Title: Using tES in Combination with Working Memory Training to Improve EEG Components in Children and Adolescents with ADHD: A Randomized, Active-Controlled Trial

Authors: Moslem Kord[1], Jalil Fath-Abadi[1]*, Shahriar Gharibzadeh[1], Reza Khosrowabadi[1]

1. Shahid Beheshti University, Tehran, Iran.

***Corresponding Author**: Jalil Fath-Abadi, Shahid Beheshti University, Tehran, Iran.

To appear in: **Basic and Clinical Neuroscience**

Received date: 2022/12/08

Revised date: 2023/04/04

Accepted date: 2023/04/10

Please cite this article as:

Kord, M., Fath-Abadi, J., Gharibzadeh, Sh., & Khosrowabadi, R. (In Press). Using tES in Combination with Working Memory Training to Improve EEG Components in Children and Adolescents with ADHD: A Randomized, Active-Controlled Trial. Basic and Clinical Neuroscience. Just Accepted publication Jul. 10, 2023. Doi: http://dx.doi.org/10.32598/bcn.2023.2547.1

DOI: http://dx.doi.org/10.32598/bcn.2023.2547.1

Abstract

Introduction: Transcranial Electrical Stimulation (tES), including tDCS and tRNS, can improve neuropsychological and cognitive deficits in attention deficit hyperactivity disorder (ADHD). Here, we investigated the effectiveness of various tES modes combined with working memory training in children and adolescents with ADHD.

Materials and Methods: Participants in this study consisted of a cohort of 13- to 17-year-old adolescents (N=45)who were diagnosed with ADHD in 2018. They were randomly assigned to three groups: tDCS, tRNS, and the active control (sham). The three groups received five sessions of tES either as an intervention or sham on the left and right prefrontal areas (F3 and F4). In addition to tES, Dual n-Back training was also used in the three groups. Wechsler's Digit Span subtest and resting state EEG data were collected before and after brain stimulation.

Results: Analysis of variance showed significant differences between the groups in some EEG channels (p .05). The absolute power analysis of the brain waves data in the pre-testand post-test phases revealed that the tDCS group had the greatest changes compared to the other two groups and that most changes in the absolute power related to theta, delta and alpha bands were found in the frontal and occipital regions.

Conclusions: Based on the results, we concluded that tES over the prefrontal area induced cortical changes in children and adolescents with ADHD. Thus, it seems that various methods of tES can be used in combination with other common types of intervention to treat ADHD.

Introduction:

Attention-deficit-hyperactivity disorder (ADHD) is a childhood-onset psychiatric disorder characterized by disproportionate levels of developmental inattention, impulsivity, and hyperactivity (American Psychological Association, 2013). The global prevalence rate of thedisorder is 5.3% in children (Mannuzza et al., 2003) and 3.4% in adults (Fayyad et al., 2007).

In spite of various research on this disorder, uncertainty still persists regarding the causes of the disorder, as it is heterogeneous and changes drastically at individual level. Sustained attention, inhibitory control, and executive functions are areas that are often affected. Specifically, Walcott, et al. (2005) showed that response inhibition and working memory are impaired in most people with ADHD . Past research has also shown that deficits in executive functions, in particular working memory deficits, are highly correlated with academic dysfunction (Lauren N. Irwin, at al.2022). Although drug treatments have proved effective against the disorder's main symptoms they have a limited effect on cognitivedeficits , especially executive dysfunction, calling for more research on treatments that target cognitive deficits .

(Lauren N. Irwin, at al.2022).

The concept of working memory refers to the active, top-down process of manipulating information stored in short-term memory and includes functions implicated in the temporal lobe prefrontal cortex that directs behavior by updating, processing, and manipulating the time/sequence of information in short-term memory. (Lara AH, Wallis JD . 2015). Working memory acts as an interface between the environment and long-term memory and is the basis of a set of learning skills, including note-taking, listening comprehension, and following instructions. Working memory also supports functions such as impulse control (Riker et al., 2012), cooperation with others, dynamic decoding of social information (Phillips et al., 2007), and tolerance of delayed gratification (McInnes A et al.,2003) (Aliyari et al., 2018), all of which are impaired in ADHD

In recent years, non-invasive brain stimulation has been introduced as a new treatment method for disorders with a neurocognitive basis. .

According to the specific evidence provided by functional magnetic resonance imaging studies, regions that are closer to the skull surface can be the target of non-invasive brain stimulation interventions.

Although there are many studies showing the effectiveness of direct current stimulation (tDCS) in improving working memory, this effect is still uncertain (H Aliyari et al., 2019). These conflicting results seem to be due to differences in study design, stimulation protocol, and inter-individual differences (Jantz, Katz, & Reuter-Lorenz, 2016).

Findings from several studies have provided support for the effectiveness of electrical stimulation with random noise flow (tRNS) in boosting cognitive functions , including perceptual learning (Fertonani et al., 2011), number discrimination (Cappetti et al., 2013), and mathematics learning (Snowball et al., 2013). Despite this, Brauer et al. (2018) did not report a better performance on a go/no-go task after stimulating the right inferior frontal cortex region using tRNS. In another study, Bruit-Abi et al. (2018) showed that three sessions of tRNSover the left dorsolateral prefrontal cortex reduced participants' reaction time on the go/no-go task, but did not affect their accuracy.

