Title: Prefrontal Modulation by Repetitive Bilateral Transcranial Direct Current Stimulation (tDCS) in Alcoholic Inpatients

Brief Title: Bilateral Prefrontal Modulation in Alcoholism (tDCS_ALCOHOL)

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NCT 02091284

Date: July 3, 2018

Study Protocol

Alcohol is a highly addictive substance and alcohol dependence is a chronically relapsing disorder. It induces tolerance such that increased doses of the alcohol are required to achieve the desired effects and is associated with adverse symptoms during its acute withdrawal. Progressing disease is accompanied with neglect of alternative interests, and social, family and occupational activities. Attempts to quit are often unsuccessful and the patient continues to use the substance despite knowledge of physical and/or psychological harm caused by alcohol (1). Alcohol dependence is thus a debilitating disorder that harms not only the individual, but inflicts significant costs to society, including loss of productivity, security challenges, crime and lawlessness, increasing health care costs and a myriad of negative social consequences (2).

Craving is a common manifestation in all drug addictions. It is defined as the "pressing, urgent and irrepressible desire to give in to the substance" (3), resulting in an uncontrolled urge to consume a drug, with strong obsessions about and irresistible compulsions to use (4), even when the individual is well aware of the consequences that its use can bring to his life. Craving is now considered as part of the diagnosis criteria for Substance Use Disorders under the A4 criteria in the DSM-5 (1, 5, 6). One reason to add craving to the diagnostic criteria was that that it activates brain regions related to the reward system (7, 8). Indeed, craving can be caused by an alteration of the relevant brain circuitry, that may persist even when the individual is not currently using the substance, but is exposed to stimuli that are associated with it (1, 9, 10), constituting a recognized central driving force for successive relapses and perpetuation of drug use (11, 12).

Psychosocial and pharmacological approaches, although essential, have shown limitations and modest efficacy in the treatment of alcohol dependence (13). Therefore, the development of more effective treatments or alternatives improving the efficacy of the current approaches is highly desired.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique in which a weak current is applied to the brain for several minutes through electrodes, resulting in a polarity-dependent modulation of brain activity (14, 15). Considering that a single bilateral tDCS, either left cathodal/right anodal or left

anodal/right cathodal, over the dorsolateral prefrontal cortex (dlPFC) showed to reduce alcohol craving in AUD patients (16), but the repetitive unilateral anodal tDCS over the left dlPFC increased instance of relapses in AUD patients (17), in the following study in AUD outpatients, we applied five consecutive sessions of bilateral tDCS, having the cathodal electrode over the left and the anodal over the right dlPFC, and showed a reduced probability of relapse to the use of alcohol (18). Half (50%) of the AUD patients treated with tDCS, as compared to only 11.8% of subjects from the sham-tDCS group, were completely abstinent at the end of six months following the intervention. However, in this study craving during the period of brain stimulation was not significantly changed (18).

The extension of tDCS sessions may clinically matters as 10 daily sessions have shown to result in more effective and long-lasting effects than 5 daily sessions (19, 20). Therefore, in the present study we aimed to investigate whether an intensified intervention with ten sessions of tDCS bilaterally applied over the dlPFC would reduce craving for alcohol use in AUD inpatients.

Material and Methods

We report this clinical trial according to CONSORT guidelines. This trial was registered under Clinical Trials.gov number NCT02091284.

Participants

AUD patients of both genders were successively recruited between June of 2015 and January of 2018 from three specialized clinics for drug dependence treatment, one public and two privates, from the State of Espírito Santo, Brazil. These specialized services applied standard protocols for the treatment of drug addiction, consisting of psychosocial approaches –conducted by a professional team of psychologists, nurses, social workers and physicians, and pharmacotherapy, including benzodiazepines, vitamin B, disulfiram and, when necessary, antidepressants, anxiolytics, antihypertensive, and gastric medications, and folic acid. Two dropouts occurred after randomization. One dropout had to be hospitalized due to clinical instability and another missed many stimulation sessions.

