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Modulation of Drug Craving in Crystalline-Heroin Users by Transcranial Direct Current Stimulation of Dorsolateral Prefrontal Cortex

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Original Article

Abstract

Background: Drug craving, the main cause of relapse and a major motivator for drug use, is a challenging obstacle in substance use treatment. Transcranial direct current stimulation (tDCS), a non-invasive neuromodulatory technique, has shown promising outcomes in treating different neuropsychiatric disorders such as drug addiction, more specifically on drug craving. The aim in the current study was to examine the effects of applying tDCS on dorsolateral prefrontal cortex (DLPFC) in reducing drug cravings in former crystalline-heroin users enrolled in methadone maintenance (MMT) programs.

Methods: The present study was a semi-experimental, crossover study with pre/post-test, and a control group. 40 right-handed men were selected from former crystalline-heroin users enrolled in MMT programs in Tehran, Iran. They were then divided into two matched groups based on age, education, and age of onset crystalline-heroin abuse. Desire for Drug Questionnaire (DDQ) was administered two times to all of the subjects, before first brain stimulation, and at the end of the last session. Experimental group received TDCS on DLPFC, and sham stimulation was applied on control subjects. The data were analyzed by analysis of covariance (ANCOVA) method using SPSS software.

Findings: The study results indicated anodal tDCS over right and cathodal TDCS over left DLPFC, and in parallel with sham, significantly decreased drug cravings among former crystalline-heroin users ($P < 0.050$).

Conclusion: This study showed that applying TDCS on DLPFC of former crystalline-heroin users reduces drug craving. The findings of this study expanded the results of previous studies on effects of this neuromodulatory technique for drug craving reduction in other drug type settings.

Keywords: Heroin; Dorsolateral prefrontal cortex; Craving; Transcranial direct current stimulation

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Introduction

According to the World Drug Report, the global prevalence of opioid use (including heroin) is about 0.7% of the population aged 15-64 years old and it is estimated that 32.4 million people use opioids all over the world.[1] "Crystalline-heroin", which is known with the street name of "heroin-crack" in Iran, is odorless and easy to use.[2]

Drug craving, a state which motivates drug dependents to seek and use drugs,[3] is the most important problem during addiction treatment,[4,5] and higher craving is known to be related to a higher risk for relapse.[6] Without any solution to this problem, patients with substance dependency problems experience numerous relapses. Recently, many studies in the field of non-invasive neuromodulatory techniques have concentrated on new brain stimulation strategies for addiction treatment and have successfully shown that transcranial direct current stimulation (tDCS) has promising affirmative results on some aspects of substance dependency such as drug craving.[7,8] Studies have indicated tDCS effect on cue-induced craving among crack-heroin abusers.[9] TDCS modulates cortical excitability in a polarity-dependent manner, that is, anodal tDCS causes depolarization increasing cortical excitability, but cathodal tDCS causes hyperpolarization which decreases cortical excitability at stimulated sites.[10]

Studies have demonstrated diminished functioning of dorsolateral prefrontal cortex (DLPFC)[11] associated with the regulation of cognitive, emotional, and motivational processes[12] in substance dependency.[13] Presumably, the above-mentioned changes in brain function are the underlying factors for relapse in substance dependency. Studies based on cerebral imaging have shown that the activity of DLPFC is associated with craving.[14] Applying tDCS on DLPFC is effective in controlling cue-induced craving for alcohol,[15,16] food,[17-19] smoking,[20,21] cannabis,[22] and methamphetamine.[7]

Craving and relapses are the key elements of drug addiction. The main treatment for opium's craving is methadone maintenance (MMT) therapy which has limited efficacy to defeat drug craving. Thus, alternative treatments are needed to improve therapeutic techniques.

The objective in this study was to test the modulation of coincident craving through applying non-invasive tDCS on DLPFC in former crystalline-heroin users enrolled in MMT programs in Iran. In the present study, the differences of anode over right DLPFC, cathode over left DLPFC, and reverse montage in parallel with sham stimulation were tested.

Methods

Subjects were recruited from among former crystalline-heroin users enrolled in MMT programs in 10 addiction treatment centers in Tehran, Iran. A total of 40 subjects were enrolled and divided into two groups, 20 each, of experimental and control. Inclusion criteria were: right handed men, age between 25 and 50, previous use of crystalline-heroin with duration of at least 12 and at most 24 months, at least five years of education, and ability to read and understand the questions. In addition, the exclusion criteria included: any current or past major clinical neurologic disorders, taking any drugs affecting central nervous system (CNS), history of epilepsy, brain surgery, brain tumor, intracranial metal implantation, or clinically significant head trauma, and any major clinical psychiatric disorders except addiction [according to Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5)]. The study protocol was accepted by ethics committee of Karaj Branch, Azad University, Karaj, Iran, and registered in Iranian Registry of Clinical Trials (IRCT) in 2016 with the code IRCT2015120625384N1.

