High-Definition Transcranial Direct Current Stimulation (HD-tDCS) enhances working memory training

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Abstract—**High-Definition transcranial direct current stimulation (HD-tDCS) is a noninvasive brain stimulation technique that can improve the performance of working memory (WM). However, the current researches have focused on the effects of stimulation, while ignored the process of stimulus and the neural mechanism. The targets of this study were to explore the effects of different stimulus categories (active or sham) applied on left dorsolateral prefrontal cortex (LDLPFC) on WM training, as well as the physiological changes in the brain after training. Behavioral and electroencephalography (EEG) results of 20 participants showed that HD-tDCS significantly enhanced training effects in the later training period. Furthermore, WM ability benefited from training combined with HD-tDCS, and active group found the time-dependent desynchronization (ERD) weakened in α and β band, while sham group increased. The results supported the viewpoint that HD-tDCS can shorten the training time and alter neurons rhythm, it may be used as psychotherapy for the patients with brain injury.**

I. INTRODUCTION

Working memory (WM) is the core of human cognition and a basic cognitive process. Miller first conducted a quantitative study of short-term memory in 1956, pointed out that young people have a memory span of about seven units (Arabic numerals, letters, words or other units) [1]. However, with the advent of information and technology, people need more and more memory capacity to store and process information. Fregni F et al. applied active or sham transcranial direct current stimulation (tDCS) on the left dorsolateral prefrontal cortex (LDLPFC) or left motor cortex (M1), subjects performed Verbal 3-back simultaneously. The results showed that the performances could be improved only when active stimulation applied to the LDLPFC, while there was no significant change in other conditions [2]. It could be concluded that the stimulation-induced effects of tDCS on WM capacity depend on locations and polarity of electrodes. In latter studies, participants underwent cognitive training combined with active tDCS or sham control, the results showed that training with tDCS had the potential to significantly ameliorate cognition [3, 4, 5]. The effects appeared to be stronger on younger adults [6, 7], which show interindividual differences related to age. In some cases, these benefits would be transferred to the learning and consolidation of other skills [8, 9]. Whence more and more studies concentrated on this region, but its potential mechanism and optimized stimulus parameters have not been clarified.

With the development of brain science, evidences were presented that EEG oscillation in α and β band reflected cognitive and memory performances [10], and LDLPFC was the key to express WM capacity. When LDLPFC received a period of active tDCS, participants could enhance the performance in higher-order cognitive tasks [11, 12, 13]. However, the traditional tDCS montage produced diffuse currents in the brain, making it difficult to establish a link between brain regions and behavioral changes [14]. Recently High-Definition transcranial direct current stimulation (HD-tDCS) has been developed to target brain regions with increased focality. Studies also found that HD-tDCS altered resting-state functional connectivity [15], and more than doubled the increase excitability over time compared to traditional tDCS [16].

In the present study we targeted to examine whether HD-tDCS (2 mA) applied to LDLPFC combined with WM training could regulate the training process, enhance the WM ability, and change the neuronal efficiency. To address this, we designed cognitive tests and WM training under two different stimulation condition, individual performance and EEG signal were recorded respectively to explore the changes of WM abilities and neurodynamic.

II. METHODS

A. Participants

Twenty healthy volunteers (male 9, female 11; age 22.3 ± 1.38, right-handed) participated in this study. All participants had normal or corrected to normal vision and were free from neurological disorders as well as contra-indications of tDCS. All participants were randomly divided into sham tDCS group (sham, n=10) or active tDCS group (active, n=10). There were no differences in basic WM scores, age, gender, or years of education between the two groups.

B. Experiment Design

This study was a single-blind, sham-controlled trial. To evaluate WM capacity as well as the changes during training combined with HD-tDCS, the whole study consisted of four parts: (a) Pretest, (b) WM training, (c) Post1 test, (d) Post2 test. (Fig. 1(a)). We employed a computerized Verbal N-back (N =

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4, 6) task in which each trial began with presentation of a letter for 500-msec followed by presentation of a fixation cross for 3000-msec, trials lasted 3500-msec. Each experimental block consisted of 80 trials, (Fig. 1(b)). Verbal N-back task involved remembering letters in the order they were present for later recall, participants pressed either left or right response key to compare whether the current letter was the same as the previous letter with an interval of N. Participants always responded using their dominant right hand and instructed to keep their gaze on the fixation cross throughout each trial. After each block was completed, participants received feedback on their performance accuracy and response time regarding their performances, then completed a questionnaire about their rating scale mental effort. In Pretest, participants completed 5 experimental blocks of Verbal 4-back and Verbal 6-back respectively with no HD-tDCS, then recorded the response accuracy and time. Pretest lasted between 50 and 70 min.