The inclusion criteria for this study were: (1) male and female patients over the age of 18 years; (2) met criteria for alcohol dependence according to the Classification of Mental and Behavioral Disorders (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), 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) without severe withdrawal signs or symptoms at baseline.

Exclusion criteria included: (1) a condition of intoxication or withdrawal due to a substance other than alcohol, (2) unstable mental or medical disorder or substance abuse or addiction other than alcohol dependence, except nicotine and/or caffeine or history of marijuana use during adolescence; (3) diagnosis of epilepsy, convulsions, or delirium tremens during the abstinence of alcohol; (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 or metal implants.

Ethical approval was provided by the Brazilian Institutional Review Board of the Federal University of Espírito Santo (CAAE 19403713.6.0000.5060), Brazil, and it was registered in clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT02091284). 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, where this study was conducted. Subjects were fully informed about the experimental protocol and voluntarily signed an informed consent form before the start of the study.

Direct Current (DC) stimulation

The intervention in this clinical trial was transcranial DC stimulation (tDCS). In each session, tDCS was applied via two carbonated silicone electrodes (35 cm^2) with a thick layer of high-conductive EEG paste on the contact surface connected to a DC-Stimulator (DC-Stimulator Plus, NeuroConn, Ilmenau, Germany) for 20 minutes with fade-in and fade-out periods of 30 seconds each. Intensity was set to 2 mA.

The cathode was placed above F3 (according to the EEG international 10 –20 system), corresponding to the left dlPFC, and the anode was positioned above the right

dlPFC (F4). 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. Sham- or real tDCS was applied once a day, every other day, including weekends, until completion of 10 sessions (Fig. 1).

Craving assessment: 5-items OCDS

Craving was scored with a brief scale composed of 5 items (1, 2, 4, 5, and 13) from the Obsessive-Compulsive Drinking Scale (OCDS) (21-23), which assesses craving in a narrow sense according to De Wildt et al. (24).

Questions of this brief scale allow quantification of thoughts and feelings (obsessions), and behavioral intentions (24), and are answered on a scale ranging from 0 to 4, resulting in a total score between 0 and 20. They ask how much of a person's time (total per day), when the drug is not used, is occupied by thoughts, ideas, desires, or impulses related to alcohol and its effects; how frequently these thoughts, ideas, desires, or impulses related to alcohol and its effects occur; how much distress or disturbance these ideas, thoughts, impulses or desire related to alcohol use cause when the person is under withdrawal; how much effort the person has to make to resist these thoughts, ideas, desires, or impulses, or how much energy he/she has to spend to think of something else when they enter the mind under withdrawal; and finally ask about the person's drive to use alcohol.

This scale was applied in the week before the beginning of the real or sham-tDCS treatment (1st measurement), during the treatment over approximately 3-weeks (2nd, 3rd and 4th measurements) and in the week after the end of the brain stimulation protocol (5th measurement).

3-months follow-up: Alcohol use relapses

After their discharge from the hospital, patients from sham- and real tDCS groups were followed-up for three months, corresponding to a period of initial remission according to DSM-5, regarding alcohol use relapses. Alcohol use relapse here was considered as the first episode of return to the previous uncontrolled pattern of alcohol use (drinks per day) (18). Information of these relapses 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 for study participation according to the inclusion and exclusion criteria described above and agreed to participate in this study signed an informed consent form (Fig. 1). All data were originally acquired from participants participating in a randomized sham-controlled double-blind clinical trial to investigate the efficacy of tDCS treatment of alcohol dependence.

After global physical and clinical examination, subjects were randomly assigned to one of the two intervention 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 recruitment) and only revealed to the co-investigator conducting treatments immediately before the first session.

Craving (5-items OCDS) was measured before and after completion of the treatment and once per week during the three-weeks treatment, resulting in five measurements (Fig. 1). Alcohol use relapses after hospital discharge were verbally obtained from patients, families or caregivers.

Participants and experimenters were blinded for brain stimulation assignments from the beginning of the study protocol up to the end of the 3-months follow-up after the end of sham-tDCS or real tDCS treatment, configuring a double-blind experimental design.

