

Modulatory effects of transcutaneous auricular vagus nerve stimulation (taVNS) on attentional processes

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ABSTRACT

Background The modulatory effect of transcutaneous auricular vagus nerve stimulation (taVNS) on attention has varied in previous studies. This inconsistency might be attributed to the combined influence of the modulation effect on the different attentional functions, including alerting, orienting and executive control.

Aims We aimed to preliminarily examine the modulatory effects of taVNS on different attentional functions.

Methods Fifty-nine healthy participants were recruited and were randomly assigned to taVNS (receiving taVNS for 20 minutes) or control (receiving taVNS for 30 seconds) groups. All participants underwent a dot-probe task before and after the taVNS/control intervention. Their behavioural performance and electroencephalographic signals during pre- and post-tests were recorded, and different observed variables were extracted and analysed to characterise different attentional systems.

Results We observed that active taVNS applied at the left ear significantly improved the overall behavioural performance, that is, shorter reaction time (RT) and lower intra-individual reaction time variability (IIRTV) for right-hand responses when compared with the control condition. In addition, active taVNS resulted in larger P3 and movement-related cortical potential (MRCP) amplitudes associated with right-hand reactions than the control condition. Active taVNS also decreased the difference between the pre- and post-tests in the power spectral density of spontaneous high- α band oscillations at C4 electrode. Importantly, parallel mediation models for right-hand responses showed that the change of P3 amplitude mediated the effects of taVNS on RT and IIRTV. In contrast, the change of MRCP amplitude suppressed the effect of taVNS on the IIRTV.

Conclusions Our results provided behavioural and brain evidence supporting the effects of taVNS on different attentional systems, and their interaction further shaped behavioural performance, suggesting a promising role of taVNS in cognitive enhancement.

INTRODUCTION

Implantable vagus nerve stimulation (iVNS) is a neuromodulation technique that has been approved by the US Food and Drug Administration to treat refractory epilepsy¹ and chronic or recurrent depression.² Its applications for treating pain conditions, sepsis, cardiovascular disease, diabetes and

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Transcutaneous vagus nerve stimulation (taVNS) has been investigated for its ability to enhance attention levels and treat attention-related disorders, but the research findings are inconsistent.
- ⇒ This might be attributed to the influence of the interactions among the modulation effects on the different attentional systems, that is, alerting, orienting and executive control.

WHAT THIS STUDY ADDS

- ⇒ taVNS could accelerate the overall reaction time (RT) contributed by the improvement in alerting, overpowering the RT delay caused by the reinforcement in the response inhibition.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ taVNS could be recognised as a promising attention modulator; it is imperative to precisely specify the attentional system estimated by the applied experimental task.

obesity have also been investigated.³ As one of the affordable and non-invasive alternatives to iVNS, transcutaneous auricular vagus nerve stimulation (taVNS) applies rhythmic electrical currents to the skin surface of the vagally innervated ear regions, allowing activation of the auricular branch of the vagus nerve (ABVN).

Two dominant views of the neural mechanisms associated with taVNS have emerged; that is, taVNS takes effect via the modulation of either the bilateral locus coeruleus-norepinephrine (LC-NE) system⁴ or the γ -aminobutyric acid (GABA) neurotransmission contralateral to taVNS.⁵ These views are supported by the strong links between vagal activities and physiological markers of LC-NE system activity (eg, P3 amplitude, pupil dilation and α -oscillations⁶), as well as between vagal activities and GABA levels (eg, short-interval intracortical inhibition⁵). Since the activities of the LC-NE⁶ and GABAergic systems⁷ are essential contributors to the

attentional processes, in recent years, researchers have assumed a modulatory effect of taVNS on attention.^{8,9} Current research has mainly focused on the modulatory effects on target detection, emotion-induced orientation and response inhibition while yielding inconsistent findings.^{9,10} The discrepancies may be not only due to methodological differences and various stimulation parameters employed in previous studies but also because the attentional tasks performed combined different aspects of attention.

According to Posner's theory of attention,¹¹ there are three attentional systems with distinct functions: alerting, orienting and executive control. Specifically, 'alerting' refers to the overall vigilance and readiness to detect incoming stimuli, which involves the level of general arousal; 'orienting' involves the selective allocation of attention to specific modalities or locations; and 'executive control' is responsible for resolving conflict among responses. Although the three are functionally orthogonal constructs, they interact with each other to shape the overall behaviour performance in the attentional tasks.¹² Therefore, the heterogeneity effects of taVNS on attentional tasks could be attributed to the combined influence of the modulation effect on the different attentional functions, further increasing the complication of the modulation effects on the observed variables. For instance, the cortical distribution of the LC-NE system, which could be activated by the taVNS, is the basis of alerting, and its excitation would facilitate the orienting by increasing the sensitivity to salient stimuli (eg, negative pictures) in the environment, thus accelerating the reaction time (RT) to the targets. On the other hand, the taVNS-induced increase in the GABA level at the sensorimotor cortex would enhance the executive attention processes in the conflict condition while prolonging the RT.^{12,13} Thus, it is critically necessary to use appropriate observed variables to explore the taVNS modulation effects on different attention systems.

In this work, we adopted a dot-probe task¹⁴ that contained warning signals (ie, fixation occurred at a fixed time prior to the target stimulus), cues (ie, faces with different expressions) and the following targets (ie, solid white dots presented on the left or right location) to conduct an exploratory study of the taVNS effects on the attentional systems. Specifically, according to the deconstruction of the attention systems¹¹ and the Attention Network Test developed by Fan *et al*,¹² alerting was determined by the overall RT of all trials warned by a fixation cross presented at 1500 ms prior to the target onset, which collapsed across affective cue-target congruency. The effects of taVNS on the electroencephalographic (EEG) components associated with alerting function (ie, the P3 component) were recorded and investigated. In addition, the orienting was measured by the difference in the RT between the validly cued-target (ie, the position of the target is congruent with that of the previous affective face) and the invalidly cued-target (ie, the position of the target is incongruent with that of the previous affective

face). Response inhibition influence in this choice reaction task (ie, left or right) was evaluated by two EEG components: the motor-related cortical potential (MRCP, a component around the sensorimotor cortex supposed to inhibit the mirror movement of the contralateral hand in the choice reaction time task¹⁵) and spontaneous brain oscillations (reflecting the cortical excitability for movement preparation¹⁶). This exploratory study would improve insight into the modulation effects of taVNS on the attentional systems and further promote the taVNS application transformation.

