Drug and Alcohol Dependence 217 (2020) 108429

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

# Multi-session electrical neuromodulation effects on craving, relapse and cognitive functions in cocaine use disorder: A randomized, sham-controlled tDCS study

Ilse Verveer [a,*], Frederik M. van der Veen [a], Alireza Shahbabaie [b], Danielle Remmerswaal [a], Ingmar H.A. Franken [a]

[a] Department of Psychology, Education and Child Studies, Erasmus School of Social and Behavioural Sciences, Erasmus University, Rotterdam, the Netherlands
[b] Cognitive Psychology Unit, Institute of Psychology, Leiden University, Leiden, the Netherlands

ARTICLE INFO

*Keywords:*
Cocaine use disorder
tDCS
Relapse
Inhibitory control
Go-NoGo
Risky decision-making

ABSTRACT

*Background:* The use of transcranial Direct Current Stimulation (tDCS) has previously shown promising results for reducing craving in cocaine use disorder. In this study we further explored the potential of tDCS as add-on intervention in the treatment of cocaine use disorder.

*Methods:* In a randomized, placebo-controlled, between subject study, we applied tDCS bilaterally with the anodal electrode targeting the right dorsolateral prefrontal cortex (DLPFC; https://clinicaltrials.gov/ct2/show/NCT03025321). Patients with cocaine use disorder were allocated to ten sessions of either active tDCS ($n$ = 29) or sham ($n$ = 30) on five consecutive days. Inhibitory control and risky decision-making were measured via a Go-NoGo task and a two-choice gambling task, respectively, each at baseline, one day after all tDCS sessions and after three months. Relapse at follow-up and craving were also assessed.

*Results:* There was no significant effect of active tDCS on the number of cocaine use days and craving. Relapse was frequent among patients who had received either active or sham tDCS (48.0 % and 69.2 %, respectively), despite an overall decrease in craving during the first two weeks of treatment. No effects were found on cognitive functions. An exploratory analysis for crack cocaine use only revealed that relapse rates were significantly reduced after active tDCS ($n$ = 17) as compared to sham ($n$ = 19).

*Conclusions:* No beneficial effects of tDCS on number of cocaine use days, craving and cognitive functions were found in the present study, but somewhat promising results were obtained regarding relapse rates among crack-cocaine users specifically. Further research is required to determine the efficacy of tDCS as a complementary treatment in cocaine use disorder.

## 1. Introduction

Psychosocial interventions are currently recommended as first-line treatment for cocaine addiction, and there is still little evidence for effective pharmacological treatments (De Crescenzo et al., 2018). In order to successfully follow psychosocial therapies, certain cognitive and emotional skills are required. This can be problematic for substance users, since they often show impairments in cognitive control functioning (Franken and van de Wetering, 2015), as a result of prefrontal cortex (PFC) dysfunction (Goldstein and Volkow, 2011). Impaired cognitive control has been associated with less treatment responsiveness (Winhusen et al., 2013) and with relapse in substance use disorders (SUDs; Volkow et al., 2016). Therefore, research on addiction treatment has recently shifted towards interventions focusing on modulating brain activity in the PFC by means of non-invasive brain stimulation (NIBS; Nakamura-Palacios et al., 2016).

Transcranial Direct Current Stimulation (tDCS) over the dorsolateral PFC has been one of the protocols of choice in studies on the clinical effectiveness of NIBS in addiction (Kekic et al., 2016; Lapenta et al., 2018). Promising results have been found for craving in a variety of SUDs when tDCS was applied over the dorsolateral prefrontal cortex (DLPFC; Jansen et al., 2013). For cocaine addiction specifically, five sessions of active bilateral tDCS (2 mA, 20 min) over the DLPFC (right anodal/left cathodal) reduced craving (Batista et al., 2015). Ten days of

* Corresponding author.
*E-mail address:* verveer@essb.eur.nl (I. Verveer).

https://doi.org/10.1016/j.drugalcdep.2020.108429
Received 20 March 2020; Received in revised form 6 November 2020; Accepted 10 November 2020
Available online 23 November 2020

tDCS (2 mA, 20 min) over the DLPFC (left anodal/right cathodal) was also associated with reduced craving in a small sample of patients with cocaine use disorder (De Almeide Ramos et al., 2016). However, no effects on craving and relapse were observed after ten tDCS sessions (2 mA, 20 min) over the DLPFC (right anodal/left cathodal) in a group of patients with cocaine use disorder that reported relatively high craving scores at baseline and more years of substance use (Klauss et al., 2018a).

Few other studies have attempted to explore the effect of tDCS on relapse in addiction. For alcohol use disorder specifically, studies with stimulation protocols where the anodal electrode was placed over the right DLPFC have generally reported a reduction in risk of relapse (Klauss et al., 2014; Klauss et al., 2018b). In addition, a recent meta-analysis has indicated that anodal tDCS over the right DLPFC with cathodal tDCS over the left DLPFC had the most positive effects on smoking behaviour (Kang et al., 2019). For the clinical effectiveness of tDCS on addictive behaviour in general, it has been reported that multi-session tDCS over the DLPFC is particularly beneficial as compared to single session tDCS, but the contribution of other parameters such as lateralized neuromodulation (left vs. right) and current intensity remains unclear (Song et al., 2019).

Investigating the underlying mechanism of the therapeutic effects of tDCS could help improve the application of NIBS in addiction treatment. It has been suggested that therapeutic effects on craving and relapse by modulating neuronal activity of the DLPFC is the result of enhanced inhibitory control and reduced risky decision-making (Brevet-Aeby et al., 2016; Lapenta et al., 2018; Naish et al., 2018; Schluter et al., 2018). Bilateral tDCS over the DLPFC (right anodal/left cathodal) has been associated with less risky decision-making in addiction (Fecteau et al., 2014; Pripfl et al., 2013). Also, risky decision-making was reduced in patients with cocaine use disorder when bilateral tDCS was applied with the anodal electrode over the right DLPFC, but results on risk-taking were more inconsistent when the anode was placed over the left DLPFC (Gorini et al., 2014). In total, only few studies have investigated tDCS for modulating decision-making in addiction and to the best of our knowledge, the effect of tDCS on inhibitory control has not previously been explored in addiction.

The current study explored inhibitory control and risky decision-making in relation to beneficial effects of tDCS on craving and relapse in a representative sample of patients with cocaine use disorder. We decided not to exclude patients with additional substance use disorders, since cocaine addiction is rarely a stand-alone SUD. It has been reported that approximately two-third of patients with cocaine use disorder report seeking help for secondary substance use disorders (World Drug Report, 2019). In addition, craving was measured by ecological momentary assessments (EMA) to collect detailed information about the duration and dynamics of the beneficial effects of tDCS (Shiffman et al., 2008). Since craving is a momentary phenomenon, EMA offers an ecologically valid alternative to retrospective self-reports by enabling repeated measurement of craving at random moments of the day (Serre et al., 2015).

