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RESEARCH

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Effects of different types of high-definition transcranial electrical stimulation on visual working memory and contralateral delayed activity

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Abstract

Background and purpose Working memory is critical for individuals and has been found to be improved by electrical stimulation of the left dorsolateral prefrontal cortex (DLPFC). However, the effects of different types of transcranial electrical stimulation on working memory are controversial, and the underlying mechanism remains uncertain. In this study, high-definition transcranial direct current stimulation (HD-tDCS) and high-definition transcranial random noise stimulation (HD-tRNS) were applied to the DLPFC to observe the different effects on visual working memory (VWM). The aim was to explore the causal relationship between the electrical activity of the DLPFC and the posterior parietal cortex (PPC) electrical activity and the contralateral delayed activity (CDA).

Methods Thirty-three healthy subjects received HD-tDCS, HD-tRNS and sham stimulation in a random order. Stimulation was applied to the left DLPFC for 20 min. The subjects underwent a color change-detection task as our VWM task and an auditory digit span test (DST) immediately after stimulation. Event-related potential (ERP) data were collected during the VWM task.

Results The results revealed significant differences between the different types of HD-tES. There was a remarkable increase in VWM capacity following HD-tDCS compared with both HD-tRNS ($p_a = 0.038$) and sham stimulation ($p_a = 0.038$). Additionally, the CDA from the PPC differed after stimulation of the DLPFC. Both HD-tDCS and HD-tRNS expanded the maximum CDA amplitude from set size of 4 to 6, whereas after sham stimulation, the maximum CDA was maintained at a set size of 4. Compared with the sham condition, only HD-tDCS induced a noteworthy increase in CDA amplitude ($p_a = 0.012$). Notably, a significant correlation emerged between the mean CDA amplitude and VWM capacity ($p < 0.001$, $r = -0.402$).

Conclusion These findings underscore the ability of HD-tDCS to target the DLPFC to augment working memory capacity while concurrently amplifying CDA amplitudes in the PPC through the frontoparietal network.

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Keywords Transcranial random noise stimulation, High-definition transcranial electrical stimulation, Working memory, Event-related potentials, Frontoparietal network

Introduction

Working memory, which temporarily stores and manipulates information, serves as a global workspace for various higher-level cognitive functions [1]. Deficits in working memory have been linked to numerous medical conditions [2–5], including cognitive impairment, aphasia, and emotional disorders [6–8]. The dorsolateral prefrontal cortex (DLPFC) is most closely related to working memory, but the mechanism by which the DLPFC regulates working memory is still unclear. Our previous study on stroke revealed that transcranial direct current stimulation (tDCS) acting on the DLPFC may affect the left frontoparietal network [9], but causal evidence is still lacking.

tDCS and transcranial random noise stimulation (tRNS) are two commonly used transcranial electrical stimulation (tES) methods [10–13]. However, they have completely different waveform patterns and therefore different mechanisms. tDCS regulates the excitability of the brain by depolarizing the membrane potential through a monophonic direct current. tRNS can moderate aftereffects in brain oscillatory activity or create stochastic resonance [14] to improve working memory in healthy people. Some even suggest that the effect of tRNS on working memory is superior to that of tDCS [15, 16].

Although researchers have conducted many studies to explore the efficacy of tDCS on working memory [17–19], there are still inconsistencies and variations in the results [20]. Conventional large-pad tDCS may struggle to induce consistent results in the PFC because of its broad coverage area. However, recent advances in high-definition tDCS (HD-tDCS), which uses multiple ring electrodes to precisely target specific brain regions with stronger current density, show promise in addressing this issue [21]. Compared with tDCS, high-definition tDCS (HD-tDCS) is considered more effective at improving working memory due to its higher definition and current density [22, 23]. However, the mechanism by which HD-tDCS improves working memory remains unclear, and current studies lack objective evaluation indicators that directly reflect changes in brain function. Moreover, studies on high-definition tRNS (HD-tRNS) are still very rare [24], and the effects and mechanisms also require further study and exploration.

Contralateral delay activity (CDA) is an event-related potential coupled with a color change-detection task used to evaluate visual working memory; this task is believed to originate from the inferior intraparietal sulcus (IPS) and is a reliable electrophysiological index of functional activity in the posterior parietal cortex (PPC) [25]. In addition, the difference in the amplitude of CDA is strongly correlated with working memory capacity [26]: the working memory capacity of healthy humans and the memory size at the maximum CDA amplitude are both 4 [27]. The values of working memory capacity, *K*, and the amplitude of CDA are both good objective indicators for evaluating working memory capacity. Indeed, several recent studies have suggested that HD-tDCS applied to the PFC can improve working memory performance, particularly in n-back tasks involving verbal working memory [23, 28, 29]. However, it remains unknown whether precise DLPFC stimulation can consistently enhance visuospatial working memory performance across participants. Additionally, the impact of stimulating the DLPFC on parietal electrical activity within the PPC is still unexplored. Therefore, in our present study, we used HD-tDCS to stimulate the DLPFC and simultaneously recorded event-related potentials (ERPs) while participants engaged in a color change-detection task. We also employed HD-tRNS as a control protocol and administered sham stimulation over the DLPFC as an additional control. We hypothesized that HD-tDCS over the DLPFC would improve working memory performance and concurrently modulate CDA in the parietal areas through the frontoparietal network.

Materials and methods

Participants

A total of 34 healthy volunteers aged 21 to 29 years (9 males, 24 females, mean age = 22.2) were recruited and provided informed consent to participate in the study. All the participants were right-handed, possessed normal or corrected-to-normal vision, were not colorblind, and had no history of neurological or psychiatric disorders. Additionally, none of the participants used recreational drugs or medications that could have affected cognitive or emotional functioning during the study. Before their participation, all individuals provided written informed consent, as required by the ethics committee at the Third Affiliated Hospital of Sun Yat-sen University.

Design

A crossover design was employed for this experiment, consisting of three distinct stages, each containing a

different stimulation session (HD-tDCS, HD-tRNS or sham) followed by an assessment, with a one-week washout period imposed between stages. According to the three different stimulations, a total of six different stimulation orders could be arranged, and each subject was randomly assigned to one of the six orders. The assessment required participants to perform a color change-detection task while their ERPs were recorded, along with a digit span task. These two tasks collectively took 40 min to complete. The assessment was performed immediately after stimulation, during which the cap manipulation took 5 to 8 min. At the end of the third stage, each participant was asked to complete a questionnaire regarding safety and to make an educated guess regarding the sequence of the three stimulation types according to how they felt (refer to Fig. 1).