MATERIALS AND METHODS

Participants

Participants who met the following inclusion criteria were recruited: (1) unacquainted with prior non-invasive neuromodulation; (2) no history of chronic pain, neurological or psychiatric illness; and (3) normal or corrected vision. People with illnesses, sensation disorders or auricular skin defects were excluded. Women who were in their menstrual period were also excluded. With these criteria, 60 healthy right-handed adults were recruited for this study. The required sample size for exploring the taVNS effect on attention was determined using G*Power software by setting the statistical power ($1-\beta$) at 0.9 with a medium effect size ($f=0.25$) and a significance level (α) at 0.05. A priori test for repeated measures analysis of variance (rmANOVA) with two groups and eight measurements yielded the minimum required sample size of 20. We recruited a total of 60 participants, which met the sample size requirements. Participants were randomly assigned to either the taVNS group or the control group to ensure that the experimental details were single-blinded. One participant was excluded from data analyses due to incomplete data collection during the EEG recording, leaving a final sample of 29 participants (16 female) in the taVNS group and 30 participants (17 female) in the control group (figure 1). Two groups were matched in terms of age, sex ratio and years of education (see online supplemental table S1). They had no significant difference in depression and trait anxiety, assessed using the Chinese version of the Beck Depression Inventory-II (BDI-II¹⁷) and the Trait-Anxiety Inventory subscale (T-AI) from the State-Trait Anxiety Inventory,¹⁸ respectively (see online supplemental table S1). Therefore, any group differences associated with taVNS observed in the present study would not be attributed to the inherent group difference in depression and trait anxiety levels. Written informed consent was obtained from each participant prior to all phases. The experimental procedures were in accordance with the ethical standards of the local ethics committee.

Transcutaneous vagus nerve stimulation

taVNS was a train of electrical pulses delivered by an electrical stimulator (SXC-4A, Sanxia, China) via two electrodes placed at the left cymba conchae (to avoid

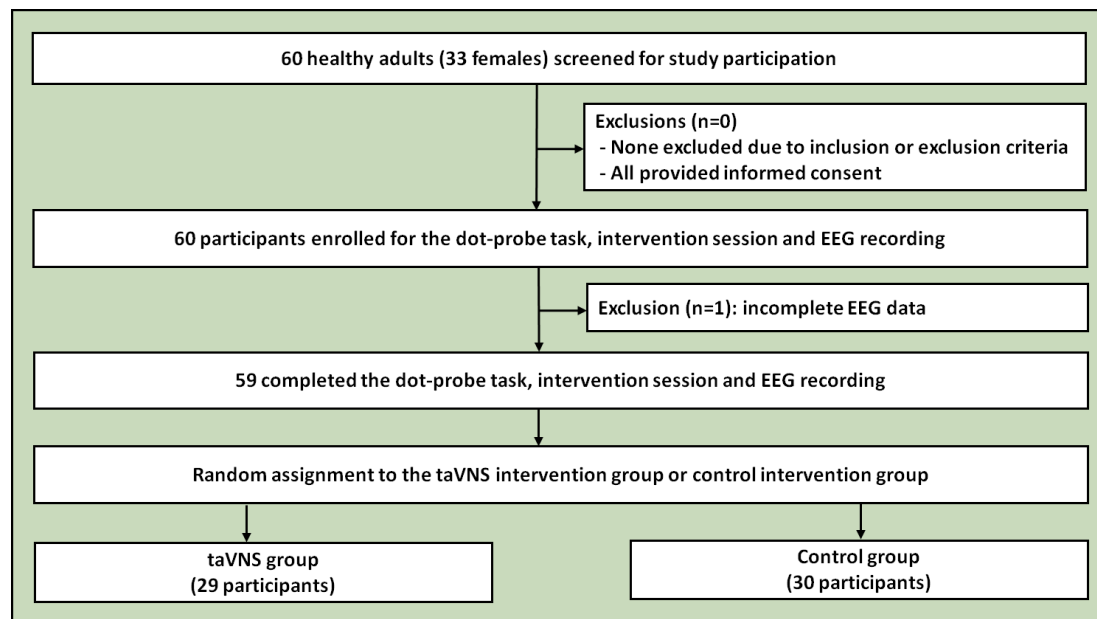


Figure 1 Flowchart of participants' recruitment. EEG, electroencephalographic; taVNS, transcutaneous auricular vagus nerve stimulation.

the possible cardiac issue caused by the innervation of the right efferent vagus fibres on the sinoatrial node¹⁹) innervated by the ABVN. The electrical stimulation was square waves with a pulse width of 250 μ s and presented at a frequency of 25 Hz; these waves are widely employed in exploring the taVNS effect on cognition.²⁰ The individually customised taVNS intensity used in this experiment was determined via the method of limit. The current intensity increased by steps of 10 μ A from 60 μ A until a rating of 4 was obtained on an 11-point Numerical Rating Scale (0–10: no sensation–extremely painful sensation, with 5 denoting pain threshold), which represented a strong but non-painful sensation. Participants in the taVNS group received taVNS with the individually determined intensity throughout the whole 20-minute intervention session. In contrast, those in the control group only received taVNS during the first 30 seconds of this session, but they were told that the stimulation would be sustained for 20 minutes. The stimulation intensity was adjusted at the 7th and 14th minutes of the modulation session for the taVNS and control groups to avoid adaptation in the taVNS group and to keep the control group unaware of inactive intervention. During the experiment, participants in both groups were followed with the same instructions and were not informed of the expected stimulation effects and the manipulation differences. Participants were asked if they felt uncomfortable or had experienced hurtful electrical stimuli after the taVNS; no one reported any side effects.

