Title: The Effect of Different tDCS Protocols on Drug Craving and Cognitive Functions in Methamphetamine Addicts

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Abstract

Background and objective: Drug craving is considered to be a major problem in addiction treatment. Neuroimaging research has revealed various areas for drug craving, among which two key areas are the dorsolateral prefrontal cortex (DLPFC) and the cerebellum. The DLPFC is involved in different cognitive tasks like the inhibitory control over seductive options harboring the promise of immediate reward. The cerebellum considered to be related to cognition and memory and gets activated by drug-related cues. Therefore based on the previous researches we decided to study the effects of applying tDCS on six different protocols in reducing Drug Craving and increasing Cognitive Functions in Methamphetamine Addicts.

Methods: The present study is a semi-experimental, with pre/post-test, and a control group. Based on a simple sampling method, 15 male methamphetamine addicts in two rehabilitation centers in Tehran were recruited. The participants were 18-65 years old with a minimum 12-month history of methamphetamine dependence. Visual Analog Scale (VAS), The Go/No-Go Task and The N-Back Task was administered before and after single session of tDCS. tDCS applied on six protocols which were: 1. The right DLPFC anodal and the left DLPFC cathodal stimulation 2. The right DLPFC cathodal and the left DLPFC anodal stimulation 3. The right DLPFC anodal and the right arm cathodal stimulation 4. The left DLPFC anodal and the left arm cathodal stimulation 5. The right cerebellar hemisphere (O2) anodal and the left cerebellar hemisphere (O1) cathodal stimulation 6. The right cerebellar hemisphere (O2) cathodal and the left cerebellar hemisphere (O1) anodal stimulation. The data were analyzed by covariance method using SPSS-22 software.

Results: Study results indicated while single session tDCS effects on craving were not significant, it increased cognitive inhibition especially in protocol 2: The right DLPFC cathodal and the left DLPFC anodal stimulation

Conclusion and discussion: Single session of tDCS has an insignificant effect on craving but it can increase cognitive inhibition significantly. These findings extend the results of previous studies on the effects of brain stimulation for drug craving reduction in other drug type settings.

Keywords: Cerebellum, Cognitive function, Dorsolateral Prefrontal Cortex (DLPFC), Drug craving, Methamphetamine addict, Trans-cranial direct current stimulation (tDCS).
Introduction

Drug craving is considered to be a major problem in addiction treatment (Skinner, M. D., & Aubin, H. J. 2010) and Greater drug craving is associated with an increased risk of relapse to drug use (Sinha, R., Garcia, M., Paliwal, P., Kreek, M. J., & Rounsaville, B. J. 2006).

Different definitions of drug craving has complicated matters further as it can be conceptualized and addressed as the history of a stable tendency toward drugs and also as the experience of an intense or compelling urge or desire (Rosenberg, H. 2009).

Recent neuroimaging researches have revealed various brain areas to be involved in drug craving, amongst which the dorsolateral prefrontal cortex (DLPFC) is an important one (Hartwell, K. J., Johnson, K. A., Li, X., Myrick, H., LeMatty, T., George, M. S., et al. 2011). The DLPFC is involved in reward, motivation and decision-making and its circuits provide the substrate for integration of cognitive and motivationally relevant information and the inhibitory control over seductive options harboring the promise of immediate reward (Goldstein RZ, Volkow ND. 2002; Bechara A. 2005).

Another important area for drug craving is cerebellum. The cerebellum is related to cognition, learning, and memory and research has shown that drug-related cues activate cerebellum. (Moreno-Rius, J., & Miquel, M. 2017)

Transcranial direct current stimulation (tDCS) is a recently developed method and has attracted wide attention among researcher circles. Many studies have focused on the effects of tDCS on DLPFC and reported a decline in drug craving following the application of tDCS. (Boggio, P. S., Sultani, N., Fecteau, S., Merabet, L., Mecca, T, et al., 2008; Fregni, F., Orsati, F., Pedrosa, W., Fecteau, S., Tome, F. A., et al., 2008; Boggio et al., 2009)

Methamphetamine (crystal meth) abuse is a prevalent addiction without any established pharmacological treatments (Farhadian et al., 2017), (Schottenfeld et al., 2018) and applied methods to reduce methamphetamine craving have been shown to be potentially useful (Shahbabaie et al., 2014). A serious challenge facing individuals with methamphetamine use disorder is executive dysfunction (Farhadian et al., 2017). Hence, the present study focused on the effect of six tDCS protocols applied to the DLPFC and cerebellar areas on reducing drug craving and enhancing executive functions, such as cognitive inhibition and working memory.
Materials and methods

Participants

A quasi-experimental pre-test and post-test research design was conducted and 15 male individuals with methamphetamine use disorder in two rehabilitation centers of Ekbatan Neshat Salamat, and Aramesh participated and received tDCS. The participants signed a written consent form and then enrolled in the study. The participants aged 18-65 years (mean = 37.06 years) with a minimum 12-month history of methamphetamine dependence. The participants had reported methamphetamine abuse at least three times a week in a period of six months. During the treatment process, the participants did not receive any opioid or stimulant medication except for cigarettes. Those with maximum two-week abstinence were excluded from the study due to ethical considerations, so were the participants with other neurological disorders like epilepsy or those receiving medications affecting the central nervous system.

