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Original Article

The Impact of Transcranial Direct Current Stimulation (tDCS) on Craving and Relapse Rates in Opioid-Dependent Patients Undergoing Methadone Maintenance Therapy

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Abstract

Background: Addiction is a chronic and debilitating condition associated with compulsive behaviors, cravings, and high relapse rates. Transcranial direct current stimulation (tDCS) is a neuromodulation technique for the treatment of substance use disorders by targeting brain areas involved in craving and inhibitory control. This study aimed to assess tDCS effectiveness in reducing cravings in opioid-dependent patients on methadone maintenance therapy (MMT).

Methods: A total of 60 opioid-dependent participants were randomly assigned to either an active intervention group or a sham group. The intervention group received ten sessions of anodal tDCS applied to the left dorsolateral prefrontal cortex (DLPFC) and cathodal tDCS over the right DLPFC. Craving was measured using the Desire for Drug Questionnaire (DDQ) before and after the intervention.

Findings: This study found no statistically significant differences in craving scores between the intervention and sham groups. There was no statistically significant difference in craving score changes between the two groups before and after the intervention.

Conclusion: The findings of this study suggest that the specific tDCS protocol used, targeting the left DLPFC with anodal stimulation and the right DLPFC with cathodal stimulation, did not significantly reduce craving in opioid-dependent patients undergoing MMT. The study highlights the need for further research to optimize tDCS protocols and explore alternative brain targets for the treatment of substance craving and relapse prevention.

Keywords: tDCS, Opioid-dependent, Craving

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Introduction

Addiction is defined as a chronic and persistent condition distinguished by features including compulsive behaviors, loss of control over substance use or actions, substance-seeking behaviors, and continuous consumption despite the social, psychological, physical, familial, and economic consequences.[1] Studies suggest that there are many risk factors for addiction, including genetic factors,[2] impulsivity,[3] social factors,[4] and clinical features.[5,6] The interaction of these risk factors contributes to a complex disease etiology, making addiction a multifactorial disorder that requires a comprehensive understanding and intervention. Epidemiological studies on a large scale have also shown that substance use disorders (SUD) have high comorbidity with mental disorders, including depression, anxiety, and attention deficit hyperactivity disorder (ADHD).[7] This comorbidity often complicates treatment approaches, highlighting the need for strategies that address both SUD and associated psychiatric conditions. Therefore, the treatment of SUD is complex and faces numerous challenges, with studies indicating an addiction treatment relapse rate of approximately 70%.[8]

Craving, one of the most challenging aspects of addiction, is defined as the anticipation of the reinforcing effects of substances and a strong inclination toward them.[9] Various studies have demonstrated that craving is a central phenomenon and a significant factor in the continuation of substance abuse and relapse after treatment. According to brain imaging studies, many brain areas are implicated in the craving mechanism, with the lateral prefrontal cortex playing a key role in craving, mood, and cognitive disorders.[10] Changes in prefrontal regions, particularly the lateral posterior prefrontal cortex, have been identified in addiction disorders, where strong inclinations toward substances and impaired inhibitory control exacerbate the problem.[11] Furthermore, according

to this study, changes in the prefrontal regions of the brain, especially in the lateral posterior prefrontal cortex, have been identified in addiction disorders. These brain changes, which are associated with craving for substances, are intensified by a strong tendency towards substances and impaired inhibitory control.[11] In general, addiction can have a profound effect on a person's actions and brain activity, resulting in uncontrollable drug use. To tackle substance abuse and addictive behaviors, a range of treatment methods have been created to reduce drug dependency, lessen the severity of relapses, and improve cognitive abilities.[8] Recent research has indicated that integrating biological, physiological, and psychological methods can improve the effectiveness of treatment. Adopting a biopsychosocial framework, which integrates the biological, psychological, and social dimensions of addiction, enables the development of more holistic and effective treatment interventions.[12]

