDCS and tRNS.

Given that subjective pain perception is greatly influenced by our expectations [27,28,33], we explored how a-tDCS and tRNS affect pain expectations. To dissociate pain expectation from pain perception, predictability cues were inserted during the pain-rating task, and participants were instructed to provide ratings of expected pain intensity upon the presentation of pain-predictability cues. Compared with sham stimulation, expected-pain ratings decreased immediately after tRNS application. Mediation analysis further revealed that tRNS application attenuated perceived-pain ratings partially via the drop in expected-pain ratings. With the knowledge that a painful event is upcoming, selective attention could be more precisely directed toward processes related to forthcoming sensorimotor events [53,54], which might manifest as suppression of cortical alpha oscillations [29,55,56]. An EEG study has reported that tRNS increases cortical alpha oscillations [57], whereby increased alpha oscillation has been associated with decreased attention resource allocation [58]. Therefore, it is likely that tRNS with a DC-offset decreased attentional resources directed towards the forthcoming pain during the anticipation stage, which led to attenuated pain perception.

Although a single-session a-tDCS reduced pain intensity for both certain-trials and uncertain-trials, pain intensity was reduced more when participants were uncertain of the stimulation outcome. That is, the degree of certainty regarding the upcoming pain would moderate the analgesic effects of a-tDCS, which finding is in line with previous studies reporting that psychological and contextual factors influenced tDCS effects [59–61]. This phenomenon may be explained by the state-dependent nature of brain stimulation [38], such that the effect of a specific stimulation protocol is affected not only by the stimulation properties (e.g., tDCS parameters) but also by the internal functional states of the neural system. For instance, cognitive and physiological effects of tDCS depended on the baseline electrophysiological state before the intervention [62]. In the uncertain contexts that could elicit anxiety and exacerbate pain perception [33,63], a-tDCS could induce greater modulation of pain perception, in which a greater range of modulation is allowed.

Human experimental models of pain use standardized noxious stimuli and assess pain perception under controlled settings. This process minimizes the influence of potentially confounding factors associated with chronic pain such as psychological comorbidities



**Fig. 6.** The mediating role of pain-expectation on the effect that tRNS had on pain-perception. The mediation model included tRNS as the independent variable (1 for tRNS group, -1 for sham group), the effects on perceived-pain ratings as the dependent variable, and the effects on expected-pain ratings as the mediator. The immediate and sustained effects on expected-pain ratings mediated the immediate (A) and sustained (B) analgesic effects of tRNS application, respectively. \*:  $p < 0.05$ , \*\*:  $p < 0.01$ , \*\*\*:  $p < 0.001$ .

[64]. Here, with experimental pain tasks applied on healthy participants, we have provided evidence that single-session a-tDCS and tRNS + DC-offset over M1 had an immediate analgesic effect, which can last for even 30 min after tRNS application. This finding supports the application of tES techniques in attenuating intractable pain for clinical patients, and tRNS with a DC-offset appears to possess even more beneficial therapeutic potential. Given that multiple-session tES may be more effective than single-session intervention [65], future studies can fully validate its effectiveness in relieving clinical pain by applying tES in repeated sessions. Moreover, our data showed that the analgesic effect of a-tDCS was more prominent when participants were not sure stimulation would be painful. This can help guide the optimization of a-tDCS application for clinical pain management, whereby patients' expectation of pain should be considered.

This study has several limitations that should be acknowledged. First, due to the size of the electrodes, we cannot with complete certainty attribute the analgesic effects solely to M1 stimulation; somatosensory or premotor areas adjacent to M1 were also likely affected by the stimulation, thus contributing to our results. Using more precise brain-stimulation techniques, such as high-definition tES, might help ensure that analgesic effects can be attributed to excitation of specific brain areas. Second, we provided behavioral evidence for the analgesic effects of single-session a-tDCS and tRNS, but we did not measure neurophysiological data that could allow us to assess the mechanisms underlying the analgesic effects. Further studies collecting neurophysiological data will be able to provide such mechanistic insights on the effects of a-tDCS and tRNS in pain perception and expectation. Third, we used a parallel design to prevent learning and order effects (e.g., training on the task, randomization of stimulation order), while evidence suggests that a crossover design is more appropriate for minimizing inter-individual variability [66]. However, the participants were randomly allocated to one of the experimental groups with age, gender and pain-sensitivity profiles well matched. Thus, the inter-individual variability introduced by the parallel design was minimized.

**Conclusions**

This study utilized standardized experimental methods of testing pain to evaluate the effects of single-session a-tDCS and tRNS on pain expectation and perception. Specifically, a-tDCS immediately reduced pain sensation, and this effect was more pronounced when pain expectation was uncertain. High-frequency tRNS + DC-offset had an immediate and sustained effects on attenuating pain, which was partially mediated by a decrease in

pain expectation. Our results revealed different temporal courses for the analgesic effects of a-tDCS and tRNS, which could be related to the more sustained effectiveness in elevating cortical excitability and plasticity induced by high-frequency tRNS + DC-offset. Although both a-tDCS and tRNS have the potential to be useful tools in attenuating intractable pain for clinical patients, our results highlight the fact that cognitive-emotion factors, including expectation and probability of experiencing pain, should be taken into consideration for maximizing the benefits of neuromodulatory treatment for pain management. Future studies should further explore the foundation of these analgesic effects in greater detail.

**CRedit authorship contribution statement**

**Junjie Yao:** Conceptualization, design of the study, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Xiaoyun Li:** Conceptualization, design of the study, Formal analysis, Writing – original draft, Writing – review & editing. **Wenyun Zhang:** Conceptualization, design of the study, Data curation, Writing – review & editing. **Xinxin Lin:** Data curation, Writing – review & editing. **Xiaohan Lyu:** Data curation, Writing – review & editing. **Wutao Lou:** Writing – review & editing. **Weiwei Peng:** Conceptualization, design of the study, Funding acquisition, Formal analysis, Writing – original draft, Writing – review & editing.

**Declaration of competing interest**

None.

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**Appendix A Supplementary data**

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2021.07.011>.

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