The dot-probe task

Visual cues were composed of 8 happy, 8 sad and 16 neutral face pictures, matched in terms of emotional intensity scores (happy: 5.74 (0.48) (mean (standard deviation, SD), the same below); sad: 6.05 (0.46); neutral: 5.88

(0.12); $p=0.382$) and emotional accuracy levels (happy: 95.79 (1.26); sad: 95.42 (1.77); neutral: 95.42 (1.77); $p=0.215$) from the Chinese Affective Picture System.²¹ All pictures were black-and-white with 300×260 pixels in size and well-matched in luminance and contrast. Neutral face pictures were separated into two comparable sets. Pictures from one set were paired one-on-one with happy face pictures, while those from the other set were paired with sad face pictures similarly, yielding 8 happy-neutral (H-N) pairs and 8 sad-neutral (S-N) pairs. In addition, pictures from the two neutral picture sets were paired with one another, yielding 8 neutral-neutral (N-N) pairs.

Each trial started with a white fixation lasting for 1000 ms in the centre of a black screen with a resolution of 1920×1080 pixels (figure 2A). Subsequently, a pair of pictures as the cue was presented side by side simultaneously for 500 ms, and then a solid white dot as a target appeared immediately in the position where one of the faces had disappeared. The dot remained on the screen for 3000 ms or until participants responded with a key press. Participants were asked to press the 'd' or 'j' button on a keyboard as quickly and accurately as possible to indicate the location of the dot (either left or right, respectively). Since the taVNS was administered at the left cymba conchae, trials with the dot on the left and right sides of the visual area were defined as ipsilateral trials (i-trials) and contralateral trials (c-trials), respectively. The arrangement of two pictures in each pair and the location of the dot were counterbalanced. Trials with H-N and S-N pairs (16 pairs×2 picture positions×2 dot positions) were presented twice, whereas those with N-N pairs (8 pairs×2 picture positions×2 dot positions) were only presented once. Consequently, the task consisted of 160 pseudo-randomised trials in total. The inter-trial

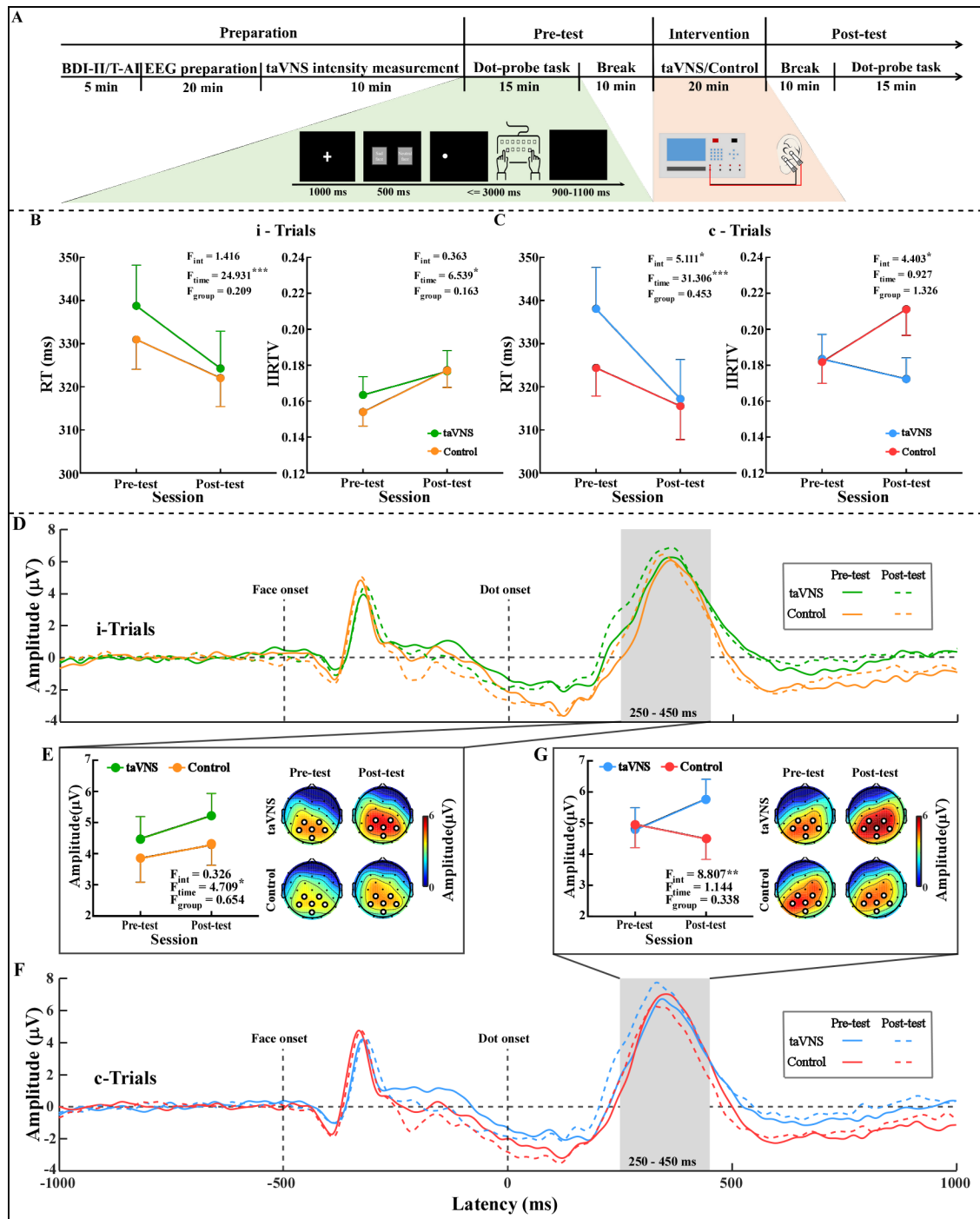


Figure 2 Experimental procedure and effects of the taVNS on behaviour performance and P3 amplitudes. (A) The experimental procedure, trial procedure and a diagram of taVNS. All participants underwent two phases—the preparation phase and the test phase in sequence. A pre-test/post-test design was employed in the test phase, in which participants completed two dot-probe tasks separately before and after a 20-minute intervention. Participants in the taVNS group received taVNS throughout the whole 20-minute intervention session, and those in the control group only received taVNS during the first 30 seconds of this session. (B, C) The effect of taVNS on RT and IIRTV. For ipsilateral trials (i-trials) (B), there was no significant time $\times$ group interaction for either RT or IIRTV. In contrast, for contralateral trials (c-trials) (C), there was a significant time $\times$ group interaction for both RT and IIRTV. (D, F) Averaged ERP waveforms of the taVNS and the control groups, respectively, at parietal electrodes in the pre-test (solid lines) and post-test (dashed lines) sessions. (E, G) The scalp topographies and statistical line charts of P3 amplitudes for i-trials and c-trials, respectively. A significant time $\times$ group interaction of P3 amplitudes was observed for c-trials but not for i-trials. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; error bar represents 1 SE. BDI-II, Beck Depression Inventory-II; EEG, electroencephalographic; ERP, event-related potential; IIRTV, intra-individual reaction time variability; RT, reaction time; SE, standard error; T-AI, Trait-Anxiety Inventory subscale; taVNS, transcutaneous vagus nerve stimulation.