In recent years, innovative treatment approaches have been explored to address addiction and reduce relapse rates. One such technique is transcranial direct current stimulation (tDCS), which has gained attention for its potential to modulate brain activity and reduce craving.[13] tDCS is used to induce neural plasticity and modulate brain cortex function by a weak direct current stimulation to the participants' scalp. Transcranial direct current stimulation (tDCS) has been extensively utilized over the past decade, contributing substantially to advancements in neuroscience and psychology. This non-invasive technique can selectively enhance or suppress cortical excitability. Anodal stimulation typically increases neuronal excitability in targeted regions, whereas cathodal stimulation reduces it. Mechanistically, tDCS modulates cortical activity by altering neuronal membrane potentials and influencing firing rates within the stimulated brain areas.[14, 15] Research studies have suggested that the use of tDCS in the prefrontal area, specifically the dorsolateral prefrontal cortex (DLPFC), may be helpful in substance use disorder subjects, as the DLPFC is critically involved in top-down inhibitory control and reward process [16]. The modulation of these neural circuits is thought to improve cognitive control and reduce compulsive substance-seeking behaviors.

Results analyzed in subjects dependent on cocaine, alcohol, crack, and cigarettes have shown the positive effects of direct transcranial electrical stimulation on quality of life[17, 18] and substance craving.[18, 19] Studies have shown that anodal stimulation of the left DLPFC improves resistance to smoking urges in smokers.[20] Similarly, anodal stimulation over the left DLPFC can effectively reduce craving in alcohol and methamphetamine users and decrease the relapse rate in these individuals. This effect is partly mediated by the activation of the ventromedial prefrontal cortex (vmPFC), which is indirectly affected by changes in the activity of DLPFC. Therefore, the regulation of VMPFC activity through indirect pathways serves as a mechanism through which tDCS promotes better self-control in addicts, improves decision-making, and reduces the risk of relapse.[21] The fronto-parieto-temporal junction and the frontopolar cortex (FPTj) represent another potential target region for tDCS in addiction treatment. For example, one study investigated the effects of inhibiting the FPTj on attentional bias towards smoking cues in smokers.[22] Another study used a similar research design. They reported the electrophysiological and imaging effects of tDCS on the lateral posterior frontal cortex in substance use disorder, particularly in alcohol and crack-cocaine users.[12] Low-resolution electromagnetic tomography analysis (LORETA), a functional imaging technique that utilizes electrophysiological and neuroanatomical principles,[23] and P3 wave data were extracted from alcohol and crack users. Findings indicated that the vmPFC region had the greatest activation towards drug-related cues in abstinent individuals; however, during and after bilateral tDCS treatment, craving decreased, possibly due to vmPFC modulation over drug-seeking behavior. In this study, bilateral DLPFC stimulation decreased relapse and craving for drug use, and increased activation of the vmPFC under drug cues, which may be crucial in controlling drug use in substance use disorder.[24]

In opioid using subjects undergoing methadone maintenance therapy (MMT), tDCS has been evaluated for its effects on relapse, craving, anxiety, depression, and cognitive function.[25,26,27] These studies employed different stimulation protocols, with varying results. Given the heterogeneity of findings, further research is warranted to clarify the effects of tDCS, particularly in the context of opioid addiction. This research seeks to investigate the impact of anodal stimulation of the left DLPFC on craving and its implications for relapse prevention. By exploring these mechanisms in a larger sample size, the study aimed to enhance our understanding of tDCS's role in supporting individuals in MMT programs. The outcomes could inform clinical practices and advance the integration of neuromodulation techniques into comprehensive addiction treatment strategies, benefiting not only relapse prevention but also mental health and rehabilitation outcomes.

Material and Methods

Participants

A total of 60 individuals with a history of opium use disorder were enrolled at Ibn-e Sina Psychiatric Hospital. The inclusion criteria were as follows: participants aged between 18 and 60 years, no diagnosis of acute or chronic psychiatric disorders other than substance addiction, negative results on a urine drug test, undergoing methadone maintenance therapy (MMT) for at least one month prior to the study, and no history of epilepsy

or severe brain injury. The exclusion criteria included the presence of significant physical illnesses, history of traumatic brain injury, diagnosis of major depressive disorder, schizophrenia, or attention-deficit/hyperactivity disorder (ADHD), history of electroconvulsive therapy, experience of manic episodes, psychological and neurological disorders, including spinal cord injury, brain tumors, epilepsy, or seizures, presence of intracranial implants, and pregnancy or breastfeeding at the time of the study.

