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Positive Effect of Transcranial Direct Current Stimulation on Visual Verbal Working Memory in Patients with Attention-Deficit/Hyperactivity Disorder

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Abstract

Background: Working memory is an executive function that plays an important role in many aspects of daily life, and its impairment in patients with attention-deficit/hyperactivity disorder (ADHD) affects quality of life. The dorsolateral prefrontal cortex (DLPFC) has been a good target site for transcranial direct current stimulation (tDCS) due to its intense involvement in working memory. In our 2018 study, tDCS improved visual-verbal working memory in healthy subjects. **Objective:** This study examines the effects of tDCS on ADHD patients, particularly on verbal working memory. **Methods:** We conducted an experiment involving verbal working memory of two modalities, visual and auditory, and a sustained attention task that could affect working memory in 9 ADHD patients. Active or sham tDCS was applied to the left DLPFC in a single-blind crossover design. **Results:** tDCS significantly improved the accuracy of visual-verbal working memory. In contrast, tDCS did not affect auditory-verbal working memory and sustained attention. **Conclusion:** tDCS to the left DLPFC improved visual-verbal working memory in ADHD patients, with important implications for potential ADHD treatments.

Keywords

Working Memory, Attention-Deficit/Hyperactivity Disorder, Dorsolateral Prefrontal Cortex, Transcranial Direct Current Stimulation

1. Introduction

Working memory, defined as the ability to temporarily hold information in order to perform a cognitive task, is considered one of the brain's executive functions. The involvement of association areas, particularly the dorsolateral prefrontal cortex (DLPFC), has been strongly implicated in working memory tasks in both monkeys and humans. In these species, the DLPFC is central to information processing and the simultaneous execution of multiple tasks. Deficits in working memory significantly impair daily life, learning, and the performance of complex tasks. In the context of psychiatric disorders, impaired working memory is particularly associated with depression in depressive disorders and is a core symptom in attention-deficit/hyperactivity disorder (ADHD) and schizophrenia [1].

Transcranial direct current stimulation (tDCS) is a method that modulates neuronal membrane potentials by applying a small electrical current (0.5 - 2 mA) from electrodes positioned on the scalp to the brain parenchyma for a specific duration. tDCS can either enhance or attenuate brain activity by targeting specific brain areas. This technology is inherently noninvasive, simple, affordable, and portable [1]. The effects of tDCS on brain function vary depending on the type of scalp current stimulation—positive (anodal) or negative (cathodal). Animal studies have shown that anodal stimulation increases excitability in the cortex below the electrode, while cathodal stimulation results in inhibition. In humans, anodal stimulation of the primary motor cortex has been shown to enhance hand EMG potentials induced by subsequent transcranial magnetic stimulation (TMS) in the same region, suggesting that anodal stimulation promotes excitatory activity in the underlying brain cortex [2].

In our previous research, administration of tDCS to the left DLPFC in healthy subjects improved performance on a test reflecting visual verbal working memory (VWM) in the anodal stimulation condition compared to the sham condition [3]. However, a limitation of this study was that it included only college students, who may not accurately represent the working memory capacity and general intellectual level of the general population. Notably, in a study that combined working memory training with concurrent 1 mA tDCS over the left DLPFC, the effectiveness of stimulation depended on the level of practice prior to training; moreover, participants with lower baseline working memory skills benefited more from tDCS, while those with higher working memory skills showed less improvement [4]. Given that ADHD is a developmental disorder that significantly impairs working memory, the effects of tDCS may be more pronounced in individuals with ADHD than in those without. An fMRI study showed that activation in regions associated with working memory was lower in the ADHD group than in normal controls and varied with task difficulty [5]. This led us to hypothesize that the effect of tDCS on working memory might be more pronounced in subjects with ADHD.

In the current study, we investigated the effect of anodal tDCS on verbal

working memory (VWM) by stimulating the left DLPFC of each participant. The methods used to assess VWM and the intellectual level of the subjects were consistent with those used in our previous study [3].

