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Comparison of the synergistic effectiveness of cognitive-behavioral therapy and transcranial direct current stimulation of the dorsolateral prefrontal cortex on clinical symptoms and neuropsychological functions in methamphetamine users

Mahdi Helmzadeh[1]; *Morteza Modares Gharavi[2]; Mahdi Ghasemi Motlagh[3]

[1]Ph.D. student in psychology, Faculty of Educational Sciences and Psychology, Islamic Azad University, Bojnord Branch, Bojnord, Iran.
[2]Department of Clinical Psychology, Psychiatry and Behavioral Sciences Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
[3]Assistant professor of psychology, Faculty of Educational Sciences and Psychology, Islamic Azad University, Bojnord Branch, Bojnord, Iran.

Abstract

Introduction: Methamphetamine (crystal meth) is a highly addictive stimulant substance with destructive effects on the human mind and body. The aim of this research was to investigate the synergistic effectiveness of Cognitive-Behavioral Therapy (CBT) and transcranial Direct Current Stimulation (tDCS) of the DorsoLateral PreFrontal Cortex (DLPFC) on clinical symptoms and neuropsychological functions in methamphetamine users.

Materials and Methods: The statistical population included all patients with clinical symptoms of crystal meth use disorder who were referred to addiction treatment centers in Mashhad, Iran, from 2022 to 2024. Forty patients were selected using the convenience sampling and randomly assigned to 3 experimental groups (CBT, tDCS, CBT + tDCS) and 1 control group (10 participants each). Data were analyzed using descriptive statistics, Independent t-test, ANOVA, and ANCOVA.

Results: The findings showed that the interventions were effective therapies, especially CBT and CBT + tDCS had significant effects ($P< 0.05$) on reducing clinical symptoms and improving neuropsychological functions in methamphetamine users.

Conclusion: The results indicated that all interventions reduced clinical symptoms and led to an improvement in neuropsychological functions, especially in the groups of cognitive-behavioral therapy and cognitive-behavioral therapy plus tDCS.

Keywords: Clinical symptoms, Cognitive-behavioral therapy, Methamphetamine abuse, Neuropsychological functions, Transcranial direct current stimulation

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***Corresponding Author:**
Psychiatry and Behavioral Sciences Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
modaresmg@gmail.com
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Introduction

Addiction to stimulant substances, especially methamphetamine (crystal meth), is considered a serious mental health challenge globally. This substance, in addition to severe effects on the central nervous system, has extensive cognitive, emotional, and behavioral consequences for users, which complicates the treatment process (1). Methamphetamine (crystal meth) dependence is associated with impaired cognitive functions and the emergence of symptoms of depression and anxiety, which are predictors of relapse in patients with substance use disorder (SUD) (2). Traditional treatment methods, especially pharmacological treatments, have not been successful in reducing these symptoms and preventing relapse, thus, attention to novel non-invasive and combined therapeutic methods is necessary (3). One of the well-known therapeutic methods is Cognitive-Behavioral Therapy (CBT), which helps patients modify maladaptive thought patterns and improve their coping skills (4). Research has shown that CBT plays an important role in reducing craving and improving emotional regulation, but its effects alone are limited and need reinforcement (5). In recent years, transcranial Direct Current Stimulation (tDCS) has gained attention as a non-invasive interventional method for modulating cortical neuronal activities. Studies show that stimulation of the DorsoLateral PreFrontal Cortex (DLPFC) can improve cognitive functions and reduce the severity of depression and anxiety symptoms in substance-dependent patients. Given that both methods have positive but limited effects, combining these two methods can be an effective strategy for enhancing treatment quality (6,7).

Some research has shown that combining these two methods can have synergistic effects and increase their effectiveness (8). For example, in one study, individuals who received combined treatment showed a significant reduction in symptoms of depression and anxiety, and an improvement in cognitive functions, whereas groups that received only one of these treatments showed less improvement (9). Results have indicated that the synergy between these two methods can be a promising strategy in treating crystal meth dependence (10). Furthermore, evidence suggests that tDCS, by regulating neural activities related to reward processing and impulse control, can improve neuropsychological functions in substance-dependent individuals (11). These effects are significant in individuals with executive dysfunctions and cognitive inhibition, which are prominent features of methamphetamine (crystal meth) users (12). The aim of this research was to investigate the synergistic effectiveness of Cognitive-Behavioral Therapy (CBT) and transcranial Direct Current Stimulation (tDCS) of the DorsoLateral PreFrontal Cortex (DLPFC) on clinical symptoms and neuropsychological functions in methamphetamine users.