We hypothesized that beneficial effects of multiple sessions of tDCS on relapse will be established by its effects on craving and cognitive functions, as shown by less craving, improved inhibitory control and reduced risky decision-making after active tDCS.

The tDCS protocol used in the current study was chosen based on previous literature showing that tDCS (2 mA) over the DLPFC (right anodal/left cathodal) seemed most effective in some substance use disorders and had the largest effect on risk-taking behaviour. In addition, tDCS was applied two times with a 20-minute break in between on each intervention day. Performing a second session during the after-effects of the first tDCS session (within 20 min) could increase the duration of combined after-effects beyond one day (Monte-Silva et al., 2013). We therefore expected that the multi-session tDCS protocol employed in the current study as add-on treatment in cocaine use disorder would decrease the number of relapse days within three months after the intervention.

## 2. Materials and methods

This clinical trial was pre-registered with identifier NCT03025321 at ClinicalTrials.gov. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands. Detailed information about the materials is provided at https://dx.doi.org/10.17504/protocols.io.bjwhkpb6.

### 2.1. Participants

All participants were fully informed by the principal investigator before they signed the written informed consent and entered the study. The study was powered for a moderate effect size (f = .25) based on the study by Batista et al. (2015). With a two-tailed p-value of 0.05 and a power of .80, we estimated to recruit about 80 participants. Seventy-eight patients (61 males, 17 females) who met the DSM-5 criteria for cocaine use disorder as assessed by a clinician were recruited between February 2017 and November 2018 from one specialized clinic for inpatient SUD treatment in Rotterdam (Antes) within one week after arrival. In total, fifty-nine patients (active tDCS $n$ = 29, sham tDCS $n$ = 30) completed the intervention week. Reasons for drop-out did not differ between groups (e.g. relapse, high load of experiment, tDCS side effects).

The inclusion criteria for the current study were: 1) Males and females aged between 18 and 65 years; 2) Meeting the DSM-5 criteria for cocaine use disorder; 3) The ability to speak, read, and write in Dutch at an eight-grade literacy level; 4) Abstinent for at least one week; 5) Owner of a smartphone. Exclusion criteria were: 1) Any self-reported withdrawal signs or symptoms at baseline; 2) Indications of severe psychopathology (i.e. history of psychoses or bipolar disorder) or unstable medical disorder as assessed by a physician; 3) A diagnosis of epilepsy, convulsions or *delirium tremens* during abstinence of cocaine; 4) Any contraindication for electrical brain stimulation procedures (i.e. electronic implants or metal implants); 5) Pregnancy or breast-feeding. In addition, all participants received treatment as usual in the inpatient clinic for approximately three weeks, including psychosocial therapies conducted by professional practitioners – sometimes combined with adjunctive pharmacotherapy including benzodiazepines and disulfiram and, if necessary, antidepressants, anxiolytics, antihypertensive and gastric medication (similar to Klauss et al., 2018).

### 2.2. Experimental design

The current study had a double-blind, randomized, sham-controlled design in which patients with cocaine use disorder received a total of ten tDCS sessions (active or sham) on five consecutive mornings in the week after arrival in the inpatient clinic (Fig. 1). Participants were first randomly assigned to either sham or active tDCS. Then, before the tDCS sessions, participants completed questionnaires regarding demographics, past drug use (Addiction Severity Index; ASI, Alcohol Use Disorders Identification Test; AUDIT), and cocaine addiction severity (Obsessive Compulsive Drug Use Scale – cocaine version; OCDUS). In addition, they performed two behavioural tasks (i.e., an inhibitory control and risky decision-making task) before the first session and one day after the last tDCS session. Participants were furthermore asked to answer questions about craving in an application on their mobile phones (EMA) for two weeks, starting the day of the first tDCS session.

Three months after the tDCS intervention, participants returned to the clinic in order to verify cocaine use in the past three months. Upon follow-up, participants completed the same behavioural tasks as at baseline.

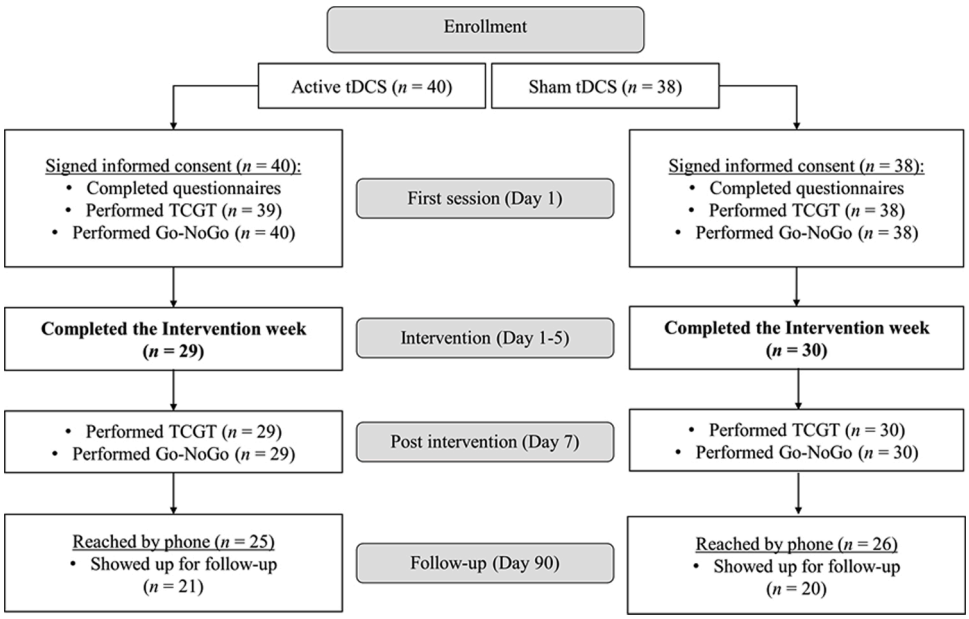


**Fig. 1.** Flow-chart of the experimental procedure. Participants were recruited from the inpatient addiction clinic, signed the informed consent, and were randomized to receive either sham or active transcranial Direct Current Stimulation (tDCS). The intervention week comprised 10 sessions of bilateral tDCS with the anodal electrode over the right DLPFC (2mA, 2x 13 min stimulation with a 20-minute rest interval in between) on five consecutive days.

### 2.3. Measures

#### 2.3.1. Relapse

Patients were followed-up 90 days after the last tDCS session regarding cocaine use relapse. Drug use was defined as the number of self-reported days that patients had used cocaine in the past 90 days. In addition, relapse rates were defined as the percentage of participants who had used cocaine (yes or no) in the last 90 days. This information was gathered by a telephone call, during which an appointment was made for the follow-up session in the clinic. If patients could not be reached by telephone, they were contacted by email. In case of no response, we contacted a family member, to request further information on how to reach the patient. During the follow-up session in the clinic, patients were asked again how many days in the past 90 days they had used cocaine, which was then verified with urine drug screens.