Sample Size

According to the findings from the study conducted by Namazpoor et al the minimum required sample size was determined to be 24 individuals per group, utilizing an alpha level of 0.05 and a beta level of 0.2.[28]

Initially, 60 participants were recruited for the study; however, only 48 completed the treatment sessions, resulting in a dropout of 12 individuals for various reasons. Specifically, five participants (three from the sham group and two from the intervention group) withdrew due to difficulties related to daily commuting for treatment. Additionally, seven participants (three from the sham group and four from the intervention group) did not respond to follow-up calls and subsequently left the study (Figure 1).

Procedure Assessment

Subjects were randomly divided into two groups (intervention and sham). The intervention group received methadone treatment for at least one month. Subjects received 10 sessions of tDCS (one session per day). In the tDCS montage, the anodal electrode was positioned over the left dorsolateral prefrontal cortex (DLPFC) at the F3 location (10-20 EEG system). In contrast, the cathodal electrode was placed over the right DLPFC (F4) to create a balanced bilateral stimulation paradigm. The intensity of the current was 2 mA, and the duration of the stimulation session was 20 minutes. In the control shame group, the tDCS protocol was conducted similarly to that of the intervention group; however, the electrical flow was automatically cut off by the device after one minute. This ensured that participants felt the initial sensation of tDCS but did not receive any actual stimulation. The ethical criteria and guidelines of the American Psychological Association and the Iranian Psychological Association were followed in this study. Before and after the intervention sessions, both the intervention and sham groups completed a questionnaire.

At the outset of the study, participants were provided with a concise and comprehensible overview of the disease and the research objectives. Eligible participants who agreed to join the study provided written informed consent, with additional biometric verification provided

