

tDCS clinical research - highlights: Addictive Disorders

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Is transcranial current stimulation (tCS, including direct current, tDCS, alternating current, tACS, or random noise stimulation tRNS) effective for the treatment of addictive disorders? Under what conditions? With what montages? We focus here on a review of the recent literature on this topic. We have relied on Google Scholar and also [PubMed](#) to carry out the search, including the terms of tDCS, tACS, tRNS as well as Addictive Disorders (**until March 2015**).

As you can read below, there quite a few encouraging results in this area, and study group sizes (the famous N) are now moderately large. We try to indicate group size and the use of a sham-controlled, double-blind experimental technique. Most studies are careful about these crucial aspects. **The typical target for treatment is anode over the right prefrontal cortex and cathode over the left prefrontal cortex (see Neuroelectrics' Wikipedia section on [multi-focal montages](#) for more information).**

As in prior posts, in what follows we concentrate on relevant, study-oriented papers with patients, and leave reviews to the end. In order to make the reading lighter, we have edited the abstracts a bit (please click on the title link if you are interested in the paper).

There are several papers with studies involving different type of addictive disorders. All these research has been focused on the tDCs stimulation of the DLPFC with a very consistent setup in all of them. Most of the literature use a common protocol with the stimulation is set to 2mA and 20 minutes of tDCs stimulation.

The studies reviewed demonstrate the efficacy of tDCS in addictive disorders. These papers have been classified as Food, Smoking and Alcohol and drugs. All these subtypes share the same concept of the stimulation at the DLPFC to reduce the addiction. The results of the papers in all subtypes are very positive and coincident.

den Uyl TE, Gladwin TE, Wiers RW. Transcranial direct current stimulation, implicit alcohol associations and craving. *Biol Psychol.* 2015 Feb;105:37-42. doi: 10.1016/j.biopsycho.2014.12.004. Epub 2014 Dec 23.

Previous research has shown that stimulation of the left dorsolateral prefrontal cortex (DLPFC) enhances working memory (e.g. in the n-back task), and reduces craving for cigarettes and alcohol. Stimulation of the right inferior frontal gyrus (IFG) improves response inhibition. The underlying mechanisms are not clearly understood, nor is it known whether IFG stimulation also reduces craving. Here, we compared effects of DLPFC, IFG, and sham stimulation on craving in heavy drinkers in a small sample (n=41). We also tested effects of tDCS on overcoming response biases due to associations between alcohol and valence and alcohol and approach, using implicit association tests (IATs). Mild craving was reduced after DLPFC stimulation. Categorization of valence attribute words in the IAT was faster after DLPFC stimulation. We conclude that

DLPFC stimulation can reduce craving in heavy drinkers, but found no evidence for tDCS induced changes in alcohol biases, although low power necessitates caution.

Nakamura-Palacios EM, de Almeida Benevides MC, da Penha Zago-Gomes M, de Oliveira RW, de Vasconcellos VF, de Castro LN, da Silva MC, Ramos PA, Fregni F. Auditory event-related potentials (P3) and cognitive changes induced by frontal direct current stimulation in alcoholics according to Lesch alcoholism typology. *Int J Neuropsychopharmacol.* 2012 Jun;15(5):601-16. doi: 10.1017/S1461145711001040. Epub 2011 Jul 22.

Frontal lobe dysfunction is a hallmark of alcohol dependence. Recent studies have shown that a simple but powerful technique of cortical modulation--transcranial direct current stimulation (tDCS)--can induce significant cognitive changes. We therefore aimed to assess the clinical and electrophysiological (as indexed by P3) effects of tDCS of left dorsolateral prefrontal cortex (DLPFC) in different types of alcoholic patients according to Lesch's typology. We enrolled 49 alcoholic subjects, aged between 18 and 75 yr, during the subacute abstinence period to participate in this study. Subjects underwent event-related potential (ERP) registration of alcohol-related and neutral sounds before, during and after active tDCS (1 mA, 35 cm², during 10 min) or sham procedure in a counterbalanced and randomized order. Frontal assessment battery (FAB) and five items of the Obsessive Compulsive Drinking Scale were applied at the beginning and at the end of each experimental session. ERP analysis showed an increase in the mean amplitude of P3 associated with alcohol-related sounds after tDCS. This effect was not seen for neutral sounds. This change was more pronounced in Lesch IV alcoholics. Secondary exploratory analysis showed a significant improvement of FAB performance after active tDCS compared to sham tDCS in Lesch IV alcoholics only. We showed clinical and electrophysiological evidence of tDCS-induced frontal activity enhancement that was specific for Lesch IV alcoholics. Given that frontal dysfunction may contribute to the loss of control over drinking behaviour, local increase in frontal activity induced by tDCS might have a beneficial clinical impact in the future.

Pripfl J, Lamm C. Focused transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex modulates specific domains of self-regulation. *Neurosci Res.* 2015 Feb;91:41-7. doi: 10.1016/j.neures.2014.09.007. Epub 2014 Sep 28.