#### 2.3.2. EMA: craving

The LifeData platform (www.lifedatacorp.com) was used to develop the application for this study and to securely collect data. After participants had downloaded the application on their smartphone during the first session, they received random prompts three times a day between 10 AM and 10 PM for 14 consecutive days to complete a random assessment (RA). Random assessments that were not completed within 120 min after the notification disappeared and were marked as missed. During random assessments, participants were asked to indicate their craving for cocaine at that moment on a Likert scale ranging from 0 to 100. In addition, participants were asked if they had used cocaine or any other drug, alcohol or cigarettes since the last time that they had filled out a random assessment. Also, questions about general mood and specific affects were included, but these are beyond the scope of this paper.

#### 2.3.3. Inhibitory control: Go-NoGo task

Previous studies have indicated that patients with cocaine use disorder perform worse on the Go-NoGo task as compared to healthy controls (e.g. Hester et al., 2013). The current study used a cocaine related Go-NoGo task to measure inhibitory control, based on the paradigm used in Luijten et al. (2011). During this task, participants were presented with a series of cocaine-related and neutral pictures. Participants were instructed to press a button with their index finger as fast as possible for Go trials, and to inhibit their response for the unexpected NoGo trials (25 % of all trials). See Fig. 2 and Materials in https://dx.doi.org/10.17504/protocols.io.bjwhkpb6 for more details about the task.

#### 2.3.4. Risky decision-making: two choice gambling task (TCGT)

An adjusted version of the computerized probabilistic two-choice gambling task (TCGT) was used for the current study (Schuermann et al., 2012). Participants were instructed to gain as many points as possible by choosing between two options that were presented on a computer screen (Fig. 3). Trial A represented a high-risk option (left) with a higher chance of losing more points than the low-risk option (right). Trial B depicts two options with equal chances of losing, but more points in the high-risk option (left) than the low-risk option (right). Trial C presents an option with low points (right) and a high chance of losing, and an option with high points and a low risk of losing (left). See https://dx.doi.org/10.17504/protocols.io.bjwhkpb6 for further details about the task.

### 2.4. Transcranial direct current stimulation

Participants received tDCS by an electric DC-plus stimulator (NeuroConn, Ilmenau, Germany) via a pair of carbon silicon electrodes with a thick layer of high-conductive EEG gel underneath them (35 $cm^2$). During each session, tDCS was applied two times for 13 min (2 mA) with a 20-minute rest interval between the stimulations (Klauss et al., 2014; Shahbabaie et al., 2018), while participants watched a neutral documentary in Dutch. Each 13-minute stimulation included a 30 s ramp up at the beginning and ramp down at the end. Monte-Silva et al. (2013) have reported that this protocol can extend after-effects of tDCS. The anodal electrode was placed over the F4 and the cathodal electrode was placed over the F3 based on 10–20 international system. Beneficial effects were found on relapse and craving with this right anodal/left cathodal positioning over the DLPFC (Klauss et al., 2014; Jansen et al., 2013; Shahbabaie et al., 2014).

The control group received sham tDCS by the DC-plus stimulator. In the sham condition, the electrodes were positioned at the same locations as in the active tDCS condition, but in this case the stimulator was

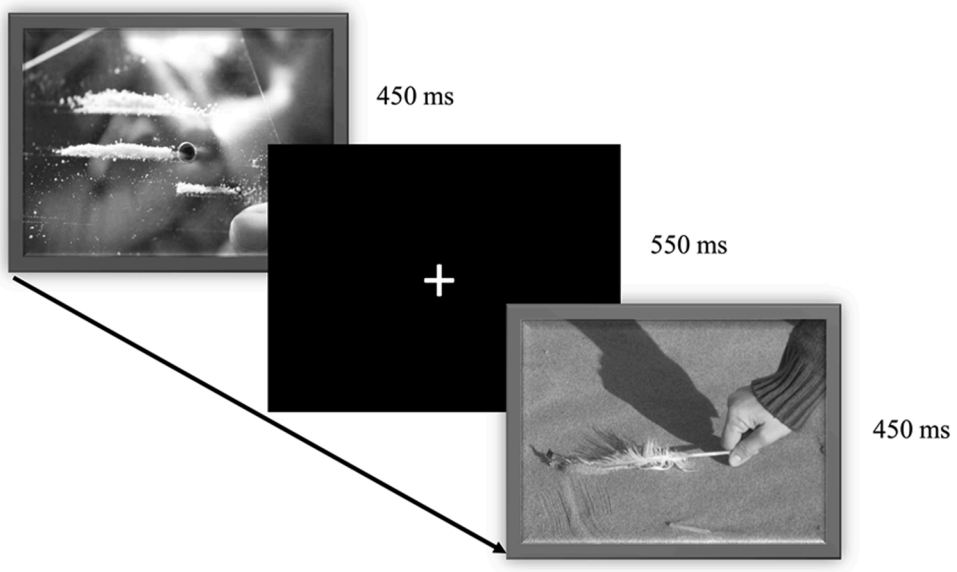


**Fig. 2.** Example of a cocaine related and neutral picture in the Go-NoGo task. The colours of the frames (either blue or yellow) indicate Go and NoGo trials.

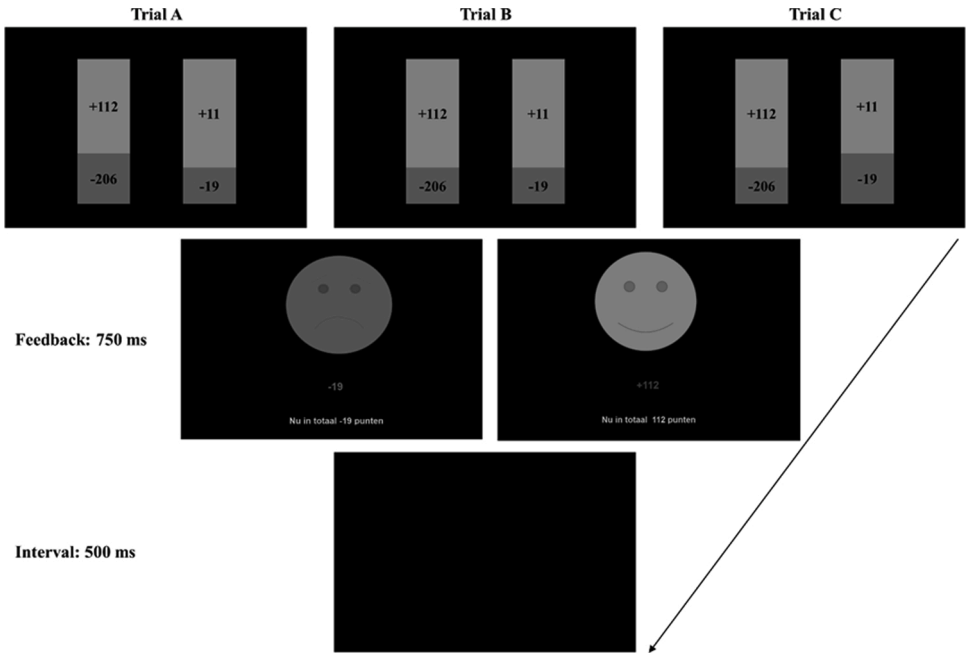


**Fig. 3.** Example of the probabilistic two choice gambling task.

gradually turned off after 30 s. Since the itching sensation of tDCS is often only experienced initially during stimulation, it was expected subjects remained blinded of the stimulation condition they received (e.g. Gandiga et al., 2006; Woods et al., 2016). The experimenter was also blinded from the tDCS condition. That is, the codes that can automatically activate sham or active tDCS, were randomly assigned to participant numbers by an independent researcher.