Interventions

HD-tES was administered via a VC-8000F tES device manufactured by Nanjing Wogao Medical Technology Co., Ltd. Each stimulation session lasted for 20 min. HD-tDCS was conducted with anodal stimulation at an intensity of 1.5 mA. HD-tRNS was administered at a frequency of 0 ~ 200 Hz, the intensity fluctuated between 0 and 1.5 mA, and the stimulus direction was randomly altered during stimulation. The same electrode configuration was used for sham stimulation, but the current was presented for only 60 s at the start and end of 20 min. The stimulating electrode was placed at F3 according to the 10–20 EEG localization method, whereas the remaining four control electrodes were placed at surrounding points F1, F5, AF3, and FC3. Among the electrodes, the stimulating electrode of the HD-tDCS montage provided a positive stimulation current, whereas the other four electrodes delivered cathodal stimulation currents.

Visual working memory test

We employed a color change-detection task as our visual working memory (VWM) test. The number of items (set size) in each hemifield varied from 2 to 6 in ascending order. Each set size condition included 48 trials, resulting in a total of 240 trials per assessment. In each trial, the arrow cue was presented for 200 ms, followed by the memory array being displayed for 100 ms. After a 900 ms blank screen, the response array appeared. The trial ended when the participant responded, after which the

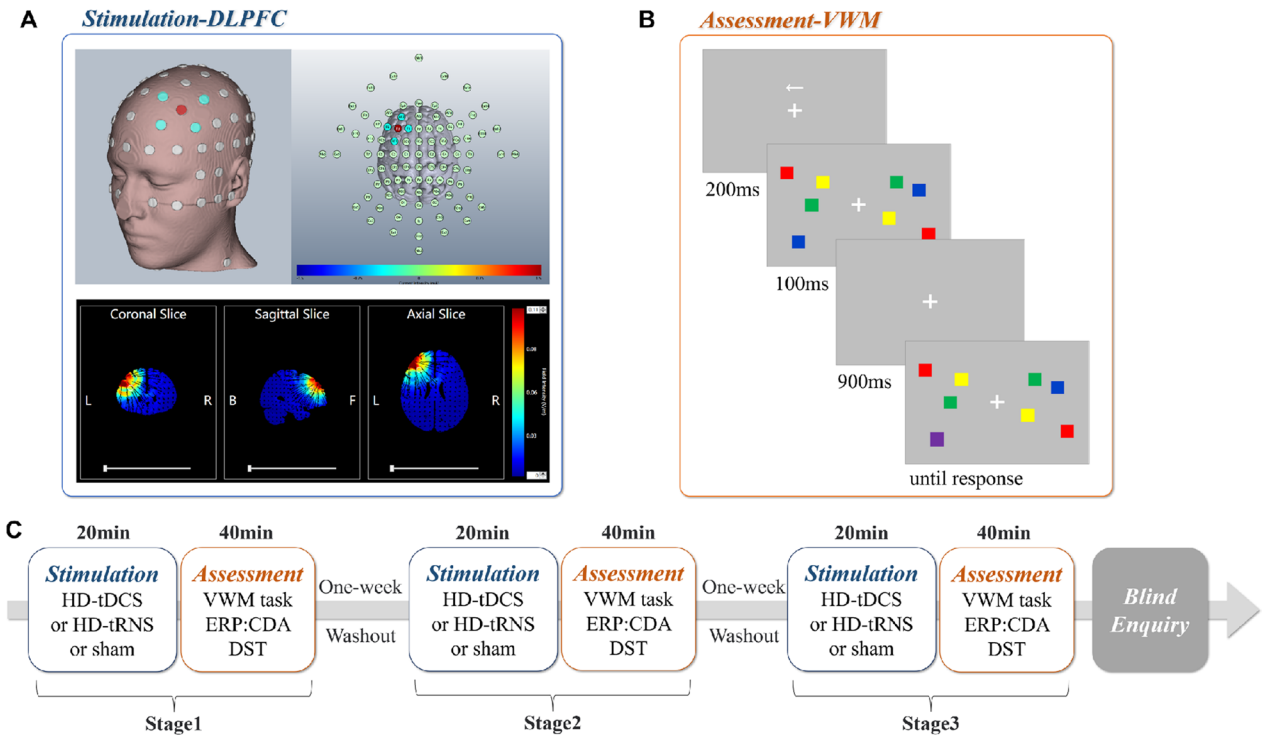

Fig. 1 Study Procedures. **A** High-definition transcranial electrical stimulation applied to the DLPFC and the current density of the effect on the brain. **B** Participants were given a visual working memory (VWM) task with five kinds of loads, including set sizes from 2 to 6. **C** Participants completed all three stages of the test, with a washout period of more than 1 week between each stage. Each stage consisted of 20 min of electrical stimulation and 40 min of assessment, and the participants received three kinds of stimulation in three stages in random order. Each participant was assessed immediately after each stimulation, including a VWM task during ERP acquisition and an auditory digit span task without ERPs. After all three sessions, a blinded questionnaire was administered

next trial began. Stimulus arrays were displayed within rectangular regions positioned to the left and right of a central fixation cross against a gray background. Each memory array consisted of 2 to 6 colored squares in each hemifield. These squares were randomly selected from a set of seven highly distinguishable colors (red, blue, purple, green, yellow, black and white), with no color repeated within a single half of the array. The positions of the stimuli were randomized for each trial to ensure an equal number of appearances on the left and right sides. In 50% of the trials, the color of one square in the test array differed from that of the corresponding item in the memory array. In the remaining trials, the colors of the two arrays were identical. At the start of each trial, a central arrow cue indicated whether the participants should remember the items in the left or right hemifield (equal number for the left and the right). The task process is shown in Fig. 1B.

Through a Chronos connected to the display, the subjects were required to respond to the response array by pressing the leftmost (same) or rightmost (different) key. To calculate visual memory capacity, we employed a formula that was initially developed by Pashler [30] and subsequently refined by Cowan and Vogel [26, 27]. The formula is $K = S \times (H\text{-}F)$, where K is the memory capacity, S is the size of the array, H is the observed hit rate, and F is the false alarm rate. This formula allows us to quantify the memory capacity based on the size of the stimulus array, the accuracy of recognizing items (hit rate), and the rate of incorrectly identifying items as present (false alarm rate).

