

Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: A double-blind, sham-controlled study

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Abstract

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 30 s 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.

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1. Introduction

Craving might be defined as a strong or inward desire. Different types of craving have been reported including smoking, food, cocaine and alcohol craving. Recent neuroimaging studies have identified cortical areas associated with craving. Most of these studies suggest that the prefrontal regions, particularly the dorsolateral prefrontal cortex (DLPFC), play a major role in craving associated with drugs and smoking (Olbrich et al., 2006; George et al., 2001; Myrick et al., 2004; McBride et al., 2006; Wilson et al., 2004; Brody et al., 2002; Due et al., 2002; Grant et al., 1996; Garavan et al., 2000; Sell et al., 2000). In addition, studies using repetitive transcranial magnetic stimulation

(rTMS), a technique that can transiently modulate focal cortical activity, show that high-frequency rTMS (i.e. excitability enhancing) delivered to DLPFC results in significant reductions in smoking craving (Eichhammer et al., 2003), food craving (Uher et al., 2005) and cocaine craving (Camprodon et al., 2007). Because alcohol craving is also associated with activity in DLPFC (Olbrich et al., 2006; George et al., 2001; Myrick et al., 2004), we decided to explore whether modulating cortical excitability in this area could change alcohol craving using another noninvasive method of brain stimulation namely, transcranial direct current stimulation (tDCS).

tDCS is a simple technique of noninvasive brain stimulation in which a weak DC current is applied into the brain for several minutes resulting in a polarity-dependent modulation of brain activity. Studies in humans have demonstrated that stimulation of the motor cortex changes its excitability depending on the stimulation polarity. Specifically, anodal stim-

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ulation increases cortical excitability while cathodal stimulation decreases it (Nitsche and Paulus, 2000; Nitsche et al., 2003). These excitability shifts during stimulation are believed to be due to subthreshold neuronal membrane depolarization (Nitsche and Paulus, 2000; Liebetanz et al., 2002) as a result of the opening or closing of voltage-gated ions induced by the electrical current flow (Purpura and McMurtry, 1965; Nitsche et al., 2003) during stimulation. On the other hand, the after-effects are shown to be regulated by NMDA receptors (Nitsche et al., 2005; Liebetanz et al., 2002).

In this study, we stimulated the DLPFC using tDCS rather than rTMS for several reasons. First, tDCS offers an advantage in that the scalp sensation associated with stimulation only lasts for a couple of seconds. Therefore, in a sham-controlled trial, subjects can be adequately blinded to the condition they are receiving (Gandiga et al., 2006). This characteristic is critical given our cross-over study design. Second, tDCS is a simple, safe and inexpensive technique and the device is highly portable. These characteristics make this treatment strategy highly appealing within the clinical setting.

Given that previous neuroimaging studies have demonstrated activity within the DLPFC in association with alcohol craving (George et al., 2001; Wilson et al., 2004), we hypothesized that modulation of this area would alter alcohol craving. Furthermore, a previous brain stimulation study carried out by our group (Fregni et al., in press) has shown that tDCS delivered to both the right and left hemisphere reduces craving for smoking. Based on these findings, we implemented a similar bilateral stimulation strategy in which we: (1) increased excitability in the left and decreased it in the right DLPFC (anodal left/cathodal right) and (2) increased excitability in the right and decreased it in the left DLPFC (anodal right/cathodal left) following a randomized, sham-controlled, double-blind, cross-over design.

2. Methods

2.1. Study subjects

We selected 13 subjects (mean age of 41.3 ± 5.7 , two females) satisfying the diagnostic criteria for alcohol dependence defined by Diagnostic and Statistical Manual of Mental Disorders (4th ed.) (DSM-IV) (American Psychiatric Association, 1994). Patients were recruited from a specialized center for alcohol and substance abuse disorders in Santana do Parnaíba, outside of Sao Paulo, Brazil. All patients were enrolled in the clinic's rehabilitation program and were abstinent for 41.0 ± 51.3 days (a minimum of 10 days). Inclusion criteria included aged between 30 and 55 years of age, alcohol dependence, and a minimum drink history (14 drinks for females and 21 drinks for males) on average per week for four consecutive weeks (during the period of drinking). Subjects were excluded if they had any current or past neuropsychiatric disorder, substantial drug abuse other than alcohol, were taking any neuropsychotropic medications or were pregnant.