Statistical Analysis

We powered the study for a small effect size given our hypothesis that tDCS would be associated with a relevant reduction in craving scores. Thus, assuming a small effect size of 0.3 specified for SPSS in G*Power 3.1 for a repeated measure (5 measures) within-between interaction analysis of variance (ANOVA) as principal statistical test for the craving analysis with a power of 80%, a two-sided probability of a type I error of 5%, a minimum of 38 subjects would be necessary; however to account for waiving or dropouts expected to be very common in this condition, we increased the estimated sample to approximately 20%, resulting in 45 to 46 subjects (22 to 23 subjects in each group).

Age, patterns of alcohol use and 5-items OCDS were normally distributed according to D'Agostino & Pearson normality test, thus they were analyzed by parametric tests.

Besides the two-way ANOVA (sham-tDCS and tDCS groups as between-subjects factor) with repeated measures (five time-points as within-subjects factor) followed by Bonferroni's multiple comparisons as *post-hoc* test, linear regression analyses were done over craving scores obtained over the respective five time-points for both groups and the slopes of the respective curves were compared using a modified version of the *t* test according to Zar (1984), which is equivalent to analysis of covariance. 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 tDCS groups with unpaired *t* tests. 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).

Age and patterns of alcohol use were compared between groups by unpaired *t*-test. For all other non-parametric data, Chi-square or Fisher tests were used to compare results between sham and real tDCS groups.

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.

References

1. DSM-5. *Diagnostic and statistical manual of mental disorders : DSM-5*. 5th ed. Washington, D.C.: American Psychiatric Association (2013). xliv, 947 p. p.
2. Daley DC. Family and social aspects of substance use disorders and treatment. *J Food Drug Anal* (2013) 21(4):S73-S6. doi: 10.1016/j.jfda.2013.09.038. PubMed PMID: 25214748; PubMed Central PMCID: PMC4158844.
3. Grall-Bronnec M, Sauvaget A. The use of repetitive transcranial magnetic stimulation for modulating craving and addictive behaviours: a critical literature review of efficacy, technical and methodological considerations. *Neurosci Biobehav Rev* (2014) 47:592-613. doi: 10.1016/j.neubiorev.2014.10.013. PubMed PMID: 25454360.
4. Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Brain Res Rev* (1993) 18(3):247-91. Epub 1993/09/01. PubMed PMID: 8401595.
5. Lupi M, Martinotti G, Santacroce R, Cinosi E, Carlucci M, Marini S, et al. Transcranial Direct Current Stimulation in Substance Use Disorders: A Systematic Review of Scientific Literature. *J ECT* (2017) 33(3):203-9. doi: 10.1097/YCT.0000000000000401. PubMed PMID: 28272095.
6. O'Brien C. Addiction and dependence in DSM-V. *Addiction* (2011) 106(5):866-7. doi: 10.1111/j.1360-0443.2010.03144.x. PubMed PMID: 21477226; PubMed Central PMCID: PMCPMC3812919.
7. Heinz A, Beck A, Grusser SM, Grace AA, Wrase J. Identifying the neural circuitry of alcohol craving and relapse vulnerability. *Addict Biol* (2009) 14(1):108-18. doi: 10.1111/j.1369-1600.2008.00136.x. PubMed PMID: 18855799; PubMed Central PMCID: PMCPMC2879014.
8. Wilson SJ, Sayette MA, Fiez JA. Prefrontal responses to drug cues: a neurocognitive analysis. *Nat Neurosci* (2004) 7(3):211-4. doi: 10.1038/nn1200. PubMed PMID: 15001989; PubMed Central PMCID: PMC2637355.
9. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry* (2016) 3(8):760-73. doi: 10.1016/S2215-0366(16)00104-8. PubMed PMID: 27475769.
10. Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F. Addiction: beyond dopamine reward circuitry. *Proc Natl Acad Sci U S A* (2011) 108(37):15037-42. doi: 10.1073/pnas.1010654108. PubMed PMID: 21402948; PubMed Central PMCID: PMCPMC3174598.
11. Weiss F. Neurobiology of craving, conditioned reward and relapse. *Curr Opin Pharmacol* (2005) 5(1):9-19. Epub 2005/01/22. doi: S1471-4892(04)00205-X [pii]