### 2.5. Data analyses

#### 2.5.1. Relapse

An independent samples *t*-test was performed in SPSS to analyse the average number of days participants had used cocaine in the 3 months after the tDCS intervention. An additional analysis was performed to test whether relapse rates, defined as the percentage of people that had relapsed within the 3 months after the intervention, differed for the active and sham tDCS group using the chi-square fisher exact test.

#### 2.5.2. Craving

Multilevel analysis was performed in R (R Core Team, 2018) using the lme4 package (Bates et al., 2014) to fit the nested data structure of Time within individuals (Level 1), and Group (sham vs. active tDCS) at Level 2. Multilevel modelling also allowed us to include data points of individuals with missing data. Missing data is almost inevitable in EMA studies, since most participants miss at least some prompts.

The outcome variable in this analysis was average craving a day. Time (day 1–14) was defined at Level 1 and patients at Level 2, with Group (sham vs. active tDCS) as a Level 2 predictor variable (see Hox, 2010). For the analyses, first a baseline model (M0) was fitted to the data with random intercepts. The baseline model was used to assess whether

multilevel analysis was required, by testing if the variance at Level 2 was significant. In the second model (M1) the Level 1 predictor Time was added to the model. In the third model (M2) random slopes were added for Time. The fourth model (M3) included the Level 2 predictor Group. Finally, the fifth model (M4) was extended by a cross-level interaction of Time at Level 1 and Group at Level 2 to assess whether the effect of time varied across groups. The fit of the models was analysed by testing the difference in deviance across models. In addition, the assumptions of normality and linearity were assessed by inspecting the residuals of each best fitted model. Unless otherwise reported, the assumptions were met.

#### 2.5.3. Behavioural tasks

For behavioural data generated during the Go-NoGo task and the TCGT, multilevel analyses were again performed in R using the lme4 package. For all outcome measures, Time (pre, post, and follow-up) was defined at Level 1 and patients were defined at Level 2 with Group (sham tDCS vs active tDCS) as predictor variable. Similar to the outcome of craving, models M0, M1, M2, M3 and M4 were fitted to behavioural outcomes.

For the outcome measures of the Go-NoGo task, different models were fitted to accuracy scores, reaction times on Go trials, and post error reaction times. Accuracy was defined as the percentage of correct NoGo trials. For both accuracy and reaction times on Go trials, Picture Type (cocaine vs. neutral) was defined as Level 1 variable in addition to Time. The main outcome variable of the TCGT was the average number of points won per trial. In addition, a separate model was built for high-risk choices, with risk-taking calculated as the percentage of times that participants choose high-risk options over low-risk options on trials A and B (Fig. 3). Trial C (Fig. 3) can be considered as control trial, since both options contain a low level of risk-taking.

#### 2.5.4. Adverse effects tDCS

After each tDCS session, participants were asked to indicate how much they experienced any of the following adverse effects on a 5-point Likert scale (ranging from none (1) to extreme (5) sensations): itching, burning, or tingling sensations, difficulties with concentrating, acute mood changes, sleepiness, neck pain, and headache. An independent samples *t*-test with Group (Active vs. Sham tDCS) as between-subject factor was performed for average intensity of adverse effects experienced by each participant. No differences between the groups (active tDCS vs sham) were observed regarding adverse effects.

## 3. Results

Demographical data and patterns of drug use are presented in Table 1. The active tDCS and sham group did not differ in baseline characteristics. It was furthermore confirmed that multilevel analyses could be performed for all outcomes, as the multilevel models with random intercepts fitted the data (i.e. variance at Level 2 was significant).

### 3.1. Relapse

There were no mismatches between urine drug screens and answers patients gave to the question whether they had relapsed or not. The number of days that participants had used cocaine did not differ between groups ($t(49) = 1.30$, $p = 0.20$). Overall, relapse rates within 90 days after the 10 tDCS sessions were high for both the active (48.0 %, $n = 12$) and sham (69.2 %, $n = 18$) tDCS group. There was no significant difference in relapse rates between both groups for the 90 days follow-up (odds-ratio = 0.42, $X^2(1) = 2.37$, $p = 0.12$).

Since previous studies analysed relapse rates for patients who use crack cocaine (Batista et al., 2015; Klauss et al., 2018), we decided to perform an exploratory analysis including only crack cocaine users (active tDCS $n = 17$; sham $n = 19$). These results show that relapse was lower for the active tDCS group (41.2 %, $n = 7$) as compared to the sham tDCS group (73.7 %, $n = 14$). The odds-ratio for the group of crack cocaine users was 0.26 ($X^2(1) = 3.90$, $p = 0.05$).

The group of patients who used cocaine in the form of crack were older as compared to the group who used powder ($t(57) = -2.48$, $p = 0.02$). Also, 11 out of 12 female participants from our sample were crack-cocaine users. Taking these variables into account did not affect the results for relapse. Furthermore, baseline comparisons between the active tDCS and sham groups within the sample of patients who used cocaine in the form of crack revealed that there were no differences in baseline characteristics (e.g. age, gender, years of use, age of onset, OCDUS scores, other substances used).