Materials and Methods

The statistical population included all patients with clinical symptoms of crystal meth use disorder who were referred to addiction treatment centers in Mashhad, Iran, from 2022 to 2024. Forty patients were selected using the convenience sampling and randomly assigned to 3 experimental groups (CBT, tDCS, CBT + tDCS) and 1 control group (10 participants each). Inclusion criteria included having a diagnosis of substance use disorder according to DSM-5, aged 18-45, having at least a six-month history of regular substance use, willingness to participate in the study, and not receiving other pharmacological or psychotherapeutic treatments. Exclusion criteria included a history of severe psychiatric disorders such as schizophrenia or bipolar disorder, having neurological diseases or brain damage, taking medications that affect cognitive function and mood, and not cooperating in treatment sessions.

Research instruments

A) tDCS Side Effects Questionnaire: To comply with the medical ethics charter and protect patients' rights, the general outline of the study, its objective, method of operation, and potential side effects of the device were explained. The option to withdraw from the study for any reason and other legal matters were also explained, and participants completed the tDCS side effects questionnaire (13).

B) Beck Depression Inventory-II (BDI-II): This inventory was developed for the first time in 1961 by Beck and colleagues. This questionnaire, which includes 21 questions, was designed to assess feedback and symptoms of depressed patients. Respondents to this test must have at least fifth or sixth-grade reading ability to understand the items. They should respond to each item on a four-point Likert scale ranging from 0 to 3. The minimum score on this test is 0,

and the maximum is 63. The sum of the scores for each item directly yields the individual's score. The Persian version of this inventory has good psychometric properties in Iranian populations (14).

C) Beck Anxiety Inventory (BAI-II): It was created by Aaron T. Beck and his colleagues in 1988. This questionnaire contains 21 items and is designed to measure anxiety in adolescents and adults. The Persian version of this inventory has good psychometric properties in Iranian populations (Cronbach's alpha= 0.92) (15).

D) Go/No-Go Behavioral Inhibition Neuropsychological Test: The Go/No-Go test, originally designed by Hoffman in 1984, has been widely used to measure behavioral inhibition and includes two categories of stimuli. Participants must respond to one category of these stimuli (GO) and refrain from responding to the other category (NO-GO). Since the number of GO stimuli is usually greater than that of NO-GO stimuli, the readiness to respond in the individual is also higher. Three separate scores are obtained from this test: the percentage of commission errors, the percentage of inappropriate inhibition, and reaction time (16).

E) Stroop Cognitive Inhibition Neuro-psychological Test: The classic Stroop test, developed by Ridley Stroop in 1935, was created to assess executive functions such as cognitive inhibition. Various other models have since been developed and utilized. In computerized models of the test, congruent (the color of the word matches the meaning of the word) and incongruent (the color of the word does not match the meaning of the word) words are presented randomly during a specific reaction time (RT), and the individual's response time, correct and incorrect responses, and conflict score are accurately measured (17).

Treatment protocol: Cognitive behavioral therapy was structured into 10 sessions, each lasting 60 minutes, while tDCS stimulation consisted of 10 sessions lasting 20 minutes each. The CBT was designed based on the standard model for addiction treatment and focused on cognitive restructuring, coping skills, and emotion regulation.

Sessions included training on addiction concepts, impulse control, cognitive restructuring of dysfunctional thoughts, problem-solving skills, enhancing self-efficacy, lapse management, and relapse prevention.

At the end of the treatment period, a review of exercises and planning for the future were conducted to consolidate cognitive and behavioral changes resulting from the treatment (4). Transcranial Direct Current Stimulation (tDCS) was performed according to the standard protocol. For stimulation, the neuroConn DC-Stimulator device was used, placing the anode electrode on the left DLPFC (F3) and the cathode electrode on the right DLPFC (F4). The current intensity was set at 2 mili amperes and each session lasted 20 minutes (9).