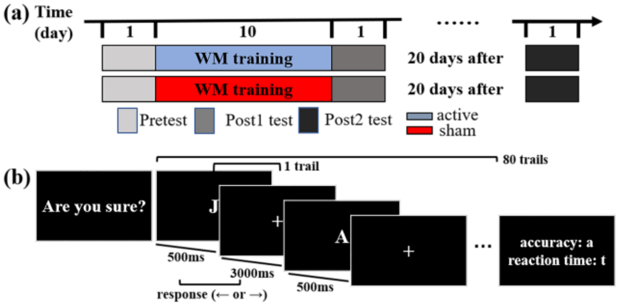

Figure 1. (a) A total experimental protocol for each condition. (b) A schematic representation of the trial procedure.

An adaptive WM training was employed in this study. Fig. 2(a) shows the protocol of the training task. Participants completed 10 training sessions on a Verbal WM task. In brief, there were 5 blocks a day, all participants began the program on Training Day 1 with a span of n, which was determined by the accuracy of Pretest. On all subsequent training days, starting span of individual was determined by performance of the prior session. At the end of block, participants received accuracy and response time regarding their performance, and the accuracy and response time were recorded. If the accuracy >85%, the span of next training session will become n+1, otherwise the span of next session would keep invariant, Fig. 2(b) shows detailed information on the third day of training, the rules applied to other sessions. Response accuracy and time were averaged within blocks.

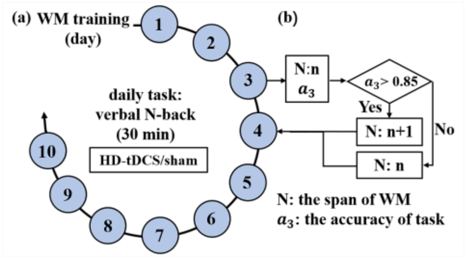

Figure 2. (a) A schematic representation of WM training. (b) The adaptive rules during the training period.

To test the effectiveness of the WM training, participants from both groups returned to perform a Post1 test that were consistent with the Pretest after training sessions. Long-term effects of the stimulus also be probed, wherefore on the 20th day after Post1 test all participants performed a Post2 test, which was the same as the Pretest. Response accuracy and time for each subject were averaged within Pretest, Post1 test, Post2 test respectively. Changes in response accuracy due to learning gains were calculated by subtracting Pretest from Post1 test, and long-term retention gains were calculated by subtracting Pretest from Post2 test.

C. Stimulation Procedure

HD-tDCS was delivered by the battery-driven Starstim system (Neuroelectrics, Barcelona, Spain) via five 3.14cm^2 saline-soaked sponge electrodes, the anodal was placed over F3 and the reference electrodes were located over FZ, FP1, FT7 and C3. For active group, a constant current of 2.0 mA intensity was delivered for 30 min and maintained for 30-sec ramp up and 30-sec ramp down. Sham group performed the same ramping of the current to 2.0 mA over 30-sec after which it was ramping down to 0 mA over 30-sec. Since the onset of tDCS usually generates a tingling or latching sensation over the first minute of stimulation, this sham procedure blinded the participant from differentiating active and sham conditions.

D. EEG Experiment and Analysis

When participants performed Verbal N-back in the Pretest, Post1 test and Post2 test, a cap which held EEG electrodes was placed on the brain of individual participant. We recorded resting-state and WM-state EEG data by SynAmps2 system (Neuroscan, USA), setting the right mastoid bone (the standard international 10–10 electrode placement: M2) as the referential electrode (impedance less than 50 KΩ; sampling rate 1,000 Hz).

Here, the recorded EEG data in Verbal 4-back and Verbal 6-back states were analyzed offline by Matlab software. First, the raw data were band-pass filtered between 1 and 45Hz, changed the reference electrodes to M1 and M2, then applied independent components analysis (ICA) to reject some artifacts such as ocular and muscular artifact (eye blink, eye movement and electromyography) by visual inspection. For each channel of WM state datasets, a total of 80 EEG epochs were extracted. Afterward, the EEG was averaged and expanded in the plane of time and frequency through time-frequency analysis. We used event-related spectrum perturbation (EPSP) to determine the frequency range of energy fluctuation. In order to show the EEG changes between Pretest and Post1 test, we calculated the value by subtracting Pretest from Post1 test. The same method was used between Posttest and Post2 test.