**Table 1**
Socio-demographic characteristics of the total sample of cocaine users (n = 59), subdivided in subjects that received the transcranial Direct Current Stimulation intervention (active tDCS: n = 29) or the sham intervention (sham tDCS: n = 30).

| | | Groups | | | |
|---|---|---|---|---|---|
| | | Sham tDCS | Active tDCS | | ***p-value*** |
| Age [mean (SD)] | | 41.9 (9.7) | 37.6 (10.7) | $t(57) = 1.62$ | 0.11 |
| Gender (% male) | | 70.0 | 89.7 | Fisher = 1.0 | 0.10 |
| Years of Education (%) | 0–8 years | 6.7 | 17.2 | X2 = 3.04 | 0.22 |
| | 9–14 years | 46.7 | 27.6 | | |
| | above 14 years | 46.7 | 55.2 | | |
| Age of onset cocaine use [mean (SD)] | | 22.1 (6.9) | 20.8 (5.6) | $t(57) = 0.80$ | 0.43 |
| Number of years cocaine use [mean (SD)] | | 17.1 (8.3) | 13.6 (10.5) | $t(57) = 1.42$ | 0.16 |
| Days of abstinence before study [mean (SD)] | | 14.3 (10.1) | 18.2 (8.5) | $t(57) = -1.63$ | 0.11 |
| OCDUS cocaine thoughts and interference | | 15.53 (6.71) | 16.66 (6.34) | $t(57) = -0.66$ | 0.51 |
| OCDUS cocaine desire and control | | 10.60 (3.78) | 10.52 (3.69) | $t(57) = 0.09$ | 0.93 |
| OCDUS cocaine resistance | | 5.67 (2.60) | 5.48 (1.82) | $t(57) = 0.32$ | 0.75 |
| How cocaine is used (%) | Snorting | 23.3 | 37.9 | X2 = 1.80 | 0.41 |
| | Smoking | 63.3 | 55.2 | | |
| | Both | 13.3 | 6.7 | | |
| Number of Other Substances Used (%) | No other substance | 20.0 | 24.1 | X2 = 0.15 | 0.93 |
| | One other substance | 36.7 | 34.5 | | |
| | Multiple | 43.3 | 41.4 | | |
| Type of other substances used (%) | Alcohol | 33.3 | 36.7 | X2 = 3.85 | 0.43 |
| | Cannabis | 26.7 | 28.3 | | |
| | Heroin | 10.0 | 10.0 | | |

### 3.2. Ema

#### 3.2.1. Compliance

The total number of completed random assessments for day 1 to day 14 was 1250 out of 2775 random assessments. Therefore, the compliance rate for completed random assessments was 45.0 %. The compliance rate was higher for the active tDCS group (49.6 %) as compared to the sham tDCS group (40.5 %), with an odds ratio of 0.69 ($X^2(1) = 22.95$, $p < .001$).

#### 3.2.2. Craving

The third model (M2) with random intercepts and slopes for time,

including Time as Level 1 predictor, was the best fitted model for average craving a day (Supplementary file; Table 3). There was an overall decrease of craving over time observed in the 14 days after the first tDCS or sham session, with an average decrease of 1.29 ($t(52) = -5.00$, $p < .001$). The results show no indication of significant differences between the sham and active tDCS group in craving over time. Additionally, the results for craving did not differ for participants who had relapsed or not three months after active or sham tDCS. Finally, there was no difference between the active and sham tDCS group in craving over time if only crack-cocaine users were included for analyses.

#### 3.2.3. Inhibitory control

For all behavioural measures of inhibitory control as measured by the Go-NoGo task (Table 2), the results indicate that the third model (M2) was the best fitted model for the data. The third model for accuracy on NoGo trials (Supplementary file; Table 4) indicates that accuracy increases over time from baseline to follow-up with an average of 5.36 ($t(58) = 2.89, p < .01$). In addition, M2 for reaction times during Go trials (Supplementary file; Table 4) suggests an average decrease of 15 ms from pre- to post intervention ($t(57) = -2.92, p < .01$). Finally, there was evidence of a general post-error slowing: reaction times post error trials were on average 27 ms slower than reaction times post correct trials ($t(154) = -11.90$, $p < .001$). The final model (M4) was never the best fitted model, and therefore no significant differences over time between groups were found for all inhibitory control outcomes.

#### 3.2.4. Risky decision-making

Descriptive statistics for outcome measures on the TCGT can be found in Table 2. The baseline model was the best fit for the average number of points won per trial (Supplementary file: Table 5). For percentage of high-risk choices, the second model (M1) with Time as fixed effect was the best fitted model (Supplementary file: Table 5). The lack of significant cross-level interaction effects indicates that risky decision-making was unaffected by tDCS.

## 4. Discussion

The present study explored multi-session tDCS over the DLPFC as add-on treatment for cocaine use disorder and its effects on cognitive functions. There was no indication of a decrease in the number of cocaine use days after three months for patients with cocaine use disorder who had received active tDCS as compared to sham. In line with the non-significant findings of tDCS on drug use in cocaine use disorder, no beneficial effects of tDCS on craving and cognitive functions were found in the present study.

**Table 2**
Descriptive data for behavioural outcomes Go/NoGo task and TCGT.

| | Baseline | | Post | | Follow-up | |
|---|---|---|---|---|---|---|
| | Active tDCS | Sham tDCS | Active tDCS | Sham tDCS | Active tDCS | Sham tDCS |
| % Correct NoGo trials | 70,7 (18,4) | 76,5 (16.0) | 73,4 (16,9) | 78,0 (14,4) | 77,7 (15,1) | 79,7 (14,2) |
| RT Go trials [ms] | 322,8 (32,3) | 342,6 (63,7) | 312,6 (27,6) | 322,6 (60,2) | 319,6 (39,4) | 330,9 (50,2) |
| RT post errors [ms] | 297,6 (34,4) | 303,4 (50,9) | 298,2 (35,6) | 300,6 (56,5) | 293,7 (25,3) | 290,8 (50,5) |
| Win per trial TCGT | 38,5 (17,9) | 36,0 (15.0) | 42,8 (18,1) | 43,9 (14,3) | 44,8 (17,7) | 37,5 (20,0) |
| % High risk choices | 49,7 (23,3) | 50,0 (23,1) | 52,9 (25,2) | 49,7 (26,2) | 50,7 (28,0) | 52,3 (23,6) |

*Note*: Mean (SD) for the % of incorrect NoGo trials, reaction times (RT) on Go trials and RT on trials post erroneous trials in ms.
Mean (SD) for win per trial and % of high risk choices on the TCGT.

### 4.1. Cocaine use during follow-up

The assessment of complete abstinence has been the golden standard to measure treatment efficacy; however, relapses often occur after treatment and a reduction of drug use to less harmful levels can be a positive outcome (Ekhtiari et al., 2019). We therefore decided to define drug use by an informative outcome measure, namely the number of days participants had used cocaine in the three months following tDCS treatment. Yet, in order to compare the results to previous reported treatment efficacy of tDCS in cocaine addiction (Klauss et al., 2018a), we also determined binary relapse rates.