So far, only one study has compared the efficacy of the two electrical stimulation techniques, i.e., tDCS and tRNS, in improving working memory in healthy individuals. Based on the results from this study, three sessions of 10-minute tDCS over the left dorsolateral prefrontal cortex area lead to improved performance on the 2-back test; however, treatment with tRNS did not yeild the same performance outcome, seemingly due to the larger electrode size used in the tRNS treatment (Molkiuni et al., 2011).

In general, several studies have shown that defects in executive functions of inhibitory control and working memory adversely affect self-management behavior, causing behavioral symptoms in people with ADHD. Given the importance of executive dysfunction in ADHD, several studies have attempted to identify the neurological and biological correlates of inhibitory control and working memory deficits in people with ADHD (Zhao and Shang, 2010; Martel et al., 2015; Sonoga-Barkey, Bitsako, and Thompson, 2010).

Considering the significant role of working memory in ADHD and the need to provide new, low-cost and comprehensive treatments for it, in the present study, we aimed to investigate the efficacy of tDCS and tRNS in ameliorating working memory and inhibitory control in individuals with ADHD.

Material and methods

Participants and Apparatus

The statistical sample included 45 adolescents with ADHD, aged 13 to 17. They were randomly selected from 110 ADHD cases referred to Baharan Psychiatric Hospital of Zahedan University of Medical Sciences in the second half of 2018 and 2019. Inclusion criteria were as follows:1- meeting the DSM-5 critera for ADHD DSM-5 along with a diagnosis of ADHD by a psychologist and a psychiatrist, 2- age 13 to 17, 3- willingness to provide informed consent (of both participants and their parents), 4- right-handedness, 5-being a male. Exclusion criteria were: 1- history of seizures and epilepsy, 2- any blow to the head, 3- history of psychiatric disorders, 4- unwillingness to participate at any time during the experiment,5 unbearable discomfort or difficulty when receiving transcranial electrical stimulation.

Participants were randomly assigned to three groups, each including 15 members: the tDCS group, the tRNS group, and the control group. In order to ensure that participants in the control group experience the same effect as participants in the tDCS and tRNS groups, we applied sham transcranial stimulation to participants in the control group. Each person in the experimental groups received 5 sessions of electrical stimulation with an interval of 24 hours between each session. EEG recording and cognitive assessment were done before the intervention, immediately after the intervention, and one week after the intervention.

Measures:

Questionnaire to measure the side effects of transcranial stimulation with direct electric current

This questionnaire includes 7 items, each referring to a particular effect reported to be possibly experienced by those receiving tDCS. They include headache, dizziness, heartburn, itchy head, feeling confused, drowsiness, and nausea. An item titled "Other" was also added to ensure participants could still report how they felt even if none of the items on the questionnaire matched their experience with tDCS (Najati et al.,).

Cognitive rehabilitation task

In this study and in line with previous research (e.g.Westwood et al., 2022) , the N-back cognitive rehabilitation task was used along with transcranial stimulation to increase working memory capacity. In this task, a sequence of stimuli is displayed on the screen one after another and the participants are required to compare the current stimulus with the one that appeared n-trials back in the sequence and press the response key if they match.

Dual n-back is a variation of the task in which two types of stimuli (visual-spatial and auditory) are presented simultaniously (Heinzel et al., 2017). Researches in the field of neurology have shown that cognitive training using dual N-back often increases brain activity in the left and right prefrontal areas, especially the left posterior-lateral area which is implicated in executive functions of woring memory including updating, Shifting and inhibition. This tool has been used in many studies and its effectiveness has been shown (Haq Nazari et al., 1401).

Digit span test

In the direct digit span memory test, lists of 3 to 9 digits are orally presented, each at a time, and participants are asked to repeat the digits in exactly the same order they hear them. In the reverse digit span memory test, however, lists of 2 to 8 digits are presented, and participants are required to repeat the digits on each list in the reverse order. Aminzadeh and Hasanabadi have reported the a reliability score of 0.8 and 0.68 for the direct and reverse versions of the task, respectively. Gathercole et al., () reported a test-retest reliability score of 0.81 for the direct digit memory test and Thompson and Gathercole () reported a test-retest reliability score of 0.71 for the reverse digit memory test. Also, he calculated the reliability model of the memory of direct and reverse digits through retesting, respectively, 0.84 and 0.60. (Abadi, 1374) (Hamed Aliyari et al., 2019).

EEG data recording and analysis

EEG data were collected using a 21-channel Contact instrumentpsych lab EEG amplifier (http://www.medinateb.com) The electrode impedances were kept below 5 kOhm. The EEG signals were recorded with a sampling frequency of 500 Hz. The electrode placed at the Right earlobe served as the reference. Moreover, the electrode on the left mastoid region was applied as the ground. Subsequently, using EEGLAB toolbox, we performed a standard preprocessing including band-pass filtering (1-40 Hz), running ICA, and reducing sampling frequency to 256 Hz to remove noise and artifacts from EEG data.

Based on their absolute power, the pre-processed data were divided into 9 components: Delta (1-4 Hz), Theta (4-8 Hz), Alpha (8-13 Hz), Alpha1(8-10 Hz), Alpha2(11-13 Hz), Beta (13-21 Hz), Beta1(13-21 Hz), Beta2(19-30 Hz).), and Gamma (30-40). The data were analyzed using a two - way ANOVA with frequency channel as within-group and stimulation type as between-group factors. T-test was applied to explore statistically significant differences between group means (Schomer and da Silva, 2012) (Shabani et al.).