Participants in the experimental group received tDCS stimulation once per week for 10 weeks. The control group underwent sham stimulation (Sham tDCS), which involved applying current for the first 30 seconds and then stopping it to create a placebo effect. Data were analyzed using SPSS version 26. Initially, descriptive statistics including means and standard deviations were calculated.

Next, to assess the normal distribution of data, the Kolmogorov-Smirnov test was used. To compare the group means, one-way Analysis of Covariance (ANCOVA) was utilized to ascertain the controlled effects of the intervention and the extent of changes in the dependent variables. Levene’s test was applied to examine the homogeneity of variances, and repeated measures analysis was used to evaluate the stability of intervention effects over time.

Results

Table 1 presents the demographic information. Table 2 shows the descriptive statistics.

Table 1. Description of demographic characteristics

Variable		Frequency	Percentage (%)
Age (Year)	20-30	12	30.0
	30-40	9	22.5
	40-50	19	47.5
Gender	Female	23	57.5
	Male	17	42.5
Marital status	Single	19	47.5
	Married	21	52.5
Education	Intermediate school	5	12.5
	Diploma	15	37.5
	Associate degree	11	27.5
	Bachelor's	9	22.5

Table 2. Description of research variables

		CBT		tDCS		CBT + tDCS		Control	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Anxiety	Pre-test	50.70	1.69	44.50	1.44	39.50	9.65	35.20	1.00
	Post-test	28.30	6.65	35.00	5.75	38.00	3.55	35.50	10.03
Depression	Pre-test	36.40	4.45	36.70	5.31	43.90	11.36	38.50	3.92
	Post-test	30.40	4.85	35.20	4.91	27.90	5.15	38.50	3.92
Cognitive inhibition	Pre-test	38.40	4.29	43.40	3.53	40.10	5.64	40.00	4.59
	Post-test	21.00	3.46	23.20	4.73	23.70	2.58	40.00	4.59
Behavioral inhibition	Pre-test	38.50	4.32	42.50	5.23	41.70	5.01	49.10	4.86
	Post-test	21.50	3.30	34.50	9.02	26.66	9.56	49.10	4.86

The analysis of the acquired results is presented. Statistical analyses, including descriptive and inferential statistics, such as Analysis of Covariance (ANCOVA) and repeated measures tests, were used for data analysis. The results of Levene's test for examining the homogeneity of variances of the research variables across the groups are reported. The F statistic from Levene's test for anxiety, depression, cognitive inhibition, and behavioral inhibition is not significant. Given this non-significant finding (P> 0.05), it can be concluded that the variances of anxiety, depression, cognitive inhibition, and behavioral inhibition across the groups are equal.

Table 3. Results of one-way analysis of covariance for differences among groups

Variable	Source	Effect size	df	F statistic	Mean squares	P	Total squares
Anxiety	Pre-test	0.143	1	5.848	245.621	0.021	245.62
	Group membership	0.326	3	5.632	236.548	0.003	709.64
	Error		35		42.002		1470.079
Depression	Pre-test	0.184	1	7.887	148.483	0.008	148.483
	Group membership	0.548	3	14.129	265.994	0.000	797.981
	Error		35		18.826		658.917
Cognitive inhibition	Pre-test	0.051	1	1.898	28.790	0.177	28.790
	Group membership	0.814	3	50.939	772.690	0.000	2318.070
	Error		35		15.169		530.910
Behavioral inhibition	Pre-test	0.086	1	3.214	153.370	0.082	153.370
	Group membership	0.500	3	11.315	539.971	0.000	1619.914
	Error		35		47.721		1622.530

The results of the one-way Analysis of Covariance indicated that the F statistic for treatment adherence in the pre-test is 5.848, which is significant at the 0.02 level, indicating that there were significant differences among the groups regarding anxiety. The effect size of 0.14 suggests that this difference was notable in the population. To assess which group means are higher in the post-test anxiety after adjusting and controlling for pre-test scores, the F statistic for treatment adherence in the pre-test is 7.88, which was significant at the 0.00 level, indicating that there were substantial differences among the groups regarding depression. The effect size of 0.18 indicates that this difference was considerable and significant in the population. To examine which group means were higher in the post-test depression after adjusting and controlling for pre-test scores, the F statistic for treatment adherence in the pre-test was 1.89, which was not significant at the 0.17 level. This indicates that there were no significant differences among the groups in cognitive inhibition. The effect size of 0.05 suggests that this difference was not significant in the population.