interval was 900–1100 ms. Response accuracy and RT were recorded for each trial. Intra-individual reaction time variability (IIRTV), achieved by dividing the mean of the RT from the intra-individual SD of the RT, is an index of dynamic variability reflecting the response stability²²; it was calculated. The validity of this task was supported by both behavioural and electrophysiological evidence (summarised in online supplemental tables S2 and S3 and online supplemental figure S1), demonstrating an attentional bias towards happy faces and a shift of attention away from sad faces.

Experimental procedure

On arrival for the study, participants' severity of depression over the past week and their trait anxiety were assessed. Subsequently, the EEG was set up, and the individually customised taVNS intensity was determined. Following the above preparation phase, all participants underwent the test phase, including sequential pretest, intervention and post-test sessions, while recording their EEG (figure 2A). During the pre- and post-test sessions, participants were asked to complete the dot-probe task. Notably, we included a pre-test as the baseline to exclude the possible influence of the inherent group difference (eg, personal traits and emotional states) on the taVNS effect. During the intervention session, all participants were required to stay awake, sit comfortably and avoid frequent movements for 20 minutes.

Data acquisition and analysis

EEG recording and preprocessing

EEG data were continuously recorded during the test phase via 32 Ag-AgCl scalp electrodes placed according to the International 10–20 system (ANT, Neuro, the Netherlands). The signals were recorded and filtered at 0.3–30 Hz with an online reference to CPz at a sampling rate of 1000 Hz. All electrode impedances were kept below 10k Ω .

EEG data were preprocessed using the open-source toolbox EEGLAB,²³ running in the MATLAB environment (2014; MathWorks, USA). EEG data were re-referenced to the averaged signals of bilateral mastoids. EEG epochs were extracted using a time window of 2000 ms (500 ms before and 1500 ms after the face onset, that is, 1000 ms before and 1000 ms after the dot onset), and the baseline was corrected using the pre-stimulus interval (–500 to 0 ms refer to the face onset). Trials contaminated by eyeblinks and movements were corrected using an independent component analysis algorithm.²³

Time domain analyses

EEG epochs were averaged separately for i-trials and c-trials in the pre- and post-test sessions to obtain event-related potentials (ERPs), yielding four averaged waveforms time-locked to the dot onset for each participant. Two components that respectively reflected alerting and executive control functions were extracted. One was the P3 component that was measured at parietal electrodes (CP1,

CP2, P3, Pz, P4 and POz) from the averaged waveform for each participant, defined as the largest positive deflection within the time interval between 250 and 450 ms after the dot being presented. The other was a positive deflection associated with movement (ie, MRCP), which was dominant at central electrodes (C3 and C4) corresponding to the location of the hand sensorimotor cortex²⁴ within the time window of 200–300 ms after dot onset. Considering the inherent differences in ipsilateral and contralateral brain regions during the preparation and execution of unilateral hand movements, comparing the modulatory effects on the MRCP at bilateral cortices was unproductive. Thus, respective analyses and representations for MRCP were performed at C3 and C4 electrodes, respectively. The amplitude of these two components for each participant was averaged over respective time windows for further analyses. Single-participant average waveforms were subsequently averaged across participants from the same group to obtain the group-level waveforms. Group-level scalp topographies of these waves were computed by spline interpolation.

Spectral analyses of spontaneous brain oscillations

To investigate the effect of taVNS on cortical excitability/inhibition, spontaneous brain oscillations (δ band: 1–3 Hz, θ band: 4–7 Hz, low- α band: 8–10 Hz, high- α band: 11–13 Hz, low- β band: 14–19 Hz, and high- β band: 20–30 Hz) before the presentation of the face were estimated for each group. A spectral analysis was applied to single-trial EEG signals within the time window of –500 to 0 ms prior to the face onset. Specifically, EEG signals were transformed to the frequency domain using a fast Fourier transform, yielding an EEG spectrum ranging from 1 to 30 Hz. Subsequently, the power spectral density (PSD) of each frequency point was normalised by dividing the total PSD across all frequencies. Afterwards, the spectrograms were averaged across trials at the single-subject level, leaving a normalised and averaged PSD at each frequency point. PSD differences at C3 and C4 electrodes (ipsilateral and contralateral to the taVNS site) were calculated by subtracting pre-test PSD from the corresponding post-test PSD for each frequency band.

Statistical analyses

Trials with incorrect responses were excluded. Furthermore, trials with unreasonably fast (RT <100 ms) or slow (RT >1500 ms) responses were classified as outliers and excluded from further analyses (except for the analyses for IIRTV), leaving 99.31% pre-test trials and 98.45% post-test trials for the taVNS group, and 99.06% pre-test trials and 98.19% post-test trials for the control group. There was no significant difference between the two groups in the pre-tests for all variables (ie, behavioural performance, ERPs and spontaneous brain oscillations). Levene's tests were performed to measure the variance homogeneity, and all dependent variables (ie, behavioural performance, ERPs and spontaneous PSD) fulfilled variance homogeneity between the two groups.

We first examined the taVNS effect on orienting towards emotional faces (either happy or sad) by comparing the normalised RT (ie, the difference in the average RT between H-N/S-N trials and N-N trials) between the two groups (taVNS vs control) with within-subject factors of time (pretest vs post-test) and congruence (the position of the dot was congruent vs incongruent with that of the emotional face) via a three-way rmANOVA. H-N trials and S-N trials were analysed separately.