This was a double-blind, randomized, and sham controlled crossover study. The study was conducted as a semi-experimental study (pre/post-test with control group). The subjects in control and experimental groups received sham stimulation in the first session. During two intervention sessions,[7] tDCS was applied in two different configurations (right cathode/left anode and right anode/left cathode) on subjects in the experimental group randomly. The sessions were conducted by an expert technician. In the experimental group, a 2 mA current was applied for 20 minutes.[23] To exclude the carryover effect of multiple stimulations, experiments were separated with a time interval of 72 hours. Before enrolling the subjects, the study was explained in detail to each participant and informed consent was obtained from them.

Table 1. Demographic characteristics and drug use profile among former crystalline-heroin users (n = 20 in each group)

Variable	Groups		t-test	
	Experimental group (mean ± SD)	Control group (mean ± SD)	df	P
Age (year)	37.950 ± 8.035	38.400 ± 7.014	38	0.851
Education (year)	11.700 ± 2.848	11.450 ± 2.416	38	0.766
Age of onset (year)	32.850 ± 66.175	30.950 ± 7.897	38	0.402

SD: Standard deviation; df: Degree of freedom

During structured interviews, demographics and substance use variables were recorded for each participant using Clinical Drug Addiction Profile (CDAP) questionnaire.[24] This profile was previously designed for structured interviews to evaluate demographics and other addiction-related aspects among drug users in Iran.

Desire for Drug Questionnaire (DDQ) was answered by the subjects in both groups at the beginning of the first session. Afterwards, direct current (DC) was applied using two electrodes with saline soaked sponge covers (5 × 7 = 35 cm^2). At the end of each session, the subjects were asked to answer DDQ again. Each session ended by filling the tDCS side effects checklist.

In each session, stimulations were carried out using one of the following three methods:

a. Anode stimulation at the right DLPFC and cathode stimulation at the left side; anodal and cathodal tDCS were attached to F4 and F3 regions, respectively.

b. Cathode stimulation at the right DLPFC and anode stimulation at the left side; anode and cathode were attached to F3 and F4 regions, respectively.

c. Sham stimulation in which the electrodes were used at the same places as with the actual stimulation. The difference was cutting the power after 30 s of stimulation. The subjects felt itching and stinging primarily.

tDCS: DC was delivered from a battery-driven, direct current stimulator (ActivaDose®II, Iontophoresis Delivery Unit, USA) and transmitted by a pair of (5 × 7 = 35 cm^2) electrodes. The electrodes were standard carbonic, covered with normal saline soaked sponge cases.

DDQ: Craving for Crystalline-heroin was evaluated using the DDQ, which consists of 14 questions and has three main elements including desire and intention to use, negative reinforcement, and deficit of control.[25]

All data were presented as mean ± standard deviation (SD) or frequency. Statistical analysis was performed by SPSS software (version 22, IBM Corporation, Armonk, NY, USA) using analysis of covariance (ANCOVA). An α level of less than 0.050 was considered to be significant.

Results

Demographics and tDCS side effects: In this study, 40 male former crystalline-heroin users enrolled in MMT programs were investigated. Demographics and drug use characteristics of the subjects are presented in table 1. All subjects experienced tDCS without any major problem. Frequencies of side effects occurring during the sessions and difference among 3 groups are presented in tables 2 and 3.

Table 2. Transcranial direct current stimulation (tDCS) side effects frequency among former crystalline-heroin users (n = 20 in each group)

Side effects	Anode right/cathode left	Cathode right/anode left	Sham
Headache	8	10	14
Vertigo	6	5	2
Tingling	9	10	10
Itching	5	8	13
Dizziness	6	5	2
Drowsiness	10	8	1
Nausea	2	1	0

DDQ subscales: Post-test means of all DDQ subscales for right anode stimulation were significantly different from their corresponding values for sham stimulation (table 4). In contrast, there were no significant differences between post-test means of DDQ subscales for right cathode stimulation and corresponding sham stimulation means (table 4).

Discussion

Results of the study indicated that applying anode right/cathode left tDCS on DLPFC significantly decreased craving among former crystalline-heroin users in comparison to sham stimulation.