This study was performed at University of Mackenzie, Sao Paulo, Brazil. Subjects gave written informed consent to participate in the study and approval was obtained from the local research ethics committee of the institution (process approval number 0020.0.272.000-06). The experimental protocol was designed and carried out according to the principles of the Declaration of Helsinki.

We were aware of the possibility that exposing patients to alcohol cues may potentially result in relapse. Given this important ethical concern, we decided, therefore, not to use real alcoholic beverages in a glass as cues. We chose images of alcoholic beverages and situations that subjects would be more typically exposed to through television commercials and advertisements.

2.2. Study protocol

This study was a randomized, double-blind, sham-controlled, cross-over study in which subjects received three different types of bilateral stimulation of DLPFC with tDCS: (1) active anodal left/cathodal right tDCS, (2) active anodal right/cathodal left tDCS and (3) sham tDCS. A 48-h inter-session interval was used to avoid the potential of any carry-over effects due to stimulation. The order of stimulation was randomized and counterbalanced across subjects using a Latin square design. Participants and the evaluating investigators (except the investigators that applied tDCS) were blinded to the treatment arm.

All stimulation sessions were carried out by the same researchers and at the same time of the day. Demographic and alcohol habits profile data were collected at baseline. The following instruments of evaluation were used:

- (1) For baseline assessment: (i) stages of change readiness and treatment eagerness scale (SOCRATES) (Figlie et al., 2004); (ii) Short Alcohol Dependence Data (SADD) questionnaire (Davidson and Raistrick, 1986).
- (2) To evaluate the effects of treatment: (i) alcohol urge questionnaire (AUQ) (Drummond and Phillips, 2002); (ii) tDCS side-effect questionnaire (side-effect checklist) (Fregni et al., in press); (iii) Visual Analogue Scale for mood domains (Fregni et al., in press).

The following steps were then performed:

- (1) *Baseline evaluation (T0)*: subjects were instructed to complete a visual analogue scale (VAS) with 16 items evaluating mood and a questionnaire to measure alcohol craving (AUQ).
- (2) *Cue-provoked craving*: subjects were then exposed to alcohol cues to increase craving that included viewing a video showing scenes of people drinking in a pleasant way different types of alcoholic beverages, such as beer, wine, vodka and 'pinga' (a popular local alcoholic beverage made from sugar cane and has an ethanol concentration that ranges from 38 to 48%). The video lasted for 5 min. Six different equivalent movies were used and randomized across subjects. In this way, subjects were exposed to a different movie before and after the three conditions of treatment.
- (3) Subjects were assessed again regarding their alcohol craving (T1).
- (4) Subjects underwent tDCS treatment for 20 min (as detailed below).
- (5) The procedure of the pre-treatment was repeated: initial craving evaluation (T2), alcohol cues to increase craving (movie) and new assessment of craving (T3) and also mood using VAS.

It is worthy of note that our urge-elicitation strategy might have increased craving processing in a manner that differs slightly from other types of naturally occurring craving. For instance, there is evidence showing that exposure to drug cues in conjunction with drug availability may produce a more intense craving than would occur without drug availability (Juliano and Brandon, 1998). However, in this study, we were interested in craving associated with alcohol abstinence and thus drinking after craving was never allowed. It is also important to mention that we did not show a neutral cue to the subjects (such as a movie of non-alcoholic beverages); however it has been shown that craving as induced by alcoholic beverage images is effective in inducing alcohol craving as compared to neutral cues (George et al., 2001).

2.3. Transcranial direct current stimulation (tDCS)

Direct current was transferred by using a saline-soaked pair of surface sponge electrodes and delivered by a custom developed, battery-driven, constant current stimulator with a maximum output of 10 mA and electrode size of 35 cm² (Nitsche and Paulus, 2000). The tDCS device has a special feature that makes it particularly reliable for double-blind study designs. We noted in our previous trials that patients try to look at the tDCS display during stimulation and encountered situations in which we had to hide the device from patients receiving sham treatment. We therefore incorporated a switch in the back of the tDCS device that can be activated by the researcher to interrupt the electrical current while maintaining the display "ON" and displaying the parameters of stimulation throughout the procedure. As described earlier, participants received three different types of treatment:

- (1) Anodal stimulation of the left DLPFC and cathodal stimulation of the right DLPFC (referred in the text as “anodal left/cathodal right”). The anode electrode was placed over F3 (using EEG 10/20 system) and the cathode electrode over F4.
- (2) Anodal stimulation of right DLPFC and cathodal stimulation of the left DLPFC (referred in the text as “anodal right/cathodal left”). The anode electrode was placed over F4 (using EEG 10/20 system) and the cathode electrode over F3.
- (3) Sham stimulation of DLPFC (referred as “sham stimulation”). For sham stimulation, the electrodes were placed at the same positions as in active stimulation; however, the stimulator was turned off after 30 s of stimulation. Therefore, the subjects felt the initial itching sensation associated with turning on the device, but received no current stimulation for the rest of the treatment period. A recent study showed that this method of sham stimulation is reliable (Gandiga et al., 2006).

The principal target for treatment was the DLPFC cortex based on prior TMS studies showing that modulation of this area results in a decrease in smoking and also food craving (Johann et al., 2003; Uher et al., 2005) and neuroimaging studies showing that the activity in this area is significantly associated with alcohol craving (Olbrich et al., 2006; George et al., 2001; Myrick et al., 2004).

A constant current of 2 mA was applied for 20 min. These parameters have been shown to be safe in healthy volunteers (Iyer et al., 2005).

2.4. Statistical analysis

Analyses were done with SAS version 9.1 statistical software (Cary, NC, USA). In this study, we had three main research questions that were addressed separately:

- *Research question 1:* did our cues (alcoholic beverage movie) increase craving? To answer this question, we merged the data of the three conditions and compared craving before (T0) and after (T1) alcohol cues, but before stimulation. We then performed an analysis of variance model in which time (T0 versus T1) was the main covariate and subsequently, we performed ANCOVA models to adjust for the effects of potential confounders such as age, gender, order of stimulation and duration of smoking.
- *Research question 2:* did active tDCS (with either anodal left/cathodal right or anodal right/cathodal left) change craving levels as compared to sham tDCS? For this analysis, we used a mixed linear model with repeated measures on time in which we modeled craving changes using the covariates of time, condition and interaction between condition and time. For the outcome measure, we summed items to produce a total craving intensity score for each time point. We compared two time-points: after cues/before stimulation (T1) versus before the second cues/after stimulation (T2).
- *Research question 3:* can tDCS induce after-effects in smoking craving? In other words, do alcohol cues viewed after tDCS stimulation change craving differently when active versus sham conditions are compared? For this assessment, we performed a similar analysis as compared to research question number 2; however, using different time-points (before the movie/after stimulation (T2) and after the movie/after stimulation (T3)).

Given we have three different questions, we corrected the p -value for multiple comparisons using Bonferroni correction. Therefore, we used a threshold for significance of $p < 0.017$ for each research question.

We defined the time points as:

- (1) T0—baseline assessment.
- (2) T1—assessment after (first) alcohol cues and before tDCS.
- (3) T2—assessment after tDCS and before (second) alcohol cues.
- (4) T3—assessment after tDCS and (second) alcohol cues.

For the other endpoints such as mood changes, we used a repeated measures analysis of variance in which the dependent variable was one of these endpoints and the independent variables were: condition (sham, anodal left/cathodal right and anodal right/cathodal left tDCS), time of treatment (pre- and post-treatment

and interaction condition versus time. When appropriate, post hoc comparisons were performed using Bonferroni correction.

At the completion of the study, a total of two subjects were lost to attrition (one dropout after one session and one dropout after two sessions of tDCS). Data that could not be obtained were handled as missing at random.

3. Results

All patients were able to well tolerate the treatment with tDCS. The demographic and clinical characteristics are summarized in Table 1. Adverse effects were rare and their frequency was not significantly different across the three conditions of treatment ($p = 0.51$, fisher's exact test). Discomfort at the site of stimulation was the most common adverse effect (1 report in the sham and 2 reports in anodal left/cathodal right and anodal right/cathodal left stimulation conditions) followed by headache (1, 0 and 2 reports, respectively), mood changes (1, 0 and 0 reports, respectively) and itching on the stimulation site (1, 0 and 0 reports, respectively). Importantly, when comparing baseline craving across the three conditions, we found no significant difference ($F_{(2,32)} = 0.09$, $p = 0.91$), suggesting no carry-over effects due to stimulation.