Transcranial electrical stimulation device (NEUROSTIM2)

This device was launched by Research & Development team of Medina Teb company in 2015. This device has two completely separate channels and is capable of applying a variety of electrical stimulation patterns with the highest quality. NeuroStim2 has two separate channels that are electrically isolated from each other and each channel can be set independently of the other to apply separate stimulations.

Transcranial brain stimulation is provided in the form of two electrodes that are placed on the target areas on the surface of the head with a weak current of 1 to 2 mA. After about 5 minutes, this weak current passes through the surface of the skull and affects the activity of nerve cells in the area where the electrodes are placed and the subcortical areas connected to them (Weber et al., 2014).

Procedure

Participants were first homogenized based on results from the Connors questionnaire (parent and teacher forms), their performance on the working memory scale of the Wechsler test (digit span, number-letter sequence) and their age. They were, then, randomly assigned to one of the three groups: the tDCS, the tRNS and sham control group Before intervention, resting state EEG recording was done and the digit span test test was administerded. Participants received 5 sessions of electrical stimulation with an interval of 24 hours between each session. To explore the transfer effect of the intervention, behavioral and psychological tests (Digit span task) were administered one week after the end of the intervention.

Results:

Behavioral data: Digit span test

Descriptive statistics of the digit span test scores a are provided in Table 1.

Table 1. Descriptive indices of subjects' scores in digit span task based on group membership and evaluation stages

the level		**Group (tDCS)**	**Group(tRNS)**	**control group**
		mean(standard deviation)	mean(standard deviation)	mean(standard deviation)
Direct digit expansion (Wechsler)	Pre-test	7.533(0/833)	7.800(0.744)	7.466(0.743)
Inverse digit expansion (Wechsler)	Post-test	10.466(0/915)	9.400(1.183)	7.800(1.207)
	Follow up	10.133(1.125)	8.400(0.736)	8.00(0.925)
Direct digit expansion (Wechsler)	Pre-test	5.933(0.703)	5.800(0.861)	5.866(0.833)
Inverse digit expansion (Wechsler)	Post-test	11.00(1.690)	7.800(1.014)	6.066(0.883)
	Follow up	9.800(1.207)	7.200(1.014)	6.400(0.736)

A mixed-design analysis of variance was applied to mean scores on the digit span test to investigate the effectiveness of tDCSandtRNS on working memory functioning in adolescents with ADHD . The results are shown in Table 2.

Table 2 Summary of the results of analysis of variance mixed with within-group and between-group factors for working memory variable

Variable	**factors**	**Sources Change**	**sum of squares**	**DF**	**mean square**	**F**	**P**	**Effect size**
Direct digit expansion (Wechsler)	In-group factor	levels	64.84	2	232.44	47.91	0.001	0.53
		Stage*group interaction	34.31	4	8.57	12.67	0.001	0.53
		Error	56.84	84	0.67			
	intergroup factor	group	59.24	2	29.62	21.41	0.001	0.50
		Error	58.08	42	1.38			
Inverse digit expansion (Wechsler)	In-group factor	levels	147.65	2	73.83	78.92	0.001	0.65
		Stage*group interaction	96.43	4	24.10	25.77	0.001	0.65
		Error	78.57	84	0.93			
	intergroup factor	group	186.41	2	93.30	69.62	0.001	0.76
		Error	56.22	42	1.33			

As shown in Table 2, the F value observed for the effect of the intervention stage (pretest, posttest, and follow-up) was significant at the 0.01 level for all components of working memory (direct and reverse digit span). As a result, there is a significant difference between scores on all components of working memory at pretest, posttest and 1-week follow-up. Regarding the between-group factor of stimulation type (tDCS, tRNS and sham stimulation), the analysis revealed statistical significance between mean scores on all components of working memory ($p<0.01$). The interaction effect between intervention stage and stimulation type was also found to be significant for all components of working memory ($p<0.001$).

The results of Bonferroni's post hoc test to compare the pairwise differences between intervention stages , and Tukey's post hoc test to compare the pairwise differences between stimulation types are shown in Tables 3 and 4.

Table 3. Pairwise comparisons of mean scores on the direct digit span test in tDCS, tRNS and sham control groups at pretest, poettest and follow-up.

levels	**Groups**		**Difference of means**	**Standard deviation error**	**Significant**
Pre-test	tDCS	tRNS	-0.267	0.287	0.357
	tDCS	Control	0.067	0.287	0.817
	tRNS	Control	0.333	0.287	0.251
Post-test	tDCS	tRNS	1.067	0.405	0.012
	tDCS	Control	2.667	0.405	0.001
	tRNS	Control	1.600	0.405	0.001
Follow up	tDCS	tRNS	1.733	0.344	0.001
	tDCS	Control	2.133	0.344	0.001
	tRNS	Control	0.400	0.344	0.252

As depicted in Table 3, no significant differences were observed between tDCS, tRNS and sham control at pretest ($p>0.05$). At posttest, however, participants in the tDCS and the tRNS groups achieved significantly higher scores than those in the sham control group ($p<0.001$). The difference between scores in the tDCS and the tRNS groups was also statistically significant at posttest ($p<0.001$), with the tDCS group getting better scores. At follow-up , the tDCS group had significantly higher scores than both the tRNS and the sham control group. However, no significant difference was found between the tRNS group and the control group ($p>0.05$).