Event-related potentials (ERPs)

ERPs were collected via a 64-lead saline electrode cap connected to a Net Amps 400 amplifier from Electrical Geodesics, Inc. The sampling rate for data acquisition was set at 1000 Hz. When participants were cued to remember the left array, the CDA was measured in the right posterior parietal region; when the array was on the right side, the CDA was measured on the left. The ERP data were preprocessed via the EEGLAB toolbox in MATLAB 2022a. This processing involved several steps, including artifact removal, bandpass filtering within the 0.1–30 Hz range, and resetting the reference to the common average of all electrodes. Artifacts such as electrocardiogram (ECG) and electrooculogram (EOG) signals were effectively removed via independent component analysis (ICA). To derive the CDA waveform, we performed the following steps. First, we subtracted the waveform of the left posterior parietal lobe from the waveform of the right posterior parietal lobe after the onset of the memory array (event onset). Conversely, when participants were cued to remember the right array, we used the waveform obtained by subtracting the right side from the left side of the posterior parietal lobe. Second, we selected electrodes based on the 10–20 EEG montage. For the left posterior parietal region of interest (ROI), we used electrodes P1, P3, P5, P7, and P9. For the right posterior parietal region, we selected electrodes P2, P4, P6, P8, and P10; the activity from these five electrodes within a given ROI was averaged to obtain a representative waveform. Finally, the waveforms corresponding to both the left and right arrays were averaged to obtain the CDA waveform for a given memory array size.

Auditory working memory test

We assessed auditory working memory via both forward (FDST) and backward (BDST) auditory digit memory span tests. These tests did not involve the acquisition of ERPs. In the FDST, participants were presented with various sequences of random numbers and were required to repeat the sequences in the order in which they had heard them. In the BDST, participants were instructed to repeat the sequences of random numbers in reverse order as they heard them. The number of random number sequences presented to participants increased progressively in difficulty. There were two random number sequences in each set, and each sequence was stated once. As long as the participants answered one of the sequences correctly, we proceeded to the next set. Scores were determined based on the highest number of correctly completed random number sequences. In other words, the score reflected the maximum number of random sequences that participants could accurately recall and repeat. These tests allowed us to evaluate auditory working memory and participants' ability to retain and manipulate sequences of random digits in both forward and backward order.

Outcome measures and statistical analyses

The primary outcome measure was visual working memory capacity, which was quantified as the mean value of K derived from all five memory array sizes. The secondary outcome measures included various aspects. (1) Mean amplitude of the CDA: This refers to the average amplitude of the CDA during the presentation of the memory array, specifically from 200 to 400 ms. This parameter serves as an indicator of the number of items maintained in visual working memory. (2) Accuracy and response time: These metrics pertained to the accuracy and response time in the VWM task. (3) FDST and BDST: Participants' performance scores on both the FDST and BDST were included as secondary outcome measures. The BDST and FDST did not involve the acquisition of ERPs.

Prior to the main study, a small preliminary experiment was conducted with a sample size of n = 4. Based on the findings from these preliminary experiments, Power Analysis & Sample Size (PASS) 15 revealed that enrolling 34 participants would yield a statistical power of 90%. This level of power was chosen to detect a minimum relevant between-stimulation difference in the K value of 0.2925 at an alpha level of 0.05.

Statistical analysis of the data was performed via crossover design ANOVA in SPSS 25.0. To minimize the potential interference of the stimulating sequence on the results, the main effect of the stimulating sequence on outcome measures was regressed out on the basis of the random sequence. The analysis considered the time sequence order of the three experimental points and the three different stimulation methods as two fixed factors, namely, "stage" and "stimulation type." The main effects of these two fixed factors on the outcomes were examined. Individual differences were considered random factors in the analysis. Factors that demonstrated significant differences among the groups were further assessed through paired t tests between any two groups. To further compare the CDA amplitude under different conditions, ANOVA or the Friedmann test was used to compare the CDA amplitude among different size sets according to the normality of CDA. If there was any difference, the CDA amplitude was further compared via paired post hoc comparisons. Corrections for multiple comparisons were applied via the false discovery rate (FDR) correction method. Additionally, partial correlation analysis was performed to explore the relationship between the mean amplitude of CDA and working memory capacity. In all analyses, statistical significance was defined as $p < 0.05$.

Results

A total of 33 subjects were included in the final statistical analysis. The general characteristics of the subjects and the orders of the actual stimulation are shown in Table 1. Among them, four reported experiencing a "stinging" sensation during the stimulation sessions. Notably, all four individuals were able to complete the stimulation sessions after the intensity was reduced to a more comfortable level (1–1.25 mA). The results of the blind questionnaire, as detailed in Table 2, indicate that participants' accuracy in guessing the type of stimulation did not significantly differ among the three stimulation conditions ($\chi^2 = 6.909$, $p = 0.141$). These findings supported the effectiveness of the blinding procedures employed in the study.

HD-tDCS enhanced visual working memory capacity

The accuracy and response time following the three types of stimulation are shown in Fig. 2. There was no significant difference in the accuracy ($F(2,62) = 0.168$, $p = 0.845$, $\eta_p^2 = 0.005$) or response time ($F(2,62) = 0.156$, $p = 0.856$, $\eta_p^2 = 0.005$) on the color change-detection task among the three different stimulation conditions.

However, there was a significant main effect of the three different types of stimulation on visual working memory capacity ($F(2,62) = 3.699$, $p = 0.030$, $\eta_p^2 = 0.107$). Specifically, participants in the HD-tDCS group presented significantly greater mean K values after stimulation than did those in the HD-tRNS condition (HD-tDCS vs. HD-tRNS difference = 0.1870, CI [0.0326, 0.3413], $p_a = 0.038$) and the sham condition (HD-tDCS vs. sham difference = 0.1768, CI [0.0224, 0.3311], $p_a = 0.038$) after FDR correction. However, there was no significant difference in visual working capacity between the HD-tRNS group and the sham group (HD-tRNS vs. sham difference = − 0.0102, CI [− 0.1645, 0.1442], $p_a = 0.896$).

These results indicate that HD-tDCS had a significant positive effect on visual working memory capacity compared with both HD-tRNS and sham stimulation, whereas there was no significant difference between HD-tRNS and sham stimulation.