To evaluate which group means are higher in the post-test cognitive inhibition after adjusting

and controlling for pre-test scores, the F statistic for treatment adherence in the pre-test was 3.214, which was not significant at the 0.08 level, indicating that there were no significant differences among the groups in behavioral inhibition. The effect size of 0.08 indicates that this difference was not significant in the population.

Table 4. Final estimated means in the group

Variable	Group	Effect size	P	t	Standard error	B
Anxiety	CBT	0.221	0.003	-3.153	3.166	-9.981
	tDCS	0.013	0.499	-0.684	2.997	-2.049
	CBT + tDCS	0.013	0.510	0.666	2.920	1.945
	Control group	.	.	.	.	0[a]
Depression	CBT	0.296	0.001	-3.833	1.953	-7.485
	tDCS	0.055	0.164	-1.423	1.949	-2.773
	CBT + tDCS	0.509	0.000	-6.029	2.020	-12.180
	Control group	.	.	.	.	0[a]
Cognitive inhibition	CBT	0.000	0.000	-10.639	1.756	-18.688
	tDCS	0.000	0.000	-9.664	1.807	-17.464
	CBT + tDCS	0.000	0.000	-9.369	1.742	-16.320
	Control group	.	.	.	.	0[a]
Behavioral inhibition	CBT	0.493	0.000	-5.745	4.008	-23.024
	tDCS	0.252	0.002	-3.382	3.474	-11.750
	CBT + tDCS	0.353	0.000	-4.307	3.712	-15.984
	Control group	.	.	.	.	0[a]

Based on Table 4, the mean of the first experimental group in anxiety was -9.981, the mean of the second experimental group was -2.049, and the mean of the third experimental group was 1.945. These differences were significant at a significance level of 0.00. Therefore, it can be said that the mean of the experimental groups in anxiety was significantly different. The beta value of the first experimental group was less than the other groups. Therefore, the first experimental group has changed more, and its effect size was 0.22. According to this finding, it can be said that cognitive-behavioral therapy and direct current stimulation therapy had a significant difference in reducing anxiety in methamphetamine (crystal) abusers. The mean of the first experimental group in depression was -7.485, the mean of the second experimental group was -2.773, and the mean of the third experimental group was -12.180. These differences were significant at a significance level of 0.00. The results of the second experimental group were not significant. Therefore, it can be said that the mean of the first and third experimental groups in depression was significantly different. The beta value of the third experimental group was less than the other groups. Therefore, the third experimental group has changed more, and its effect size was 0.50. According to this finding, it can be said that cognitive-behavioral therapy and direct current stimulation therapy had a significant difference in reducing depression in methamphetamine (crystal) abusers.

The mean of the first experimental group in cognitive inhibition was -18.688, the mean of the second experimental group was -17.464, and the mean of the third experimental group was -16.320. These differences were significant at a significance level of 0.00. According to this finding, cognitive-behavioral therapy and direct current stimulation therapy had a significant difference in cognitive inhibition in methamphetamine (crystal) abusers. Analysis of covariance was used to investigate the effect of cognitive-behavioral therapy and direct current stimulation therapy on behavioral inhibition in methamphetamine (crystal) abusers. The mean of the first experimental group in behavioral inhibition was -23.024, the mean of the second experimental group was -11.750, and the mean of the third experimental group was -15.984. These differences were significant at a significance level of 0.00. According to this finding, cognitive-behavioral therapy and direct current stimulation therapy had a significant difference in behavioral inhibition in methamphetamine (crystal) abusers. The first experimental group with an effect size of 0.493 has been most affected.