Table 4. Pairwise comparisons of mean scores on the direct digit span test at pretest, posttest and follow-up in tDCS, tRNS and sham control groups

levels	Levels		Difference of means	Standard deviation error	Significant
tDCS	Pre-test	Post-test	-2.933	0.313	0.001
	Pre-test	Follow up	-2.600	0.284	0.001
	Post-test	Follow up	0.333	0.303	0.277
tRNS	Pre-test	Post-test	-1.600	0.313	0.001
	Pre-test	Follow up	-0.600	0.284	0.041
	Post-test	Follow up	1.00	0.303	0.002
Control	Pre-test	Post-test	-.0.333	0.313	0.294
	Pre-test	Follow up	-0.533	0.284	0.068
	Post-test	Follow up	-0.200	0.303	0.512

Table 5. Pairwise comparisons of mean scores on the reverse digit span test in tDCS, tRNS and sham control groups at pretest, poettest and follow-up.

levels	Groups		Difference of means	Standard deviation error	Significant
Pre-test	tDCS	tRNS	0.133	0.293	0.652
	tDCS	Control	0.067	0.293	0.821
	tRNS	Control	-0.067	-0.293	0.821
Post-test	tDCS	tRNS	3.200	0.455	0.001
	tDCS	Control	4.933	0.455	0.001
	tRNS	Control	1.733	0.455	0.001
Follow up	tDCS	tRNS	2.600	0.367	0.001
	tDCS	Control	3.400	0.367	0.001
	tRNS	Control	0.800	0.367	0.035

As revealed in Table 5, there were no significant differences between reverse digit span scores in tDCS, tRNS and sham control groups at pretest scores ($p>0.05$). At posttest and follow-up, however, a significant difference was observed between the groups: participants in the tDCS and tRNS groups got dignificantly higher scores than those in the control group ($p<0.001$). In addition, the results showed that the tDCS group performed significantly better than the tRNS group on the reverse digit span test($p<0.001$).

Table 6 Pairwise comparisons of mean scores on the reverse digit span test at pretest, posttest and follow-up in tDCS, tRNS and sham control groups

levels	levels		Difference of means	Standard deviation error	Significant
tDCS	Pre-test	Post-test	-5.067	0.327	0.001
	Pre-test	Follow up	-3.867	0.311	0.001
	Post-test	Follow up	1.200	0.413	0.006
tRNS	Pre-test	Post-test	-2.00	0.327	0.001
	Pre-test	Follow up	-1.400	0.311	0.001
	Post-test	Follow up	0.600	0.413	0.153
Control	Pre-test	Post-test	-0.200	0.327	0.544
	Pre-test	Follow up	-0.533	0.311	0.094
	Post-test	Follow up	-0.333	0.413	0.424

Results from pairwise analysis on mean scores on the the reverse digit span test (Table 6)showed a significant difference between the pretest and posttest ($p<0.001$) and pre-test and follow-up stages in the tDCS group ($p<0.001$); However, no significant difference was found between the posttest and follow-up ($p>0.05$). In the tRNS group, the results showed significant differences at pretest, posttest and follow-up ($p<0.05$). In the control group, no significant differences were found between different intervention stages ($p>0.05$).

Data analysis of brain signals (EEG)

This study analyzed brain wave patterns over time. Different scores are presented at different time points per second for ten brain wave rhythms. These figures facilitate understanding of the changes in the participants' brain waves during the treatment period. The pattern of brain waves was examined in the tRNS, the tDCS and the sham control group.The results are presented in table 7.

Table7 Results of hree-way ANOVA on absolute power values with factors channel, frequency, and group

	Sum Sq.	DF	Mean sq.	F	Prop>F
Channel	3.24559e+12	20	1.62279e+11	0.26	0.9996
Frequency	9.64548e+13	9	1.07172e+13	17.32	0
Group	1.97632e+14	2	9.88161e+13	159.7	0
Channel*Frequency	4.05079e+12	180	2.25044e+11	0.04	1
Channel * Group	7.65507e+12	40	1.91377e+11	0.31	1
Frequency *group	2.15581e+14	18	1.19767e+12	19.36	0
Channel* Frequency* Group	9.37873e+12	360	2.6052e+10	0.04	1
Error	5.45743e+15	8820	6.1873e+11	------	-------
Total	5.9914e+15	9449	------------	---------	-------

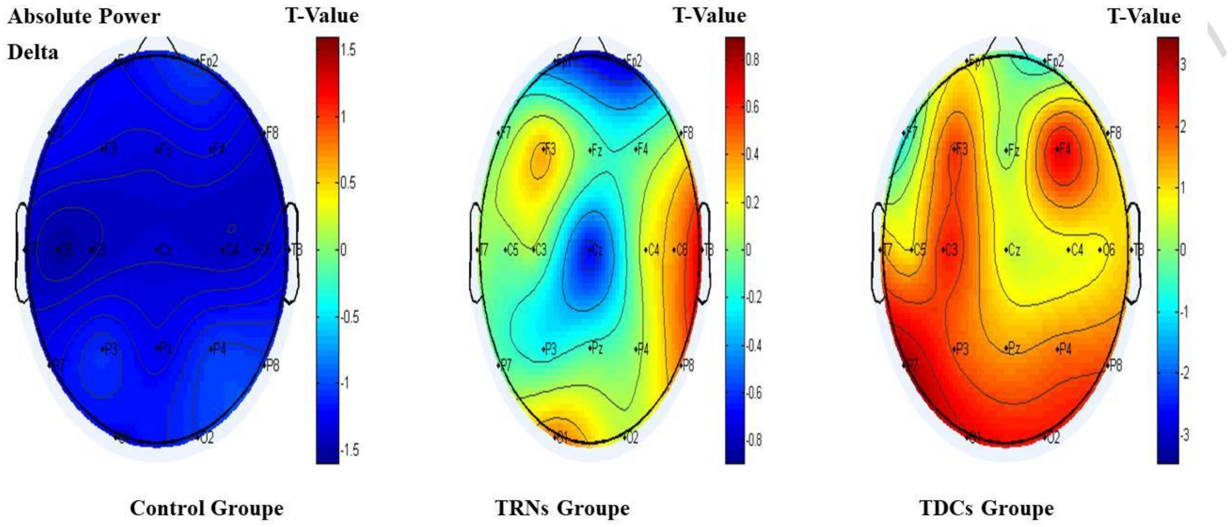
Table 7 outlines the results of a three-way analysis of variance (ANOVA) for sbsolute power values using the factors channel, frequency and group. Asignificant difference was found in the group and frequency factors, and based on this, subsequent t-tests were taken. Table No.7 The intra-group post hoc t-test for comparing the pre-test and post-test shows the absolute power in each group.