2. Materials and Methods

2.1. Participants

Nine right-handed participants (age 32.8 years ± 10.4, 5 female) were recruited for the experiment between February and September 2021. Each subject completed the entire experiment twice, under sham and active conditions, with a sufficient interval (>2 weeks) between sessions. All nine ADHD patients were diagnosed according to DSM-5 criteria, and seven were taking anti-ADHD medication (5 on methylphenidate OROS, 1 on atomoxetine, and 1 on guanfacine). Mean full-scale IQ, as measured by the WAIS-III, was 112 ± 4.9. Participants were assigned to either sham or active conditions in a single-blind fashion. ADHD symptoms were assessed using the Adult ADHD Self-Report Scale Symptom Checklist-v1.1 (ASRS), an 18-item self-report scale [6]. The mean full score ± SD of the ASRS was 29.6 ± 9.7 for the sham trials and 29.8 ± 14.5 for the active trials, with no significant difference between the two conditions. Exclusion criteria were as follows: Full score IQ < 80 on the WAIS-III, history of adverse reactions to TMS or tDCS, history or family history of seizure or stroke, history of severe head injury or brain surgery, medication other than anti-ADHD medication that could affect cognitive performance, and pregnancy. Our study was approved by the Ethics Committee of Chiba University (approval number 3517) and adhered to the tenets of the 1995 Declaration of Helsinki (as revised in Seoul 2008). Participants received a detailed explanation of the study. Written informed consent was obtained from all participants and their guardians if they were under 18 years of age. To monitor adverse effects, participants completed the tDCS Adverse Effects Questionnaire after stimulation.

2.2. Experimental Procedure

The study used a single-blind, sham-controlled, randomized, crossover design. The experiment consisted of three sessions (pre-, online, and post-session). The pre, online, and post sessions included a visual verbal 3-back task, an auditory verbal 3-back task, and a modified version of the Rapid Visual Information Processing (RVIP) task. Active or sham stimuli were delivered during the online session. The pre-, online, and post-sessions each lasted approximately 16 minutes. There was a 15-min rest period between the online and post sessions. Thus, the total duration of the experiment was approximately 63 min (**Figure 1**).

2.3. Cognitive Tasks

Visual VWM was assessed using a visual 3-back task similar to that used elsewhere [7]. A set of 20 letters (*i.e.,* J) was presented pseudorandomly for 10 ms each at a rate of 2 s per stimulus. Participants were asked to press the space bar

on the keyboard with their left hand when the currently presented letter matched one of the three previously presented stimuli. The task consisted of 60 stimuli, including 20 target stimuli, and lasted approximately 2 min. Outcome measures were change in hit rate (H), false alarm rate (F), reaction time for correct responses (RT), and A, which is a measure of sensitivity used in signal detection theory [8] and calculated as A = 1/2 + (H − F)(1 + H − F)/4H(1 − F). Auditory VWM was assessed using an auditory 3-back task. The task was identical except for the stimulus modality. In the auditory 3-back task, a set of 20 letters (*i.e.*, J) was presented aurally pseudorandomly for 600 ms each at a rate of 1 stimulus every 2 seconds. The task consisted of 60 stimuli, including 20 target stimuli, and lasted approximately 2 minutes. Outcome measures were the same as for the visual 3-back task. Figure 2 shows graphical models of the visual and auditory VWM tasks.
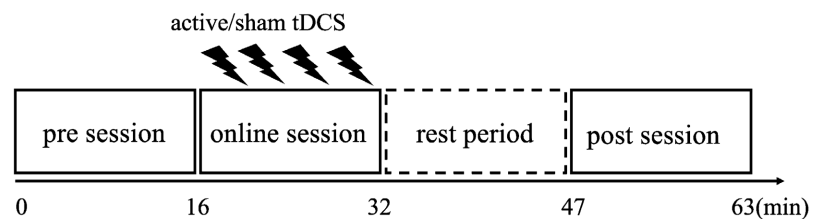