HD-tDCS over the DLPFC modulated CDA in the PPC

The waves of CDA are shown in Fig. 3, and the corresponding statistical results are summarized in Fig. 4. After the normality test, we found that the amplitudes of the CDAs did not all conform to a normal distribution. To assess the significance of the differences in CDA amplitudes, we first compared the CDA amplitudes of different sizes after each stimulation condition via the Friedmann test and found significant differences between them ($p_{\text{HD-tDCS}} < 0.001$, $p_{\text{HD-tRNS}} = 0.010$, $p_{\text{sham}} = 0.007$). Then, Wilcoxon signed-rank tests were conducted between different memory array sizes under the same stimulation conditions. All p values were subjected to FDR correction. The specific statistical results are as follows. After HD-tDCS, the absolute amplitudes of CDA at set sizes of 3 ($Z = -2.296$, $p_a = 0.037$), 4 ($Z = -3.118$, $p_a = 0.020$), 5 ($Z = -2.367$, $p_a = 0.036$) and 6 ($Z = -2.886$, $p_a = 0.020$) were significantly greater than those at a set size of 2. Additionally, the absolute amplitudes of CDA at set sizes of 4 ($Z = -2.421$, $p_a = 0.036$) and 6 ($Z = -2.546$, $p_a = 0.036$) were also larger than those at a set size of 3. After HD-tRNS stimulation, the absolute amplitudes of CDA at set sizes 3 ($Z = -2.796$, $p_a = 0.037$), 4 ($Z = -2.796$, $p_a = 0.037$), 5 ($Z = -3.314$, $p_a = 0.044$) and 6 ($Z = -3.582$, $p_a = 0.003$) were also significantly greater than those at a set size of 2. Furthermore, the absolute amplitude of CDA at a set size of 6 ($Z = -2.314$, $p_a = 0.044$) was also greater than that at a set size of 3. In contrast, after sham stimulation, only set sizes 3 ($Z = -3.332$, $p_a = 0.010$) and 4 ($Z = -2.689$, $p_a = 0.035$) resulted in significantly greater

Table 1 Characteristics of the subjects

No	Age	Sex	Type of order	Type of stimulation		
				Stage 1	Stage 2	Stage 3
1	22	Male	1	HD-tRNS	HD-tDCS	Sham
2	23	Female	2	HD-tRNS	Sham	HD-tDCS
3	**22**	**Female**	**5**	**Sham**	**Withdraw**	**Withdraw**
4	24	Female	4	HD-tDCS	Sham	HD-tRNS
5	22	female	3	HD-tRNS	Sham	HD-tDCS
6	22	Female	2	HD-tRNS	Sham	HD-tDCS
7	22	Female	1	HD-tRNS	HD-tDCS	Sham
8	22	Female	6	Sham	HD-tDCS	HD-tRNS
9	22	Female	6	Sham	HD-tDCS	HD-tRNS
10	22	Female	3	HD-tDCS	HD-tRNS	Sham
11	21	Male	1	HD-tRNS	HD-tDCS	Sham
12	24	Male	3	HD-tDCS	HD-tRNS	Sham
13	22	Male	5	Sham	HD-tRNS	HD-tDCS
14	21	Male	6	Sham	HD-tDCS	HD-tRNS
15	21	Female	6	Sham	HD-tDCS	HD-tRNS
16	21	Female	5	Sham	HD-tRNS	HD-tDCS
17	27	Male	6	Sham	HD-tDCS	HD-tRNS
18	21	Female	3	HD-tDCS	HD-tRNS	Sham
19	21	Female	2	HD-tRNS	Sham	HD-tDCS
20	21	Female	3	HD-tDCS	HD-tRNS	Sham
21	21	Female	2	HD-tRNS	Sham	HD-tDCS
22	24	Female	4	HD-tDCS	Sham	HD-tRNS
23	21	Female	2	HD-tRNS	Sham	HD-tDCS
24	22	Male	1	HD-tRNS	HD-tDCS	Sham
25	21	Female	2	HD-tRNS	Sham	HD-tDCS
26	24	Female	4	HD-tDCS	Sham	HD-tRNS
27	22	Female	3	HD-tDCS	HD-tRNS	Sham
28	22	Female	4	HD-tDCS	Sham	HD-tRNS
29	29	Male	4	HD-tDCS	Sham	HD-tRNS
30	21	Female	4	HD-tDCS	Sham	HD-tRNS
31	21	Male	1	HD-tRNS	HD-tDCS	Sham
32	21	Female	5	Sham	HD-tRNS	HD-tDCS
33	21	Female	6	Sham	HD-tDCS	HD-tRNS
34	21	Female	5	Sham	HD-tRNS	HD-tDCS

The information of the dropped subject is shown in bold

Table 2 Results of the blind questionnaire

Real stimulation Participant guessing	tDCS	tRNS	Sham	Total
tDCS	11	15	7	33
[%]	(33.3)	(45.5)	(21.2)	(100)
tRNS	12	11	10	33
[%]	(36.4)	(33.3)	(30.3)	(100)
Sham	10	7	16	33
[%]	(30.3)	(21.2)	(48.5)	(100)
Total	33	33	33	–

absolute CDA amplitudes than did set size 2. However, there was no significant difference in the absolute CDA amplitudes at a set size of 5 ($Z=-2.099$, $p_a=0.082$) or 6 ($Z=-2.189$, $p_a=0.082$) compared with those at a set size of 2.

We used the mean amplitude of CDA among the five memory array sizes for each participant to represent the number of items maintained in visual working memory. The effects of the three types of stimulation on the mean amplitude of CDA were significantly different ($F(2,62)=4.538$, $p=0.014$, $\eta_p{}^2=0.128$). Specifically, the