Table 8 post-hoc t-test on brainwave channels and components

Channel_No	abs_Power_delta		abs_Power_theta		abs_Power_alpha		abs_Power_alpha1		abs_Power_alpha2		abs_Power_beta		abs_Power_beta1		abs_Power_beta2		abs_Power_gamma		abs_Power_total	
	T	P	T	P	T	P	T	P	T	P	T	P	T	P	T	P	T	P	T	P
FP1							1.87493	0.081002									-4.11152	0.000337		
FP2																			2.46575	0.019916
F7							1.81044	0.090975									-3.07144	0.005983		
F3	2.16938	0.047072	3.07144	0.005983	2.3447	0.032389					2.4047	0.022399	3.085463	0.005107			2.65756	2.66E-02	2.258687	0.046586
FZ																				
F4	2.65354	0.036584	3.365486	0.004869	2.28174	0.037727	2.10343	0.053054	3.60142	0.002764	2.94834	0.010015	2.43447	0.027718	2.18278	0.046121	2.41424	0.028714	2.38048	0.03119
F8																	-2.01937	0.05391		
T7							2.16938	0.047072												
C5							2.00876	0.062881												
C3	2.3447	0.032389	2.6369	0.018393			2.28174	0.037727			2.5656	0.017857	2.38233	0.027567	2.10644	0.047354	-2.72797	0.011117	2.38803	0.027067
Cz							2.10343	0.053054												
C4																				
C6																				
T8																	-4.5341	0.000122		
P7	3.23275	0.004839	3.48246	0.003356	3.7375	0.001925	3.60142	0.002764	2.4193	0.02505	3.26547	0.003962	3.73347	0.001678	2.35182	0.028198			3.81239	0.001388
P3	2.03019	0.055954	2.95672	0.00996	2.54536	0.02235	2.94834	0.010015			2.49975	0.02255	2.87124	0.01114			-4.8029	5.39E-05	2.63704	0.017643
Pz			2.44445	0.027482			2.43447	0.027718											2.01078	0.060675
P4			2.0897	0.054762			2.18278	0.046121									-5.33123	5.87E-05		
P8	2.04471	0.058376	2.28615	0.037979			2.46563	0.026977												
O1	2.75171	0.013343	2.69057	0.017101			2.41424	0.028714			2.3097	0.034373	2.30417	0.034607			-2.31437	0.028889	2.21395	0.042485
O2	2.42747	0.025768	2.64424	0.019175			2.38048	0.03119			2.09355	0.054673							2.22341	0.043093

In the following, the within-group post hoc t-test was done to compare absolute power values at pretest and posttest in each group. Significant channels in each group are shown in Table 8.

Figure 1 . The difference in absolute delta power in tDCS, tRNS and sham control groups.



The brain map diagram of the difference in absolute delta power between the three groupsis shown in Figure 1. In this diagram, the closer the color of the brain channels to blue, the higher the absolute power of the wave. As can be seen in the figure above, the temporal areas in the tRNS group and the occipital and frontal areas in the tDCS group had the most activity in absolute delta power.

The pattern of brain waves in the tRNS group was different from that in the tDCS and control group. A mixed design two-way repeated measure analysis of variance (Two-way ANOVA 2*3) was applied to channel*frequency and group.

	Sum Sq.	DF	Mean sq.	F	Prop>F
Channel	0.003	20	0.00015	0.09	1
Frequency	0.5258	9	0.065772	38.99	0
Group	0.0073	2	0.00367	2.18	0.13
Channel*Frequency	0.1166	160	0.00073	0.43	1
Channel * Group	0.0068	40	0.00017	0.1	1
Frequency *group	0.2025	16	0.01265	7.51	0
Channel* Frequency* Group	0.2822	320	0.00088	0.52	1
Error	13.3812	7938	0.00169	------	-------
Total	14.5254	8504	------------	---------	-------

As can be seen in Table 9, there is a significant difference between the group and the channel. To gain a better understanding of the intergroup significance, a t-test was performed between groups in different frequencies and channels.

According to Table 10, the most significant effect has occurred in the absolute power and the difference in theta and delta frequencies.

Table 10. Comparison between tDCS and control groups in absolute power at different frequencies.