Figure 1. Experimental procedure. Participants performed three experimental sessions including pre, on-line, and post sessions. They received 16 min of active or sham tDCS during the on-line session. The post sessions started after a 15-minute rest period.
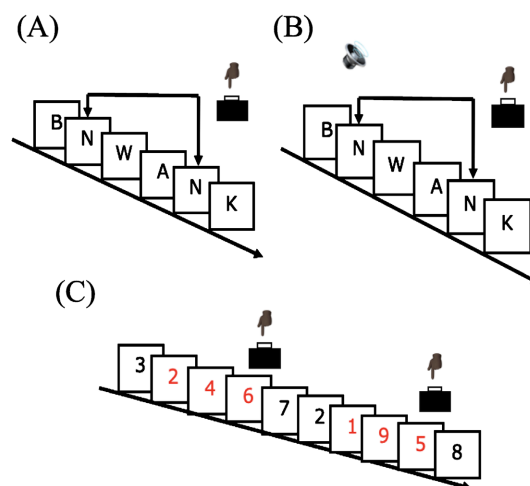

Figure 2. Graphical models of visual and auditory VWM tasks. (A) visual verbal 3-back task. (B) auditory verbal 3-back task. (C) RVIP task.

Sustained attention was assessed using a modified version of the RVIP task in which participants performed a sustained attention task with concurrent cognitive load. This task was introduced to determine whether tDCS has an effect on sustained attention, as tDCS may improve sustained attention, which could potentially affect working memory [9]. In the task, the session consisted of three phases (encoding, RVIP, and recall phase). In the encoding phase, participants

memorized a set of 4 or 5 digits. The number of digits was determined by their performance on the WAIS III forward digit span. In the RVIP phase, participants were shown a series of digit stimuli (from 1 to 9) and were asked to press the space bar on the keyboard with their left hand when they detected a series of three consecutive odd or three consecutive even digits. A stimulus was displayed for 600 ms with no time interval between two consecutive stimuli. The RVIP phase consisted of 150 stimuli, including 10 target stimuli, and lasted approximately 1.5 min. During the RVIP phase, participants were asked not to forget a sequence of digits that had been memorized during the encoding phase. In the recall phase, participants were asked to write down the encoded digit sequence. Outcome measures were change in hit rate and reaction time for correct responses. All stimuli were presented and results recorded using Matlab R2016b (MathWorks) with Psychtoolbox [10].

2.4. Transcranial Direct Current Stimulation

tDCS was delivered by a current stimulator using a pair of electrodes (Starstim tCS, Neuroelectrics Inc.) The current intensity was 1.5 mA, and the current was ramped up or down during the first and last 3 seconds of stimulation. The anode electrode was placed over the left frontal cortex (F3, corresponding to the 10 - 20 system), corresponding to the left DLPFC, and the cathode electrode was placed over the right prefrontal cortex (Fp4, corresponding to the 10 - 20 system) (Figure 3). In the active condition, stimulation was delivered continuously for 16 minutes. In the sham condition, the electrodes were placed at the same locations and the current was delivered for 30 seconds only at the beginning of the online session.
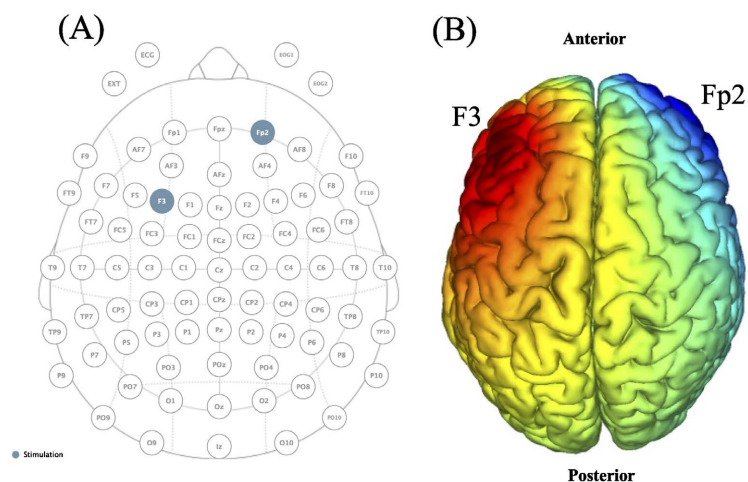