To illustrate the taVNS effects on alerting and executive control, further analyses mainly focused on the overall behavioural performance and its neural correlates. The overall RT, IIRTV, P3 amplitudes and MRCP amplitudes were calculated regardless of cue types. Considering the laterality effect of taVNS⁵ as well as the differences between dominant and non-dominant hands in behaviour and brain responses for movement, we isolated the effects of taVNS on the functions of the left (i-trials) and right (c-trials) hands by separately analysing the data for the two hands to get clear and precise results. Two-way rmANOVAs were conducted on behavioural measures and ERP amplitudes with factors of time and group. In addition, two-way rmANOVAs involving factors of group and region (C3 vs C4 electrodes) were conducted on post-pre PSD differences prior to the onset of the face for each frequency band. Partial eta squared (η_p^2) was calculated to reflect the effect size for the F-tests. Simple effect analyses were conducted when there was a significant interaction. Bonferroni correction was applied for multiple comparisons when necessary.

Finally, we adopted parallel mediation models (ie, group $\rightarrow$ ERP amplitude differences and spontaneous PSD differences $\rightarrow$ behavioural differences) to characterise the interaction effect of the different attentional systems via Hayes' PROCESS macro-V.4.0 for SPSS. Standardised estimate (b) and 95% CI were reported for both direct and indirect effects. The estimate was considered statistically significant when the 95% CI (based on 5000 bootstrap samples) excluded zero.

RESULTS

The effect of taVNS on behavioural performance

Neither the main effect of the group nor the interactions involving the factor of the group were significant for both the H-N and S-N trials (all $p > 0.05$), suggesting that orienting towards emotional faces was not modulated by the taVNS (see online supplemental table S4).

In contrast, active taVNS facilitated participants' responses when the target dot was located on the right side, regardless of the valence of the preceding face pictures, as suggested by a significant time $\times$ group interaction on RT for c-trials ($p = 0.028$) but not for i-trials (left panel in figure 2B,C). Although simple effect analysis on c-trials demonstrated that RT was significantly decreased in the taVNS group (pre-test: 338.06 ± 51.67 ms; post-test: 317.19 ± 49.04 ms; $p < 0.001$) and marginally-significantly decreased in the control group (pre-test: 324.37 ± 35.58

ms; post-test: 315.51 ± 42.44 ms; $p = 0.050$), the magnitude of such decrease was larger in the taVNS group than in the control group (see online supplemental table S5). Similarly, there was a significant time $\times$ group interaction on IIRTV only for c-trials ($p = 0.040$; figure 2C, right panel) but not for i-trials (see online supplemental table S6). Simple effect analysis showed a significant group difference in the post-test session, in which the IIRTV was smaller for the taVNS group compared with the control group (taVNS group: 0.17 ± 0.06 ; control group: 0.21 ± 0.08 ; $p = 0.045$) and a significant increase from pre-test to post-test in the control group (pre-test: 0.18 ± 0.07 ; post-test: 0.21 ± 0.08 ; $p = 0.033$).

The effect of taVNS on ERPs

Two-way rmANOVA on P3 amplitudes showed a significant time $\times$ group interaction for c-trials only (pre-test: taVNS group, 4.78 ± 3.82 μ V, control group, 4.96 ± 4.10 μ V; post-test: taVNS group, 5.77 ± 3.40 μ V, control group, 4.49 ± 3.64 μ V; $p = 0.004$; figure 2D–G; online supplemental tables S5 and S7). Simple effect analysis showed that participants from the taVNS group exhibited larger P3 amplitudes in the post-test session than in the pre-test session ($p = 0.006$), while no such effect was observed in the control group.

For MRCP amplitude, a significant time $\times$ group interaction was found at C4 for c-trials only (pre-test: taVNS group, 1.68 ± 3.48 μ V, control group, 2.30 ± 6.08 μ V; post-test: taVNS group, 3.63 ± 3.06 μ V, control group, 2.63 ± 5.41 μ V; $p = 0.006$, after multiple comparison correction; figure 3; online supplemental tables S5 and S7). Simple effect analysis showed that participants from the taVNS group exhibited a larger MRCP amplitude in the post-test session compared with the pre-test session ($p < 0.001$), while no such effect was observed in the control group.

The effect of taVNS on spontaneous PSD

There was a significant region $\times$ group interaction on spontaneous PSD difference in the high- α band (C3: taVNS group, $0.14\% \pm 0.61\%$, control group, $0.28\% \pm 0.86\%$; C4: taVNS group, $-0.08\% \pm 0.67\%$, control group, $0.36\% \pm 0.73\%$; $p = 0.018$ after multiple comparison correction; figure 4; online supplemental table S8). Simple effect analyses demonstrated that the spontaneous PSD difference of high- α band oscillations was smaller at C4 than at C3 in the taVNS group ($p = 0.002$). Moreover, the spontaneous PSD difference of high- α band oscillations at C4 was significantly smaller in the taVNS group in comparison to the control group ($p = 0.020$). No other significant interactions or main effects for spontaneous PSD differences were found at other frequency bands (see online supplemental table S9).

Mediation analyses

According to the above results, parallel mediation models for right-hand responses were established to assess whether brain activity differences mediated the effect of interventions on RT or IIRTV differences (see figure 5). We observed a positive mediating effect of P3 amplitude