III. RESULTS

A. WM Training Analyses

Training data (i.e. final N of daily training sessions) were analyzed by non-paired two-sample t-test to examine the between-group effects of Stimulation Group (active or sham) in WM training sessions, the significant difference was set at p value of less than 0.05. Comparing Final N of every day, WM span showed an upward trend in both groups, but there were significant differences between the two groups at the later stage of WM training, p-value see Table 1. Importantly, active group exhibited higher WM spans compared with sham group (Fig. 3). These results supported for the idea that active HD-tDCS applied to the LDLPFC accelerated the process of training over time.

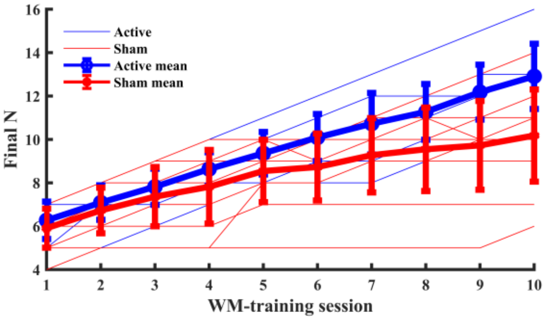

Figure 3. The results of daily training. Active HD-tDCS over LDLPFC significantly enhanced performance on the Verbal WM task than sham group.

TABLE 1. UNPAIRED TWO-SAMPLE T-TEST ANALYSES OF FINAL N IN THE DAILY WM TRAINING

session	active HD-tDCS	sham HD-tDCS	p-value Active *vs* Sham
1	6.27±0.86	5.91±0.90	0.307
2	7.09±0.79	6.73±1.05	0.420
3	7.82±0.83	7.36±1.37	0.320
4	8.64±0.77	7.82±1.70	0.181
5	9.36±0.98	8.55±1.44	0.146
6	10.09±1.08	8.73±1.54	0.040*
7	10.73±1.42	9.27±1.71	0.083
8	11.27±1.29	9.55±1.92	0.047*
9	12.18±1.27	9.73±2.05	0.010**
10	12.91±1.50	10.18±2.12	0.010**

Values were described as the mean ± SD.

* presents $p \le 0.05$, ** represents $p \le 0.01$.

B. *Pretest, Post1 test, and Post2 test Analysis*

To analyze the training gains (Post1-Pre) and the retention gains (Post2-Pre), non-paired two-sample t-test examining was used to identify the stimulation effects by comparing performance gains between two groups. For the Verbal 4-back tasks, both groups improved the response accuracy and shortened time from Pretesting to Post1 test and Post2 test. Statistics revealed that the active HD-tDCS group had significantly larger short-term training gains in terms of response accuracy (T=2.01, p=0.05), while the gains of sham group did not differ significantly. Reaction time did not find differ significantly in both groups (Fig. 4).

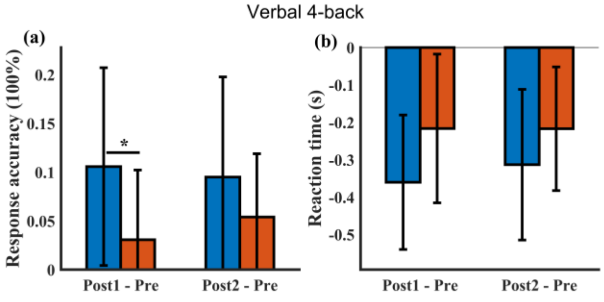

Figure 4. Training and retention gains, compared active HD-tDCS group with sham group in Verbal 4-back. (a) Response accuracy (b) reaction time

For the Verbal 6-back test, both groups improve from Pretest to Post1 test and Post2 test in terms of response accuracy and time. The active stimulus group improved more than the sham stimulus group both in response accuracy and time. However, statistics revealed that gains between two groups during training and retention did not differ significantly between two groups (Fig. 5).