Figure 3. Electrode montage and the simulated pattern of current strength in the active condition. (A) Electrode montage used for both active and sham conditions (anode: F3; cathode: Fp2). (B) Simulated pattern of field intensity induced by active stimulation.

2.5. Statistical Analysis

For all outcome measures, the Kolmogorov-Smirnov test and the Shapiro-Wilk test confirmed the normality of the distribution. For outcome measures in the

visual 3-back task, the auditory 3-back task, and the modified version of the RVIP task, a two-way mixed ANOVA with a 2 (condition: sham, active) × 2 (time: online-pre, post-pre) design was used. Post hoc comparisons were performed using the Bonferroni test. All data are presented as mean ± SD. Effect sizes were partial η^2. For the results of adverse events, one-way ANOVA was used to compare the scores assessed at the two time points (immediately after tDCS stimulation and 30 minutes after stimulation) separately in the two conditions (sham and active). In addition, to identify the possible effect of adverse events on the scores of each task, Spearman's correlation coefficients were used for the correlation between the outcome measures of each task and the scores of adverse events. All data were analyzed using IBM SPSS Statistics version 28.0.

3. Results

3.1. Behavioral Results

Participants performed the visual and auditory 3-back tasks during the pre, online, and post sessions, and changes in task performance from the pre to the online and post sessions were examined. In the visual 3-back task, a significant main effect was observed between the sham and active conditions [$F(1, 16)$ = 7.27, p =0.016, $p\eta^2$ = 0.312]. The post hoc Bonferroni test showed that the increase in hit rate (H) in the post-pre session was significantly higher in the active group than in the sham group (p < 0.05). Such a significantly higher increase was not observed in the online-pre session in either the active or the sham group. Prefrontal tDCS did not affect performance on the auditory 3-back task or the modified version of the RVIP task. Outcome measures for all tasks are shown in Table 1.

Table 1. Outcome measures of all the tasks conducted in the present study.

Task	outcome measures	Online-Pre			Post-Pre		
		Sham	Active	Partial η^2	Sham	Active	Partial η^2
Visual 3-back task	Change in H (%)	2.51 ± 14.8	8.84 ± 30.5	0.019	**−5.43 ± 16.7**	**12.4 ± 17.6**	**0.232**
	Change in F (%)	−6.93 ± 99.9	−20.9 ± 38.5	0.01	21.2 ± 108.2	−26.3 ± 40.5	0.087
	Change in RT (ms)	−36.7 ± 88.5	−41.7 ± 78.7	0.001	−39.5 ± 85.7	−73.1 ± 126.2	0.027
	Change in A	2.71 ± 14.6	7.93 ± 18.9	0.011	−0.22 ± 10.5	10.1 ± 15.9	0.141
Auditory 3-back task	Change in H (%)	6.52 ± 19.3	19.5 ± 21.8	0.1	4.16 ± 15.1	22.2 ± 32.6	0.124
	Change in F (%)	−44.9 ± 52.4	−42.6 ± 50.0	0.001	−8.20 ± 65.1	−39.3 ± 51.8	0.073
	Change in RT (ms)	−70.2 ± 62.2	−47.9 ± 71.1	0.03	−99.2 ± 91.5	−120.0 ± 158.2	0.007
	Change in A	7.19 ± 14.2	12.8 ± 11.4	0.037	5.57 ± 11.3	11.9 ± 11.8	0.077
Modified Version of RVIP task	Change in H (%)	23.0 ± 79.4	13.9 ± 24.1	0.007	39.8 ± 88.5	22.8 ± 33.3	0.09
	Change in RT (ms)	21.5 ± 39.0	−6.23 ± 32.8	0.143	−5.11 ± 89.8	5.28 ± 64.5	0.007

Significant difference was observed in the post-pre sessions of ADHD patients between the sham and active conditions (in bold).

