RESEARCH

The effect of bilateral tDCS over dorsolateral prefrontal cortex on the cognitive abilities of men with opioid use disorder under methadone therapy: A sham-controlled clinical trial

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Abstract

Background/aim: Opioid use disorder (OUD) can have negative impact on cognitive functions. This study aims to evaluate the effect of bilateral transcranial direct-current stimulation (tDCS) over the right/left dorsolateral prefrontal cortex (DLPFC) on the cognitive abilities of OUD men.

Methods: This study is a double-blind sham-controlled randomized clinical trial with a pretest/posttest design. Participants were 31 men with OUD living in Zanjan, Iran, assigned to three groups of left anode/right cathode tDCS, right anode/left cathode tDCS, and sham tDCS. The two active groups received tDCS (2 mA) at 10 sessions each for 10–20 min. The Cognitive Abilities Questionnaire (CAQ) in Persian was used to measure their cognitive abilities before and after intervention. Collected data were analyzed in SPSS v.22 software.

Results: Bilateral DLPFC stimulation resulted in a significant improvement in cognitive flexibility, planning, decision making, inhibitory control/selective attention, and memory of patients in the two active tDCS groups, while the sham tDCS had no significant effect on their cognitive abilities.

Conclusion: Bilateral tDCS over DLPFC, as an effective and complementary treatment, can improve the cognitive abilities of men with OUD.

Trial registration: This study is a double-blind sham-controlled clinical trial (Parallel, IRCT20170513033946N5. Registered 19 Jan 2019, https://en.irct.ir/trial/36081).

Keywords: Transcranial Direct-Current Stimulation, Dorsolateral prefrontal cortex, Cognitive function, Opioid use

Introduction

Opioid Use Disorder (OUD) is a chronic and relapsing disease that imposes heavy costs on patients and society [1]. It includes an overpowering desire to obtain and take opioids, such as heroin, morphine, and opium despite social and professional consequences. OUD causes various medical complications, opioid craving, increased opioid use, and withdrawal symptoms [2]. Nearly, 3 million people in the US and nearly 16 million people worldwide have current or past OUD [3, 4], and the total OUD-related costs are estimated at 55.7 billion dollars annually [5]. In Iran, a study reported that the 12-month prevalence of OUD among 15–64-year-old people in 2011

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was 2.4%, where the most widely used drug was opium. Moreover, its rate was higher in men than in women [6]. The etiology of OUD is multifaceted. It is influenced by biologic, environmental, genetic, and psychosocial factors. A notable side effect of OUD is its negative impact on cognitive functioning which refers to multiple mental abilities, including inhibitory control, remembering, decision making, planning, cognitive flexibility, and attention [7]. Substance abuse can cause impairments in these abilities [8–12]. Cognitive flexibility is described as the ability of the mind to switch between two different subjects and the ability to think about multiple concepts simultaneously [13]. This ability allows the individual to adapt to different situations quickly and efficiently. Chronic opioid use is associated with deficits in cognitive flexibility [14]. Planning ability is an important cognitive skill that forms our executive functions. It is defined as ability to "think about the future" or mentally anticipate the right way to carry-out a task or reach a specific goal [15]. Another cognitive ability that is impaired by substance abuse is the decision-making ability. It is a process, where a decision maker selects at least one option from among a set of possible options. This process seems to be easy, but it is complicated and somehow difficult, because the decision sometimes is a choice between conflicting values. Studies show that opioid users prefer short-term benefits of their decisions instead of long-term benefits [16]. Another study component is attention which has different types (focused, sustained, selective, and divided attention). It is the ability to choose and concentrate on relevant stimuli. Attention may be impaired by a variety of disorders [17]. Various studies have reported a bias in attention in people with substance abuse, such as alcohol [18] and nicotine users [19]. Memory is another cognitive component that can temporarily hold information, and is important for reasoning, learning, and the guidance of decision-making and behavior [20, 21]. Studies have shown the destructive effect of drug addiction on memory. Memory bias has been reported in opioid users [22]. Cortico-striatal circuits, amygdala, hippocampus, nucleus accumbens, and prefrontal cortex that are negatively affected by exposure to drugs, are involved in memory and cognition [23–26]. The final cognitive component is inhibitory control (response inhibition) which is defined as the ability to control one's attention, behavior, thoughts, and/or emotions to override a strong internal predisposition, and do what is more needed [20, 27]. Inhibitory control has an important role at different stages of the addiction cycle, i.e., 1) initial use of substance; 2) transition from recreational use to heavier use and abuse; 3) continuation of use for those who get addicted; 4) relapse after abstinence [28]. Multiple studies have focused on the relationship between chronic substance use and inhibitory control, but findings are equivocal [27, 29].