Exploratory analysis evaluating mood effects showed that a single session of tDCS induced no significant effects in these subjects except for the item “worried/unconcerned” ($p = 0.02$). Interestingly, after anodal right/cathodal left DLPFC stimulation, subjects had an increased rating towards “worried” as compared to anodal left/cathodal right and sham stimulation.

3.1. Question 1: craving increase by alcohol cues

In order to analyze the initial question of whether our strategy to induce craving was effective (movie of alcoholic beverage consumption), we compared alcohol craving before and after alcohol cues (T0 versus T1) using an analysis of variance model in which we include time (T0 and T1) as the main covariate and subsequently, we performed ANCOVA models to adjust the results for potential confounders such as age, gender and order and years of drinking. We found a significant increase in craving of 8.1% ($\pm 8.8\%$, $F_{(1,34)} = 29.26$, $p < 0.0001$) after alcohol cues. Similar results were obtained when we performed ANCOVA models including age, gender, order of stimulation and years of drinking as confounders ($P < 0.0001$ when adjusting for all these potential confounders). Interestingly, age and years of drinking were significantly associated with an increase in craving from T0 to T1 ($p = 0.0162$ and $p = 0.0076$, respectively) (Table 2).

Table 1
Demographic and clinical characteristics

	Mean/N (S.D.)
Age	41.3 (5.7)
Gender (F/M)	2/11
Age at onset of drinking (years)	15.0 (4.6)
Alcohol intake (g/l)	227.7 (123.2)
Number of drinks per day	10.0 (4.6)
SADD	27.4 (7.8)

F/M—females/males; SAAD—Short Alcohol Dependence Data.

Table 2
Craving levels throughout the study

	T0	T1	T2	T3
Sham tDCS	37.9 (15.0)	35.8 (15.5)	35.2 (15.7)	32.5 (15.8)
Anodal left/cathodal right tDCS	35.2 (17.0)	33.0 (17.3)	39.6 (14.8)	38.7 (14.9)
Anodal right/cathodal left tDCS	37.3 (16.1)	32.7 (15.7)	41.5 (10.4)	40.0 (13.0)

Note that the scale for craving (alcohol urge questionnaire) is an instrument with eight questions measuring craving. For some of the questions, lower values means more craving and for other items is the opposite. We therefore, made the necessary adjustments in order to have all the items going in the same direction; and therefore, calculated a composite score for each patient that ranges from 0 to 56 in which 0 indicates *maximal craving* and 56 indicates *no craving*. Therefore, an increase in this scale (e.g. from 33 to 37) indicates less craving and a decrease (e.g. from 40 to 37) indicates more craving. T0 corresponds to baseline assessment: pre tDCS, pre first cue exposure. T1 corresponds to pre tDCS, post first cue exposure. T2 corresponds to post tDCS, pre second cue exposure. T3 corresponds to post tDCS, post second cue exposure.

3.2. Question 2: effects of tDCS treatment

In order to analyze whether tDCS reduced craving, we compared craving levels before and after tDCS treatment (T1 versus T2), performing a mixed model with repeated measures on time. This model revealed a significant interaction time versus condition ($F_{(5,52)} = 7.4, p < 0.0001$), suggesting that craving changes were different across the different conditions of treatment. Indeed, when comparing the three conditions of treatment, we found a significant difference between anodal left/cathodal right versus sham stimulation ($p = 0.02$) and anodal right/cathodal left versus sham stimulation ($p < 0.0001$), but not between anodal left/cathodal right versus anodal right/cathodal left ($p = 0.53$). The mean craving change was -2% ($\pm 6\%$), $+20\%$ ($\pm 29\%$) and $+27\%$ ($\pm 20\%$) for sham, anodal left/cathodal right and anodal right/cathodal left DLPFC stimulation, respectively (see Fig. 1 and Table 2). Finally, we tested whether gender, order, age and years of drinking were significant confounders and found that these terms were not significant ($p > 0.05$) and did not change the results of our model.