Channel_No	abs_Power_delta		abs_Power_theta		abs_Power_alpha		abs_Power_beta		abs_Power_beta1		abs_Power_beta2		abs_Power_gamma		abs_Power_total	
	T	P	T	P	T	P	T	P	T	P	T	P	T	P	T	P
F3	2.915426	0.008461	4.14478	0.00147	2.89247	0.012543	2.44678	0.027856					3.14595	0.00475	2.32145	0.033214
F4	2.24768	0.043568	3.56742	0.003472			2.80145	0.011476					3.15478	0.006532	2.40975	0.02647
F8			2.58642	0.017564												
T7			2.35658	0.032548												
Cz			2.51436	0.025421												
T8			2.41458	0.028745												
Pz	2.20356	0.045866	3.24156	0.004325			2.15564	0.043252								

Figure 2. The difference in absolute theta power in the control and tRNSgroups

Figure 2. tata frequency comparison in two groups and its difference. As can be seen, the absolute power in the central areas was significantly different in the two groups, and in the final comparison of the frontal, central, and occipital channels, there is a difference.

Discussion

In the current study, we aimed to see how an intervention program of brain stimulation along with working memory training could help adolescents with ADHD enhance their working memory performance. Further, we sought to compare the efficacy of two different stimulation techniques, i.e., tDCS and tRNS in boosting working memory. The results indicated the effectiveness of electrical stimulation (TDCs) on working memory. In the following, we will discuss these results in detail.

Promising findings are obtained from studies on the effectiveness of tDCSin the treatment ofADHD. To date, eight studies have been conducted using tDCS in children and adolescents with ADHD: five randomized, double-blind, sham-controlled trials (Pern-Christensen et al., 2014; Munz et al., 2015; Nejati et al., 2017; Saf et al., 2017; Sotnikova et al., 2017) (Moein et al., 2022), two randomized, single-blind, sham-controlled trials (Sultaninejad et al., 2015; Breitling et al., 2016) and an open-label randomized controlled trial with matching participants (Bandira et al., 2016). These studies have mainly focused on memory consolidation, working memory, and inhibitory control using applying different tDCS protocols applied over the posterior lateral prefrontal cortex .

In a pilot study, Bandira et al. (2016) investigated the effects of applying anode stimulation on the left posterolateral prefrontal cortex in a sample of 9 children and adolescents with ADHD. The anode electrode was placed on the F3 area and the cathode electrode on the upper area of the right eye. Stimulation was performed daily in five consecutive 30-min sessions. During each session, stimulation was performed at an intensity of 2 mA (except for the first and last minute of stimulation, when the current was reduced to 1 mA). Importantly, in order to activate the posterolateral prefrontal cortex, the participants were asked to participate in a card-matching game by matching pictures and making connections between them . The effects of anodal stimulation on several executive functions, including working memory and attention (assessed with the digit span subtest of the Wechsler III), inhibitory control (assessed with of the Nepsey II subtest), visual working memory and visual attention (assessed with the chair test), and visual attention (assessed with attention task) were explored.

These tests were performed before the first and after the last stimulation session. In addition, at the end of the last session, parents were asked to evaluate their children’s overall clinical improvement during the treatmentthe treatment process. At the end of each stimulation session, participants were asked about any side effects during or after treatment. Mild and moderate levels of headache, neck pain, itching, burning, and tingling sensation at the location of the anode, local redness, and drowsiness were often observed as side effects. In addition, a mild level of shock was also reported. Probably, the higher intensity of stimulation, compared to the 1-mA current mainly used in other studies , was the cause of the discomfort. Overall, improvements were also observed in parents' reports, with the exception of worsening behavior in one child (the child also had oppositional defiant disorder). notably, the absence of a sham control group does not allow for a thorough evaluation of of the efficacy of the treatment. Furthermore, as both participants and parents were aware of the stimulation conditions, the occurrence of placebo effects cannot be excluded (Shabani et al., 2022).

Unlike the previous study, Skaff et al. (2017) used a double-blind randomized crossover design with a sham control group to evaluate the effects of anode stimulation over the left posterolateral prefrontal cortex on working memory and the clinical course of ADHD . The logical reason for using anode stimulation in this brain region with the aim of improving working memory was to observe the decrease in the activity of this region in people with ADHD and the possibility of improving working memory performance in healthy participants by stimulating the anode of the left posterolateral prefrontal cortex. Fifteen teenagers withADHD participated in the study. Each participant received either anode or sham stimulation for 5 days with a two-week interval between the two treatment sessions. A One-milliamp current was applied for either 20 minutes (anode stimulation) or 23 seconds (sham stimulation) using the anode electrode in the region (F3) and the cathode electrode on the top of the head (Cz). Electrical stimulation with direct current was applied while participants performed a computer task based on the N-back working memory paradigm. In the evaluation session, the assessment of participants' performance on the tasks was combined with the amount of motor activity to evaluate the main symptoms, i.e., attention, hyperactivity, and impulsivity. In addition, working memory performance and parents' reports of the severity of symptoms were also evaluated at the beginning of the stimulation, on the fifth day of stimulation, and one week after the end of stimulation. All participants completed the test and the protocol was well tolerated by the participants. Tingling and slight itching under electrodes were the most common side effects. Only one participant developed a headache. Anodal stimulation improved symptoms of ADHD compared to sham stimulation. Compared to the baseline, a long-term reduction in inattention and hyperactivity was observed 7 days after the end of the treatment,, with no significant effect on impulsivity. Interestingly, in another study (Sotnikova et al., 2017), the authors reported the results of a functional magnetic resonance imaging study performed during the first session of anodic or sham stimulation while doing the n-back task. Compared to sham stimulation, anode stimulation stimulated more of the sub-electrode region, i.e., the left posterolateral prefrontal cortex, as well as ipsilateral Barrington nucleus, sensorimotor area, and precuneus regions, suggesting that stimulation of the left posterolateral prefrontal cortex likely affects the entire network. Neurologically related to working memory function is effective. However, the limited sample size of these studies only confirmed that transcranial stimulation with direct current can be used to reduce the symptoms of people withADHD , and more studies are still needed to confirm the effectiveness of this method.