There are a variety of approaches for rehabilitation of OUD patients including: cognitive–behavioral approaches, education, reward cooperation, and medications (e.g., methadone, buprenorphine and naltrexone), and non-pharmacological methods [30]. Despite significant advances in treatments for OUD, these methods have some limitations that emphasize the need for new approaches [31]. For example, despite the effective clinical use of methadone, some neuropsychological studies have shown that methadone has negative effects on cognitive function including attention, memory and information processing [32]. Recently, new therapies, such as non-invasive brain stimulation have emerged for treatment of addiction, one of which is Transcranial Direct-Current Stimulation (tDCS) [33]. It is a non-invasive technique that involves the application of low voltage (usually 0.5–2 mA) electrical current over the scalp through two electrode surfaces (one anode and one cathode). Anodal tDCS causes a depolarization of neurons and thus increases cortical excitability, while cathodal tDCS causes neuronal hyperpolarization and reduces cortical excitability [34]. The current penetrates the skull, reaching the cerebral cortex, and thus regulating neural activity. Due to the ease of implementation of this method, its low side effects and costs, it has been used in many studies [35–37]. tDCS-induced modulations of cortical excitability have been proposed as being able not only to affect human cognitive functions but also to modify addictive behaviors [38]. In most of tDCS-related studies, the dorsolateral prefrontal cortex (DLPFC) is selected for stimulation [38–40], because the DLPFC is involved in decision making, cognitive control, and attention [41, 42]. Due to the lack of access to traditional therapies, or the failure of gold standard treatment regimens (on methadone or buprenorphine), drug addicts can be benefited from alternative non-invasive methods, such as tDCS. No study was found on the effect of bilateral tDCS on cognitive abilities of patients with OUD. In this regard, this study aimed to evaluate the effect of bilateral tDCS over the DLFC on the cognitive functions of men with OUD. It is hypothesized that anodal stimulation of left DLPFC lead to facilitation and cathodal stimulation of left DLPFC lead to inhibition and vice versa in the right DLPFC.

Methods
Study design and samples
This study is a randomized sham-controlled double-blind clinical trial (Parallel) with a pretest/posttest design. The study population consisted of all men with OUD living in Zanjan, Iran in 2018. Their addiction was diagnosed

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using Structured Clinical Interview for DSM, axis I and II (SCID-I and SCID-II). The GPower software was used to determine the sample size by setting alpha error probability as $P = 0.05$ and the effect size as 6%, which was obtained 36. Study samples were selected using a convenience sampling technique based on the inclusion criteria (age 18–50 years, at least a middle school education, history of opium use and its derivatives, being under methadone therapy for at least 2 weeks, and not receiving any psychological or technological treatment in the past 1 month). Having suicidal thoughts, severe mental disorders, such as schizophrenia, history of head trauma, epileptic seizures, existence of any implanted pacemaker, and absent for more than two sessions in the intervention program were the criteria for exclusion from the study. Participants were randomly divided into three groups of A = Left anode/right cathode tDCS ($n = 12$), B = Right anode/left cathode tDCS ($n = 12$), and C = Sham tDCS ($n = 12$) in the Sealed Envelope website (https://www.sealedenvelope.com/). Figure 1 plots the flowchart of the study process.

Assessment tools

After obtaining ethical approval from the Research Ethics Committee and an informed written consent from the participants, their information (Age, marital status, education, disease duration) were recorded using a demographic form. Then, they completed the Cognitive Abilities Questionnaire (CAQ) developed by Nejati et al. [43] in Persian. It has 30 items and 7 subscales (memory, inhibitory control/selective attention, planning, decision making, sustained attention, social cognition, and cognitive flexibility). The items are scored on a 5-point Likert