Relapse rates three months after active tDCS (48.0 %, $n = 12$) and sham (69.2 %, $n = 18$) were similar to previously reported relapse rates in a sample of patients with cocaine use disorder (52.9 % active tDCS vs. 66.7 % for sham; Klauss et al., 2018a). An exploratory analysis for the crack-cocaine users in the current study revealed that relapse rates were significantly lower after active tDCS (41.2 %, $n = 7$) as compared to sham (73.7 % $n = 14$), but this was not the case for the powder-cocaine users. Perhaps, tDCS has better treatment success in patients who use cocaine in the form of crack instead of powder, although the difference in relapse rates after active vs. sham tDCS had previously not reached significance in crack-cocaine users (Batista et al., 2015; Klauss et al., 2018a, 2018b). It is unclear why in the current study tDCS may have been more effective in crack-cocaine users and caution should be taken when interpreting these results as relapse rates are still high after active tDCS for patients who used cocaine in the form of crack and the sample of this group was small ($n = 36$). Arguably, larger sample sizes are needed, with an equal number of patients who use cocaine in the form of crack and powder, to increase the power and to be able to better detect an effect of tDCS on both crack- and powder cocaine addiction, if present.

It may also be useful to consider alternative outcome measures of relapse. Future investigations may use the percentage of relapse days and the time until the first relapse as (additional) informative primary outcome measures of treatment success. Alternatively, self-set treatment goals of patients could be considered to determine individual definitions of treatment success, since these goals may differ per patient depending on the preference and obtainability of treatment outcomes.

### 4.2. Craving

Craving levels for patients with cocaine use disorder were measured with EMA while participants were inside the inpatient addiction clinic. No significant difference between the active tDCS and sham group was found on craving levels, but we observed a general decrease of craving over time after both active and sham tDCS. These results are consistent with observations from Klauss et al. (2018a). It could be the case that there was a floor effect of craving levels by the lack of environmental cues or stress inside the clinical setting (den Uyl et al., 2017). Future studies could best measure craving with EMA outside the clinic. If one decides to measure craving while patients are inside the clinic, it would be recommended to induce craving by means of cue-exposure, as a reflection of craving levels outside the clinic (Ekhtiari et al., 2019).

### 4.3. Cognitive functions

To the best of our knowledge, this is the first time that the effect of multi-session tDCS on inhibitory control has been investigated in addicted patients (Naish et al., 2018; Schluter et al., 2018). Inhibitory control improved for both groups over time, as indicated by increased accuracy and faster reaction times on the Go-NoGo task. Yet, tDCS had no additional effect on improved inhibitory control. It has been suggested that the DLPFC would be more involved in proactive rather than reactive response inhibition on the Go-NoGo task (Brevet-Aeby et al.,

2016). However, the current study provides no evidence for this hypothesis. Alternatively, tDCS may be more effective when applied during the task (online) instead of before or after (offline). It has been reported that the effects of anodal tDCS may be particularly increased after online stimulation as compared to offline stimulation for response accuracy in patients (Dedoncker et al., 2016).

We also found no effect of multiple tDCS sessions on risky decision-making in patients with cocaine use disorder. For both healthy and addicted individuals it has been reported that risky decision-making decreased after bilateral tDCS with the anodal electrode over the right DLPFC. However, there have been exceptions where tDCS over the DLPFC did not effectively reduce risky decision-making (Gorini et al., 2014; Pripfl et al., 2013). This seems particularly the case when gambling paradigms are used, involving indications of the reward probability before decisions are made, such as the Risk Task (Fecteau et al., 2014) and the TCGT. In fact, active tDCS even increased risk-taking behaviour in marijuana users during the Risk Task (Boggio et al., 2010), and in smokers during the TCGT (Verveer et al., Unpublished results). Inconsistent findings may therefore depend on task characteristics. Clearly, more research is needed to better understand how risky decision-making is involved in therapeutic effects of tDCS.

### 4.4. Limitations

The current results should be interpreted with several limitations in mind. Although the sample size was slightly larger as compared to previous studies on tDCS in cocaine use disorder, the drop-out rate for follow-up sessions reduced the power for relapse outcomes. Another limitation is the relatively low EMA compliance rate. This may not come as a surprise, given the marginalized population of patients with (crack) cocaine use disorder. However, as participants were inpatients and other addiction studies have reported a higher average compliance of 69.8 % (Jones et al., 2019), we would have expected higher compliance rates. It is challenging to increase compliance rates, as it remains unclear what factors affect EMA compliance rates in populations with an addiction, (Jones et al., 2019). Nevertheless, EMA can be regarded as a strength of study design, since individual patterns of craving over time can be estimated in an ecologically valid manner. Finally, almost all (but 2) participants were tobacco smokers, and the timing of smoking in relation to each session could have affected tDCS effects and cognitive control performance. Future studies should control for this possibility.

### 4.5. Future directions tDCS

It is important to note that still little is known about the contribution of different tDCS parameters to the clinical effectiveness of tDCS in addiction. The effects of anodal and cathodal stimulation have varied considerably, depending on current brain state, inter-individual differences in neurophysiology, clinical status, cognitive capacity, and stimulation parameters such as the duration and intensity of tDCS stimulation (Ekhtiari et al., 2019; Jamil et al., 2017; Luigjes et al., 2019). It could well be that more than a total of ten sessions may be needed to induce long-term after-effects. For example, typically 20–30 neurostimulation sessions are considered for the treatment of major depression (Luigjes et al., 2019). Additionally, a recent study in smokers showed that 20 sessions of tDCS resulted in similar abstinence rates as bupropion treatment (Behnam et al., 2019). The results of this study also indicated that weekly boosting sessions after the actual tDCS intervention may increase the effectiveness of tDCS. More research is needed to provide further insights in the optimal tDCS protocol.

Another particularly promising way forward is to consider individual differences in order to optimize stimulation parameters for addiction treatment. One approach could be to fit the tDCS protocol to the patients' neurobiological or cognitive profile (Luigjes et al., 2019). For example, it could be investigated whether tDCS treatment outcomes may be modulated by baseline DLPFC-striatal functional connectivity, as is the case for TMS in the treatment of depression (Avissar et al., 2017). In addition, motivation to quit drug use and the engagement in treatment may be taken into account in future studies, as these factors could affect the effect of tDCS on treatment success (De Souza Brangioni et al., 2018).

### 4.6. Conclusions

The findings thus imply that multiple sessions of bilateral tDCS with the anodal electrode over the right DLPFC has no significant beneficial effects on relapse and craving, or on cognitive control functions in patients with cocaine use disorder. However, some evidence was provided that relapse rates decrease after tDCS for crack-cocaine users specifically. Future investigations should examine different effects of tDCS depending on type of substance use, age, severity of substance use, and motivation to quit.

## Role of funding source

Nothing declared.

## Contributors

Ilse Verveer (I.V.), Dr. Frederik M. van der Veen (F.V.), Dr. Alireza Shababaie (A.S.), Dr. Danielle Remmerswaal (D.R.), Prof. Dr. Ingmar H. A. Franken (I.F.): I.V., F.V., D.R., and I.F. conceived on the presented idea. I.V. and I.F. developed the study protocol, preregistered the study and applied for ethical approval. I.V. carried out the experiment and statistical analyses. A.S. verified the analytical methods. All authors discussed the results and contributed to the final manuscript.