3.3. Question 3: after-effects of tDCS

We hypothesized that tDCS effects would last for several minutes after the end of the stimulation period. In order to investigate this effect, we evaluated whether craving could be increased in

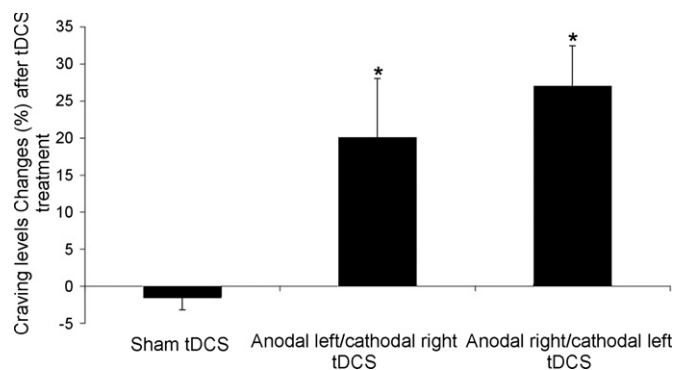


Fig. 1. Craving changes after stimulation (T2) as compared with baseline. Each column represents mean craving changes and error bar represents standard error of mean (S.E.M). *Statistically significant when compared with baseline ($p < 0.017$). This figure shows that craving was significantly changed after active stimulation only. Note that a positive change indicates craving reduction and a negative change indicates craving increase.

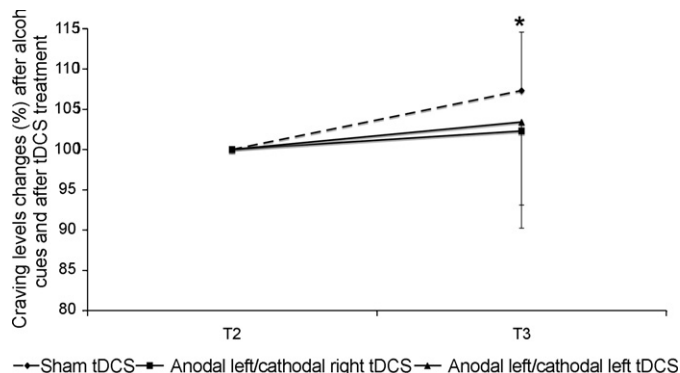


Fig. 2. Craving changes after the second alcohol cues exposure (after treatment—from T2 to T3) in the three conditions of treatment: anodal left/cathodal right DLPFC (dorsolateral prefrontal cortex) tDCS, anodal right/cathodal left tDCS and sham tDCS. Each time point represents mean craving and error bar represents standard error of mean (S.E.M). *Statistically significant when compared with baseline ($p < 0.017$). This figure shows that after the treatment craving could be significantly increased only in subjects who received sham stimulation. Note that normalized craving levels increase indicates craving increase.

patients that received active stimulation as compared with sham stimulation. We therefore performed another model in which the dependent measure was craving level and had three independent variables: time (T2 and T3), condition (sham, anodal left/cathodal right and anodal right/cathodal left) and the interaction condition with time. We found a significant interaction effect ($F_{(5,52)} = 5.7, p = 0.0003$). Indeed, craving could not be increased by alcohol cues in the two conditions that received active stimulation ($p = 0.12$ and $p = 0.64$, anodal left/cathodal right and anodal right/cathodal left stimulation conditions, respectively); however, there was a significant craving increase in the condition that received sham stimulation after alcohol cues (mean craving change of 7.3% ($\pm 7.8\%$)— $p = 0.007$)—see Fig. 2 and Table 2. When including potential confounders in the model (age, gender, order of stimulation, years of drinking), the results for the interaction term did not change and these terms were not significant, except for gender that was marginally significant ($p = 0.04$).

4. Discussion

Our results show that both anodal left/cathodal right and anodal right/cathodal left DLPFC stimulation significantly decreased alcohol craving as compared to sham stimulation. In

addition, alcohol craving could not be increased by alcohol cues in the active stimulation conditions after treatment.

Because we targeted the dorsolateral prefrontal cortex, it is conceivable that stimulation was associated with a change in the activity of this area. Indeed, other tDCS studies targeting stimulation of DLPFC showed that modulation of this area is associated with behavioral changes, such as cognitive changes in healthy subjects (Fregni et al., 2005; Kincses et al., 2004) and patients with major depression (Fregni et al., 2006b) and also mood changes in patients with depression (Fregni et al., 2006a).