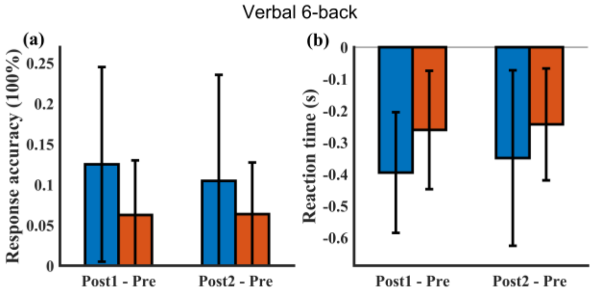

Figure 5. Training and retention gains, compared active HD-tDCS group with sham group in Verbal 6-back. (a) Response accuracy (b) reaction time

C. *Neurophysiology Analysis*

We selected electrode F3 to demonstrate physiological changes on LDLPFC (Fig. 6). It indicated the exemplary illustrations in state of Verbal 4-back, in which the black dotted line indicated the time that letter appeared, the abscissa represented time (msec) and ordinate was frequency (Hz). (a)(b) denotes the sham group, (c)(d) denotes the active group. Blue meant energy went down, red meant energy went up, and larger value indicates stronger energy. This might be considered that a decrease or an increase in synchrony of the underlying neuronal populations, respectively. The former case is called as event-related desynchronization (ERD), and the latter as event-related synchronization (ERS). Compared with the changes from Pretest to Post1 test and Post2 test between two groups, we found that the ERD of active group decreased significantly after training in α and β band. Nevertheless, while the ERD of sham group increased the energy. The changes of ERS in sham group were weaker than that in the active group.

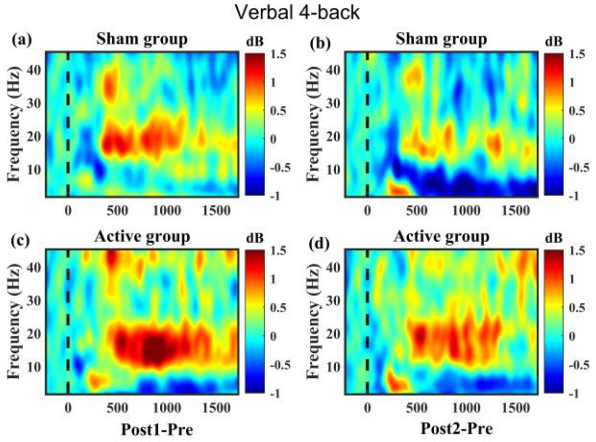

Figure 6. ERSP from Pretest to Post1 test and Post2 test between two groups located F3 in state of Verbal 4-back. (a) - (d) expressed ERSP. (a) Sham group in state of Post1-Pre. (b) Sham group in state of Post2-Pre. (c) Active group in state of Post1-Pre. (d) Active group in state of Post2-Pre.

It suggested the exemplary illustrations in state of Verbal 6-back (Fig. 7), (a)(b) denotes the sham group, (c)(d) denotes the active group. The results were similar the Verbal 4-back task, but the changes of EEG between Pretest and Post2 test were weaker than that between Pretest and Post1 test in both groups.

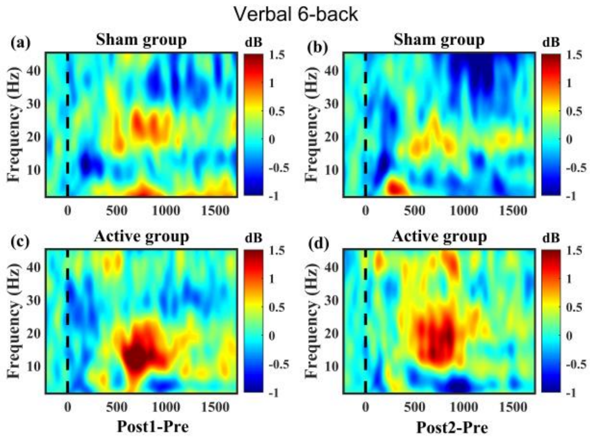

Figure 7. ERSP from Pretest to Post1 test and Post2 test between two groups located F3 in state of Verbal 6-back.

ERD was a phenomenon that EEG were inhibited due to the asynchronous activation of neurons. In the study, the weakening of ERD indicated that WM training with stimulation improved the efficiency of neuronal task processing, as well as suggested that LDLPFC played an important role in the regulation of WM ability. These results showed the evidences that HD-tDCS as an intervention means can promote WM capacity and change EEG energy in healthy person, which may be helpful in cognitive dysfunction population.