Recent neuroscience theories suggest that different kinds of self-regulation may share a common psychobiological mechanism. However, empirical evidence for a domain general self-regulation mechanism is scarce. The aim of this study was to investigate whether focused anodal transcranial direct current stimulation (tDCS), facilitating the activity of the dorsolateral prefrontal cortex (dlPFC), acts on a domain general self-regulation mechanism and thus modulates both affective and appetitive self-regulation. Twenty smokers participated in this within-subject sham controlled study. Effects of anodal left, anodal right and sham tDCS over the dlPFC on affective picture appraisal and nicotine craving-cue appraisal were assessed. Anodal right tDCS over the dlPFC reduced negative affect in emotion appraisal, but neither modulated regulation of positive emotion appraisal nor of craving appraisal. Anodal left stimulation did not induce any significant effects. The results of our study show that domain specific self-regulation networks are at work in the prefrontal cortex. Focused tDCS modulation of this specific self-regulation network could probably be used during the first phase of nicotine abstinence, during which negative affect might easily result in relapse. These findings have implications for neuroscience models of self-regulation and are of relevance for the development of brain stimulation based treatment methods for neuropsychiatric disorders associated with self-regulation deficits.

Gorini A, Lucchiari C, Russell-Edu W, Pravettoni G. Modulation of risky choices in recently abstinent dependent cocaine users: a transcranial direct-current stimulation study. *Front Hum Neurosci.* 2014 Aug 27;8:661. doi: 10.3389/fnhum.2014.00661. eCollection 2014.

Previous neurobiological and neuropsychological investigations have shown that risk-taking behaviors and addictions share many structural and functional aspects. In particular, both are characterized by an irresistible need to obtain immediate rewards and by specific alterations in brain circuits responsible for such behaviors. In this study, we used transcranial direct-current stimulation over the dorsolateral prefrontal cortex (DLPFC) of two samples of subjects (18 dependent cocaine users and 18 control subjects) to investigate the effects of left and right cortical excitability on two risk tasks: (1) the balloon analog risk task (BART) and (2) the game of dice task (GDT). All subjects randomly received a left anodal/right cathodal stimulation (LAN+), a right anodal/left cathodal stimulation (RAN+), and a sham (placebo) stimulation each run at least 48 h apart. Participants were asked to perform the BART and the GDT immediately before and after each stimulation. Our results reveal that the activation of the DLPFC (left and right) results in a reduction of risky behaviors at the BART task both in controls subjects and cocaine dependent users. The effect of tDCS on GDT, instead, is more complex. Cocaine users increased safe behavior after right DLPFC anodal stimulation, while risk-taking behavior increased after left DLPFC anodal stimulation. Control subjects' performance was only affected by the anodal stimulation of the right DLPFC, resulting in an increase of safe bets. These results support the hypothesis that excessive risk propensity in dependent cocaine users might be due to a hypoactivation of the right DLPFC and an unbalance interhemispheric interaction. In conclusion, since risky decision-making seems to be, at least in part, responsible for maintenance and relapse of addiction, we argue that a neuromodulation-based approach could represent a valuable adjunct in the clinical treatment of addiction.

Lapenta OM, Sierve KD, de Macedo EC, Fregni F, Boggio PS. Transcranial direct current stimulation modulates ERP-indexed inhibitory control and reduces food consumption. *Appetite.* 2014 Dec;83:42-8. doi: 10.1016/j.appet.2014.08.005. Epub 2014 Aug 13.

Food craving can be defined as the "urge to eat a specific food". Previous findings suggest impairment of inhibitory control, specifically a regulatory deficit in the lateral prefrontal circuitry that is associated with a compulsion for food. As demonstrated by three previous studies, bilateral transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) (anode right/cathode left) reduces food craving and caloric intake. We designed the present study to evaluate the neural mechanisms that underlie these effects. We replicated the design of one of these previous studies but included electroencephalographic assessments to register evoked potentials in a Go/No-go task that contained pictures of food and furniture (a control visual stimulus). We collected data from nine women (mean age = 23.4 ± 2 years) in a crossover experiment. We observed that active DLPFC tDCS (anode right/cathode left), compared with sham stimulation, reduced the frontal N2 component and enhanced the P3a component of responses to No-go stimuli, regardless of the stimulus condition (food or furniture). Active tDCS was also associated with a reduction in caloric intake. We discuss our findings in the context of cortico-subcortical processing of craving and tDCS effects on inhibitory control neural circuitry.

Klauss J, Penido Pinheiro LC, Silva Merlo BL, de Almeida Correia Santos G, Fregni F, Nitsche MA, Miyuki Nakamura-Palacios E. A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. *Int J Neuropsychopharmacol.* 2014 Nov;17(11): 1793-803. doi: 10.1017/S1461145714000984. Epub 2014 Jul 10.