Several neuroimaging studies have correlated activity in the dorsolateral prefrontal cortex with alcohol craving. In a recent study, George et al. (2001) reported that alcoholic subjects exhibited increased activity in the left dorsolateral prefrontal cortex while viewing alcohol cues presented within a scanner environment. Furthermore, this change was not observed when alcoholic patients viewed control pictures (such as non-alcoholic beverages) and in social drinkers (George et al., 2001). Activity in the dorsolateral prefrontal cortex area is also associated with craving for other substances, such as smoking and cocaine. Previous studies investigating neural responses to cues in nicotine abusers demonstrated that the anterior cingulate, amygdala, insula, orbitofrontal and dorsolateral prefrontal cortex are associated with craving (Wilson et al., 2004).

As the effects of alcohol and other drugs might be related to activity in mesolimbic dopamine pathways (Berridge and Robinson, 1998), this might explain the involvement of the dorsolateral prefrontal cortex (through the mesofrontolimbic connections). Several dopaminergic antagonists have demonstrated a significant effect in reducing alcohol craving such as clozapine and olanzapine (Green et al., 1999; Hutchison et al., 2006). Given that the mesolimbic pathways are associated with reward behavior, this might explain the addiction behavior as alcohol consumption plays a critical role in incentive sensitization of dopamine receptors. Therefore, with a lack of alcohol or when there is a cue associated with alcohol such as images of the alcoholic beverages or people drinking alcohol, this creates a response in the mesolimbic pathways generating an increase in DLPFC activity that in part may be responsible for the drug-seeking behavior. It would follow that if the activity of DLPFC is modulated externally by tDCS, this might block this cascade of events due to the competition with the input coming from tDCS that can ultimately decrease the signal to noise in the neural system associated with reward.

One aspect that warrants further discussion is the fact that both strategies of DLPFC stimulation, that is, anodal left/cathodal right and anodal right/cathodal left stimulation, resulted in craving reduction. Indeed, neuroimaging studies showed that either the right (Olbrich et al., 2006) or left (George et al., 2001) DLPFC are involved in alcohol craving. Therefore, it might be conjectured that anodal stimulation or cathodal inhibition of either right or left DLPFC ruptured the balance between the right and left DLPFC activity that might be normally necessary for craving states. Support for this notion of balanced bilateral activation of DLPFC during craving states has been shown in neuroimaging studies (Wilson et al., 2004). Finally, modulation of the DLPFC might have modulated other

areas associated with craving such as the orbitofrontal cortex (London et al., 2000; Fowler and Volkow, 1998) that also has extensive connections to other brain areas such as the striatum and amygdala; therefore, integrating the cortical and subcortical processing of motivational behavior and reward. This hypothesis is also supported by recent data showing that tDCS results in widespread changes in regional brain activity in this same network (Lang et al., 2005).

Although we showed that DC stimulation of the prefrontal cortex reduces alcohol craving, further studies are needed to establish the use of tDCS as a viable clinical and therapeutic application. One potential advantage of developing tDCS as an alternative therapeutic strategy is the fact that the effects of tDCS are immediate. Because craving levels are highly variable and dependent on social and even circadian influences, a single treatment that can transiently block craving levels quickly would be highly desirable compared to drug treatment therapies that are typically more long-lasting and lead to tonic effects and thus cannot capture craving variations. In addition, if tDCS does prove to have clinical value, it has additional advantage because it is safe and has a low incidence of only very mild adverse effects.

Some potential limitations of this study should be discussed. First, we studied a relatively small sample size of 13 patients. However, this study used a cross-over design and therefore the results would be comparable to a parallel design study with 39 subjects (13 subjects times 3 different conditions). Second, though not formally assessed in our study, the use of a 48-h washout period appears to be sufficient given that we showed that baseline craving values were not significantly different across different days of testing. Third, there was no neutral cue condition; thus, it is difficult to interpret conclusively whether or not tDCS reduced cue-specific craving or whether the effects were a result of a general attenuation in craving report. As shown by our data, tDCS had an effect on both types of craving as it reduced cue-provoked craving and also baseline craving. We decided not to implement a neutral cue condition given that several studies have reported that images of non-alcoholic beverages as compared with alcoholic beverages are not effective to elicit craving (George et al., 2001). Finally, we cannot determine, based on our findings, whether the effects of tDCS on alcohol craving were due to anodal or cathodal stimulation (or combination of both). Future studies using different electrode montages and sizes are critical to explore this matter further.

All together, this evidence suggests that noninvasive brain stimulation might be an efficacious method to reduce different types of craving and thus further investigation with studies including larger sample sizes and also evaluating the clinical benefits of this treatment are warranted.

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