scale from 1 = almost never to 5 = almost always. The total score of CAQ ranges from 36 to 180. With a Cronbach's alpha of 0.83, the CAQ have proper reliability for evaluation of cognitive abilities [43]. It should be mentioned that assessments before and after treatment were performed by another expert (MS in Clinical Psychology) who was unaware of the results.
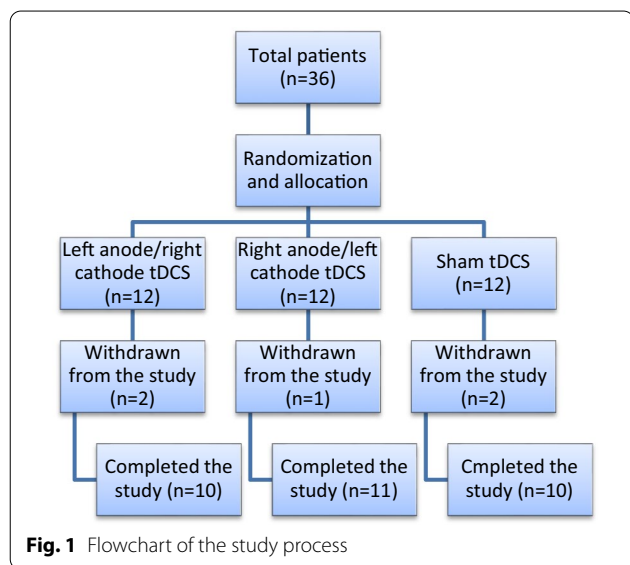
Intervention

Patients in A and B groups received active tDCS over DLPFC (anode left/cathode right and anode right/cathode left stimulation) for 20 min, once a day, for 10 consecutive days (2-mA intensity) using a FDA-approved device (ActivaDose ll, ActivaTeK Inc., Taiwan), while the C group received sham tDCS. The number of sessions was determined according to De Almeida et al. [44] In the active groups, two electrodes (positive anode and negative cathode) were positioned in the subjects' head over DLPFC (anode position over F3 and cathode over F4 in one group, and anode position over F4 and cathode over F3 in other group, according to the EEG 10–20 International System) covered by a sponge soaked in saline.

Data analysis

Immediately after the end of intervention, cognitive abilities of subjects were measured again. Out of 36 subjects, 6 were withdrawn from the study (2 in group A due to the death of close relatives, one in group B due to travel, and 2 in group C due to relapse). At the end, the data of 31 subjects were analyzed in SPSS software using descriptive statistics (mean, standard deviation) and statistical tests including Chi-square test (for examining the difference between groups in terms of demographic factors at baseline), one-way ANCOVA (for examining the difference between groups in terms of cognitive abilities after intervention) and Bonferroni test (for pairwise comparison of groups). Before conducting parametric tests, the normality assumption was examined by Kolmogorov–Smirnov (KS) test and the equality of variances was assessed by Levene's test. The KS test results reported the normal distribution of demographic factors ($p > 0.05$), and the Levene's test results showed the equal variances for these factors ($P < 0.05$).

Results

Table 1 presents the demographic characteristics of participants in three groups. The mean age of participants and their disease duration in group A were 34.40 ± 7.66 and 11.90 ± 4.93 years, respectively; in group B, the values were 32.27 ± 9.99 and 12.36 ± 5.76 years; and in the sham group, as 32.70 ± 9.34 and 12.50 ± 6.58 years. As shown in Table 1, at baseline, there was no significant difference between the groups in terms of marital

Fig. 1 Flowchart of the study process

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Table 1 Demographic statistics of participants in the three study groups

Characteristics		Group A (*n* = 10) N (%)	Group B (*n* = 11) N (%)	Group C (*n* = 10) N (%)	P value*
Marital status	Single	5(50)	4(36.4)	5(50)	0.92
	Married	4(40)	5(45.5)	4(40)	
	Divorced	1(10)	2(18.2)	1(10)	
Education	Middle school	4(40)	7(63.6)	4(40)	0.51
	High school	2(20)	–	2(20)	
	Diploma	3(30)	4(36.6)	4(40)	
	Associate degree	1(10)	–	–	
	Mean ± SD		**Mean ± SD**	**Mean ± SD**	**P value****
Age		34.40 ± 7.66	32.27 ± 9.99	32.70 ± 9.34	0.99
Disease duration (year)		11.90 ± 4.93	12.36 ± 5.76	12.50 ± 6.58	0.97

*Chi-square test, **One-way ANOVA

status and education according to Chi-square test results ($P > 0.05$), and no significant difference in terms of age and disease duration according to ANOVA results ($P > 0.05$). Table 2 presents the mean scores of CAQ dimensions before and after intervention. As can be seen, the score of cognitive flexibility, planning, decision making, inhibitory control/selective attention, and memory increased after brain stimulation in the two active groups, while their level were decreased or remained unchanged in the sham group. One-way ANCOVA results showed that these changes in the active groups were statistically significant ($p < 0.05$), but

the changes in sustained attention and social cognition were not significant (Table 3). The partial eta squared value showed that 43, 38, 36, 34 and 37% of variances in cognitive flexibility, planning, decision making, inhibitory control/selective attention and memory are explained by the tDCS. Bonferroni post hoc test was used to discover which specific means differed. The results are presented in Table 4. There was no significant differences between active groups A and B in any dimensions of cognitive functioning after intervention ($p > 0.05$), but the difference in the post-intervention level of cognitive abilities was significant between groups A and C and between B and C ($p < 0.05$).