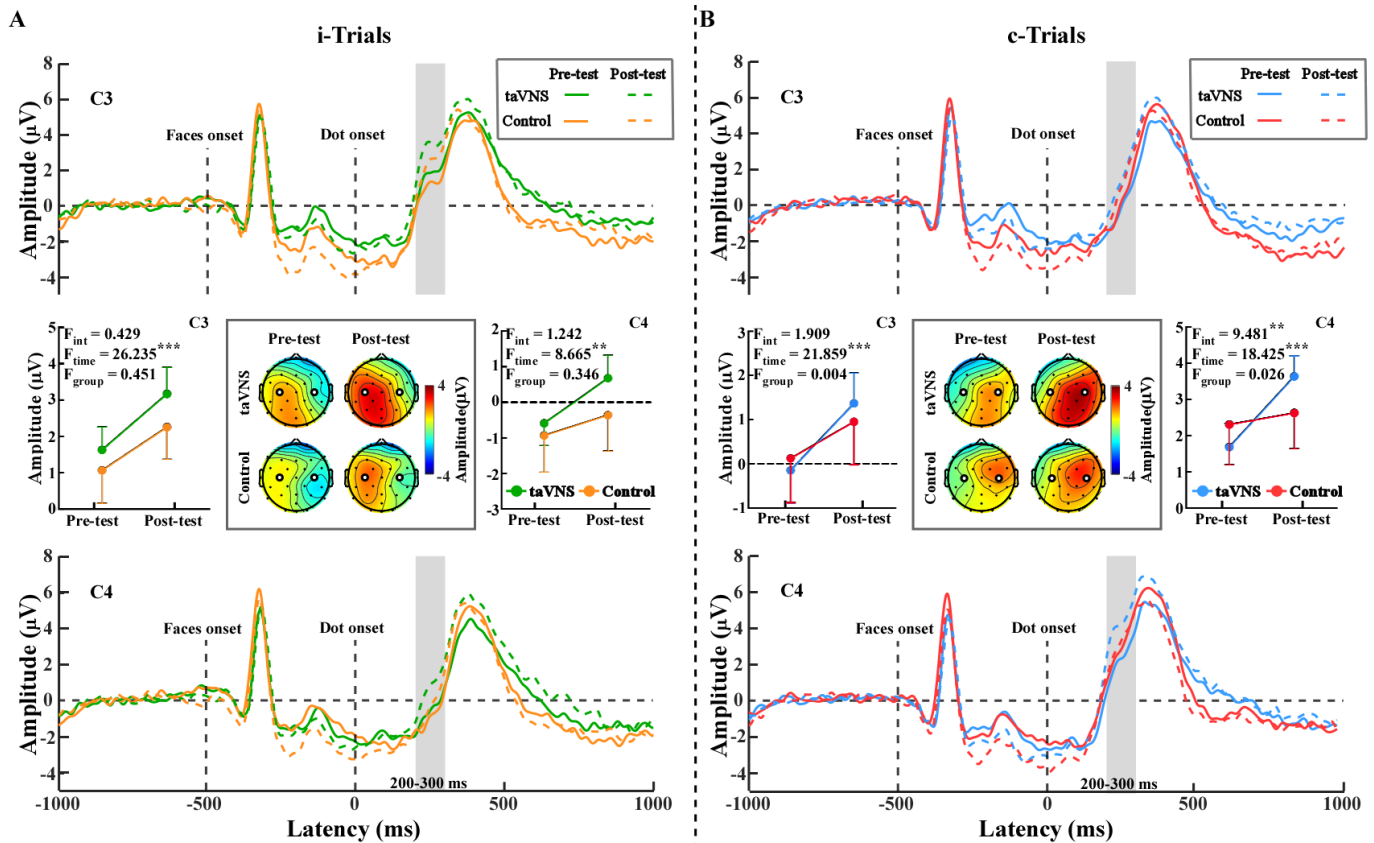


Figure 3 The effect of the taVNS on the motor-related cortical potential amplitudes. (A, B) The averaged waveforms of ERPs at C3 (upper) and C4 (lower) electrodes for ipsilateral trials (i-trials) (A) and contralateral trials (c-trials) (B) in the pre-test (solid lines) and post-test (dashed lines) sessions. Middle panels displayed scalp topographies and statistical line charts of MRCP amplitudes for i-trials and c-trials. A significant time $\times$ group interaction of MRCP amplitudes was only observed at C4 for c-trials. ** $p < 0.01$; *** $p < 0.001$; error bar represents 1 SE. ERPs, event-related potentials; MRCP, motor-related cortical potential; taVNS, transcutaneous auricular vagus nerve stimulation.

on the association between the group and the RT. In addition, there was a positive mediation effect of the P3 amplitude and a negative mediation effect of the MRCP amplitude on the association between the group and the IIRTV (see online supplemental table S10). Importantly, as the mediations were accounted for, the direct mediation effects of the group on behavioural differences were still significant (RT difference: standardized $b = 0.599$, 95% confidence interval (CI): 0.053 to 1.143; IIRTV difference: standardized $b = 0.679$, 95% CI: 0.151 to 1.206).

DISCUSSION

Main findings

In the present study, we examined the modulatory effects of taVNS on attentional functions using a dot-probe task. By measuring and comparing behavioural performance and EEG responses, we found that active taVNS applied at the left ear significantly facilitated right-hand responses. Specifically, participants from the taVNS group exhibited shorter RT, smaller IIRTV and larger P3 and MRCP amplitudes associated with right-hand responses than those from the control group. Meanwhile, active taVNS

decreased spontaneous PSD differences of high- α band oscillations at C4 as compared with the control group. Overall, behavioural and brain evidence preliminarily illustrated the effects of taVNS on the interaction of different attentional functions.

The facilitation effect of taVNS on alerting

Although it has been suggested that taVNS could inhibit the orienting towards sad faces in patients with depression²⁵ and the orienting towards threat pictures among people with chronically worrying,²⁶ no modulatory effect of taVNS was found in the present study on the orienting towards valenced faces. However, this observation agrees with previous studies conducted in patients with tension-type headaches²⁵ and healthy populations,^{8,9,26} suggesting a null effect of taVNS on the affective-driven orientation in people without emotional disorders.