10.1016/j.coph.2004.11.001. PubMed PMID: 15661620.
12. Self DW. Neural substrates of drug craving and relapse in drug addiction. *Ann Med* (1998) 30(4):379-89. Epub 1998/10/23. PubMed PMID: 9783837.
13. Miller PM, Book SW, Stewart SH. Medical treatment of alcohol dependence: a systematic review. *Int J Psychiatry Med* (2011) 42(3):227-66. Epub 2011/01/01. PubMed PMID: 22439295; PubMed Central PMCID: PMC3632430.
14. Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: State of the art 2008. *Brain Stimul* (2008) 1(3):206-23. doi: 10.1016/j.brs.2008.06.004. PubMed PMID: 20633386.
15. den Uyl TE, Gladwin TE, Wiers RW. Transcranial direct current stimulation, implicit alcohol associations and craving. *Biol Psychol* (2015) 105:37-42. doi: 10.1016/j.biopsycho.2014.12.004. PubMed PMID: 25541515.
16. Boggio PS, Sultani N, Fecteau S, Merabet L, Mecca T, Pascual-Leone A, et al. Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: a double-blind,

sham-controlled study. *Drug Alcohol Depend* (2008) 92(1-3):55-60. Epub 2007/07/21. doi: S0376-8716(07)00250-5 [pii]

10.1016/j.drugalcdep.2007.06.011. PubMed PMID: 17640830.
17. da Silva MC, Conti CL, Klauss J, Alves LG, do Nascimento Cavalcante HM, Fregni F, et al. Behavioral effects of transcranial direct current stimulation (tDCS) induced dorsolateral prefrontal cortex plasticity in alcohol dependence. *J Physiol Paris* (2013) 107(6):493-502. doi: 10.1016/j.jphysparis.2013.07.003. PubMed PMID: 23891741.
18. Klauss J, Penido Pinheiro LC, Silva Merlo BL, Correia Santos Gde A, Fregni F, Nitsche MA, et al. A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. *Int J Neuropsychopharmacol* (2014) 17(11):1793-803. Epub 2014/07/11. doi: 10.1017/S1461145714000984

S1461145714000984 [pii]. PubMed PMID: 25008145.
19. Valle A, Roizenblatt S, Botte S, Zaghi S, Riberto M, Tufik S, et al. Efficacy of anodal transcranial direct current stimulation (tDCS) for the treatment of fibromyalgia: results of a randomized, sham-controlled longitudinal clinical trial. *J Pain Manag* (2009) 2(3):353-61. PubMed PMID: 21170277; PubMed Central PMCID: PMCPMC3002117.
20. Kuo MF, Paulus W, Nitsche MA. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *Neuroimage* (2014) 85 Pt 3:948-60. doi: 10.1016/j.neuroimage.2013.05.117. PubMed PMID: 23747962.
21. Anton RF, Moak DH, Latham P. The Obsessive Compulsive Drinking Scale: a self-rated instrument for the quantification of thoughts about alcohol and drinking behavior. *Alcohol Clin Exp Res* (1995) 19(1):92-9. Epub 1995/02/01. PubMed PMID: 7771669.
22. Anton RF, Moak DH, Latham PK. The obsessive compulsive drinking scale: A new method of assessing outcome in alcoholism treatment studies. *Arch Gen Psychiatry* (1996) 53(3):225-31. Epub 1996/03/01. PubMed PMID: 8611059.
23. Anton RF. Obsessive-compulsive aspects of craving: development of the Obsessive Compulsive Drinking Scale. *Addiction* (2000) 95 Suppl 2:S211-7. Epub 2000/09/26. PubMed PMID: 11002915.
24. de Wildt WA, Lehert P, Schippers GM, Nakovics H, Mann K, van den Brink W. Investigating the structure of craving using structural equation modeling in analysis of the obsessive-compulsive drinking scale: a multinational study. *Alcohol Clin Exp Res* (2005) 29(4):509-16. Epub 2005/04/19. doi: 00000374-200504000-00004 [pii]. PubMed PMID: 15834215.