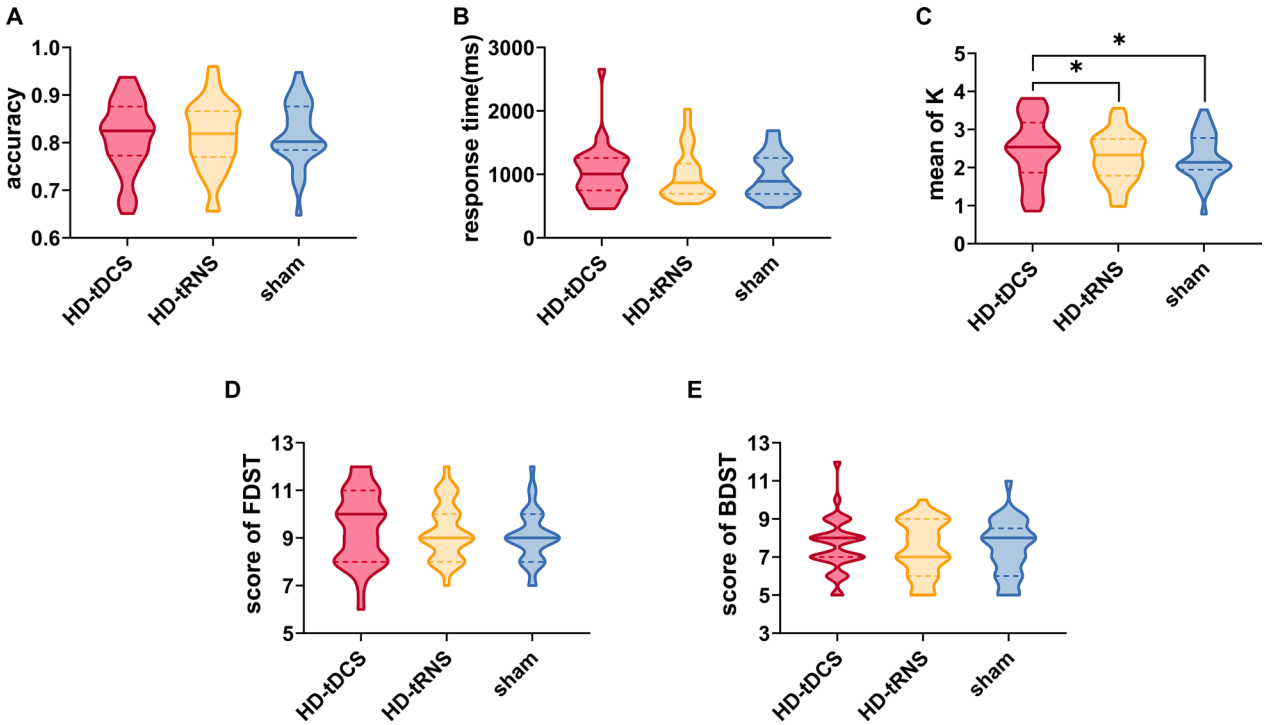

Fig. 2 Results of working memory. **A**, **B** Accuracy and response time in the VWM task showed no group differences among the three stimulation conditions. **C** The mean visual working memory capacity (*K*) of the HD-tDCS group was significantly greater than those of the HD-tRNS group and sham group. **D**, **E** DSTs in both forward and backward order showed no pairwise group differences. * indicates $p < 0.05$ after FDR correction. The solid line represents the median, whereas the dashed line represents the quartile

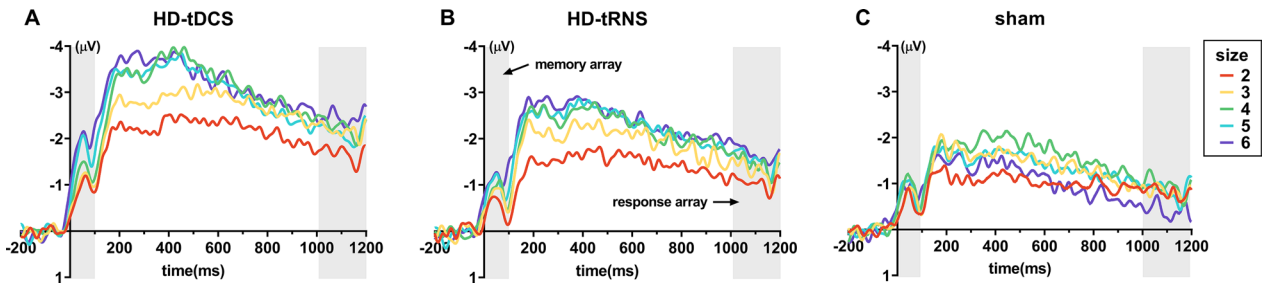

Fig. 3 Waveforms of contralateral delay activity. **A**–**C** The amplitude of the CDA was recorded from the beginning of the memory array. The waveforms in different colors represent changes in the CDA amplitude of the set size from 2 to 6. After HD-tDCS and HD-tRNS stimulation, the amplitude of the CDA increased with increasing set size from 2 to 4 and was maintained at approximately 4 to 6 thereafter. However, after sham stimulation, the amplitude of CDA was the highest when the set size was 4, and the amplitude of CDA showed a decreasing trend when the set size was from 4 to 6

mean amplitude of CDA following HD-tDCS was significantly greater than that following sham stimulation (HD-tDCS vs. sham difference = − 1.5201, CI [− 2.5238, − 0.5164], $p_a = 0.012$) after FDR correction, but the mean amplitude of CDA following HD-tRNS did not differ significantly from that following HD-tDCS (HD-tRNS vs. HD-tDCS difference = 0.7696, CI [− 0.2341, 1. 7732], $p_a = 0.140$) or sham (HD-tRNS vs. sham difference = − 0.7505, CI [− 1.7542, 0.2531], $p_a = 0.140$) conditions.

In addition to the observed differences in visual working memory capacity and CDA among the different stimulation methods, there was a significant correlation between the mean amplitude of the CDA and the mean value of *K* ($p < 0.001$, $r = -0.402$). Notably,