Preliminary small studies have shown that transcranial direct current stimulation (tDCS) reduces craving in alcoholic subjects. It is unclear whether tDCS also leads to changes in clinically meaningful outcomes for alcohol dependence in a properly powered phase II randomized clinical trial. We aimed to investigate whether repetitive tDCS changes the risk of alcohol use relapse in severe alcoholics from outpatient services. Thirty-five subjects were randomized to receive active bilateral [left cathodal/right anodal over the dorsolateral prefrontal cortex (dlPFC)] repetitive (five consecutive days) tDCS (2 mA, 35 cm², two times daily stimulation for 13 min with a 20-min interval) or sham-tDCS. There were two dropouts before treatment. From 33 alcoholic subjects, 17 (mean age 45.5±8.9 s.d., 16 males) were randomized to sham and 16 (44±7.8 s.d., 16 males) to real tDCS treatment. By the end of the six months of follow-up, two subjects treated with sham (11.8%) and eight treated with real tDCS (50%) were still alcohol-abstinent [p=0.02, Long-rank (Mantel-Cox) Test, HR=0.35 (95% CI, 0.14-0.85)]. No differences with regard to changes on scores of craving, frontal function, global mental status, depressive or anxiety symptoms were observed between groups. However, subjects from the tDCS group improved with regard to their overall perception of quality of life (p=0.02), and increased their scores in the environment domain (p=0.04) after treatment. Bilateral tDCS over dlPFC reduces relapse probability in severe alcoholic subjects and results in improved perception of quality of life.

Shahbabaie A, Golesorkhi M, Zamanian B, Ebrahimipour M, Keshvari F, Nejati V, Fregni F, Ekhtiari H. State dependent effect of transcranial direct current stimulation (tDCS) on methamphetamine craving. *Int J Neuropsychopharmacol.* 2014 Oct;17(10):1591-8. doi: 10.1017/S1461145714000686. Epub 2014 May 14.

Transcranial direct current stimulation (tDCS) has been shown to modulate subjective craving ratings in drug dependents by modification of cortical excitability in dorsolateral prefrontal cortex (DLPFC). Given the mechanism of craving in methamphetamine (meth) users, we aimed to test whether tDCS of DLPFC could also alter self-reported craving in abstinent meth users while being exposed to meth cues. In this double-blinded, crossover, sham-controlled study, thirty two right-handed abstinent male meth users were recruited. We applied 20 min 'anodal' tDCS (2 mA) or 'sham' tDCS over right DLPFC in a random sequence while subjects performed a computerized cue-induced craving task (CICT) starting after 10 min of stimulation. Immediate craving was assessed before the stimulation, after 10 min of tDCS, and after tDCS termination by visual analog scale (VAS) of 0 to 100. Anodal tDCS of rDLPFC altered craving ratings significantly. We found a significant reduction of craving at rest in real tDCS relative to the sham condition (p = 0.016) after 10 min of stimulation. On the other hand, cue-induced VAS craving was rated significantly higher in the real condition in comparison with sham stimulation (p = 0.012). Our findings showed a state dependent effect of tDCS: while active prefrontal tDCS acutely reduced craving at rest in the abstinent meth users, it increased craving during meth-related cue exposure. These findings reflect the important role of the prefrontal cortex in both cue saliency evaluation and urge to meth consumption.

Fecteau S, Agosta S, Hone-Blanchet A, Fregni F, Boggio P, Ciraulo D, Pascual-Leone A. Modulation of smoking and decision-making behaviors with transcranial direct current stimulation in tobacco smokers: a preliminary study. *Drug Alcohol Depend.* 2014 Jul 1;140:78-84. doi: 10.1016/j.drugalcdep.2014.03.036. Epub 2014 Apr 16.

Most tobacco smokers who wish to quit fail to reach their goal. One important, insufficiently emphasized aspect of addiction relates to the decision-making system, often characterized by dysfunctional cognitive control and a powerful drive for reward. Recent proof-of-principle studies indicate that transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex (DLPFC) can transiently modulate

processes involved in decision-making, and reduce substance intake and craving for various addictions. We previously proposed that this beneficial effect of stimulation for reducing addictive behaviors is in part mediated by more reflective decision-making. The goal of this study was to test whether nicotine intake and decision-making behaviors are modulated by tDCS over the DLPFC in tobacco smokers who wished to quit smoking. Main findings include a significant decrease in the number of cigarettes smoked when participants received active as compared to sham stimulation. This effect lasted up to four days after the end of the stimulation regimen. In regards to decision-making, smokers rejected more often offers of cigarettes, but not offers of money, after they received active as compared to sham stimulation at the Ultimatum Game. No significant change was observed at the Risk Task with cigarettes or money as rewards.

Conti CL, Moscon JA, Fregni F, Nitsche MA, Nakamura-Palacios EM. Cognitive related electrophysiological changes induced by non-invasive cortical electrical stimulation in crack-cocaine addiction. *Int J Neuropsychopharmacol.* 2014 Sep;17(9):1465-75. doi: 10.1017/S1461145714000522. Epub 2014 Apr 28.