## Declaration of Competing Interest

The authors report no declarations of interest.

## Acknowledgements

We thank Dr. Ben van der Wetering and Dr. Mary Janssen van Raay for making our research possible by providing access to Antes clinic Rotterdam where the current study was conducted. We are grateful to Britt van Waardhuizen and Coert Bredewout for their effortful contribution to the data collection.

## References

Avissar, M., Powell, F., Ilieva, I., Respino, M., Gunning, F.M., Liston, C., Dubin, M.J., 2017. Functional connectivity of the left DLPFC to striatum predicts treatment response of depression to TMS. Brain Stimul. 10 (5), 919–925. https://doi.org/10.1016/j.brs.2017.07.002.

Bates, D., Mächler, M., Bolker, B., Walker, S., 2014. Fitting Linear Mixed-Effects Models Using lme4. arXiv Preprint arXiv:1406.5823.

Batista, E.K., Klauss, J., Fregni, F., Nitsche, M.A., Nakamura-Palacios, E.M., 2015. A randomized placebo-controlled trial of targeted prefrontal cortex modulation with bilateral tDCS in patients with crack-cocaine dependence. Int. J. Neuropsychopharmacol. 18 (12), pyv066. https://doi.org/10.1093/ijnp/pyv066.

Behnam, S.G., Mousavi, S.A., Emamian, M.H., 2019. The effects of transcranial direct current stimulation compared to standard bupropion for the treatment of tobacco dependence: a randomized sham-controlled trial. Eur. Psychiatry 60, 41–48. https://doi.org/10.1016/j.eurpsy.2019.04.010.

Boggio, P.S., Zaghi, S., Villani, A.B., Fecteau, S., Pascual-Leone, A., Fregni, F., 2010. Modulation of risk-taking in marijuana users by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). Drug Alcohol Depend. 112 (3), 220–225. https://doi.org/10.1016/j.drugalcdep.2010.06.019.

Brevet-Aeby, C., Brunelin, J., Iceta, S., Padovan, C., Poulet, E., 2016. Prefrontal cortex and impulsivity: Interest of noninvasive brain stimulation. Neurosci. Biobehav. Rev. 71, 112–134. https://doi.org/10.1016/j.neubiorev.2016.08.028.

De Crescenzo, F., Ciabattini, M., D'Alò, G.L., De Giorgi, R., Del Giovane, C., Cassar, C., et al., 2018. Comparative efficacy and acceptability of psychosocial interventions for individuals with cocaine and amphetamine addiction: a systematic review and network meta-analysis. PLoS Med. 15 (12), e1002715. https://doi.org/10.1371/journal.pmed.1002715.

De Souza Brangioni, V., Maria, C., Pereira, D.A., Thibaut, A., Fregni, F., Brasil-Neto, J.P., Boechat-Barros, R., 2018. Effects of prefrontal transcranial direct current stimulation and motivation to quit in tobacco smokers: a randomized, sham controlled, double-blind trial. Front. Pharmacol. 9, 14. https://doi.org/10.3389/fphar.2018.00014.

Dedoncker, J., Brunoni, A.R., Baeken, C., Vanderhasselt, M.A., 2016. A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. Brain Stimul. 9 (4), 501–517. https://doi.org/10.1016/j.brs.2016.04.006.

den Uyl, T.E., Gladwin, T.E., Rinck, M., Lindenmeyer, J., Wiers, R.W., 2017. A clinical trial with combined transcranial direct current stimulation and alcohol approach bias retraining. Addict. Biol. 22 (6), 1632–1640. https://doi.org/10.1111/adb.12463.

Ekhtiari, H., Tavakoli, H., Addolorato, G., Baeken, C., Bonci, A., Campanella, S., et al., 2019. Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: a consensus paper on the present state of the science and the road ahead. Neurosci. Biobehav. Rev. 104, 118–140. https://doi.org/10.1016/j.neubiorev.2019.06.007.

Fecteau, S., Agosta, S., Hone-Blanchet, A., Fregni, F., Boggio, P., Ciraulo, D., Pascual-Leone, A., 2014. Modulation of smoking and decision-making behaviors with transcranial direct current stimulation in tobacco smokers: a preliminary study. Drug Alcohol Depend. 140, 78–84. https://doi.org/10.1016/j.drugalcdep.2014.03.036.

Franken, I.H., van de Wetering, B.J., 2015. Bridging the gap between the neurocognitive lab and the addiction clinic. Addict. Behav. 44, 108–114. https://doi.org/10.1016/j.addbeh.2014.11.034.

Gandiga, P.C., Hummel, F.C., Cohen, L.G., 2006. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin. Neurophysiol. 117 (4), 845–850. https://doi.org/10.1016/j.clinph.2005.12.003.

Goldstein, R.Z., Volkow, N.D., 2011. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat. Rev. Neurosci. 12 (11), 652. https://doi.org/10.1038/nrn3119.

Gorini, A., Lucchiari, C., Russell-Edu, W., Pravettoni, G., 2014. Modulation of risky choices in recently abstinent dependent cocaine users: a transcranial direct-current stimulation study. Front. Hum. Neurosci. 8, 661. https://doi.org/10.3389/fnhum.2014.00661.

Hester, R., Bell, R.P., Foxe, J.J., Garavan, H., 2013. The influence of monetary punishment on cognitive control in abstinent cocaine-users. Drug Alcohol Depend. 133 (1), 86–93. https://doi.org/10.1016/j.drugalcdep.2013.05.027.

Hox, J.J., 2010. Multilevel Analysis: Techniques and Applications. Routledge, New York, NY.

Jamil, A., Batsikadze, G., Kuo, H.I., Labruna, L., Hasan, A., Paulus, W., Nitsche, M.A., 2017. Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. J. Physiol. 595 (4), 1273–1288. https://doi.org/10.1113/JP272738.

Jansen, J.M., Daams, J.G., Koeter, M.W., Veltman, D.J., van den Brink, W., Goudriaan, A.E., 2013. Effects of non-invasive neurostimulation on craving: a meta-analysis. Neurosci. Biobehav. Rev. 37 (10), 2472–2480. https://doi.org/10.1016/j.neubiorev.2013.07.009.

Jones, A., Remmerswaal, D., Verveer, I., Robinson, E., Franken, I.H., Wen, C.K.F., Field, M., 2019. Compliance with ecological momentary assessment protocols in substance users: a meta-analysis. Addiction 114 (4), 609–619. https://doi.org/10.1111/add.14503.

Kang, N., Kim, R.K., Kim, H.J., 2019. Effects of transcranial direct current stimulation on symptoms of nicotine dependence: a systematic review and meta-analysis. Addict. Behav. https://doi.org/10.1016/j.addbeh.2019.05.006.