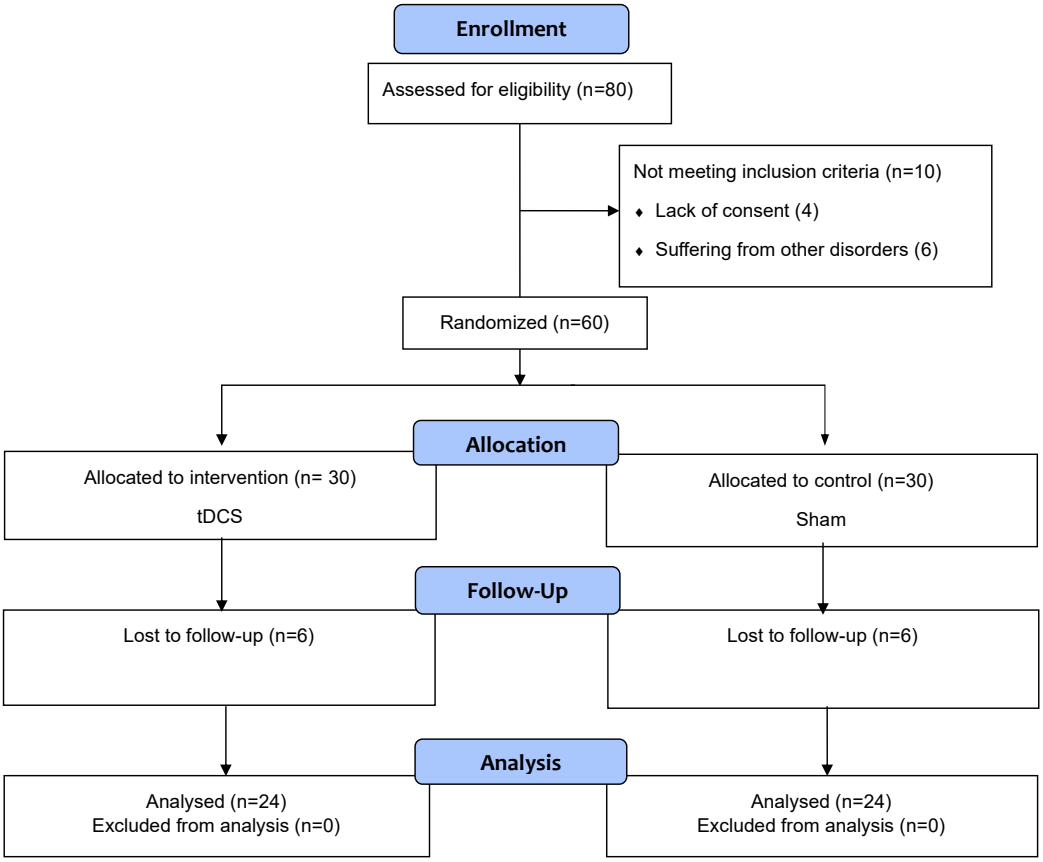

Figure 1. consort flow diagram

through fingerprint documentation to ensure protocol adherence. All medical procedures associated with this research were offered to participants at no cost.

Block Randomization Methodology

This study utilized a block randomization technique to generate a sequence of random numbers, ensuring balanced allocation across treatment groups. This method involved the creation of blocks of varying sizes, specifically 10 blocks of size 4 and 4 blocks of size 2, using combinations of the letters A and B. These combinations were selected through a random number table to ensure randomness and reduce selection bias. For blocks of size 2, the possible combinations were 1- AB and 2- BA. For blocks of size 4, the combinations included 1- AABB, 2- ABBA, 3- BBAA, 4- BAAB, 5- BABA, and 6- ABAB. The selection process for the blocks of size two involved drawing four random numbers from the random number table. If a number fell between 0 and 4, the first block (AB) was selected; if it was between 5 and 9, the second block (BA) was chosen. Similarly, for blocks of size 4, ten random numbers ranging from 1 to 6 were drawn. The number determined the block selection as follows: a number of 1 corresponded to the first block (AABB), a number of 2 to the second block (ABBA), and so forth for the remaining blocks. This structured approach to randomization ensured that each treatment group was equally represented, thereby enhancing the reliability and validity of the study's findings. Both participants and outcome assessors were blinded to group allocation to minimize bias and ensure the integrity of the results.

Desires for Drug Questionnaire (DDQ)

The DDQ is a 13-item questionnaire developed by Franken et al. The questionnaire is a derivative of the Alcohol Urge Questionnaire and is also used for heroin-dependent individuals. However, due to its ability to assess different types of substance use, it has been used to assess craving for other substances as well.[29] This tool consists of 3 subscales: urge and intention to use substances, negative reinforcement, and perceived control over substance use.[29] The questionnaire is based on a 7-point Likert scale (ranging from completely disagree to completely agree). Participants responded to the items based on their current thoughts or feelings. The scale was rated as follows: 1- not at all, 2- mild, 3- mild to moderate, 4- moderate, 5- moderate to severe, 6- severe, and 7- approximately complete. The evaluations from this questionnaire pertain to the current moment and present time. Additionally, a normal score for this questionnaire is not specified, and the significance of the changes is the criterion for evaluation. Franken et al reported the overall reliability of this scale using Cronbach's alpha as 0.85. For the subscales of urge and intention to use substances, negative reinforcement, and perceived control over substance use, Cronbach's alpha was 0.77, 0.80, and 0.75, respectively. In the study by Poor-Seyed et al the overall Cronbach's alpha values for users of different substances were reported as follows: 0.96 for methamphetamine, 0.95 for crack, 0.90 for methamphetamine, 0.94 for heroin smoking, and 0.98 for heroin injection.[30]

Data were analyzed using SPSS software version 25 and R software. A significance threshold of $P < 0.05$ was applied to all statistical analyses. The normality of quantitative data was evaluated using the Shapiro-Wilk test. For comparisons between the two groups, independent *t*-tests were employed for normally distributed quantitative variables, while chi-square tests were used to analyze qualitative variables. To adjust for the baseline craving level effect, analysis of covariance (ANCOVA) was utilized. The effect of the intervention on the outcome of relapse was examined using a modified logistic regression model with the logistic package in R.

Results

Demographical Results

Table 1 displays the demographic information, indicating that the two groups did not differ significantly in many parameters, including age, years of education, marital status, employment status, and type of drugs used.