3.2. Adverse Events

Participants completed adverse event ratings at two time points, immediately after stimulation and at the end of the experiment (30 minutes after stimulation). One subject, a 16-year-old boy with ADHD, was not able to tolerate the stimulation and quit the on-line session, so his data were excluded from the study. The severity of adverse events is shown in Table 2. All participants who completed the experiments tolerated the stimulation well. The severity score of all adverse events was in the range of none to mild, and no significant difference was observed between the scores in the sham and active conditions at the two time points. In addition, no significant association was observed between the hit rate (H) in the post-pre session in the active group and any of the adverse event scores (data not shown).

Table 2. Results of the tDCS adverse events effects questionnaire.

Symptom	Immediately after the stimulation		30 min after the stimulation	
	Sham	Active	Sham	Active
Headache	1.2 ± 0.7	1.3 ± 0.7	1.2 ± 0.4	1.2 ± 0.6
Neck pain	1.1 ± 0.3	1.3 ± 0.7	1.2 ± 0.4	1.2 ± 0.4
Scalp pain	1.2 ± 0.4	2.0 ± 1.0	1.1 ± 0.3	1.6 ± 1.0
Burning	1.3 ± 0.5	1.4 ± 1.0	1.0 ± 0.0	1.5 ± 1.1
Tingling	2.0 ± 0.5	2.7 ± 1.0	1.1 ± 0.3	1.4 ± 1.0
Itching	1.9 ± 0.3	2.0 ± 1.1	1.7 ± 1.1	1.4 ± 0.5
Concentration	1.6 ± 0.7	1.9 ± 1.0	1.7 ± 0.7	2.0 ± 1.0

Symptoms were rated on a scale of 1 (absent), 2 (mild), 3 (moderate), and 4 (severe).

4. Discussion

In this study, we present, for the first time to our knowledge, a comparison of the effects of transcranial direct current stimulation (tDCS) on verbal working memory (VWM) in ADHD patients across visual and auditory modalities. This builds on our previous research with healthy subjects [3]. Consistent with our previous findings, we observed that tDCS applied to the left dorsolateral prefrontal cortex (DLPFC) enhanced visual VWM in ADHD patients. In particular, sustained attention, as assessed by a modified version of the Rapid Visual Information Processing (RVIP) task, remained unaffected during and after stimulation. Thus, the observed improvement in visual VWM performance in the current study cannot be attributed to changes in sustained attention, confirming our previous findings.

ADHD patients have been reported to have working memory deficits associated with hypoactivation of the DLPFC [11]. Functional MRI (fMRI) studies have shown that the N-back task activates the DLPFC, but this activation appears to be impaired in ADHD patients [12]. Therefore, we hypothesized that

anodal tDCS stimulation of the DLPFC would have a greater positive effect on task processing in ADHD patients, given the expected lower working memory capacity compared to healthy individuals. Interestingly, an fMRI study showed that ADHD subjects experienced increased difficulty when the task escalated from a 2-back to a 3-back level [13]. Our current results show that tDCS had beneficial effects on ADHD patients, all of whom were inattentive and had high ASRS scores. This suggests that, as expected, neurostimulation techniques such as tDCS may have a more pronounced therapeutic effect in populations with impaired woking memory capabilities.