Table 3. Difference among three groups in terms of frequency of transcranial direct current stimulation (tDCS) side effects

Sources	Sum of squares	df	Mean square	F	P
Between groups	2.000	2	1.000	0.055	0.947
Within groups	329.143	18	18.286		
Total	331.143	20	-		

df: Degree of freedom

Ineffectiveness of right cathode/left anode current stimulation on DLPFC in reduction of drug craving among crystalline-heroin users was also observed.

The results showed significant effect of right anodal current stimulation on DLPFC in reduction of crystalline-heroin craving among the subjects. This is in agreement with the studies conducted by Boggio et al.[15,22] regarding craving for alcohol and cannabis, Fregni et al.[18,21] on craving for food and cigarettes, Goldman et al.[17] on craving for food, Conti and Nakamura-Palacios[26] on craving for crack-cocaine, Fecteau et al.[27] on craving for cigarettes, and Shahbabaie et al.[7] on craving for methamphetamine, who found significant reduction in cravings due to different drugs with right anodal/left cathodal current stimulation on DLPFC.

The results regarding cathode right/anode left stimulation are in agreement with Boggio et al.[22] who showed that there was no relationship between right cathode/left anode stimulation and craving for cannabis. On the other hand, the results of the present study were in disagreement with studies by Boggio et al.[15] on craving for alcohol, Fregni et al.[18] on craving for food, and Fregni et al.[21] on craving for cigarettes, which indicated that right anodal/left cathodal and right cathodal/left anodal DLPFC stimulation had significant relationship with reduction of craving among users of the afore-mentioned drugs. Moreover, da Silva et al.[16] argued that right cathodal stimulation of DLPFC had significant relationship with reduction of cravings for alcohol.

Chronic use of addictive substances leads to an increase in the activity of the dopaminergic reward pathway.[28] Furthermore, drug abstinence is associated with a reduction in the activity of the dopaminergic reward pathway which in turn activates craving and relapse.[29] Human and animal model studies have indicated that frontal cortex stimulation leads to dopamine release in the mesolimbic pathway. The increased stimulation in the dopaminergic pathway may act like substance effect in the mesolimbic pathway leading to temporary reduction in craving.[30] Another possibility is that phasic dopamine release promotes drug seeking behaviour and motivates individuals to focus on stimuli and approach goal directed behaviour.[31] Prefrontal cortex is the area regulating attention and motor output.[32] Stimulation of DLPFC by tDCS may cause an increase in phasic dopamine release, hence leading to reduction in drug seeking behaviour.

According to the findings, two-sided stimulation of DLPFC is more effective than the one sided approach; it increases activity on one side and decreases activity on the other side.[33] Simultaneous right anodal/left cathodal stimulation of DLPFC facilitates neuronal activities and improves neuroplasticity. Probably, right anodal stimulation increases DLPFC activity, which may result in a decrease in drug seeking behavior.[34] Craving in crystalline-heroin dependent smokers activates specific circuits in their brain.

Table 4. Scores of Desire for Drug Questionnaire (DDQ) subscales during right anode/left cathode and right cathode/left anode in comparison to sham transcranial direct current stimulation (tDCS) among crystalline heroin users (n = 40)

DDQ subscales	Right anode tDCS		P	Right cathode tDCS		P
	Before stimulation (mean ± SD)	After stimulation (mean ± SD)		Before stimulation (mean ± SD)	After stimulation (mean ± SD)	
Desire and intention	10.800 ± 1.735	9.550 ± 1.356	0.001*	11.800 ± 1.673	11.750 ± 1.713	0.974
Negative reinforcement	10.650 ± 4.030	8.200 ± 3.503	0.001*	7.000 ± 3.356	7.700 ± 3.213	0.283
Deficit of control	5.700 ± 2.866	4.500 ± 2.503	0.006*	6.400 ± 2.186	6.050 ± 2.235	0.177

DDQ: Desire for Drug Questionnaire; tDCS: Transcranial direct current stimulation; SD: Standard deviation
*Denotes a statistically significant difference

The prefrontal circuitry has been strongly implicated in regulating functions related to the control of behaviours such as response-inhibitory and compulsive desire to consume drugs.[12] Therefore, the neuromodulations induced by stimulation may contribute to the improvement of inhibitory control,[35] and as a result, reduce drug seeking behavior.[31]

There were some limitations in this study. Firstly, the subjects in this work were patients under treatment; their brain activity might be different from current users or abstinent subjects. Secondly, the current study did not include a follow-up period in order to find out whether tDCS effect on craving reduction would be maintained. Additional studies with more participants and therapeutic sessions, as well as follow-up studies in current heroin users, abstinent subjects, and subjects enrolled in MMT programs who were previously addicted to heroin are suggested.