IV. CONCLUSION

Our study elucidated that HD-tDCS can ameliorate the WM behaviors and boost the rate of training over time on the healthy adults, suggesting that training combined with anodal HD-tDCS can modulate attention/speed of processing and working memory intervention, and change nervous rhythm to modulate attention and cognitive behavioral, it may serve as a potential neuromodulation measure. Meanwhile the potential neuro-electrophysiology mechanisms might be the improvement of neural synchronization and decrease of neural desynchronization in LDLPFC regions, which can improve the processing efficiency of neurons and influence the cortical oscillations.

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REFERENCES

[1] George A. Miller, "The magical number seven, plus or minus two: Some limits on our capacity for processing information," *The Psychological Review*, vol. 63, no. 2, pp. 81–97, Mar. 1956.

[2] Fregni F, Boggio P S, and Nitsche M, "Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory," *Experimental Brain Research*, vol. 166, no.1, pp. 23-30, Jul. 2005.

[3] Woods A J, Cohen R, and Marsiske M, "Augmenting cognitive training in older adults (The ACT Study): Design and Methods of a Phase III tDCS and cognitive training trial," *Contemporary Clinical Trials*, vol. 65, pp. 19-32, Nov. 2017.

[4] Benwell Christopher S.Y. Learmonth G, and Miniussi C, "Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: Evidence from biparietal tDCS influence on lateralized attention bias," *Cortex*, vol. 69, pp. 152-165, Jun. 2015.

[5] Iuculano T, and Cohen Kadosh R, "The Mental Cost of Cognitive Enhancement," *Journal of Neuroscience*, vol. 33, no. 10, pp. 4482-4486, Mar. 2013.

[6] Gbadeyan O, Mcmahon K, and Steinhauser M, "Stimulation of Dorsolateral Prefrontal Cortex Enhances Adaptive Cognitive Control: A High-Definition Transcranial Direct Current Stimulation Study," *The Journal of Neuroscience*, vol. 36, no. 50, pp. 12530-12536, Dec. 2016.

[7] Ciechanski P, and Kirton A, "Transcranial Direct-Current Stimulation Can Enhance Motor Learning in Children," *Cerebral Cortex*, vol. 27, no. 5, pp. 2758-2767, May. 2017.

[8] Richmond L L, Wolk D, and Chein J, "Transcranial Direct Current Stimulation Enhances Verbal Working Memory Training Performance over Time and Near Transfer Outcomes," *Journal of Cognitive Neuroscience*, vol. 26, no. 11, pp. 2443-2454, Oct. 2014.

[9] Richmond L L, Morrison A B, and Chein J M, "Working memory training and transfer in older adults," *Psychology and Aging*, vol. 26, no. 4, pp. 813-822, Dec. 2011.

[10] Balconi M, and Vitaloni S, "The tDCS effect on alpha brain oscillation for correct vs. incorrect object use. The contribution of the left DLPFC," *Neuroscience Letters*, vol. 517, no.1, pp. 25-29, Apr. 2012.

[11] Martin A K, Ilvana Dzafic I, and Ramdave S, "Causal evidence for task-specific involvement of the dorsomedial prefrontal cortex in human social cognition," *Social Cognitive and Affective Neuroscience*, vol. 12, no. 8, pp. 1209-1218, Apr. 2017.

[12] Hsu W Y, Zanto Theodore P, and Anguera Joaquin A, "Delayed enhancement of multitasking performance: Effects of anodal transcranial direct current stimulation on the prefrontal cortex," *Cortex*, vol. 69, pp. 175-185, Aug. 2015.

[13] Guo H, Zhang Z, and Da S, "High-definition transcranial direct current stimulation (HD-tDCS) of left dorsolateral prefrontal cortex affects performance in Balloon Analogue Risk Task (BART)," *Brain & Behavior,* vol. 8, no. 2, pp. e00884, Oct. 2017.

[14] Hogeveen J, Grafman J, and Aboseria M, "Effects of High-Definition and Conventional tDCS on Response Inhibition," *Brain Stimulation*, vol. 9, pp. 720-729, Apr. 2016.

[15] Sheng J, Xie C, and Fan D Q, "High definition-transcranial direct current stimulation changes older adults subjective sleep and corresponding resting-state functional connectivity," *International Journal of Psychophysiology*, vol. 129, pp. 1-8, May. 2018.

[16] Fischer D B, Fried P J, and Ruffini G, "Multifocal tDCS targeting the resting state motor network increases cortical excitability beyond traditional tDCS targeting unilateral motor cortex," *NeuroImage*, vol. 157, pp.34-44, May. 2017.