Kekic, M., Boysen, E., Campbell, I.C., Schmidt, U., 2016. A systematic review of the clinical efficacy of transcranial direct current stimulation (tDCS) in psychiatric disorders. J. Psychiatr. Res. 74, 70–86. https://doi.org/10.1016/j.jpsychires.2015.12.018.

Klauss, J., Penido Pinheiro, L.C., Silva Merlo, B.L., Correia Santos, G.D.A., Fregni, F., Nitsche, M.A., Miyuki Nakamura-Palacios, E., 2014. A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. Int. J. Neuropsychopharmacol. 17 (11), 1793–1803. https://doi.org/10.1017/S1461145714000984.

Klauss, J., Anders, Q.S., Felippe, L.V., Ferreira, L.V.B., Cruz, M.A., Nitsche, M.A., Nakamura-Palacios, E.M., 2018a. Lack of additional effects of extended sessions of transcranial Direct Current Stimulation (tDCS) over dorsolateral prefrontal cortex on craving and relapses in crack-cocaine users. Front. Pharmacol. 9, 1198. https://doi.org/10.3389/fphar.2018.01198.

Klauss, J., Anders, Q.S., Felippe, L.V., Nitsche, M.A., Nakamura-Palacios, E.M., 2018b. Multiple sessions of transcranial direct current stimulation (tDCS) reduced craving and relapses for alcohol use: a randomized placebo-controlled trial in alcohol use disorder. Front. Pharmacol. 9, 716. https://doi.org/10.3389/fphar.2018.00716.

Lapenta, O.M., Marques, L.M., Rego, G.G., Comfort, W.E., Boggio, P.S., 2018. tDCS in addiction and impulse control disorders. J. ECT 34 (3), 182–192. https://doi.org/10.1097/YCT.0000000000000541.

Luigjes, J., Segrave, R., de Joode, N., Figee, M., Denys, D., 2019. Efficacy of invasive and non-invasive brain modulation interventions for addiction. Neuropsychol. Rev. 29 (1), 116–138. https://doi.org/10.1007/s11065-018-9393-5.

Luijten, M., Littel, M., Franken, I.H., 2011. Deficits in inhibitory control in smokers during a Go/NoGo task: an investigation using event-related brain potentials. PLoS One 6 (4), e18898. https://doi.org/10.1371/journal.pone.0018898.

Monte-Silva, K., Kuo, M.F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., Nitsche, Ma., 2013. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimul. 6 (3), 424–432. https://doi.org/10.1016/j.brs.2012.04.01.

Naish, K.R., Vedelago, L., MacKillop, J., Amlung, M., 2018. Effects of neuromodulation on cognitive performance in individuals exhibiting addictive behaviors: a systematic review. Drug Alcohol Depend. https://doi.org/10.1016/j.drugalcdep.2018.08.018.

Nakamura-Palacios, E.M., Lopes, I.B.C., Souza, R.A., Klauss, J., Batista, E.K., Conti, C.L., et al., 2016. Ventral medial prefrontal cortex (vmPFC) as a target of the dorsolateral prefrontal modulation by transcranial direct current stimulation (tDCS) in drug addiction. J. Neural Transm. 123 (10), 1179–1194. https://doi.org/10.1007/s00702-016-1559-9.

Pripfl, J., Neumann, R., Köhler, U., Lamm, C., 2013. Effects of transcranial direct current stimulation on risky decision making are mediated by 'hot' and 'cold' decisions, personality, and hemisphere. Eur. J. Neurosci. 38 (12), 3778–3785. https://doi.org/10.1111/ejn.12375.

Schluter, R., Daams, J., van Holst, R.J., Goudriaan, A.E., 2018. Effects of noninvasive neuromodulation on executive and other cognitive functions in addictive disorders: a systematic review. Front. Neurosci. 12, 642. https://doi.org/10.3389/fnins.2018.00642.

Schuermann, B., Endrass, T., Kathmann, N., 2012. Neural correlates of feedback processing in decision-making under risk. Front. Hum. Neurosci. 6, 204. https://doi.org/10.3389/fnhum.2012.00204.

Serre, F., Fatseas, M., Swendsen, J., Auriacombe, M., 2015. Ecological momentary assessment in the investigation of craving and substance use in daily life: a systematic review. Drug Alcohol Depend. 148, 1–20. https://doi.org/10.1016/j.drugalcdep.2014.12.024.

Shahbabaie, A., Golesorkhi, M., Zamanian, B., Ebrahimpoor, M., Keshvari, F., Nejati, V., et al., 2014. State dependent effect of transcranial direct current stimulation (tDCS) on methamphetamine craving. Int. J. Neuropsychopharmacol./Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP) 17 (10), 1591–1598. https://doi.org/10.1017/S1461145714000686.

Shahbabaie, A., Hatami, J., Farhoudian, A., Ekhtiari, H., Khatibi, A., Nitsche, M.A., 2018. Optimizing electrode montages of transcranial direct current stimulation for attentional Bias modification in early abstinent methamphetamine users. Front. Pharmacol. 9 (August), 1–12. https://doi.org/10.3389/fphar.2018.00907.

Shiffman, S., Stone, A.A., Hufford, M.R., 2008. Ecological momentary assessment. Annu. Rev. Clin. Psychol. 4, 1–32. https://doi.org/10.1146/annurev.clinpsy.3.022806.091415.

Song, S., Zilverstand, A., Gui, W., Li, H.J., Zhou, X., 2019. Effects of single-session versus multi-session non-invasive brain stimulation on craving and consumption in individuals with drug addiction, eating disorders or obesity: a meta-analysis. Brain Stimul. 12 (3), 606–618. https://doi.org/10.1016/j.brs.2018.12.975.

Verveer, I., van der Veen, F.M., & Franken, I. F. A. Feedback Processing during Risky Decision Making in Tobacco Smokers: A tDCS-EEG study. (Unpublished results).

Volkow, N.D., Koob, G.F., McLellan, A.T., 2016. Neurobiologic advances from the brain disease model of addiction. N. Engl. J. Med. 374 (4), 363–371. https://doi.org/10.1056/NEJMra1511480.

Winhusen, T.M., Somoza, E.C., Lewis, D.F., Kropp, F.B., Horigian, V.E., Adinoff, B., 2013. Frontal systems deficits in stimulant-dependent patients: evidence of pre-illness dysfunction and relationship to treatment response. Drug Alcohol Depend. 127 (1-3), 94–100. https://doi.org/10.1016/j.drugalcdep.2012.06.017.

Woods, A.J., Antal, A., Bikson, M., Boggio, P.S., Brunoni, A.R., Celnik, P., et al., 2016. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin. Neurophysiol. 127 (2), 1031–1048. https://doi.org/10.1016/j.clinph.2015.11.012.

World Drug Report, 2019. Stimulants. United Nations Office on Drugs and Crime, Booklet 4 (Accessed 10 March 2020). https://wdr.unodc.org/wdr2019/prelaunch/WDR19_Booklet_4_STIMULANTS.pdf.