Prefrontal dysfunction is a hallmark in drug addiction, yet interventions exploring modulation of prefrontal cortex function in drug addiction have not been fully investigated with regard to physiological alterations. We tested the hypothesis that non-invasive prefrontal stimulation would change neural activity in crack-cocaine addiction, investigating the effects of transcranial Direct Current Stimulation (tDCS) of Dorsolateral Prefrontal Cortex (DLPFC) induced cortical excitability modulation on the visual P3 Event Related Potentials (ERP) component under neutral and drug cue exposition in crack-cocaine addicts. Thirteen crack-cocaine users were randomly distributed to receive five applications (once a day, every other day) of bilateral (left cathodal/right anodal) tDCS (20 min, 2 mA, 35 cm²) or sham tDCS over the DLPFC. Brain activity was measured under crack-related or neutral visual-cued ERPs. There were significant differences in P3-related parameters when comparing group of stimulation (active vs. sham tDCS) and number of sessions (single vs. repetitive tDCS). After a single session of tDCS, P3 current intensity in the left DLPFC increased during neutral cues and decreased during crack-related cues. This effect was opposite to what was observed in the sham-tDCS group. In contrast, repetitive tDCS increased current density not only in the DLPFC, but also in a wider array of prefrontal areas, including presumably the frontopolar cortex (FPC) orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC), when subjects were visualizing crack-related cues. Thus, single and repetitive application of tDCS can impact cognitive processing of neutral and especially crack-related visual cues in prefrontal areas, which may be of importance for treatment of crack-cocaine addiction.

Meng Z, Liu C, Yu C, Ma Y. Transcranial direct current stimulation of the frontal-parietal-temporal area attenuates smoking behavior. *J Psychiatr Res.* 2014 Jul;54:19-25. doi: 10.1016/j.jpsychires.2014.03.007. Epub 2014 Mar 25.

Many brain regions are involved in smoking addiction (e.g. insula, ventral tegmental area, prefrontal cortex and hippocampus), and the manipulation of the activity of these brain regions can show a modification of smoking behavior. Low current transcranial direct current stimulation (tDCS) is a noninvasive way to manipulate cortical excitability, and thus brain function and associated behaviors. In this study, we examined the effects of inhibiting the frontal-parietal-temporal association area (FPT) on attention bias to smoking-related cues and smoking behavior in tobacco users. This inhibition is induced by cathodal tDCS stimulation. We tested three stimulation conditions: 1) bilateral cathodal over both sides of FPT; 2) cathodal over right FPT; and 3) sham-tDCS. Visual attention bias to smoking-related cues was evaluated using an eye tracking system. The measurement for smoking behavior was the number of daily cigarettes consumed before and after tDCS treatment. We found that, after bilateral cathodal stimulation of the FPT area, while the attention

to smoking-related cues showed a decreased trend, the effects were not significantly different from sham stimulation. The daily cigarette consumption was reduced to a significant level. These effects were not seen under single cathodal tDCS or sham-tDCS. Our results show that low current tDCS of FPT area attenuates smoking cue-related attention and smoking behavior. This non-invasive brain stimulation technique, targeted at FPT areas, might be a promising method for treating smoking behavior.

Meng Z, Liu C, Yu C, Ma Y. Transcranial direct current stimulation of the frontal-parietal-temporal area attenuates smoking behavior. J Psychiatr Res. 2014 Jul;54:19-25. doi: 10.1016/j.jpsychires.2014.03.007. Epub 2014 Mar 25.

Many brain regions are involved in smoking addiction (e.g. insula, ventral tegmental area, prefrontal cortex and hippocampus), and the manipulation of the activity of these brain regions can show a modification of smoking behavior. Low current transcranial direct current stimulation (tDCS) is a noninvasive way to manipulate cortical excitability, and thus brain function and associated behaviors. In this study, we examined the effects of inhibiting the frontal-parietal-temporal association area (FPT) on attention bias to smoking-related cues and smoking behavior in tobacco users. This inhibition is induced by cathodal tDCS stimulation. We tested three stimulation conditions: 1) bilateral cathodal over both sides of FPT; 2) cathodal over right FPT; and 3) sham-tDCS. Visual attention bias to smoking-related cues was evaluated using an eye tracking system. The measurement for smoking behavior was the number of daily cigarettes consumed before and after tDCS treatment. We found that, after bilateral cathodal stimulation of the FPT area, while the attention to smoking-related cues showed a decreased trend, the effects were not significantly different from sham stimulation. The daily cigarette consumption was reduced to a significant level. These effects were not seen under single cathodal tDCS or sham-tDCS. Our results show that low current tDCS of FPT area attenuates smoking cue-related attention and smoking behavior. This non-invasive brain stimulation technique, targeted at FPT areas, might be a promising method for treating smoking behavior.

Kekic M, McClelland J, Campbell I, Nestler S, Rubia K, David AS, Schmidt U. The effects of prefrontal cortex transcranial direct current stimulation (tDCS) on food craving and temporal discounting in women with frequent food cravings. Appetite. 2014 Jul;78:55-62. doi: 10.1016/j.appet.2014.03.010. Epub 2014 Mar 20.