Discussion

Methamphetamine addiction (crystal meth) is one of the most complex challenges in the field of mental health, leading to physical dependence (21). Users often face issues such as increased anxiety, depression, impaired decision-making, reduced cognitive inhibition, and emotional regulation difficulties, which make the treatment process more challenging (22). Conventional treatment methods, such as pharmacotherapy and classical psychotherapy, have shown limited effectiveness in reducing cravings and improving cognitive and emotional functioning in these individuals (23). Therefore, it is necessary to employ innovative and combined interventions that can more effectively target the various dimensions of substance use disorder (24).

The findings of this study indicated that combined therapy was more effective in reducing depression, and inhibition than either treatment method alone. These results align with those of Rimmer (24) and Camacho-Conde et al. (10). Specifically, the combined intervention group showed a significant reduction in depression (25,26), along with notable improvements in cognitive inhibition (27) and craving reduction (28).

The results demonstrated that combined therapy not only facilitates cognitive processes but may also enhance regulation of brain activity related to impulse control and reward processing (29). Research suggests that combined interventions can amplify therapeutic effects, likely due to synergistic interactions between the cognitive and neural mechanisms of the two treatment approaches (30). While CBT helps individuals modify maladaptive cognitive patterns and develop new coping skills (31), tDCS facilitates the execution of these skills by stimulating brain regions associated with self-control and decision-making. The dorsolateral prefrontal cortex (DLPFC)—the primary target of tDCS in this study—plays a key role in impulse control, emotional regulation, and cognitive processing (32). Dysfunction in this region is a hallmark of methamphetamine (crystal meth) dependence, leading to increased impulsive behavior and reduced ability to resist cravings (33). Thus, stimulating this area via tDCS may help improve cognitive inhibition. Additionally, the results showed that depression reduction in the combined intervention group was significantly greater than in other groups, consistent with findings from Muench et al. (4). This suggests that tDCS may not only directly affect executive functions but also modulate activity in emotion-processing regions (e.g., amygdala and orbitofrontal cortex), thereby contributing to reduced anxiety and depression (20). On the other hand, CBT focuses on modifying negative beliefs and teaching emotion regulation skills, helping patients develop more effective stress and negative emotion management strategies (32). The combination of these two approaches likely enables patients to not only change cognitive patterns but also achieve greater neurophysiological adaptation to new conditions (11).

Compared to previous studies, the findings of this research highlight the superiority of combined therapy over single-method treatments (18). Importantly, when tDCS was used alongside CBT, the effects were more sustained, with participants showing continued improvement not only in the short term but also in later treatment stages. This is because CBT induces lasting cognitive and behavioral changes that stabilize the effects of tDCS (7).

However, this study has several limitations. A key challenge was the lack of long-term follow-up to assess the durability of therapeutic effects. While the results confirmed the efficacy of combined intervention, it remains unclear how long these effects persist. Some studies suggest that long-term follow-ups could provide valuable insights into the sustainability of these changes. Additionally, the sample size was relatively small, and future research with larger, more diverse groups could improve the generalizability of the results.

Conclusion

The findings of this study demonstrated that the combination of cognitive-behavioral therapy and transcranial direct current stimulation is an effective approach for reducing clinical symptoms and improving neuropsychological functioning in methamphetamine (crystal meth) users. This intervention can serve as a novel, non-invasive treatment option, enhancing patients' quality of life and facilitating their recovery process.

Given the limitations of traditional treatments, the use of such combined methods may provide more effective solutions for substance dependence treatment.

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Conflict of Interest

The authors declare no conflict of interest.

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Ethical Considerations

This article is derived from a study approved by the Research Ethics Committee of Islamic Azad University, Bojnourd Branch.

Code of Ethics

IR.IAU.BOJNOURD.REC.1401.024. IRCT code: IRCT20230318057753N1

Authors' Contributions

Morteza Modarres Gharavi: Study design, writing and editing the manuscript, Mahdi Helmzadeh: Data analysis, writing, and revising the manuscript, Mahdi Ghasemi Motlagh: Data interpretation.

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