Instruments

In this study the following instruments were used.

The tDCS which was an ActivaTek system for stimulating the skin/scalp, made in the USA.

Visual Analog Scale (VAS)

Visual analog scale (VAS) is a commonly used technique to assess the level of craving based on a 0 to 10 scale and includes two sides, one side with numbers which indicates the craving and the other side is without numbers). Participants show their levels of drug craving on the not numbered side and the examiner records the numbers from the back side of this tool. Each participant is asked to show the level of his drug craving on the scale, which represents the level of his tendency, temptation, and desire for the drug in question (Rosenberg, H. 2009).

Go/No-Go Task

This Go/No-Go task measures the inhibitory control, which allegedly plays a major role in daily life. This requires the capacity to choose the right behavior and to control, inhibit, and
suppress negative and disturbing behaviors, which is called response inhibition (Barkley, R. A. 1997).

*N-Back Task*

The N-back task is considered a very effective and widely used method to measure working memory since it includes both recording and manipulation of cognitive information (Chen, Y. N., Mitra, S., & Schlaghecken, F. 2008).

Procedures

All participants received 6 protocols for one session with a 72 hour washout period randomly in a cross over method. Current intensity of 2 mA for 20 minutes was applied to the participants in each session using the tDCS system through two anode and cathode electrodes in the form of the following protocols:

1. The first protocol was the right DLPFC anodal stimulation and the left DLPFC cathodal stimulation.
2. The second protocol was the right DLPFC cathodal stimulation and the left DLPFC anodal stimulation
3. The third protocol was the right DLPFC anodal stimulation and the right arm cathodal stimulation
4. The fourth protocol was the left DLPFC anodal stimulation and the left arm cathodal stimulation
5. The fifth protocol was the right cerebellar hemisphere (O2) anodal stimulation and the left cerebellar hemisphere (O1) cathodal stimulation
6. The sixth protocol was the right cerebellar hemisphere (O2) cathodal stimulation and the left cerebellar hemisphere (O1) anodal stimulation

The participants were asked to describe their temptation for methamphetamine in detail (e.g. date and time). Then, they were given a checklist to report any possible side effects in each group. All participants did a self-report scale for measuring craving (VAS), Go/No-Go Task, and N-Back Task before and after each tDCS intervention.
Data Analysis

The analysis of covariance (ANCOVA) was employed for data analysis to test the study’s hypotheses according to the study’s quasi-experimental design (pre-test and post-test) and the study’s objectives. The pre-test effect was considered as a covariate. The pre-test was aimed to measure the drug craving with VAS. The pre-test effect obtained using ANCOVA was excluded as a precaution as it has typically no learning effect but have possibly unmeasurable disturbing effects as a latent variable.

Results

The ANCOVA results for the main hypothesis are listed in Table 1. It should be also noted that the ANCOVA pre-assumptions, including the normal data distribution, variance homogeneity, and regression slope homogeneity, were all examined and then validated through statistical tests.

Table 1. The significant tests of between-subjects effects of drug craving and cognitive inhibition of 15 male individuals with methamphetamine use disorder.

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Source</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craving</td>
<td>Corrected Model</td>
<td>6</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Pre-VAS</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Cognitive inhibition</td>
<td>Corrected Model</td>
<td>6</td>
<td>0.043</td>
</tr>
<tr>
<td></td>
<td>Intercept</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Protocol</td>
<td>5</td>
<td>0.027</td>
</tr>
<tr>
<td>Elimination Error</td>
<td>Intercept</td>
<td>1</td>
<td>0.003</td>
</tr>
<tr>
<td>Presentation Error</td>
<td>Intercept</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Average Response Time</td>
<td>Intercept</td>
<td>1</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Table 2: The significant pairwise comparisons of cognitive inhibition and presentation error of 15 male individuals with methamphetamine use disorder.