Bulimia nervosa, binge-eating disorder, and some forms of obesity are characterised by compulsive overeating that is often precipitated by food craving. Transcranial direct current stimulation (tDCS) has been used to suppress food cravings, but there is insufficient evidence to support its application in clinical practice. Furthermore, the potential moderating role of impulsivity has not been considered. This study used a randomised within-subjects crossover design to examine whether a 20-minute session of sham-controlled bilateral tDCS to the dorsolateral prefrontal cortex (anode right/cathode left) would transiently modify food cravings and temporal discounting (TD; a measure of choice impulsivity) in 17 healthy women with frequent food cravings. Whether the effects of tDCS on food craving were moderated by individual differences in TD behaviour was also explored. Participants were exposed to food and a film of people eating, and food cravings and TD were assessed before and after active and sham stimulation. Craving for sweet but not savoury foods was reduced following real tDCS. Participants that exhibited more reflective choice behaviour were more susceptible to the anti-craving effects of tDCS than those that displayed more impulsive choice behaviour. No differences were seen in TD or food consumption after real versus sham tDCS. These findings support the efficacy of tDCS in temporarily lowering food cravings and identify the moderating role of TD behaviour.

Conti CL, Nakamura-Palacios EM. Bilateral transcranial direct current stimulation over dorsolateral prefrontal cortex changes the drug-cued reactivity in the anterior cingulate cortex of crack-cocaine addicts. Brain Stimul. 2014 Jan-Feb;7(1):130-2. doi: 10.1016/j.brs.2013.09.007. Epub 2013 Oct 12.

BACKGROUND:

Patients addicted to crack-cocaine routinely have difficulty sustaining treatment, which could be related to dysfunctional cerebral activity that occurs in addiction.

OBJECTIVE:

To investigate the indirect electrophysiological effects of single transcranial direct current stimulation (tDCS) on cocaine-addicted brains.

METHODS:

The patients received either left cathodal/right anodal or sham stimulation over the DLPFC. The region of interest was the anterior cingulate cortex (ACC) during the N2 time window (200-350 ms). Event-related potentials in the ACC were measured during visual presentation of crack-related cues or neutral cues.

RESULTS:

Low-resolution brain electromagnetic tomography (LORETA) indicated that exposure to crack-related images led to increased activity in the ACC in the sham group, while the tDCS group showed decreased ACC activity after visualization of drug cues.

CONCLUSION:

Prefrontal tDCS specifically modulated the ACC response during exposure to visual drug cues in crack-cocaine users.

Xu J, Fregni F, Brody AL, Rahman AS. Transcranial direct current stimulation reduces negative affect but not cigarette craving in overnight abstinent smokers. Front Psychiatry. 2013 Sep 20;4:112. doi: 10.3389/fpsyt.2013.00112. eCollection 2013.

Transcranial direct current stimulation (tDCS) can enhance cognitive control functions including attention and top-down regulation over negative affect and substance craving in both healthy and clinical populations, including early abstinent (~1.5 h) smokers. The aim of this study was to assess whether tDCS modulates negative affect, cigarette craving, and attention of overnight abstinent tobacco dependent smokers. In this study, 24 smokers received a real and a sham session of tDCS after overnight abstinence from smoking on two different days. We applied anode to the left dorsolateral prefrontal cortex and cathode to the right supra-orbital area for 20 min with a current of 2.0 mA. We used self-report questionnaires Profile of Mood States (POMS) to assess negative affect and Urge to Smoke (UTS) Scale to assess craving for cigarette smoking, and a computerized visual target identification task to assess attention immediately before and after each tDCS. Smokers reported significantly greater reductions in POMS scores of total mood disturbance and scores of tension-anxiety, depression-dejection, and confusion-bewilderment subscales after real relative to sham tDCS. Furthermore, this reduction in negative affect positively correlated with the level of nicotine dependence as assessed by Fagerström scale. However, reductions in cigarette craving after real vs. sham tDCS did not differ, nor were there differences in reaction time or hit rate change on the visual task. Smokers did not report significant side effects of tDCS. This study demonstrates the safety of tDCS and its promising effect in ameliorating negative affect in overnight abstinent smokers. Its efficacy in treating tobacco dependence deserves further investigation.

Jansen JM, Daams JG, Koeter MW, Veltman DJ, van den Brink W, Goudriaan AE. Effects of non-invasive neurostimulation on craving: a meta-analysis. Neurosci Biobehav Rev. 2013 Dec;37(10 Pt 2): 2472-80. doi: 10.1016/j.neubiorev.2013.07.009. Epub 2013 Jul 31.

This meta-analysis was conducted to evaluate the available evidence regarding the effects of non-invasive neurostimulation of the dorsolateral prefrontal cortex (DLPFC), on craving in substance dependence and craving for high palatable food. Non-invasive neurostimulation techniques were restricted to repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS). A total of 17 eligible studies were identified. Random effects analysis revealed a pooled standardized effect size (Hedge's g) of 0.476 (CI: 0.316-0.636), indicating a medium effect size favouring active non-invasive neurostimulation over sham stimulation in the reduction of craving ($z=5.832$, $p<0.001$). No significant differences were found between rTMS and tDCS, between the various substances of abuse and between substances of abuse and food, or between left and right DLPFC stimulation. In conclusion, this meta-analysis provides the first clear evidence that non-invasive neurostimulation of the DLPFC decreases craving levels in substance dependence.

da Silva MC, Conti CL, Klauss J, Alves LG, do Nascimento Cavalcante HM, Fregni F, Nitsche MA, Nakamura-Palacios EM. Behavioral effects of transcranial direct current stimulation (tDCS) induced dorsolateral prefrontal cortex plasticity in alcohol dependence. J Physiol Paris. 2013 Dec;107(6): 493-502. doi: 10.1016/j.jphysparis.2013.07.003. Epub 2013 Jul 25.