Desires for Drug Questionnaire (DDQ) Results

According to the results in Table 2, the mean post-test scores in the intervention and sham groups were 65.25 ± 17.45 and 62.35 ± 03.16, respectively. The independent *t*-test results indicated that there was no significant difference in the mean post-test scores between the intervention and sham groups ($P = 0.833$). Additionally, we compared the changes in craving levels between the two groups. The mean changes in the intervention group were reported as −18.27 ± 12.40 and in the sham group as −8.18 ± 96.48. Despite the greater changes in craving scores in the intervention group compared to the sham group, the independent *t*-test results showed that these changes were not significantly different ($P = 0.181$).

In the next step, the mean scores of each group before and after the tDCS intervention were also reported, as presented in Table 2. The mean pretest scores of this questionnaire in the intervention and sham groups were 62.25 and 62.53, respectively. These scores in the post-test phase for the intervention and sham groups were 45.17 and 53.62, respectively. Analysis of covariance showed that the two groups did not differ significantly regarding post-intervention craving levels ($P = 0.877$).

The result of the independent *t*-test showed that the mean post-test scores in the two groups did not have a significant difference ($P = 0.833$). Additionally, we compared the changes in craving between the two groups. The mean changes in the intervention group were reported as −18.27 ± 12.40, and in the sham group

Table 1. Demographic and clinical characteristics of study participants (presented as mean ± standard deviation)

Variable	Intervention group *n* = 24	Sham group *n* = 24	*P* value
Age (mean)	12.12 ± 13.42	8.41 ± 58.41	0.139
Gender			
Female	4 (16.7%)	5 (20.8%)	999.0
Male	20 (83.3%)	19 (79.2%)	
Marital status			
Single	7 (29.2%)	9 (37.5%)	0.540
Married	17 (70.8%)	15 (62.5%)	
Employment status			
Government employee	6 (25.0%)	1 (4.2%)	0.134
Self-employed	12 (50.0%)	12 (50.0%)	
Unemployed	6 (25.0%)	10 (41.6%)	
Farmer	0	1 (4.2%)	
Education			
Bachelor	4 (16.7%)	1 (4.2%)	0.229
Postgraduate	0	1 (4.2%)	
High school diploma	6 (25.0%)	10 (41.6%)	
Below high school diploma	14 (58.3%)	12 (50.0%)	
Type of drug			
Opium	11 (45.9%)	12 (50.0%)	0.074
Refined opium	2 (8.3%)	4 (16.7%)	
Mixed-use	11 (45.8%)	4 (16.7%)	
Crystal	0	2 (8.3%)	
Tramadol	0	2 (8.3%)	
Average duration of use	120 (156)	108 (129)	0.152♣
Mean pretest scores	65.17 ± 25.45	03.16 ± 62.53	0.092

The data are described as frequency (percentage) for qualitative variables, mean ± standard deviation for normally distributed quantitative variables, and median (interquartile range) for non-normally distributed quantitative data. Duration of use: months.

Table 2. Results of the scores of the two groups before and after the intervention, and calculation of the group effect and pretest effect

Craving score	Intervention group	Sham group	*P* value
Pretest	65.25 ± 17.42	62.35 ± 03.16	0.833
Post-test	45.17 ± 25.65	53.62 ± 16.03	0.877
p-value	0.004	0.026	
Craving score changes	−18.27 ± 12.40	−8.18 ± 96.48	0.181
Covariance test result	*P* value	*F*	

Table 3. The effect of the intervention on relapse

Groups	Odds ratio	Coefficient estimates	95% confidence interval	*P* value
Sham group	7.97	2.07	(0.78–1196)	0.0986
Intervention group	Reference (group1)	-	-	-

as −8.18 ± 96.48. Based on the obtained results, despite the greater changes in craving scores in the intervention group compared to the sham group, the results of the independent *t*-test indicated that these changes were not significantly different between the two groups ($P = 0.181$).

Additionally, according to Table 3, the adjusted logistic regression model was analyzed to examine the effect of the intervention on relapse outcomes. This model indicated that the odds of relapse in the sham group were 7.97 times higher than in the intervention group; however, this difference was not statistically significant ($P = 0.0986$; OR = 7.97; 95% CI: 0.78–1196).

