

Original Article

Effectiveness of Transcranial Direct Current Stimulation (tDCS) on Methamphetamine Craving

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Abstract

Introduction: Transcranial Direct-Current Stimulation is one of the most challenging version of non-invasive brain stimulation. Although it has promised effects on drug-cravings, it has not been approved by FDA as an intervention.The purpose of this study was to investigate the effectiveness of tDCS on reducingmethamphetamine craving.

Method: This study was a quasi-experimental design with the pre-test, post-test and control group. The statistical population included all the methamphetamine users who were referred to the HematPayrovan Institute for treatment in 2019. The sample population were 60 males assigned randomly into two groups of experimental and control group. We applied 20 minutestDCS (2 Ma, Anode F4/Cathode FP1) for experimental group. Data were collected using the Individual Student Assessment Plan (ISAP), The Leeds Dependence Questionnaire (LDQ), and Desires for drug questionnaire (DDQ). The data were analyzed through multivariate analysis of covariance (MANCOVA).

Results: The result showed that t DCS significantly decreases methamphetamine craving in the experimental group ($P<0.03$).

Discussion: This finding has important implications pertaining the education and mental health of methamphetamine users. Based on the results, repeated DLPFC stimulation could be a promising approach for therapeutic intervention in decreasing methamphetamine craving.

Declaration of Interest: None

Keywords: Transcranial Direct-Current Stimulation, Methamphetamine, Craving

Introduction

Drug addiction, also known as substance use disorder (SUD), is a severe threat to physical and psychological health of individuals, which affects at least 275 millions of people all over the world (1,2). This medical condition is defined as the compulsive active use of substances regardless of the potential harms. The diagnostic criteria include withdrawal symptoms, craving, physical and mental illness, etc. (3). Methamphetamine is an extremely addictive psycho-stimulant drug that has developed early in the 20th century from its parent drug, amphetamine, and was used originally in nasal decongestants and bronchial inhalers (4). The clinical effects of methamphetamine include increased alertness and aggression, loss of appetite and insomnia. (5). Medically it may be indicated for the treatment of attention deficit hyperactivity disorder and as a short-term treatment for weight loss (6,7), but these uses are limited and it is rarely prescribed.Also, the prescribed doses are far lower than those typically abused (8). This substance is mostly popular among young adults, due to its availability, long duration of psychoactive effects, and comparatively low costs (4,7). Methamphetamine is a powerful, highly addictive stimulant that affects the central nervous system and the monoamine neurotransmitter system of the brain (9).

Addictions involve persistent, compulsive, and uncontrolled behaviors that are both maladaptive and destructive (1,3). The role of mesocorticolimbic dopaminergic and glutaminergic pathways, intracellular mechanisms, and relevant brain regions in compulsive drug drive and inhibitory dyscontrol have been the focus of these sections on drug relapse (9,10). Most kinds of SUDs are generally considered to originate from abnormality in dopamine (DA) system (11) and increase extracellular concentrations of mesolimbic dopamine (12,13). Meth-craving is stronger comparative to other drugs probably based on its high speed of inducing mesolimbic dopamine (10).Its abstinence period is longer than others due to its recurrent cravings which made the treatment so hard (14). The bunch of imaging studies have revealed that the repeated use of amphetamine-like substances will down-regulate DA release and DA receptor availability (14) which results in the attenuation of projections to the cortical areas such as the dorsolateral prefrontal cortex (DLPFC), and orbitofrontal cortex (15). These regions of brain are responsible for executive control functions or salience attribution to the external stimuli (16). This might explain why the abusers are hardly able to control the craving and consumption of drugs (16,17). In general, the dysfunction of dopamine system plays a central role in drug addiction (14) and this notion has inducted the development of neurobiological treatments including brain stimulations.

Transcranial direct current stimulation (tDCS) is the last generation of non-invasive brain stimulation (NIBS)which has broad applications in cognitive enhancement and treatments (18).tDCS modulates brain activity noninvasively (18,19). tDCS is of major current contribution to the treatment of different brain disorders such as stroke, epilepsy, aphasia after stroke, depression, and binge eating disorder (20-23). In other applications, tDCS has been successfully

employed on healthy subjects e.g. to increase motor function (24) and cognitive brain function (25). The findings of the studies indicate that the anode tDCS could increase excitability in motor areas, while cathodaltDCS induces inhibition (18). Although inducing direct action potential is not imagined because of its weak electric currency, it could raise/lower neural threshold through increasing/decreasing cell membrane Na^{+}/Ca^{2+} permeability in a polarity dependent manner (26). Its restricted penetration is not only considered as limitation, but also advantageous element which could satisfy fastidious psychiatrics for its restricted side effects (18,19).