In contrast, we observed significantly modulatory effects of taVNS on overall right-hand performance, as reflected by shorter RT and smaller IIRTV in response to the targets presented on the right side of the screen after receiving taVNS, compared with control manipulation. In other words, active taVNS applied at the left ear facilitated

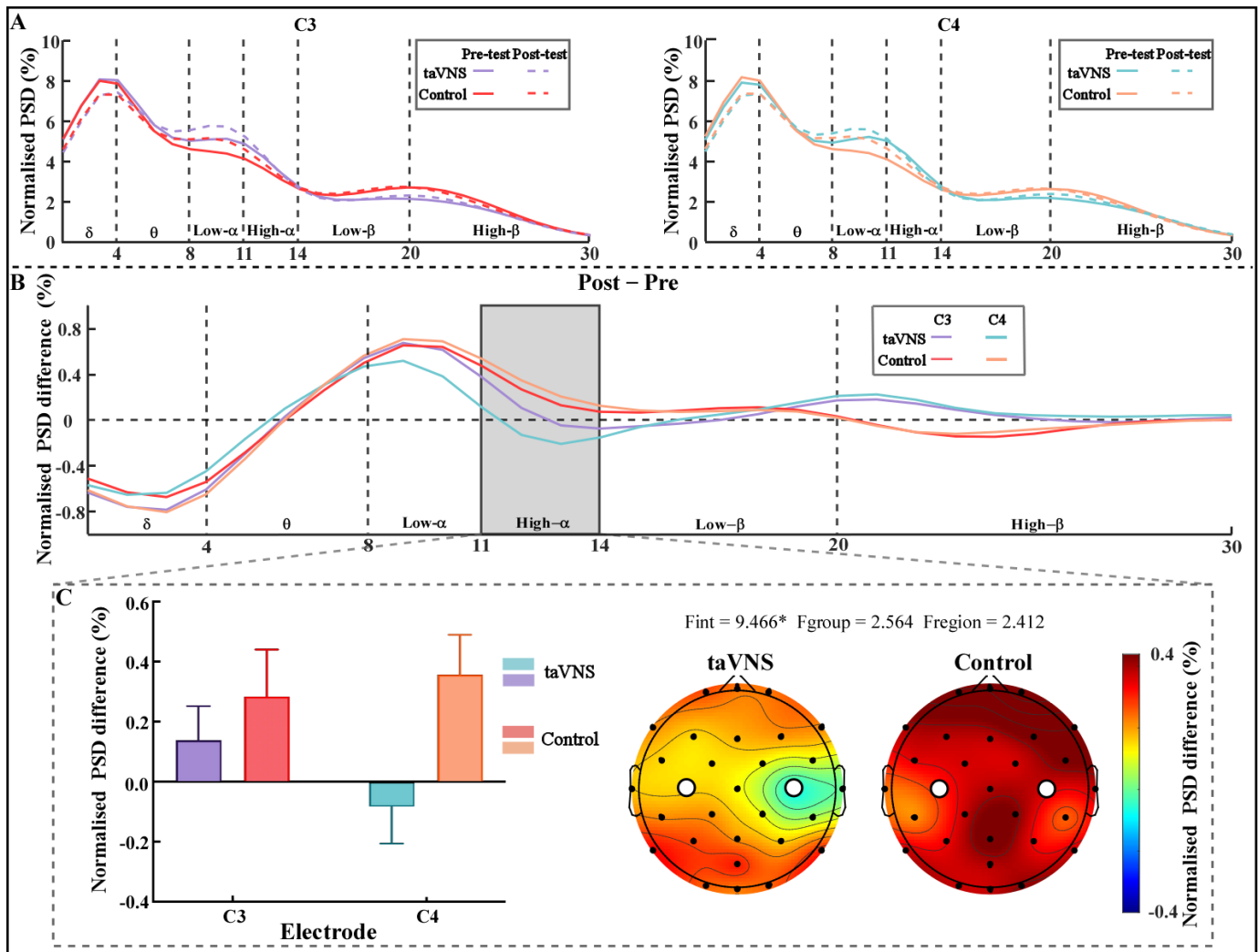


Figure 4 The effect of the taVNS on the spontaneous PSD prior to the face onset. (A) The normalised-averaged PSD for each frequency band at C3 and C4 electrodes, respectively. (B) The PSD differences at C3 and C4 were calculated by subtracting pre-test PSD from the corresponding post-test PSD. (C) The bar charts and scalp topographies of PSD difference for high- α band oscillations. There was a significant region $\times$ group interaction for high- α band oscillations. * $p < 0.05$; error bar represents 1 SE. PSD, power spectral density; SE, standard error; taVNS, transcutaneous auricular vagus nerve stimulation

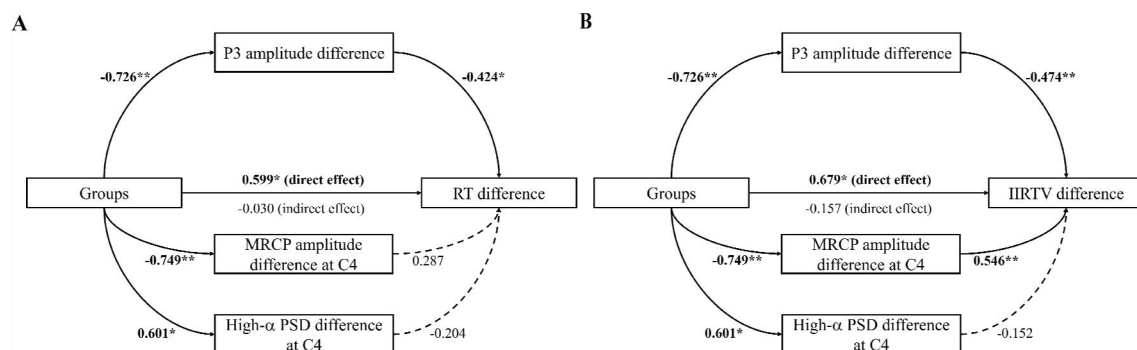


Figure 5 Parallel mediation analyses for right-hand responses. (A, B) Parallel mediation analyses of the modulated effects of taVNS on RT and IIRTV, respectively. Groups (ie, taVNS and control) showed a direct effect on RT and IIRTV with indirect effects via different brain responses. The mediating effect of P3 amplitude on the association between the group and the RT was significant, and the mediating effects of P3 and MRCP amplitudes on the association between the group and the IIRTV were significant. Solid and dashed lines represented significant and insignificant effects, respectively. * $p < 0.05$; ** $p < 0.01$. IIRTV, intra-individual reaction time variability; MRCP, movement-related cortical potential; PSD, power spectral density; RT, reaction time; taVNS, transcutaneous auricular vagus nerve stimulation.

right-hand responses to the target and persisted the investment of the attention resources over time.²⁷

The modulatory effect of taVNS on alerting was further supported by ERP results, where a significantly increased P3 amplitude was found for the taVNS group rather than the control group. As an indicator of the extent to which attention is paid to the target,²⁸ the P3 component measured at parietal electrodes is a widely accepted proxy for the activity of the LC-NE system.⁶ As suggested, the activity of the LC-NE system closely correlates with maintaining alertness and mediates arousal.¹¹ Direct evidence from neuroimaging studies showed LC activity was higher during taVNS when compared with resting state or sham manipulation at the earlobe.⁴ In line with this, P3 amplitude exhibited a positive mediating effect on the link between the group and the RT as well as the IIRTV (figure 5), demonstrating a possible mechanism of improved alerting after taVNS, that is, through the enhancement of the activity in the LC-NE system.

