

**Title:** Prefrontal Modulation by Repetitive Bilateral Transcranial Direct Current Stimulation (tDCS) in Crack-Cocaine Inpatients

**Brief Title:** Bilateral Prefrontal Modulation in Crack-Cocaine Addiction (tDCS\_CRACK)

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Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation tool which has proven to be efficient in modulating brain activity (George and Aston-Jones, 2010). Previous studies already demonstrated favorable effects of tDCS compared to sham stimulation in substance use disorders and craving. Accordingly, we have demonstrated that in crack-cocaine dependent subjects, five sessions of right anode/left cathode bilateral stimulation of the dlPFC was able to significantly reduce craving both during and after treatment in the real tDCS group as compared to a sham-tDCS group (Batista et al., 2015). Thus, we hypothesized that extension of repetitive bilateral dlPFC tDCS to ten sessions would have a more pronounced effect on craving in crack-cocaine substance use disorder, considering that a successful management of craving during treatment is highly desirable to prevent dropouts and relapses.

## **Material and Methods**

We report this clinical trial according to CONSORT guidelines. This trial was registered under Clinical Trials.gov number NCT02091167.

### *Participants*

All subjects were informed about the purposes of the experiment by the principal investigator and signed a written consent before entering the study.

Thirty-five patients, 29 men and 6 women, who met DSM V criteria for cocaine (crack) use disorder were recruited between June of 2015 and April of 2018 from three specialized clinics for drug use disorder treatment (one public and two private hospitals) from Espírito Santo State, Brazil. They all received standard treatment given by the clinics, consisting of psychosocial approaches – conducted by a professional team of psychologists, nurses, social workers and physicians – sometimes combined with adjunctive pharmacotherapy including benzodiazepines, B-complex vitamins, disulfiram and, if necessary, antidepressants, anxiolytics, antipsychotics, antihypertensive and gastric medication. It must be mentioned that in the public hospital, from where half of the patients was recruited, they were not allowed to have any medication, except non-opioid pain relievers when absolutely necessary, after they had been admitted to the hospital. Therefore, half of the patients were free of medication during the sham- or DC-stimulation. From the other half patients coming from the two private clinics, few of them were medicated (antipsychotics, antidepressants or mood stabilizers) during brain stimulation procedures.

There were two dropouts in the sham-tDCS group that were excluded after randomization. One patient escaped from the treatment facility and the other had to be discontinued because of precocious discharge from the clinic for misconduct.

The inclusion criteria for this study were: (1) male and female patients over the age of 18 years; (2) met criteria for crack-cocaine use disorder according to the ICD-10 Classification of Mental and Behavioral Disorders and the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, as

determined by clinical evaluation; (3) in stable clinical condition with no need for emergency care; (4) able to read, write, and speak Portuguese; and (5) no severe withdrawal signs or symptoms at baseline.

Furthermore, exclusion criteria included: (1) a condition of intoxication or withdrawal due to a substance other than crack-cocaine, (2) unstable mental or medical disorder or substance abuse or addiction other than crack-cocaine use disorder, except nicotine and/or caffeine; (3) diagnosis of epilepsy, convulsions, or delirium tremens during abstinence from crack-cocaine; (4) a previous history of drug hypersensitivity or adverse reactions to diazepam or other benzodiazepines and haloperidol; (5) any contraindication for electrical brain stimulation procedures such as electronic implants or metal implants.

The study was approved by the Brazilian Institutional Review Board of the Federal University of Espírito Santo (CAAE 19403713.6.0000.5060), Brazil, and all patients signed a written informed consent form. The study was conducted in strict adherence to the Declaration of Helsinki and is in accordance with the ethical standards of the Committee on Human Experimentation of the Federal University of Espírito Santo, ES, Brazil.

### *DC stimulation*

A randomized double-blind clinical trial tDCS protocol was used in the study. Stimulation was done using a DC stimulator (DC-Stimulator Plus, NeuroConn, Ilmenau, Germany) with two carbonated silicone electrodes (35 cm<sup>2</sup>) with a thick layer of high-conductive EEG gel beneath them according to our previous study (Nakamura-Palacios et al.,2012). Electrodes were placed

based on the international 10-20 electrode placement system. For tDCS, the cathode was placed over the left dlPFC (F3) while the anode was placed over the right dlPFC (F4). Each session of tDCS lasted for 20 minutes with fade-in and fade-out periods of 30 seconds each. Intensity was set to 2 mA. For sham tDCS, the electrodes were placed at the same positions.

During active tDCS treatment, subjects typically reported tingling sensations under the electrodes area, which rapidly faded (Batista et al., 2015). Our sham intervention was therefore designed to provide an initial period of tingling - the stimulator was automatically switched off after 30 seconds of either anodal or cathodal stimulation - so that similar sensations are perceived during active and sham tDCS protocols, thus serving as an ideal control condition (Nitsche et al., 2003;Gandiga et al., 2006;Batista et al., 2015). Data and instructions in the device display are identical in active and sham settings.

For the sham stimulation procedure, the stimulator automatically switched off after 30 seconds of either anodal or cathodal stimulation yielding sensations typically elicited by tDCS.

### *Craving assessment*

Craving was scored through a brief scale composed of five items (1, 2, 4, 5, and 13) of the Obsessive-Compulsive Cocaine Use Scale, also known as the Obsessive-Compulsive Cocaine Scale (OCCS), which are based on the Obsessive-Compulsive Drinking Scale (Anton et al., 1995;Anton et al., 1996;Anton, 2000), as proposed by Hormes et al. (Hormes et al., 2012) and

Vorspan et al. (Vorspan et al., 2012). These five-item scales assess craving in a narrow sense according to De Wildt et al. (de Wildt et al., 2005).