Table 2 Mean and standard deviation (SD) of COQ scores before and after intervention

Cognitive abilities		Group A (*n* = 10), mean ± SD	Improvement rate (%)	Group B (*n* = 11), mean ± SD	Improvement rate (%)	Group C (*n* = 10), mean ± SD	Improvement rate (%)
Cognitive flexibility	Posttest	14.60 ± 2.31	39	14.81 ± 2.63	31	13.80 ± 4.07	10
	Pretest	10.50 ± 2.71		11.27 ± 2.68		15.40 ± 3.33	
Social cognition	Posttest	7.90 ± 2.64	6	7.09 ± 2.50	13	7.30 ± 3.26	3
	Pretest	8.40 ± 2.98		8.18 ± 2.60		7.10 ± 3.44	
Inhibitory control/ selective attention	Posttest	22.70 ± 4.76	41	20.27 ± 4.47	30	20 ± 5.14	6
	Pretest	16.10 ± 6.04		15.54 ± 4.22		21.30 ± 4.69	
Decision Making	Posttest	17.80 ± 4.7	60	17.72 ± 4.83	45	18.50 ± 3.43	5
	Pretest	11.2 ± 3.08		12.2 ± 4.24		17.60 ± 4.35	
Sustained attention	Posttest	10 ± 2.49	33	11.09 ± 2.54	47	10.60 ± 3.06	4
	Pretest	7.50 ± 3.50		7.54 ± 2.91		10.20 ± 3.52	
Planning	Posttest	11.20 ± 2.57	49	10.63 ± 2.37	48	10.70 ± 2.86	2
	Pretest	7.50 ± 2.71		7.18 ± 1.72		10.9 ± 2.13	
Memory	Posttest	17.60 ± 5.66	51	20.45 ± 3.38	48	18.20 ± 7	3
	Pretest	11.60 ± 5.16		13.81 ± 5.68		18.80 ± 6.95	

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Table 3 Test of between-subjects effects after intervention

Variable	Type III sum of squares	df	Mean Square	F	Sig.	Partial eta squared
Cognitive flexibility*	157.736	2	78.868	10.531	0	0.43
Social cognition	8.27	2	4.135	0.702	0.504	0.04
Inhibitory control/selective attention*	263.671	2	131.835	7.027	0.003	0.34
Planning*	86.706	2	43.353	8.858	0.001	0.38
Decision Making*	216.834	2	108.417	7.77	0.002	0.36
Sustained attention	49.389	2	24.694	2.659	0.088	0.165
Memory*	304.236	2	152.118	8.092	0.002	0.37

*The mean difference is significant at $p < 0.05$

Table 4 Pairwise comparison results using the Bonferroni test

Variable	Group	Mean difference	Std. error	Sig.
Cognitive flexibility	A vs. B	− 0.692	1.196	1.000*
	A vs. C	− 5.197	1.231	0.001
	B vs. C	− 4.505	1.208	0.003
Planning	A vs. B	0.318	0.967	1.000*
	A vs. C	− 3.400	0.989	0.006
	B vs. C	− 3.718	0.967	0.002
Decision Making	A vs. B	− 1.097	1.632	1.000*
	A vs. C	− 6.168	1.674	0.003
	B vs. C	− 5.071	1.637	0.014
Inhibitory control/selective attention	A vs. B	− 0.797	1.937	1.000*
	A vs. C	− 6.704	1.991	0.007
	B vs. C	− 5.906	1.893	0.013
Memory	A vs. B	− 0.040	1.942	1.000*
	A vs. C	− 6.742	1.941	0.005
	B vs. C	− 6.703	1.924	0.005

*The mean difference is not significant ($p > 0.05$)