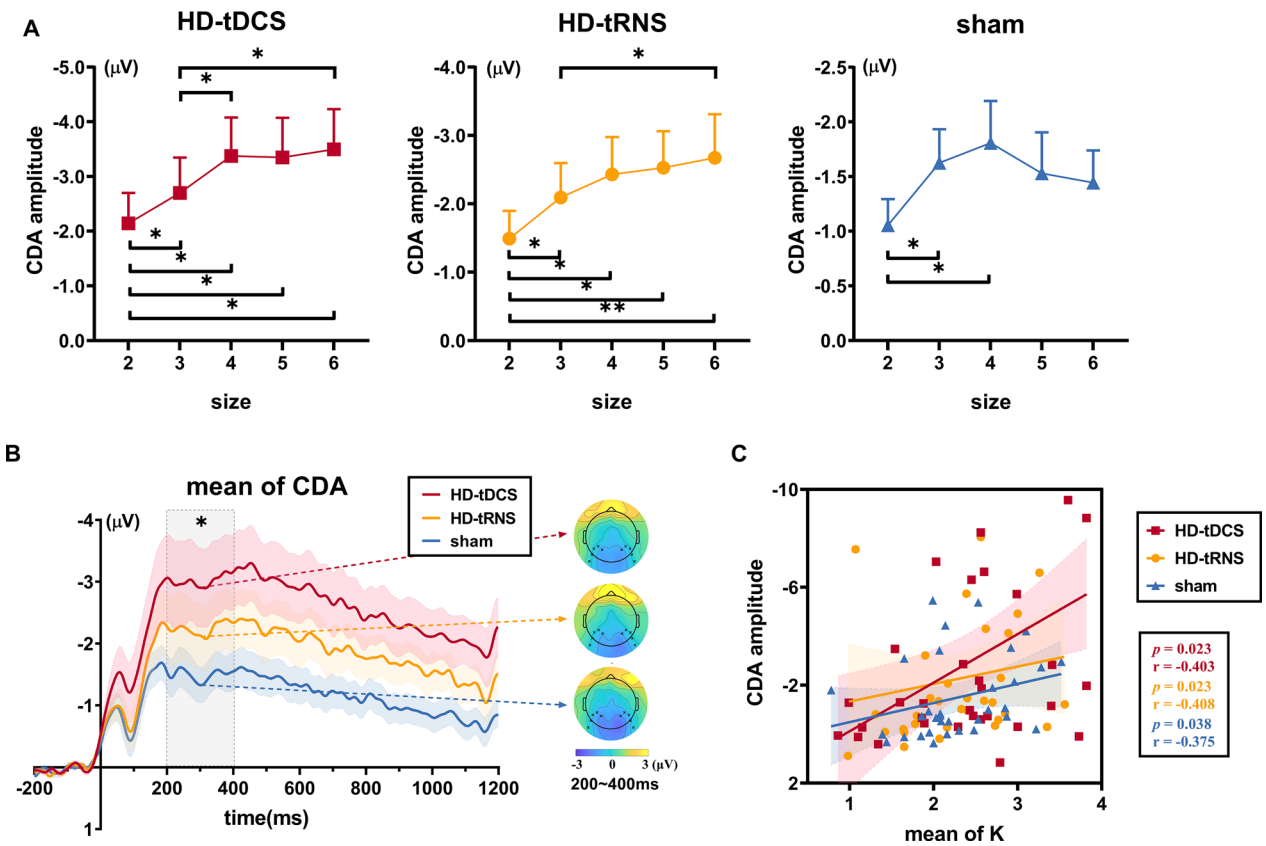

Fig. 4 Contralateral delay activity and its correlation with working memory capacity. **A** The amplitudes of CDA after all three stimulations were more negative at set size 3 and set size 4 than at set size 2, and the amplitudes of CDA at set size 5 and set size 6 after HD-tDCS and HD-tRNS were still more negative than those at se -size 2 but not for sham stimulation. **B** The mean amplitude and SEM (shade) of CDA for all item-number memory arrays after the three stimulations. The mean amplitude of CDA after HD-tDCS was significantly greater than that after sham stimulation. On the right is the EEG topography of CDA in the 200–400 ms time window after HD-tDCS, HD-tRNS, and sham stimulation. The waveforms of the CDA were selected for averaging the leads at the marked points. **C** The mean amplitude of the CDA was moderately strongly correlated with the mean working memory capacity. * indicates p < 0.05 after FDR correction; ** indicates p < 0.01 after FDR correction

this correlation was consistent across all three different stimulation protocols. These results are shown in Fig. 4.

High-definition stimulation over the DLPFC did not increase auditory working memory

Performance in the auditory digit span test, which serves as an indicator of verbal working memory, did not significantly differ among the three different stimulations for either forward ($F(2,62) = 1.772$, $p = 0.178$, $\eta_p^2 = 0.054$) or backward ($F(2,62) = 0.466$, $p = 0.630$, $\eta_p^2 = 0.015$) order (Fig. 2).

A detailed description of the above outcomes can be found in the Supplementary materials (Supplemental Table 1).

Stage effects affected working memory performance but not CDA

The main effects of stage on working memory and CDA are shown in Fig. 5. The accuracy ($F(2,62) = 6.242$, $p = 0.003$, $\eta_p^2 = 0.168$) and response time ($F(2,62) = 14.001$, $p < 0.001$, $\eta_p^2 = 0.311$) of the VWM task significantly differed across the three different stages. The accuracy of stage 3 (stage 3 vs. stage 1 difference = 0.0250, CI [0.0101, 0.0398], $p_a = 0.003$) and stage 2 (stage 2 vs. stage 1 difference = 0.0198, CI [0.0049, 0.0346], $p_a = 0.014$) was substantially greater than that of stage 1, and the response times of stage 3 (stage 3 vs. stage 1 difference = − 282.6123, CI [− 395.2066, − 170.0181], $p_a < 0.001$) and stage 2 (stage 2 vs. stage 1 difference = 224.1056, CI [− 336.6998, − 111.5113], $p_a < 0.001$) were also substantially faster than those of stage 1. Moreover, the *K* values in stage 3 (stage 3 vs. 1 difference = 0.2263, CI [0.0720, 0.3806], $p_a = 0.015$) and stage 2 (stage 2 vs. 1 difference = 0.1780, CI [0.0237, 0.3324], $p_a = 0.036$) were significantly greater than that in stage 1 after FDR correction, whereas no significant difference was found between stages 2 and 3 (stage 3 vs. stage 2 difference = 0.0483, CI [− 0.1061, 0.2026], $p_a = 0.534$). As the