Through this brief scale it is possible to quantify thoughts and feelings (obsessions), and behavioral intentions (de Wildt et al., 2005), answered on a scale ranging from 0 to 4, resulting in a total score between 0 and 20. Patients are questioned on how much of the time (total per day), when the drug is not used, is occupied by thoughts, ideas, desires, or impulses related to crack-cocaine and its effects; how frequently these thoughts, ideas, desires, or impulses related to crack-cocaine and its effects occur; how much distress or disturbance these ideas, thoughts, impulses or desire related to crack-cocaine use cause when the person is under withdrawal; how much effort they have to make to resist these thoughts, ideas, desires, or impulses, or how much energy they have to spend to think of something else when they enter the mind under withdrawal; and finally ask about their drive to use crack-cocaine.

The OCCS was applied in the week before the beginning of the real or sham-tDCS treatment, during the treatment (second, third and fourth weeks) and in the week after the end of the brain stimulation application, resulting in five time-points measurements.

#### *Relapses in 30- and 60-days follow-up*

After their discharge from the hospital, patients from sham- and real tDCS groups were followed-up for at least 60 days regarding crack-cocaine use relapses. A use relapse was defined as the first episode of return to the

previous uncontrolled pattern of crack-cocaine use (rocks per day) (Klauss et al., 2014). Information about relapse were gathered directly when patients regularly returned to the hospital for clinical follow-up after their discharge and/or by self-report or reports of family members by telephone calls.

### *Procedures*

Those patients who were eligible according to inclusion and exclusion criteria described above and agreed to participate in this study signed an informed consent sheet. All data were originally acquired from participants entering this single research center clinical trial to investigate the efficacy of tDCS treatment.

After global physical and clinical examination subjects were randomly assigned to one of the two groups (sham- and real tDCS) in a 1:1 ratio using a computer-generated block randomization sequence that was kept with the unblinded study coordinator (not involved in the recruitment). The co-investigator conducting treatments was only given a list of 5-number blinding codes to be loaded to the DC-stimulator before each session of brain stimulation. The device is previously settled with specific settings for the study.

After patients had been admitted to the hospitals, they were maintained under regular treatment for 30 days in average or until they had reached a global clinical stabilization, to have them started in the sham- or real tDCS treatments. The brain stimulation application was then performed in one 20-min session a day, every other day, including weekends, up to a total of 10

sessions, always in the afternoon period, in the following five weeks and they were followed-up after the end of the stimulation treatment for up to 60 days after their discharge from the hospitals.

Craving was measured once a week over five weeks (once before the beginning of the stimulation sessions, three times over the stimulation sessions and once more after the end of stimulation sessions) with a total of five time-points measurements. Relapses were collected after discharge from the hospital up to 60 days after intervention.

Participants and experimenters were blinded for brain stimulation assignments from the beginning of the study protocol up to the end of the 60-days follow-up after the end of sham- or real tDCS treatment, resulting in a double-blind experimental design.

### *Statistical Analysis*

We powered the study for a medium effect size based on the results of our previous study (Batista et al., 2015) in which the effect size (partial  $\eta^2$ ) for the main within-subject factor in the respective two-way ANOVA with repeated measures was 0.10384 when comparing craving scores once before, twice during and once after 5-sessions of tDCS (four time-points). The tDCS electrode montage was identical in the studies, and patient populations of crack-cocaine users were similar. We used the correction for SPSS input into the G\*Power 3.1.9.2. With this effect size, for the two-way mixed model ANOVA of the present study with the within factor craving measurements, the



between-subject factor tDCS condition, the dependent variable craving score, and craving measurements x condition interaction as the primary outcome parameter, with a power of 80%, and a two-sided probability of a type I error of 5%, the resulting minimum sample size was 30 participants. To account for waiving or dropouts, which were expected to be very common in this condition, we increased the estimated sample size to approximately 10%, resulting in 33 subjects in total (approximately 16 to 17 subjects in each group).

Most of data (age, patterns of crack-cocaine use, 5-items OCCS) were normally distributed according to the D'Agostino & Pearson normality test, thus they were analyzed by parametric tests. Between-group (sham- and real tDCS) comparisons were conducted by unpaired *Student's t*-tests. For all other non-parametric data (gender, schooling, employment, marital state and tobacco use), Chi-square or Fisher tests were used to compare sham and real tDCS groups.

Besides the two-way ANOVA with repeated measures followed by Bonferroni-corrected t-tests, linear regression analyses were done over craving scores obtained along the 4-week treatment (five time-points measurements) for both groups. Additional comparisons between initial and final OCDS scores were done by paired t-tests for each group, and differences between final and initial scores were compared between sham-tDCS and real tDCS groups with unpaired t-test. Effect sizes were calculated using Cohen's *d* and corrected by Hedges's  $g_s$  for unpaired and Hedges'  $g_{av}$  for paired t-tests (Lakens, 2013).

A two-tailed p-value of 0.05 or less was considered to indicate statistical significance. SPSS Statistics Base 24.0 (SPSS Inc, USA) and GraphPad Prism

7.0 (GraphPad Software Inc, USA) were employed for statistical analysis and graphic presentations.