Numerous studies suggest the effects of brain stimulation on the dopamine system. Some studies show that tDCS could induce DA release (27). Likewise, DA transporter accessibility in caudate nucleus goes up after a high-frequency repetitive transcranial magnetic stimulation (rTMS) on DLPFC in a recent case study (28). Moreover, tDCS on bilateral DLPFC elicits DA increase in the same region as well (29). A meta-analysis investigated the effect of NIBS toward DLPFC on craving for food or stimulants and reported a medium treatment effect (30). These findings may be indicative of the effectiveness of brain stimulation in reducing meth craving through changes in DA. Accordingly, and considering the need for effective therapeutic approaches to reduce meth craving, this study investigated the effects of repeated tDCS over the DLPFC on decrease meth craving.

Method

This research has been conducted by a semi-experimental method with pretest-posttest design and control group. In this research, treatment methods have been considered as independent variables at two levels (tDCS and no intervention), and meth craving has been considered as dependent variable. The research population includes all the methamphetamine users who were referred to the HematPayrovan Institute for treatment in 2019. The sample includes 60 methamphetamine users who have been selected by convenience sampling and randomly assigned to experimental and control groups. The sample size was determined by using the following formula. As the population was specific and limited, the sample size was obtained by the following formula with an accuracy of 5% and a confidence level of 95%.

$$n = \frac{N Z^2_{\frac{\alpha}{2}} pq}{(N-1)d^2 + Z^2_{\frac{\alpha}{2}} pq}$$

The inclusion criteria included: passing SCID-8 as an approved drug-dependent criterion, history of methamphetamine use at least 6 months based on DSM-V criteria, use at least 3 times per week over the past 6 months, male with at the age of 21-50 years. The exclusion criteria included: female gender, history of brain trauma, epilepsy, brain surgeries/metal implants or tumors.

Data collection was done by using the following tools:

- Individual Student Assessment Plan (ISAP): ISAP is a standard demographic questionnaire that is initiated by Iranian National Center for Addiction Studies (INCAS) for evaluating demographic characteristics and different addiction-related dimensions.

- The Leeds Dependence Questionnaire (LDQ): LDQ is a self-reported, 10-item questionnaire, validated to be used in

addiction and psychiatric settings for alcohol and opiate consumers to measure substance dependence severity [19, 20]. The LDQ (31) is composed of 10 items, which are scored with 4 digits: 0-1-2-3 (0 = never, 1 = sometimes, 2 = often, 3 = nearly always) measuring the severity of dependence upon substances, independent of the pharmacological properties or the quantity of substances overused. The operational definitions given to the 10 cognitive and behavioral markers of substance dependence by Raistrick et al. (31), representing the ICD-10 and DSM-IV criteria for substance dependence, are pre-occupation, salience, compulsion to start, planning, maximize effect, narrowing of repertoire, compulsion to continue, primacy of effect, constancy of state and cognitive set (items from 1 to 10, respectively). The LDQ total score increases with the degree of substance dependence, but no cut-off score indicating dependence has been identified. High LDQ scores are associated with cognitive preoccupation with substance use, a compulsion to use, continual use, planning and organizing future use, maximization of the subjective experience of substance use, a reduced repertoire of behaviour with the primacy of substance use and substance use as an existential coping strategy.

- Desires for drug questionnaire (DDQ):

The original DDQ includes 13 questions for three main craving components, desire and intention to drug use (questions 1, 2, 4, 6, 10, 13 and 14), negative reinforcement (questions 5, 9, 11 and 12), and control (questions 3 and 8). We restored the question, which had been excluded from the final questionnaireby Franken, et al (2002), in order to increase the internal consistency of its respective component, in our questionnaire (R: question 7). Participants answer questions on a seven-step Likert-scale answer sheet based on what he/she feels or thinks at the moment. The items were 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.