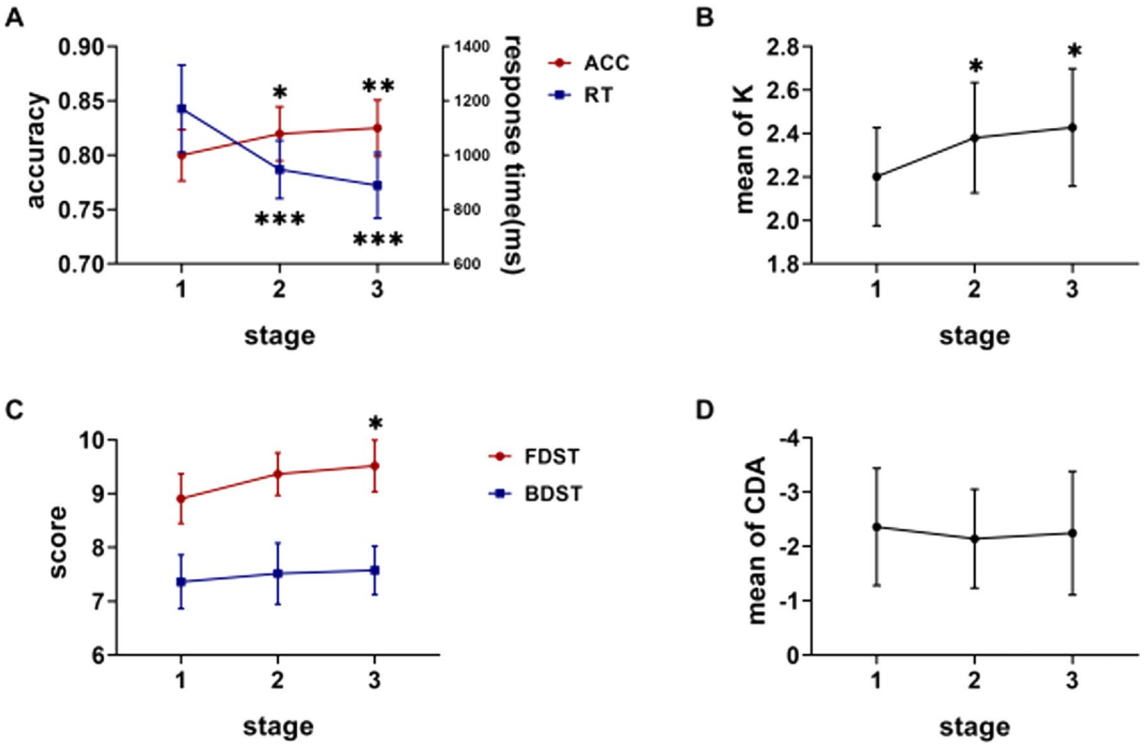

Fig. 5 Main effect of stage. **A** Compared with those in stage 1, the accuracy and response time in the VWM task significantly improved in both stage 2 and stage 3. **B** The mean visual working memory capacity was significantly greater in both stage 2 and stage 3 than in stage 1. **C** The forward-order DST score was significantly greater in both stage 2 and stage 3 than in stage 1, but the change in the backward-order DST score was not significant. **D** The amplitude of CDA was not significantly different among the three stages. Symbols and bars represent the means and 95% confidence intervals of the data for each group. * represents $p < 0.05$ after FDR correction;** represents $p < 0.01$ after FDR correction; *** represents $p < 0.001$ after FDR correction

stage progressed, the performance in the FDST improved ($F(2,62) = 4.389$, $p = 0.016$, $\eta_p^2 = 0.124$). The FDST scores in stage 3 (stage 3 vs. stage 1 difference = 0.6061, CI [0.1758, 1.0363], $p_a = 0.021$) were significantly higher than those in stage 1, indicating a learning effect. However, the performance in the BDST did not significantly improve across the different stages ($F(2,62) = 0.466$, $p = 0.630$, $\eta_p^2 = 0.015$). Moreover, the amplitude of CDA did not differ among the three stages ($F(2,62) = 0.048$, $p = 0.953$, $\eta_p^2 = 0.002$).

Discussion

In the present study, different types of HD-tES produced inconsistent effects on working memory and CDA. The application of HD-tDCS over the DLPFC demonstrated an absolute advantage in improving VWM capacity, accompanied by an increase in the amplitude of CDA observed in the PPC. However, HD-tRNS did not significantly improve VWM capacity or CDA amplitude. Notably, an intriguing correlation was observed between overall working memory capacity and CDA amplitude, independent of stimulation conditions.

Effect of HD-tDCS over the DLPFC on working memory

The observed waveform characteristics of CDA after sham stimulation in our study align with previous research, where CDA typically has the most negative values at a set size of 4 and decreases as the set size increases. However, our findings introduce an intriguing departure from this conventional trend in the context of HD-tDCS. In our study, after HD-tDCS, not only did we observe an increase in the average amplitude of CDA from set sizes 2 to 4, but this increase persisted as the set size expanded from 4 to 6. This novel observation suggests that human working memory capacity may possess untapped potential for extension, and HD-tDCS could serve as a means to unlock this capacity. The mechanism underlying this effect might be linked to the depolarization of neuronal resting membrane potentials induced by anodal tDCS, a phenomenon supported by prior research [31]. We hypothesize that this depolarization effect, initiated by left DLPFC stimulation, may propagate to the parietal lobe, ultimately resulting in an amplified CDA response. These findings suggest that HD-tDCS may have the unique ability to augment working memory

beyond its typical limits, a prospect that warrants further exploration and elucidation of the underlying neural mechanism.

However, top-down control from the PFC is closely related to working memory [32]. Prior investigations involving conventional tDCS applied to the DLPFC yielded inconsistent outcomes [9, 33, 34]. This outcome can largely be attributed to the poor definition of the stimulation procedure. The DLPFC has a highly intricate structure and multifaceted functionality, actively participating in various neural networks. In conventional bielectrode prefrontal tDCS, the cathode is positioned over the right supraorbital region, near the left prefrontal anode electrode. This proximity creates a situation where the electrical current has the potential to influence both the right and left prefrontal lobes simultaneously. This possibility has two notable consequences: first, it diminishes the definition of the stimulation targeting the left DLPFC, as the current diffuses across a broader area. Second, the excessive electrode size leads to a lower current density, potentially diluting the overall impact of tDCS on the prefrontal region. In contrast to conventional tDCS, HD-tDCS is a more promising approach. This technique is believed to be more effective in enhancing working memory in healthy individuals because of its ability to provide highly focused and prolonged stimulation effects [22].

Consequently, in our current study, by adopting HD-tDCS, we address the previous shortcomings associated with tDCS and open new avenues for investigating the potential of noninvasive brain stimulation in augmenting cognitive functions, particularly working memory, in healthy individuals. This represents a considerable advance in our quest to unlock the full potential of neural modulation techniques.

This remote effect is in line with previous research findings [35–37] and indicates that HD-tDCS has the ability to modulate brain regions beyond the directly stimulated area. Specifically, the CDA component, which is thought to originate in the IPS [38], reflects changes in parietal lobe activity induced by DLPFC stimulation. These findings underscore the intricate network of brain regions involved in working memory and suggest that the frontoparietal network is a key player in mediating the effects of HD-tDCS on working memory improvement.