Conclusion

In conclusion, the findings in this study suggest that 20 minutes right anodal/left cathodal DLPFC stimulation might be able to reduce craving for crystalline-heroin. It is likely that, repeating the intervention may prolong the effects, which can be subject for future studies. Moreover, follow-up studies can show the long-time efficacy of this method for treatment of heroin users. It is believed that there is no single method of therapy for solving the drug addiction problem. Therefore, given complicacy of pathological aspects of drug dependence disorders, the best approach is the one that deals with different aspect of the problem at the same time, and is free of shortcomings such as recurrence, short-term effectiveness, and side effects. This concept needs further examinations.

Conflict of Interests

The Authors have no conflict of interest.

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تغییرات ولع مصرف در مصرف‌کنندگان کراک- هروئین با استفاده از تحریک الکتریکی مستقیم ناحیه پیش‌پیشانی پشتی- جانبی مغز از روی جمجمه

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مقاله پژوهشی

چکیده

مقدمه: ولع مصرف مواد، عنصری کلیدی در بازگشت و آغازگر اصلی استفاده از مواد و مانع چالش‌برانگیز در درمان مصرف مواد است. تحریک الکتریکی مستقیم مغز از روی جمجمه، نوعی روش غیر تهاجمی تحریک مغز می‌باشد که نتایج امیدبخشی در درمان اختلالات عصب- روان‌شناختی مانند اعتیاد به مواد و به ویژه ولع مصرف مواد دارد. پژوهش حاضر با هدف بررسی اثربخشی تحریک الکتریکی مستقیم ناحیه پیش‌پیشانی پشتی- جانبی مغز از روی جمجمه بر کاهش ولع مصرف در مصرف‌کنندگان سابق کراک- هروئین تحت درمان نگهدارنده با متادون انجام شد.

روش‌ها: این مطالعه از نوع شبه آزمایشی مقطعی، با مراحل پیش‌آزمون و پس‌آزمون و گروه شاهد بود. بر اساس روش نمونه‌گیری در دسترس، ۴۰ مرد راست دست از میان مصرف‌کنندگان سابق کراک- هروئین تحت درمان نگهدارنده با متادون در تهران انتخاب شدند و از نظر سن، تحصیلات و زمان شروع مصرف کراک- هروئین، در دو گروه همتا قرار گرفتند. پرسش‌نامه ولع مصرف پایه (Desire for Drug Questionnaire یا DDQ) دو بار، قبل از اولین تحریک و در پایان تحقیق برای همه شرکت‌کنندگان تکمیل شد. تحریک الکتریکی مستقیم ناحیه پیش‌پیشانی پشتی- جانبی مغز برای گروه آزمایش و تحریک شم برای گروه شاهد انجام گردید. داده‌ها با استفاده از روش کواریانس در نرم‌افزار SPSS مورد تجزیه و تحلیل قرار گرفت.

یافته‌ها: تحریک آندال راست/ کاتدال چپ به طور معنی‌داری ولع مصرف را در مصرف‌کنندگان سابق کراک- هروئین در مقایسه با تحریک شم کاهش داد.

نتیجه‌گیری: استفاده از روش تحریک الکتریکی مستقیم مغز از روی جمجمه بر ناحیه پیش‌پیشانی پشتی- جانبی مصرف‌کنندگان سابق کراک- هروئین می‌تواند ولع مصرف را کاهش دهد. یافته‌های به دست آمده، منجر به گسترش نتایج مطالعات پیشین بر اثرات تحریک مغزی در کاهش ولع مصرف انواع دیگر مواد می‌شود.

واژگان کلیدی: هروئین، ناحیه پیش‌پیشانی پشتی- جانبی، ولع، تحریک الکتریکی مستقیم مغز از روی جمجمه

ارجاع: شریفی فردشاد مونا، مهربان اشتهاردی مهدی، شمس اسفندآباد حسن، شریعتی‌راد شوان، مولوی نادر، حسنی ابهریان پیمان. **تغییرات ولع مصرف در مصرف‌کنندگان کراک- هروئین با استفاده از تحریک الکتریکی مستقیم ناحیه پیش‌پیشانی پشتی- جانبی مغز از روی جمجمه.** مجله اعتیاد و سلامت ۱۳۹۷؛ ۱۰ (۳): ۱۷۹-۱۷۳.

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