Non-pharmacological treatment options using non-invasive brain stimulation will be useful in this regard. One important reason for the use of non-invasive brain stimulation in the treatment of ADHD comes from studies showing that abnormal excitability of the cerebral cortex in ADHDis due to reduced motor inhibition (Buchman et al., 2003), as well as studies showing that two groups of ADHD drugs work by altering cortical excitability (Gilbert et al., 2006). Therefore, considering that non-invasive brain stimulation can affect the excitability of the cerebral cortex, it can be suggested as an effective alternative for drugs. Behavioral deficits in patients with ADHDcan be attributed to defective inhibitory processes that lead to dysfunctional executive control, impulsive and hyperactive behavior (inhibition-based model), or deficits in motivation and reward processing [functional disorder model (Sepda et al. , 2000; Sonoga-Barke, 2005)]

It is suggested that for future research, other cognitive variables be investigated in different age groups not only in ADHD, but also in other (developmental) disorders. Moreover, using measurement tools such as FMRI in future research can help better discover the neural foundations of disorders.

One of the limitations of this research is the lack of access to female participants.

Conclusion

This study evidenced the efficacy of electrical stimulation of prefrontal areas in improving working memory in adolescents with ADHD. The results showed that tDCS had a beneficial effect on working memory performance in the early stages. This effect had been identified with theta/beta ratio and other predictors previously. Our study showed that tDCS and tRNS affect working memory differently, with tDCS stimulation being more effective. There is evidence that multi-session tDCS intervention improves memory performance and that these effects are maintained for weeks to months after stimulation. This suggests that repeated application of tDCS can improve neural plasticity during stimulation.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub.

Aron, A. R. (2011). From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. *Biological psychiatry*, *69*(12), e55-e68.

Baddeley, A., Chincotta, D., & Adlam, A. (2001). Working memory and the control of action: evidence from task switching. *Journal of experimental psychology: General*, *130*(4), 641.

Blair, C., & Ursache, A. (2011). A bidirectional model of executive functions and self-regulation. *Handbook of self-regulation: Research, theory, and applications*, *2*, 300-320.

Chaieb, L., Kovacs, G., Cziraki, C., Greenlee, M., Paulus, W., & Antal, A. (2009). Short-duration transcranial random noise stimulation induces blood oxygenation level dependent response attenuation in the human motor cortex. *Experimental brain research*, *198*(4), 439-444.

Chambers, C. D., Bellgrove, M. A., Stokes, M. G., Henderson, T. R., Garavan, H., Robertson, I. H., ... & Mattingley, J. B. (2006). Executive "brake failure" following deactivation of human frontal lobe. *Journal of cognitive neuroscience*, *18*(3), 444-455.

Coffman, B. A., Clark, V. P., & Parasuraman, R. (2014). Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. *Neuroimage*, *85*, 895-908.

Eisenberg, N., Spinrad, T. L., & Eggum, N. D. (2010). Emotion-related self-regulation and its relation to children's maladjustment. *Annual review of clinical psychology*, *6*, 495-525.

Fayyad, J., De Graaf, R., Kessler, R., Alonso, J., Angermeyer, M., Demyttenaere, K., & Lepine, J. P. (2007). Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. *The British Journal of Psychiatry*, *190*(5), 402-409.

Herpertz, S. C., Wenning, B., Mueller, B., Qunaibi, M., Sass, H., & Herpertz-Dahlmann, B. (2001). Psychophysiological responses in ADHD boys with and without conduct disorder: implications for adult antisocial behavior. *Journal of the American Academy of Child & Adolescent Psychiatry*, *40*(10), 1222-1230.

McInnes A, Humphries T, Hogg-Johnson S, Tannock R. Listening comprehension and working memory are impaired in attention-deficit hyperactivity disorder irrespective of language impairment. J Abnorm Child Psychol. 2003 Aug;31(4):427-43. doi: 10.1023/a:1023895602957. PMID: 12831231.

Mannuzza, S., Klein, R. G., & Moulton III, J. L. (2003). Persistence of attention-deficit/hyperactivity disorder into adulthood: what have we learned from the prospective follow-up studies? *Journal of attention disorders*, *7*(2), 93-100.

Mazaheri, A., Fassbender, C., Coffey-Corina, S., Hartanto, T. A., Schweitzer, J. B., & Mangun, G. R. (2014). Differential oscillatory electroencephalogram between attention-deficit/hyperactivity disorder subtypes and typically developing adolescents. *Biological psychiatry*, *76*(5), 422-429.

Mazaheri, A., Nieuwenhuis, I. L., Van Dijk, H., & Jensen, O. (2009). Prestimulus alpha and mu activity predicts failure to inhibit motor responses. *Human brain mapping*, *30*(6), 1791-1800

Mrug S, Hoza B, Gerdes A (2001) Children with attention-deficit/hyperactivity disorder: peer relationships and peer-oriented interventions. In: Nangle DW, Erdley CA (eds) The role of friendship in psychological adjustment. Jossey-Bass, San Francisco, pp 51–77

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of physiology*, *527*(3), 633-639.