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>(I) protocol</th>
<th>(J) protocol</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive inhibition</td>
<td>R.DLPFC.A/L.DLPFC.C</td>
<td>R.DLPFC.C/L.DLPFC.A</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>R.DLPFC.A/L.DLPFC.C</td>
<td>R.DLPFC.A/R.Arm.C</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>R.DLPFC.C/L.DLPFC.A</td>
<td>R.DLPFC.A/L.DLPFC.C</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>R.DLPFC.C/L.DLPFC.A</td>
<td>L.DLPFC/L.Arm.C</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>R.DLPFC.A/R.Arm.C</td>
<td>R.DLPFC.A/L.DLPFC.C</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>R.DLPFC.A/R.Arm.C</td>
<td>L.DLPFC/L.Arm.C</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>L.DLPFC/L.Arm.C</td>
<td>R.DLPFC.C/L.DLPFC.A</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>L.DLPFC/L.Arm.C</td>
<td>R.DLPFC.A/R.Arm.C</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>L.DLPFC/L.Arm.C</td>
<td>R.O2.C/L.O1.A</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>R.O2.C/L.O1.A</td>
<td>L.DLPFC/L.Arm.C</td>
<td>0.033</td>
</tr>
<tr>
<td>Presentation Error</td>
<td>R.DLPFC.A/L.DLPFC.C</td>
<td>R.DLPFC.C/L.DLPFC.A</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td>R.DLPFC.C/L.DLPFC.A</td>
<td>R.DLPFC.A/L.DLPFC.C</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td>R.DLPFC.C/L.DLPFC.A</td>
<td>L.DLPFC/L.Arm.C</td>
<td>0.011</td>
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<tr>
<td></td>
<td>L.DLPFC/L.Arm.C</td>
<td>R.DLPFC.C/L.DLPFC.A</td>
<td>0.011</td>
</tr>
</tbody>
</table>

*L: left  R: right  A: anodal  C: cathodal  DLPFC: dorsolateral prefrontal cortex  O1: left cerebellar hemisphere  O2: right cerebellar hemisphere

According to the table 1, the pre-test effect on craving was significant. When pre-test effect was eliminated, the tDCS effect was insignificant. Thus, the first hypothesis of the study was rejected.

The effect of the pre-test (covariate) on cognitive inhibition was not statistically significant, whereas that of tDCS was significant (Table 1). According to the results of the test, the biggest effect was produced by Protocol 2 (right DLPFC cathodal stimulation and the left DLPFC anodal stimulation) (Table 2).

Neither the pre-test effect nor the tDCS effect on the elimination error were statistically significant (Table 1).
The effect of the pre-test on the presentation error was not significant, whereas the tDCS error was significant (Table 1). The results of the test indicated that the biggest effect was produced by Protocol 4 (Table 2).

Neither the pre-test effect nor the tDCS effect on the average response time were significant (Table 1).

The test results can be summarized as follows; the tDCS effect on cognitive inhibition was significant with the biggest effect produced by Protocol 2. Also, the tDCS effect on presentation error was also significant with the biggest effect produced by Protocol 4.

**Discussion**

The results of the present study are inconsistent with the research findings of Fregni, F., Orsati, F., Pedrosa, W., Fecteau, S., Tome, F. A., et al. (2008), Shariatirad, S., Vaziri, A., Hassani-Abharian, P., Sharifi Fardshad, M., Molavi, N., et al. (2016), and Da Silva, M. C., Conti, C. L., Klauss, J., Alves, L. G., do Nascimento Cavalcante, H. M., et al. (2013), which reported that tDCS intervention was effective in declining drug craving. Nevertheless, the results are consistent with those reported by Ehgartner, D (2012), who showed the ineffectiveness of tDCS therapeutic intervention, which can be attributed to the implementation of each protocol for only one session. Attendance of participants in more intervention sessions is recommended.

The present study also showed that tDCS intervention significantly enhanced the level of cognitive inhibition. This finding is consistent with the reports by Goldman, R. L., Borckardt, J. J., Frohman, H. A., O’Neil, P. M., Madan, A., et al. (2011) and Wolkenstein, L., & Plewnia, C. (2013).

According to the findings, one session of different six protocols was not effective to reduce drug craving. However, it increased cognitive inhabitation, which plays an important role in addiction recovery.

Therefore, although attendance in more sessions of tDCS are needed for reducing drug craving, even minimal use of tDCS might be useful in helping the individuals to recover from addiction by increasing their cognitive inhabitation. Besides its effectiveness, tDCS is easy to
use, has a low cost, and is a safe device. Therefore, in addition to recovery from addiction, it can be used as a complementary treatment for a number of other interventions like psychotherapy and pharmacotherapy.

For best results with tDCS in addiction recovery, it’s suggested to use right DLPFC cathodal stimulation and left DLPFC anodal stimulation Protocol.

The self-report tool for the assessment of craving was one of the limitations of this study as the participants might have been unwilling to report their real level of drug craving due to the fear of undergoing a longer treatment course. Another limitation of our study was the sampling method. Our participants were those individuals who were actively seeking treatment in rehabs under controlled conditions, which naturally reduces their craving. Furthermore, the present study focused solely on male participants and, consequently, neglected the gender-related differences.

For future studies, it is recommended to adopt an indirect objective assessment approach to obtain more suitable measure of drug craving. Also, use of random sampling method and conducting the tests on active male and female individuals with drug use disorder under both real and uncontrolled conditions is recommended.
References