Transcranial Direct Current Stimulation (tDCS) has been shown to reduce acute substance craving in drug addicts, and improve cognition in neuropsychiatric patients. Here we aimed to explore further tDCS induced behavioral and neurophysiological modulation including assessment of relapse rate over a prolonged time course in alcoholism. We examined the effects of repeated anodal tDCS (2mA, 35 cm², 20min) over the left dorsolateral prefrontal cortex (DLPFC) on relapse to the use of alcohol in alcoholics from outpatient services, who received additional routine clinical treatment. Furthermore, event related potentials (ERPs), cognitive and frontal executive processes, craving, depressive and anxiety symptoms were obtained before and after treatment. From thirteen alcoholic subjects, seven were randomized to sham-tDCS and six to real tDCS treatment (once a week for five consecutive weeks). Depressive symptoms and craving were reduced to a larger extent in the tDCS group compared to the sham group ($p=0.005$ and $p=0.015$, respectively). On the other hand, active tDCS was able to block the increase in neural activation triggered by alcohol related and neutral cues in prefrontal cortex (PFC) as indexed by ERP as seen in the sham-tDCS group. Finally, there was a trend for increased change in executive function in the tDCS group compared to the sham-tDCS group ($p=0.082$), and, similarly, a trend for more relapses in the tDCS group compared to sham tDCS (four alcoholic subjects (66.7%) vs. one (14.3%), $p=0.053$). These results confirm the previous findings of tDCS effects on craving in alcoholism and also extend these findings as we showed also tDCS-related mood improvement. However, potential increase in relapse is possible; thus the clinical value of an increase in craving and improvement in depression and executive function needs to be carefully assessed in further studies; including investigation of optimal parameters of stimulation.

Goldman RL, Borckardt JJ, Frohman HA, O'Neil PM, Madan A, Campbell LK, Budak A, George MS. Prefrontal cortex transcranial direct current stimulation (tDCS) temporarily reduces food cravings and increases the self-reported ability to resist food in adults with frequent food craving. Appetite. 2011 Jun;56(3):741-6. doi: 10.1016/j.appet.2011.02.013. Epub 2011 Feb 23.

This study examined whether a 20-min session of prefrontal transcranial direct current stimulation (tDCS) (anode over the right prefrontal cortex and cathode over the left prefrontal cortex) would reduce food cravings and increase the self-reported ability to resist foods in 19 healthy individuals who reported frequent food cravings. Participants viewed computerized images of food and used computerized visual analogue

scales to rate food cravings and inability to resist foods before, during, and after receiving either real or sham tDCS. This study employed a randomized within-subject crossover design; participants received both real and sham tDCS and were blind to the condition. Food cravings ratings were reduced in both conditions, however, the percent change in cravings ratings from pre- to post- stimulation was significantly greater for real stimulation than for sham. The percent change in inability to resist food from pre- to post-stimulation also showed a greater decrease in the real condition than for sham. Post hoc analyses suggest that active prefrontal tDCS acutely and significantly decreased food cravings ratings for sweet foods and carbohydrates more so than sham tDCS. No significant differences were seen in the amount of food ingested between real and sham tDCS. These findings in healthy subjects indicate that tDCS is able to temporarily reduce food cravings and improve the self-reported ability to resist foods.

Boggio PS, Zaghi S, Villani AB, Fecteau S, Pascual-Leone A, Fregni F. Modulation of risk-taking in marijuana users by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). *Drug Alcohol Depend.* 2010 Dec 1;112(3):220-5. doi: 10.1016/j.drugalcdep.2010.06.019. Epub 2010 Aug 21.

Cognitive deficits that are reported in heavy marijuana users (attention, memory, affect perception, decision-making) appear to be completely reversible after a prolonged abstinence period of about 28 days. However, it remains unclear whether the reversibility of these cognitive deficits indicates that (1) chronic marijuana use is not associated with long-lasting changes in cortical networks or (2) that such changes occur but the brain adapts to and compensates for the drug-induced changes. Therefore, we examined whether chronic marijuana smokers would demonstrate a differential pattern of response in comparison to healthy volunteers on a decision-making paradigm (Risk Task) while undergoing sham or active transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). Twenty-five chronic marijuana users who were abstinent for at least 24h were randomly assigned to receive left anodal/right cathodal tDCS of DLPFC (n=8), right anodal/left cathodal tDCS of DLPFC (n=9), or sham stimulation (n=8); results on Risk Task during sham/active tDCS were compared to healthy volunteers from a previously published dataset. Chronic marijuana users demonstrated more conservative (i.e. less risky) decision-making during sham stimulation. While right anodal stimulation of the DLPFC enhanced conservative decision-making in healthy volunteers, both right anodal and left anodal DLPFC stimulation increased the propensity for risk-taking in marijuana users. These findings reveal alterations in the decision-making neural networks among chronic marijuana users. Finally, we also assessed the effects of tDCS on marijuana craving and observed that right anodal/left cathodal tDCS of DLPFC is significantly associated with a diminished craving for marijuana.