Regarding the modalities of VWM, a significant difference was observed only in the visual, but not in the auditory task—mirroring the results of our previous study. Notably, neuroimaging studies have shown that both auditory and visual VWM tasks activate the DLPFC, but auditory VWM elicits higher DLPFC activation than visual VWM. The occipital cortex and hindbrain regions show higher activation during visual tasks compared to auditory tasks [14] [15]. These studies suggest a greater recruitment of the DLPFC in auditory than in visual VWM processing. At first glance, our findings that tDCS has a greater effect on visual VWM may seem counterintuitive. As speculated in our previous study, tDCS may have reached a ceiling effect on DLPFC neural excitation during auditory VWM tasks, whereas its enhanced function during visual tasks led to more efficient performance. However, this remains speculative due to the lack of neurophysiological and neuroimaging data in our study. Interestingly, an fMRI study observed significant differences in cortical activity and task performance between normal and ADHD subjects when performing a visual VWM task with auditory distractors [16]. Their results suggest that enhancing left DLPFC function could potentially mitigate the effects of auditory distraction in individuals with ADHD. Combined with our results, this suggests that ADHD individuals, particularly those who are prone to auditory distraction, may perform better on visual VWM tasks in noisy environments following tDCS to the left DLPFC.

Regarding sensory stimulation during task performance, tDCS is considered noninvasive but may cause scalp discomfort. Therefore, in this study, discomfort was assessed using a questionnaire immediately after tDCS stimulation and 30 minutes later in both sham and active conditions. Importantly, no correlation was found between hit rate scores and discomfort scores in the visual VWM task, suggesting that tDCS-induced scalp sensation does not affect task performance. To our knowledge, there are no reports of sensory discomfort during tDCS clearly affecting task performance outcomes. However, some ADHD patients may be hypersensitive to cutaneous sensations [17], and one patient in this study had to discontinue tDCS due to discomfort. It has been reported that the use of a local anesthetic cream, the Eutectic Mixture of Local Anesthetics (EMLA) cream, prior to tDCS stimulation significantly reduced discomfort, particularly with cathode stimulation, which appears to be more painful than anode stimulation [18]. Future studies may need to consider the discomfort of tDCS stimulation for certain participants, such as patients with ADHD.

It is proposed that both medication and neurostimulation, such as tDCS or rTMS, may improve performance by activating neural networks associated with working memory, including the DLPFC. Medications such as methylphenidate and atomoxetine, commonly used for ADHD, have been reported to improve working memory by addressing prefrontal inefficiencies [11] [13] [19]. Previous single-session tDCS studies in ADHD patients targeting the DLPFC are summarized in Table 3 [20]-[26]. As shown in Table 3, most studies show promising results when using tDCS to assess cognitive function in ADHD patients. However, due to the variety of protocols, a definitive method to effectively improve cognitive function in ADHD is still elusive. Regarding electrode placement, anodal stimulation over the left DLPFC is commonly selected in tDCS-ADHD studies, and positive results have also been reported with cathodal placement over the left DLPFC or anodal stimulation over the right DLPFC, as detailed in a recent review [27]. ADHD is a diverse syndrome with heterogeneity extending to symptom subtypes, anatomical differences, cognitive functions, emotional control, intelligence, EEG states, and other factors. In one study, DLPFC current density during a 3-back task in healthy subjects correlated with performance scores, suggesting that individual anatomical differences may contribute to the inconsistent results of tDCS [28]. Therefore, the variability in tDCS results for ADHD is not unexpected. Future tDCS protocols for ADHD may need to be adjusted for individual differences, and Lipka *et al.* have suggested protocol optimization based on computational simulations for more homogeneous patient groups.

Table 3. Previous Studies of tDCS on ADHD with single session targeting DLPFC.