Effect of HD-tRNS over the DLPFC on working memory

In our study, HD-tRNS did not meaningfully improve visual working memory capacity. Although hf-tRNS had a subtle effect on increasing the amplitude of CDA, it was less effective than HD-tDCS. This finding is similar to the results of some previous studies of tRNS [39], including studies on improving working memory [40]. The mechanisms underlying tRNS involve desynchronizing pathological cortical rhythms. This unique approach might have influenced the results, especially when applied to a population of healthy individuals who typically lack pathological cortical rhythms. However, other studies have produced results that differ from ours. High-frequency tRNS is effective in improving facial memory [41]. In addition, Murphy's study revealed that direct current offset (DC-offset) tRNS improved working memory due to tDCS [15]. The discrepancies between our study and previous studies regarding the effects of tRNS on working memory could be attributed to the following factors. Importantly, previous studies have not directly compared HD-tDCS with HD-tRNS, and conventional tDCS with two electrodes may have diluted the relative effects of tDCS. Additionally, differences in stimulation parameters, such as the frequency of tRNS and the absence of DC offset, may have contributed to the varying outcomes.

In our study, owing to the parameter limitations of the device, we used a specific frequency of 0 – 200 Hz for HD-tRNS without a DC offset, which distinguishes it from previous tRNS protocols. For example, several scholars have reported the beneficial effects of high-frequency tRNS (100 – 640 Hz) on healthy people [42]. In addition, the DC offset used by previous studies can cause tRNS to have single-phase current characteristics similar to those of tDCS, which improves its effect on the working memory of healthy people [15]. Unfortunately, the electrical stimulator we used could not modulate the above parameters of tRNS, which may be one of the main reasons for the differences between our findings and those of previous studies.

Nonetheless, our findings suggest that HD-tRNS demonstrated a subtle potential to enhance working memory, as evidenced by mild improvements in the VWM task and increased CDA amplitudes for larger memory arrays (5- and 6-item). As stated in the introduction, tRNS can also enhance task-related stochastic resonance through subthreshold modulation. Even in healthy individuals, HD-tRNS can potentially affect the frontoparietal network via the above mechanism, including the IPS, as evidenced by changes in CDA amplitude. These observations highlight the complex interplay of neural mechanisms and stimulation parameters that determine the effects of tRNS on working memory. However, the parameter tunability of both tRNS and HD-tRNS is greater than that of HD-tDCS, and the tunability of tRNS has been studied far less completely than that of HD-tDCS. This finding suggests the potential of HD-tRNS to improve cognition, which warrants further investigation in future studies.

The use of CDA to evaluate working memory

The utilization of CDA in recent research has significantly enriched our understanding of VWM and yielded numerous noteworthy findings [1, 25, 43, 44]. The choice to employ a basic version of the VWM task in this study, which is consistent with prior literature, allowed us to observe performance types similar to those reported by Vogel [26]. This once again demonstrated the robust stability and reproducibility of CDA as an evaluation method. This alignment between our findings and those of prior research underscores the validity of using CDA as a valuable metric for assessing the impact of transcranial electrical stimulation (tES) on VWM.

Furthermore, we established a consistent correlation between CDA and working memory capacity, further confirming the utility of CDA as a sensitive and reliable measure of cognitive function. Interestingly, while the accuracy and reaction time in the VWM task, as well as the scores in the auditory digit span test (DST), improved with repeated testing, they failed to significantly differ between the various stimulation conditions. These findings suggest that these behavioral metrics may have limited sensitivity when used alone. While practice and familiarity with tasks may lead to performance improvements, distinguishing the specific effects of HD-tDCS stimulation can be challenging.

In contrast, the amplitude of the CDA remained unaffected by repeated testing, making it a more reliable and stable measure. Importantly, there were significant differences between the different stimulation types. These factors indicate that CDA, as an endogenous cognitive activity originating from the parietal lobe, remains relatively immune to the confounding effects of time and learning, providing a better reflection of the intrinsic function of the parietal lobe or the brain as a whole. Consequently, compared with task performance measures, CDA may emerge as a more objective and dependable electrophysiological evaluation metric with the requisite sensitivity. Future studies should consider CDA as a valuable tool for revealing the effects of tES on cognitive processes.

Limitations

This study has several limitations that should be acknowledged. First, the research focused only on healthy participants to examine the impact of various forms of HD-tES on working memory. These findings should be extrapolated to populations with cognitive disorders or medical conditions with caution, as the effects of HD-tES may differ in individuals with specific medical or neurological conditions. Further research is needed to explore the potential therapeutic applications of HD-tES in patient populations.

Second, the study investigated only the immediate effects of a single session of HD-tES stimulation. Although this study provides valuable insights into the acute effects of HD-tES on working memory, it does not address potential long-term or cumulative effects that may result from repeated sessions of stimulation. However, the cumulative effect of repeated stimulation is the key to its therapeutic role in clinical practice, and the long-term effect is the focus of clinical treatment, which was not reflected in our study.

In summary, while this study contributes valuable insights into the immediate effects of HD-tES on working memory and the associated electrophysiological responses in healthy individuals, further research is essential to explore its applicability in clinical populations and to investigate the potential long-term effects of repeated stimulation. These considerations will be crucial for advancing our understanding of HD-tES as a neuromodulation tool and its potential use in therapeutic interventions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12984-024-01498-4.

Additional file 1

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Author contributions

Y.A.: Conceptualization, Methodology, Resources, Software, Investigation, Formal analysis, Visualization, Writing—original draft. M.Y.: Investigation, Data Curation, Formal analysis, Validation, Writing—Review & Editing. L.Z.: Writing—Review & Editing, Project administration. H.H., H.Z. and W.F: Writing—Review & Editing. Y.K.: Methodology, Validation, Writing—Review & Editing, Supervision, Funding acquisition. X.H.: Conceptualization, Methodology, Project administration, Writing—Review & Editing, Supervision, Funding acquisition.

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Availability of data and materials
All the data supporting the results and conclusions are included within the article or Supplemental Materials. Raw data and code are also available at https://osf.io/3wrvu/.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University (No. II2023-158-02), and all the subjects volunteered to participate and signed informed consent forms.

Consent for publication
Consent to publish was obtained from all the participants.

Competing interests
The authors declare no competing interests.

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