Discussion

To our knowledge, this study is the first sham-controlled clinical trial that investigates the effect of tDCS over the right and left DLPFC on different cognitive abilities of opioid users. Our findings showed that both left and right DLPFC stimulation resulted in improvement of cognitive flexibility, planning, decision-making, inhibitory control, and memory in men with OUD. There are some similar studies that have used tDCS over the DLPFC in different patients. In most of the studies on addicts, the tDCS has been applied over the DLPFC [39, 44–46] which indicates the role and importance of this brain region in cognitive functions and its impairment by drug addiction. The prefrontal cortex plays an important role in cognitive control, which determines goals and how to achieve it. It regulates cognitive functions, such as inhibitory control, attention, planning, and risk-taking. Low activity of the prefrontal cortex may lead to defects in these functions and more cognitive and motor impulsivity [44]. DLPFC, as one of the most important areas of the prefrontal cortex, is responsible for diagnosing and determining actions, and evaluating the future consequences of current behavior. Stimulation of this area can improve the mentioned abilities [45]. Dadashi et al. [46] in their study also showed that anodal tDCS over the left DLPFC reduced attentional bias in opium addicts. In Gorini et al.'s study [38] on cocaine users, tDCS over the right and left DLPFC resulted in a reduction of risk-taking behaviors. Teti Mayer et al. [42] applied tDCS over the DLPFC for 5 consecutive days in 50 patients with borderline personality disorder, and reported its effect on the reduction of their impulsivity as a risky behavior. In the study by Cheng and Lee [40], tDCS also significantly reduced risky decision-making in impulsive individuals. These findings are consistent with our results; however, Boggio et al. [47] showed that both right anodal and left anodal DLPFC stimulation increased the propensity for risk-taking in marijuana users which is against the results of present study. This discrepancy may be due to the difference in substance and study area.

Metzuyanim-Gorlick and Mashal [48] suggested that tDCS can improve response inhibition for the long term in healthy adults, which is in agreement with our findings. Inhibitory control ability prevents automatic responses and stops inappropriate cognitive processes that may disrupt the proper performance of a purposeful action. Therefore, it can be said that inhibitory control acts as a filter and is associated with social competence and behavioral and emotional control, and its impairment may cause impulsivity [49]. Andrews et al. [50] found out that anodal tDCS to the left DLPFC combined with cognitive activity can result in greater improvement in working memory performance in healthy subjects, while Keshvari et al. [51] reported that bilateral stimulation of DLFC is not a useful procedure to improve working memory.

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Our results showed no significant effect of bilateral tDCS on sustained attention and social cognition of addicts. This may be because addicts in our study were under methadone therapy. Despite the effective clinical use of methadone, some neuropsychological studies have shown that methadone has negative effects on cognitive function including attention, memory and information processing [32]. Henry et al. [52] reported significant impairment in psychomotor performance/attention and episodic memory of patients under methadone maintenance. Stonsaovapak et al. [53] in a sham-controlled trial, examined the effect of anodal tDCS over the right DLPFC on cognitive function in patients with mild cognitive impairment. Their results revealed a significant improvement in visual sustained attention, spatial working memory and visual memory. In terms of sustained attention, their results are against our findings which may be due to the difference in samples and the duration of stimulation. In our study, it was performed for 10 sessions (once a day) on opioid addicts, while participants in their study had mild cognitive impairment treated 3 times per week for 4 weeks (12 sessions).

The results obtained from the current study can be valuable for establishing new concepts for the treatment of opioid addicts. In addition, providing new information regarding the possible effects of tDCS on their cognitive abilities can be useful in the study of mechanisms underlying cognitive behavior. Our study had some disadvantages including: low number of participants, existence of comorbid diseases (e.g., depression, anxiety, and infectious diseases) and not assessing their effect on the study outcome, studying only males with OUD (since women face significant stigmatization regarding their substance use in Iran and are reluctant to receive treatment), lack of a follow-up for relapse (due to the aggressive behavior of addicts), and use of a subjective scale. In this regard, further studies are recommended using a higher sample size, an objective scale (e.g., Wisconsin Card Sorting Test or Trail Making Test), females with OUD, and a follow-up period. The use of advanced MR imaging techniques such as functional MRI (fMRI) and MR spectroscopy are also suggested to identify brain changes caused by tDCS or performing QEEG guided-based neurofeedback treatment.

Conclusion
The bilateral tDCS over the DLPFC can improve cognitive functioning in opioid users. As a non-invasive and complementary treatment, it can be used in improving and enhancing the cognitive abilities of opioid addicts.

Abbreviations
OUD: Opioid use disorder; DLPFC: Dorsolateral prefrontal cortex; KS: Kolmogorov–Smirnov; SCID-I: Structured Clinical Interview for DSM, axis I; SCID-II: Structured Clinical Interview for DSM, axis II; CAQ: Cognitive Abilities Questionnaire; tDCS: Transcranial Direct-Current Stimulation.

Availability of data and materials
The data sets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975. A written informed consent was obtained from all patients for being included in the study and ethical approval was then obtained from Zanjan University of Medical Sciences in Iran (code: IR.ZUMS.REC.1397.127).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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