Boggio PS, Liguori P, Sultani N, Rezende L, Fecteau S, Fregni F. Cumulative priming effects of cortical stimulation on smoking cue-induced craving. *Neurosci Lett.* 2009 Sep 29;463(1):82-6. doi: 10.1016/j.neulet.2009.07.041. Epub 2009 Jul 18.

Smoking cue-provoked craving is an intricate behavior associated with strong changes in neural networks. Craving is one of the main reasons subjects continue to smoke; therefore interventions that can modify activity in neural networks associated with craving can be useful tools in future research investigating novel treatments for smoking cessation. The goal of this study was to use a neuromodulatory technique associated with a powerful effect on spontaneous neuronal firing - transcranial direct current stimulation (tDCS) - to modify cue-provoked smoking craving. Based on preliminary data showing that craving can be modified after a single tDCS session, here we investigated the effects of repeated tDCS sessions on craving behavior. Twenty-seven subjects were randomized to receive sham or active tDCS (anodal tDCS of the left DLPFC). Our results show a significant cumulative effect of

tDCS on modifying smoking cue-provoked craving. In fact, in the group of active stimulation, smoking cues had an opposite effect on craving after stimulation - it decreased craving - as compared to sham stimulation in which there was a small decrease or increase on craving. In addition, during these 5 days of stimulation there was a small but significant decrease in the number of cigarettes smoked in the active as compared to sham tDCS group. Our findings extend the results of our previous study as they confirm the notion that tDCS has a specific effect on craving behavior and that the effects of several sessions can increase the magnitude of its effect. These results open avenues for the exploration of this method as a therapeutic alternative for smoking cessation and also as a mean to change stimulus- induced behavior.

Fregni F, Liguori P, Fecteau S, Nitsche MA, Pascual-Leone A, Boggio PS. Cortical stimulation of the prefrontal cortex with transcranial direct current stimulation reduces cue-provoked smoking craving: a randomized, sham-controlled study. J Clin Psychiatry. 2008 Jan;69(1):32-40.

OBJECTIVE:

Because neuroimaging studies have shown that cue-provoked smoking craving is associated with changes in the activity of the bilateral dorsolateral prefrontal cortex (DLPFC), we aimed to investigate whether a powerful technique of noninvasive brain stimulation, transcranial direct current stimulation (tDCS), reduces cue-provoked smoking craving as indexed by a visual analog scale.

METHOD:

We performed a randomized, sham-controlled crossover study in which 24 subjects received sham and active tDCS (anodal tDCS of the left and right DLPFC) in a randomized order. Craving was induced by cigarette manipulation and exposure to a smoking video. The study ran from January 2006 to October 2006.

RESULTS:

Smoking craving was significantly increased after exposure to smoking-craving cues ($p < .0001$). Stimulation of both left and right DLPFC with active, but not sham, tDCS reduced craving significantly when comparing craving at baseline and after stimulation, without ($p = .007$) and with ($p = .005$) smoking-craving cues. There were no significant mood changes in any of the conditions of stimulation. Adverse events were mild and distributed equally across all treatment conditions.

CONCLUSIONS:

Our findings extend the results of a previous study on the use of brain stimulation to reduce craving, showing that cortical stimulation with tDCS is beneficial for reducing cue-provoked craving, and thus support the further exploration of this technique for smoking cessation.

Fregni F, Orsati F, Pedrosa W, Fecteau S, Tome FA, Nitsche MA, Mecca T, Macedo EC, Pascual-Leone A, Boggio PS. Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. Appetite. 2008 Jul;51(1):34-41. doi: 10.1016/j.appet.2007.09.016. Epub 2007 Dec 23.

We aimed to assess whether modulation of the dorsolateral prefrontal cortex (DLFPC) with noninvasive brain stimulation, namely transcranial direct current stimulation (tDCS), modifies food craving in healthy subjects. We performed a randomized sham-controlled cross-over study in which 23 subjects received sham and active tDCS (anode left/cathode right and anode right/cathode left) of the DLPFC. Subjects were exposed to food and also watched a movie of food associated with strong craving. Desire for food consumption was evaluated by visual analogue scales (VAS) and food consumption before and after treatment. In addition we measured visual attention to food using an eye tracking system. Craving for viewed foods as indexed by VAS was reduced by anode right/cathode left tDCS. After sham stimulation, exposure to real food or food-related movie increased craving; whereas after anode left/cathode right tDCS, the food-

related stimuli did not increase craving levels, as revealed by the VAS scale. Moreover, compared with sham stimulation, subjects fixated food-related pictures less frequently after anode right/cathode left tDCS and consumed less food after both active stimulation conditions. These changes were not related to mood changes after any type of tDCS treatment. The effects of tDCS on food craving might be related to a modulation of neural circuits associated with reward and decision-making.

Boggio PS, Sultani N, Fecteau S, Merabet L, Mecca T, Pascual-Leone A, Basaglia A, Fregni F. Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: a double-blind, sham-controlled study. *Drug Alcohol Depend.* 2008 Jan 1;92(1-3):55-60. Epub 2007 Jul 19.