- Transcranial direct current stimulation (tDCS)

Direct currents of 2 mA generated by an electrical stimulator were applied through a pair of saline-soaked sponge electrodes (7 × 5 cm) for 20 min. In both, active and sham conditions, to stimulate the left DLPFC, the anode electrode was vertically positioned over F4 the cathodal reference electrode was horizontally positioned over FP1. The electrode placement and method of localization is in accordance with previous tDCS studies, and has shown to produce significant effects on reducing cravings in a range of studies. For sham stimulation, the person receiving the tDCS did not know that they are not receiving prolonged stimulation. The experimenter who applied tDCS was blind to the study hypotheses but not to the tDCS condition (active vs sham).All of participants could tolerated repeated sessions with no major side effect and none of them given up for this reason, Most prevalent side effects are numbness or tingling 20%, headache 14%, sleepiness 5%.

Before intervention, participants were divided in test and sham group accidentally in a double-blinded manner and were hidden throughout the intervention. Participants filled LDQ and DDQ in 5^{th}, $12^{th}15^{th}$, 18^{th}, 42^{th}, 72^{th}, 102^{th}, 132^{th} and 162^{th} day in order to have cross sectional assessment of craving through

and after the research. Consequently, we had 4 variables (3 component of DDQ and 1 from LDQ) indicating four dimensions of Meth-craving from 2 separate groups. Data were analyzed in SPSS 21 software.

Result

We start with 60 Meth-dependent males but only 46 people could complete the study. According to table 1 the test group contains 23 males (28 ± 6) and the control one has also 23 males (38 ± 8). Their first age of drug consumption was 21± 5 and 24 ± 7 respectively. Both groups have the average duration of dependency for 7 ± 4.5 years.

Table 1: Demographic descriptive information of test and control group

		Experimental group	Control group
Age		28 ± 6	31 ± 8
Education level		10 ± 2	10 ± 2
Marital status	Married	4.4%	22%
	single	86.9%	60%
	Divorced	8.8%	17.4 %
Injection history		13%	26%
Record of imprisonment		26%	26%
History of drug trafficking		39%	35%
Methamphetamine abuse	Age of onset of consumption	21±5	24±7
	Number of years of consumption	7 ± 4.5	7 ± 4.5
Nicotine and Tobacco	Number of years of consumption	14 ± 7	11 ± 8
Opioids	Number of years of consumption	2 ± 2.5	2 ± 3
Alcohol	Number of years of consumption	9 ±7	8 ± 8

Table 2 presents the mean and standard deviation of quality of life for patients affected by macular degeneration in control and experimental groups based on the pretest and posttest results.

Table 2: Mean and standard deviation of depression scores of control and experiment groups in pretest and posttest

Quality of life		Experimental group		Control group	
		Mean	SD	Mean	SD
DDQ1	Pretest	41.51	15.98	40. 14	18.04
	Posttest	6.78	1.43	28.68	15.12
DDQ2	Pretest	34.89	18.86	31.36	16.97
	Posttest	7.49	1.92	18.89	13.88
DDQ3	Pretest	25.98	22.31	21.41	15.59

	Posttest	9.61	6.49	10.33	9.56
LDQ	Pretest	16.17	5.38	15.87	5.35
	Posttest	3.96	2.74	10.30	4.94

As seen in the table, there is asignificant difference between the mean posttest scores of DDQ and LDQ in the control and experimental groups; in the experimental group, the mean scores of DDQ and LDQ in posttest are lower than the scores of pretest.

In order to observe the assumptions of parametric tests, Box and Levene's tests were used before using the parametric test of multivariate analysis of covariance. The results of the Box test were not significant for any of the variables; based on this test, the presumption of homogeneity of variance/covariance matrixes have been well observed (Box=3.17, F=0.88, P=0.29). According to the results of Levene's test, the presumption of equality of intergroup variances has been observed for posttest and its insignificant results for all variables ($p>0.05$). P-value was not lower than 0.05 in One-Sample Kolmogorov-Smirnov Test, which means that the distribution is not normal then non-parametric evaluation is needed. So, multivariate analysis of covariance can be done. The results of Wilks Lambda showed that there is a significant difference between the posttest of the studied groups in terms of at least one of the dependent variables (Wilks Lambda= 0.74, F=4.89, $P < 0.001$). According to the results of eta-squared, it was found that the difference between the two groups is significant regarding the dependent variables and this difference in posttest is 73% based on Wilks Lambda (eta squared=0.73); i.e. 73% of the variance is related to the difference between the two groups which results from the mutual effect of dependent variable of DDQ and LDQ.