The inhibition effect associated with taVNS

In addition to the facilitation effect of taVNS on alerting, the present study also showed preliminary evidence suggesting a modulated executive control, as we observed that taVNS induced a larger MRCP amplitude at C4 electrode for c-trials. Previous studies found a similar ipsilateral positivity-going deflection of the premotor waveform to the response hand over the sensorimotor cortex, reflecting an inhibition process of incorrect responses in a choice situation.¹⁵ This process would facilitate accuracy but prolong response initiation.¹⁵ At the same time, it was reported that greater top-down executive control was required in participants with high IIRTV.²² As a support, parallel mediation analyses showed that the mediating effect of MRCP amplitude difference on the association between the group and IIRTV was significant (see figure 5B and online supplemental table S10). This result illustrated the suppression effects of the post-pre alternations at the manipulated-contralateral sensorimotor cortex on the regression coefficient between the group and behavioural performance.²⁹ Combining the positive mediating effect of P3 amplitude, our results might reflect an interaction between the alerting and response inhibition functions. Notably, given that the MRCP amplitude could be contaminated by the positivity of the P3 component (they are maximal at different brain regions, though), further study could add a mask slice to separate different processing or record electromyograms to isolate response-locked waveforms.

In addition, the taVNS group showed smaller spontaneous high- α band PSD prior to the face onset at C4 than the control group. Since alpha-oscillations are associated with the overall synchronised neural spiking pattern, our result might reveal a change in the thalamocortical excitability modulated by taVNS.¹⁶ We observed that the decrement in the spontaneous alpha oscillations only presented at the modulation-contralateral (ie, right) sensorimotor cortex, which might illustrate a lateralised

release of inhibition and attentional buffer to prepare for the following stimuli. Capone *et al*⁵ demonstrated a similar lateralised but opposite trend modulation of cortical excitability after 60 minutes taVNS (30 seconds on for every 5 minutes), revealed by an enhancement of short-interval cortical inhibition (SICI) around the manipulated-contralateral sensorimotor cortex. However, as the distinct neurophysiological processes between SICI (only reflecting GABAergic neural activity) and spontaneous alpha oscillation (involving a wide range of neural networks and neurotransmission systems), our results did not conflict with the former and might illustrate a similar lateralised modulatory effect.

It was worth noting that the modulatory effects of taVNS on behaviours and ERPs were mainly shown in c-trials. It is possible that the inhibition process around the right sensorimotor cortex after taVNS had a greater effect on left-hand movements compared with right-hand movements. In addition, a significant modulation of non-dominant hand responses (ie, left-hand responses in the present study) might require a greater taVNS-induced psychophysiological change than the dominant hand, as the visuomotor tasks completed with non-dominant hands are usually associated with greater recruitment resources³⁰ and bilateral sensorimotor cortex involvement.³¹ To better understand the lateralised effect of the taVNS modulation, a larger sample size and left-handed participants are necessary for future explorations.

Unlike previous studies using earlobe stimulation as a sham setting,⁹ we employed a placebo manipulation that contained a short-term stimulation (ie, the first 30 seconds) in the modulation session, in which participants were told that the stimulation would be sustained for 20 minutes. Previous evidence suggested that such manipulation would result in solid subject blinding and not recruit potentially therapeutic nerves.³² Moreover, not stimulating the earlobe could avoid the unpredictable modulation effect of the stimulation.³² However, in our experimental design, we cannot rule out the possible effect of the different amounts of electrical activity between the two groups on our results. A questionnaire designed for measuring subjective feelings and expectations regarding the electrical stimulation is necessary in further investigations to rule out the possibility that our results could be driven by the strong difference in body sensations evoked by electrical stimulation. However, we believe that this possibility is not likely to be true. Please note that a previous study with a similar experimental design (the effect of the intervention was assessed by comparing pre-test and post-tests) observed that strong but non-painful transcutaneous electrical nerve stimulation could not evoke significant changes in EEG oscillations.³³ This observation suggested that the effect of strong body sensory stimulation on electrophysiological signals, although existent, may not be sustained for a prolonged period.

Limitations

There are some limitations in the present study. First, our results only illustrated the short-term after-effects of taVNS (ie, ~10 minutes after the stimulation stopped); the long-term effects of taVNS should be further explored. Second, the small attentional bias towards sad or happy faces in healthy populations might leave a floor effect, thus limiting the taVNS effects on the modulation of orientation. Further studies are necessary to explore the taVNS effects on orientation in special populations with strong or abnormal attentional bias. Third, although 25 Hz was commonly used in previous studies, other parameters should be investigated further to optimise the modulation effects. Notably, it is reported that taVNS with 100 Hz frequency, compared with 10 Hz and 25 Hz frequencies, could produce the highest functional magnetic resonance imaging responses in LC.³⁴

Implications

In summary, the present study demonstrated an offline modulatory effect of taVNS on alerting linking to LC-NE activity via a dot-probe task. Additionally, since the taVNS induced evident alternations of brain activities in the motor cortex, our study also demonstrated an interaction effect of taVNS on modulating alerting and executive inhibition systems. As such attentional systems are crucial for a wide range of cognitive processes, our findings suggest that taVNS could be a cognitive enhancer in healthy populations. Additionally, inspired by the enhanced behaviour performance and the bottom-up modulation of the LC-NE system, taVNS might be a promising treatment for patients with cognitive disorders. Notably, the LC-NE system was one of the main targets in treating disorders with low cognitive performance, such as attention-deficit/hyperactivity disorder and autism spectrum disorder. The application of taVNS in special populations should be taken cautiously and be based on solid clinical evidence in the future.

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