Author (year)	Number of subjects	age range	study design	Anode/Cathode	Amplitude (mA)/ Duration (min)	Cognitive tasks	Outcome
Cosmo *et al.* (2015)	60 (active 30/sham 30) ADHD	18~65	RCT	rt DLPFC/ ltDLPFC	1.0/20	Go/No Go task	No difference between the conditions
Soltaninejad *et al.* (2015)	20 ADHD	15~17	single-blind/ crossover	lt DLPFC/ rtSpraorbital	1.5/15	Go/No to task, Stroop	Increased correct responses in Go of Go/No Go task
				rtSpraorbital/ ltDLPFC			Increased inhibition accuracy of the inhibition stage Go/No Go task
				Sham			
Breitling *et al.* (2016)	21 (ADHD), 21 (HC)	13~17	trial	rt IFG/ pt lt mastoid	1.0/20	Flanker task	Increased interference control in ADHD = in Anodal group
				lt pt mastoid/ rt IFG			
				sham			

Continued

Bandeira *et al.* (2016)	9 (ADHD)	6~16	trial	lt DLPFC/rt supraorbital	2.0/30	TAVIS-3, NEPSY- Ⅱ	improved selected attention (part of the visual attention test), time to check information and the frequency of errors
Cachoeira *et al.* (2017)	17 (ADHD)	18~45	RCT	rt DLPFC/ lt DLPFC	2.0/20	ASRS, Sheehan Disability Scales	ASRS score improved :not significantly, Sheehan Disability Scales lower in active group
Soff *et al.* (2017)	15 (ADHD)	12~16	RCT crossover	lt DLPFC/ Vertex	1.0/20	n-back/fMRI	reduction in inattention and impulsively(FBB-ADHD by parents), reduction in inattention and hyperactivity by QbTest
Sotnikova *et al.* (2017)	16 (ADHD)	12~16	RCT crossover	lt DLPFC/ Vertex	1.0/20	n-back/fMRI	fMRI showed increased activation in the anode area(lt DLPFC, lt premotor cortex, lt supple motor cortex, precuneus), improvement in reaction time
Jacoby and Lavidor (2018)	20 (ADHD), 15 (HC)	19~29	RCT crossover	rt lt DLPFC/1 cm below inion	1.8/20	MOXO-CPT test, PANAS	in ADHD patients, hyper activity (assessed by MOXO-CPT) improved and not in the HC
Allenby *et al.* (2018)	37 (ADHD)	18~65	RCT crossover	lt DLPFC/ rt supraorbital	2.0/19	n-back task, CPT	fewer false positive errors in active tDCS
						stop signal reaction time task	response time, SSRT scores, and effect of false positive errors did not persist at follow-up
Nejati *et al.* (2021)	25 (ADHD)	10 (2.3)* 9 (1.8)* *mean (SD)	RCT crossover	lt DLPFC/ rt DLPFC lt DLPFC/ rt orbitofrontal cortex (OFC)	1.0/15	Go/No-go, Stroop, n-back task, WCST	anodal lt DLPFC improved executive control functions, cathodal lt DLPFC improved inhibitory control, and combined DLPFC-OFC benefited cognitive flexibility/task switching

The present study has several limitations. It has three limitations in common with our previous research [3]: a small sample size, the lack of a cathodic condition group, and a single-blind design in which only the participants were blinded to the conditions, not the experimenters. In addition, the current study with ADHD subjects only partially replicated our previous study with healthy subjects. We did not observe performance gains during tDCS, but we did find improvements after tDCS, which may be due to a possible delay in brain activation in ADHD patients compared to healthy controls. It should also be noted that the two studies used different devices: HD-tDCS previously and a general tDCS device currently. There is a study which reported the differences in post-stimulus task performance between HD-tDCS and general tDCS [2]. Whether our results

are due to the different devices or to the subject characteristics—healthy vs. ADHD requires further investigation.

5. Conclusion

In conclusion, this study provides the first evidence that tDCS can improve visual VWM performance in ADHD patients. We believe that this is consistent with our previous results with healthy subjects, showing that tDCS has a comparable effects on patients, providing important insights into the potential for ADHD treatment.

Acknowledgements

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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