BACKGROUND:

Functional neuroimaging studies have shown that specific brain areas are associated with alcohol craving including the dorsolateral prefrontal cortex (DLPFC). We tested whether modulation of DLPFC using transcranial direct current stimulation (tDCS) could alter alcohol craving in patients with alcohol dependence while being exposed to alcohol cues.

METHODS:

We performed a randomized sham-controlled study in which 13 subjects received sham and active bilateral tDCS delivered to DLPFC (anodal left/cathodal right and anodal right/cathodal left). For sham stimulation, the electrodes were placed at the same positions as in active stimulation; however, the stimulator was turned off after 30s of stimulation. Subjects were presented videos depicting alcohol consumption to increase alcohol craving.

RESULTS:

Our results showed that both anodal left/cathodal right and anodal right/cathodal left significantly decreased alcohol craving compared to sham stimulation ($p < 0.0001$). In addition, we found that following treatment, craving could not be further increased by alcohol cues.

CONCLUSIONS:

Our findings showed that tDCS treatment to DLPFC can reduce alcohol craving. These findings extend the results of previous studies using noninvasive brain stimulation to reduce craving in humans. Given the relatively rapid suppressive effect of tDCS and the highly fluctuating nature of alcohol craving, this technique may prove to be a valuable treatment strategy within the clinical setting.

Fecteau S, Pascual-Leone A, Zald DH, Liguori P, Théoret H, Boggio PS, Fregni F. Activation of prefrontal cortex by transcranial direct current stimulation reduces appetite for risk during ambiguous decision making. *The Journal of Neuroscience*, 6 June 2007, 27(23): 6212-6218; doi: 10.1523/JNEUROSCI.0314-07.2007

As adult humans, we are continuously faced with decisions in which proper weighing of the risk involved is critical. Excessively risky or overly cautious decision making can both have disastrous real-world consequences. Weighing of risks and benefits toward decision making involves a complex neural network that includes the dorsolateral prefrontal cortex (DLPFC), but its role remains unclear. Repetitive transcranial magnetic stimulation studies have shown that disruption of the DLPFC increases risk-taking behavior. Transcranial direct current stimulation (tDCS) allows upregulation of activity in the DLPFC, and we predicted that it might promote more cautious decision making. Healthy participants received one of the following treatments while they performed the Balloon Analog Risk Task: (1) right anodal/left cathodal DLPFC tDCS, (2) left anodal/right cathodal DLPFC tDCS, or (3) sham tDCS. This experiment revealed that participants receiving either one of the bilateral DLPFC tDCS strategies adopted a risk-averse response style. In a control experiment, we tested whether unilateral DLPFC stimulation (anodal tDCS over the right

or left DLPFC with the cathodal electrode over the contralateral supraorbital area) was sufficient to decrease risk-taking behaviors. This experiment showed no difference in decision-making behaviors between the groups of unilateral DLPFC stimulation and sham stimulation. These findings extend the notion that DLPFC activity is critical for adaptive decision making, possibly by suppressing riskier responses. Anodal tDCS over DLPFC by itself did not significantly change risk-taking behaviors; however, when the contralateral DLPFC was modulated with cathodal tDCS, an important decrease in risk taking was observed. Also, the induced cautious decision-making behavior was observed only when activity of both DLPFCs was modulated. The ability to modify risk-taking behavior may be translated into therapeutic interventions for disorders such as drug abuse, overeating, or pathological gambling.

Fecteau S, Knoch D, Fregni F, Sultani N, Boggio P, Pascual-Leone A. Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. *J Neurosci.* 2007 Nov 14;27(46):12500-5.

Studies have shown increased risk taking in healthy individuals after low-frequency repetitive transcranial magnetic stimulation, known to transiently suppress cortical excitability, over the right dorsolateral prefrontal cortex (DLPFC). It appears, therefore, plausible that differential modulation of DLPFC activity, increasing the right while decreasing the left, might lead to decreased risk taking, which could hold clinical relevance as excessively risky decision making is observed in clinical populations leading to deleterious consequences. The goal of the present study was to investigate whether risk-taking behaviors could be decreased using concurrent anodal transcranial direct current stimulation (tDCS) of the right DLPFC, which allows upregulation of brain activity, with cathodal tDCS of the left DLPFC, which downregulates activity. Thirty-six healthy volunteers performed the risk task while they received either anodal over the right with cathodal over the left DLPFC, anodal over the left with cathodal over the right DLPFC, or sham stimulation. We hypothesized that right anodal/left cathodal would decrease risk-taking behavior compared with left anodal/right cathodal or sham stimulation. As predicted, during right anodal/left cathodal stimulation over the DLPFC, participants chose more often the safe prospect compared with the other groups. Moreover, these participants appeared to be insensitive to the reward associated with the prospects. These findings support the notion that the interhemispheric balance of activity across the DLPFCs is critical in decision-making behaviors. Most importantly, the observed suppression of risky behaviors suggests that populations with boundless risk-taking behaviors leading to negative real-life consequences, such as individuals with addiction, might benefit from such neuromodulation-based approaches.