Posner, M. I., Rothbart, M. K., & Rueda, M. R. (2013). Developing attention and selfregulation in infancy and childhood. *Comprehensive developmental neuroscience: Neural circuit development and function in the healthy and diseased brain*, 395-411.

Rubia, K. (2018). fMRI-Based Neurotherapies for ADHD. *The ADHD Report*, *26*(6), 1-11.

Saturnino, G. B., Antunes, A., & Thielscher, A. (2015). On the importance of electrode parameters for shaping electric field patterns generated by tDCS. *Neuroimage*, *120*, 25-35.

Walcott, C. M., & Landau, S. (2004). The relation between disinhibition and emotion regulation in boys with attention deficit hyperactivity disorder. *Journal of clinical child and adolescent psychology*, *33*(4), 772-782.

Weber, M. J., Messing, S. B., Rao, H., Detre, J. A., & Thompson- Schill, S. L. (2014). Prefrontal transcranial direct current stimulation alters activation and connectivity in cortical and subcortical reward systems: A tDCS- fMRI study. *Human brain mapping*, *35*(8), 3673-3686.

Westwood, S. J., Bozhilova, N., Criaud, M., Lam, S. L., Lukito, S., Wallace-Hanlon, S., ... & Rubia, K. (2022). The effect of transcranial direct current stimulation (tDCS) combined with cognitive training on EEG spectral power in adolescent boys with ADHD: A double-blind, randomized, sham-controlled trial. IBRO neuroscience reports, 12, 55-64

Willcutt, E. G., Doyle, A. E., Nigg, J. T., Faraone, S. V., & Pennington, B. F. (2005). Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Biological psychiatry*, *57*(11), 1336-1346.

Irwin LN, Soto EF, Chan ESM, Miller CE, Carrington-Forde S, Groves NB, Kofler MJ. Activities of daily living and working memory in pediatric attention-deficit/hyperactivity disorder (ADHD). Child Neuropsychol. 2021 May;27(4):468-490. doi: 10.1080/09297049.2020.1866521. Epub 2021 Jan 18. PMID: 33459154; PMCID: PMC8035253.

Haqnazari, F., Nejati, V., Pouretemad, H. (2022). Effectiveness of Computerized Working Memory Training on Sustained Attention and Working Memory of Male School Students. The Scientific Journal of Rehabilitation Medicine, 11(1), 2-13. [Persian]

Holmes J, Hilton KA, Place M, Alloway TP, Elliott JG, Gathercole SE. Children with low working memory and children with ADHD: same or different? Front Hum Neurosci. 2014 Dec 9;8:976. doi: 10.3389/fnhum.2014.00976. PMID: 25538599; PMCID: PMC4260512.

Lara, A. H., & Wallis, J. D. (2015). The role of prefrontal cortex in working memory: A mini review. Frontiers in Systems Neuroscience, 9, Article 173. https://doi.org/10.3389/fnsys.2015.00173.

McInnes A, Humphries T, Hogg-Johnson S, Tannock R. Listening comprehension and working memory are impaired in attention-deficit hyperactivity disorder irrespective of language impairment. J Abnorm Child Psychol. 2003 Aug;31(4):427-43. doi: 10.1023/a:1023895602957. PMID: 12831231.

Phillips SM, Moore DR, Tang JE. A critical examination of dietary protein requirements, benefits, and excesses in athletes. Int J Sport Nutr Exerc Metab. 2007 Aug;17 Suppl:S58-76. doi: 10.1123/ijsnem.17.s1.s58. PMID: 18577776.

Aliyari, H., Hosseinian, S., Sahraei, H., & Menhaj, M. (2019). Effect of proximity to high-voltage fields: Results of the neural network model and experimental model with macaques. *International Journal of Environmental Science and Technology*, *16*, 4315-4326.

Aliyari, H., Hosseinian, S. H., Menhaj, M. B., & Sahraei, H. (2019). Analysis of the effects of high-voltage transmission line on human stress and attention through electroencephalography (EEG). *Iranian Journal of Science and Technology, Transactions of Electrical Engineering,* *43*, 211-218.

Aliyari, H., Sahraei, H., Daliri, M. R., Minaei-Bidgoli, B., Kazemi, M., Agaei, H., Sahraei, M., Hosseini, S. M. A. S., Hadipour, M. M., & Mohammadi, M. (2018). The beneficial or harmful effects of computer game stress on cognitive functions of players. *Basic and clinical neuroscience*, *9*(3), 177.

Moein, N., Rostami, R., Mohamadi, R., Zomorrodi, R., Nitsche, M., Ostadi, A., & Shabani, M. (2022). Electrophysiological correlates of stuttering severity: An ERP study. *Journal of Clinical Neuroscience*, *101*, 80-88.

Shabani, M., Salehi, J., & Khosrowabadi, R. Gender Effect on Neural Correlates of Autobiographical False Memories for Brand Images. *Basic and clinical neuroscience*, 0-0.

Shabani, M., Salehi, J., & Khosrowabadi, R. (2022). Comparing Autobiographical Brand Images and Neutral Images Regarding False Memory Formation. *Basic and clinical neuroscience*, *13*(4), 489-500.