Discussion

The present study aimed to investigate the effectiveness of tDCS on craving for substance use in opioid users. The results indicated that tDCS had no significant effect on reducing craving or other parameters in substance users. The results of this study are in line with other studies demonstrating that tDCS (F3: cathode and F4: anode) reduced depression, anxiety, and stress; however, it demonstrated no significant effects on the relapse rate parameter among opioid users during MMT.[26] These results, however, contradict other studies indicating that tDCS (F3: cathode and F4: anode) decreases craving in opioid users.[31] To explain these differing findings, it can be considered that the methods used to place electrodes in the right and left DLPFC were different. In addition, the effect of tDCS may vary across different populations and types of addiction.[13] Recent results of a meta-analysis study demonstrated that tDCS slightly decreased cravings in opioid, methamphetamine, cocaine, and tobacco users; however, no significant impact was observed for cannabis or alcohol. The variability observed in the meta-analysis highlights the diverse effects of tDCS among different participants, treatments, and results.[13] These results suggest that different forms of addiction disorders (SUDs) and other factors may influence the effects of transcranial direct current stimulation (tDCS). In our study, 45% of participants in the intervention group were mixed substance users, which may have impacted the treatment outcomes. Recent studies indicate that tDCS effectively decreases cravings in individuals with substance addiction, particularly when targeting the DLPFC. The DLPFC is linked to various cognitive functions, including executive functions, working memory, reward processing, motivation, attentional control, decision-making, and cognitive regulation.[32] Moreover, this brain area plays a role in the control of cravings.[13] Patients with drug or alcohol dependence showed decreased resting and functional activity in the prefrontal cortex.[13] Besides, tDCS is thought to influence neural functions by altering the membrane potential, cerebrovascular flow, synaptic transmission, neural oscillations, neural connectivity, and levels of various neurotransmitters.[33] Based on brain function and the mechanisms of tDCS, the DLPFC protocol may be effective in reducing cravings. One study

suggested that managing cravings is linked to balancing activity between the brain hemispheres.[34] Additionally, an animal study showed that placing the cathode over the frontal lobe led to an increase in dopamine levels in the basal ganglia.[35] Dopamine is essential to the reward system, as it influences pleasurable sensations, drives incentive motivation, and helps form associations between stimuli and reward processes.[36] Some research has indicated that continuous substance use leads to neural adaptation and sensitivity to substances; these adaptations ultimately result in the phenomenon of tolerance and craving for substances during abstinence periods. Regarding the mechanism of action, it is hypothesized that tDCS is effective by influencing the dopaminergic pathway and improving patients' cognitive function. The application of tDCS in the DLPFC area reduces risk-taking behavior and arousal, may enhance resistance to cravings, and can increase response inhibition.[37] Furthermore, another study demonstrated that tDCS may have positive effects on response inhibition.[38] On the other hand, researchers have pointed out that tDCS stimulation can also reduce risk-taking behavior.[39] Modulating dopamine levels in these subjects through tDCS may be a possible mechanism for reducing cravings.

In our study, the anodal electrode was positioned over the left dorsolateral prefrontal cortex (DLPFC), while the cathodal electrode was placed over the right DLPFC. However, a recent meta-analysis suggested that right anodal stimulation is more effective in reducing cravings. This finding indicates that the right DLPFC is more involved in inhibitory control and craving regulation.[40] The meta-analysis also demonstrated that combining anodal stimulation on the right DLPFC with cathodal stimulation on the left DLPFC is more successful in decreasing cravings compared to anodal stimulation solely on the left DLPFC.[13] In contrast to the approach used in our study, these findings may explain the non-significant outcomes observed with respect to electrode placement.

Limitations

There are many limitations to this study. First, cognitive parameters and psychological parameters, such as depression and anxiety, were not evaluated before and after the interventions. In addition, some subjects in this study also used other drugs, which may have affected the results of the study. Moreover, the inclusion of many mixed users might have impacted the final results.

Conclusion

Overall, the results of this study indicated that the left anodal and right cathodal tDCS protocol did not significantly decrease cravings. Future studies should compare this protocol with other protocols in larger populations.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request. However, they are not publicly accessible due to restrictions, such as the inclusion of information that may compromise participant confidentiality.

Ethical Approval

The study was approved by the Mashhad University of Medical Sciences ethics committee (ethics code: IR.MUMS.MEDICAL.REC.1400.418).

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