Table 3. The results of the analysis of covariance

Variable	Source of change	SS	Df	MS	F	Eta squared
DDQ1	Group	6555.55	1	6555.55	11.03	0.20
	Error	26162.62	44	594.61		
DDQ2	Group	2843.81	1	2843.81	4.95	0.10
	Error	25293.73	44	574.86		
DDQ3	Group	11.31	1	11.31	0.02	0.00
	Error	240.94	44	2.83		
LDQ	Group	774.28	1	774.28	8.84	0.17
	Error	3853.18	44	87.57		

As presented in table 3, with the controlled effect of pretest, there is a significant difference between the posttest results of experimental and control groups in terms

of the mean scores of DDQ1 (F=11.03), DDQ2 (F=4.95), and LDQ (F=8.84), ($P < 0.05$). In other words, in posttest of the experimental group, tDCS has significantly decreased DDQ and LDQ in methamphetamine users.

Discussion and Conclusion

The aim of this study was to determine the effectiveness of tDCS in reducing meth craving. According to the findings of the study, tDCS had an effect on reducing meth craving in methamphetamine users, which is consistent with the results of previous studies (27-30, 33, 34). In this study the best montage for meth craving which was 2 ml A, 20 min on Anode F4 and cathode FP1which was on consensus of pervious researches. Fregni et al. (33) showed that anodal stimulation of both left and right DLPFC with active, but not sham, tDCS reduced smoking craving compared to baseline. Furthermore Boggio et al. (34) found that both anodal left/cathodal right and anodal right/cathodal left tDCS significantly decreased alcohol craving compared to sham stimulation. Finally, this effect was also found for marijuana craving. Boggio et al. (2010) observed that right anodal/left cathodaltDCS of DLPFC reduced craving for marijuana.

Different underlying mechanisms have been suggested for tDCS considering its varied effects. The wide variation of its effects on the same disorders which decrease its significance is also explained by different levels of extracellular dopamine. tDCS was proposed to have the potential ability to act through different neural mechanisms in different time courses. Its Anode's after effect is attributed to cell membrane permeability to positive ions which could reduce neural threshold excitability (27). Neuro-modulatory effects of tDCS, especially on dopamine, would be the first candidate for its durable effects on drug-craving. Since tDCS has enough time to neutralize meth-induced dopamine receptors gradually from down-regulation (29), this would be a good explanation for its neuro-plastic effects on addiction-induced neuro-adaptations.

Often tDCS studies had targeted the DLPFC area as a current location for the stimulation brain. It is well indicated that the DLPFC is critically involved in the processing of drug craving. Furthermore, drug-dependent individuals exhibit lower resting and metabolic activity in PFC (28). The DLPFC integrates cognitive, emotional, and motivational information in order to make a decision and regulate emotion, motivation, and internal state and uses this information to regulate drug seeking and drug avoiding behaviors (21,28). According to these findings, and considering mechanisms of anodal tDCS in facilitating spontaneous neuronal activity and reinforcing local plasticity (30), we conjecture that anodal stimulation enhances DLPFC activity, which may inhibit drug-seeking behavior.

According to conceptualization of drug addiction, the craving stage involves neuro-plastic changes in the brain reward system, stress, and executive function systems (33). Here, PFC regions play a critical role, especially the DLPFC. Deficits in executive functionsin individuals with SUD are reflected by decreases in frontal cortex activity that interfere with decision-making, self-control, emotionregulation, and planning, which lead tocompulsive drug use and deficiency of control in addiction (21). On the basis of previous studies and the present results, we speculate that

stimulation of the DLPFC with anodal tDCS may have increased excitability and functional connectivity in this region and other networks involved in addiction and thereby resulted in increased control of drug-seeking behavior.

tDCS anodal excitation could play a semi-natural role in neural activities because of its gentle and gradual influences. Its potentiality of being repeated provides enough time for changing receptor activities (33). This opportunity is not available for any drug because of their limitations due to their side effects (34). Additionally, drugs lead to a similar neuro-adaptation with is proposed as the basic underlying mechanism of addiction. Other NIBS such as rTMS could not be repeated because of its strong annoying effects.

Our findings indicated that active prefrontal tDCS reduces craving at meth users. This may reflect the role of the prefrontal cortex in top-down craving modulation. These results offer initial promising information to support further studies investigating tDCS as a clinical application for meth craving in methamphetamine users.

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