Cortical Stimulation of the Prefrontal Cortex With Transcranial Direct Current Stimulation Reduces Cue-Provoked Smoking Craving: A Randomized, Sham-Controlled Study

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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.

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Smoking craving is a powerful desire to smoke elicited by smoking deprivation or exposure to situations or cues that are associated with smoking, such as seeing or being near other smokers or smoking materials.[1] The craving is an important factor in provoking smoking relapse in subjects who try to quit smoking.[2–4] Several approaches, such as nicotine substitution, drugs, and psychotherapy, have been proposed to decrease smoking craving. However, efficacy and side effects limit the use of these techniques.

The dorsolateral prefrontal cortex (DLPFC) is critically involved in processing the craving of smoking[5–8] and drugs such as cocaine,[9,10] alcohol,[11] and opiates.[12] Specifically, craving is associated with enhanced activity of this area. Increasing the activity of the DLPFC by noninvasive brain stimulation, and thus likely mimicking its reward-related activation, has been demonstrated to be effective in decreasing craving symptoms in cigarette smokers. High-frequency repetitive transcranial magnetic stimulation (rTMS) of the DLPFC, which increases cortical excitability, reduces smoking craving[13] and cigarette smoking.[14]

We hypothesize that another noninvasive method of brain stimulation, namely, transcranial direct current stimulation (tDCS), could also reduce smoking craving. Transcranial direct current stimulation modulates brain activity significantly in a safe, powerful, and painless way, and its after-effects can last for more than an hour.[15–17] It is a technically simple tool in which a continuous weak electric current is applied to the brain via large electrodes that are placed on the scalp of the subject. The effects of tDCS depend on the direction of the electric current: anodal stimulation increases brain activity and excitability, and cathodal stimulation reduces it.[16] Several well-conducted studies in animals and humans have confirmed the behavioral and neurophysiological effects of this technique.[16,18,19] Furthermore, we have recently shown that the effects induced by tDCS are beneficial for the treatment of neuropsychiatric disorders such as pain,[20] tinnitus,[21] and stroke.[22]

In this study, we tested the hypothesis that excitability-enhancing anodal tDCS of the right or left DLPFC is suited for reducing cue-dependent craving in cigarette smokers. In addition, we tested the hypothesis that this intervention would also reduce general smoking craving (comparing craving after the treatment with baseline). Therefore, we conducted a sham-tDCS–controlled, randomized, double-blind, crossover study. To elicit craving, we used a cue-reactivity paradigm that has been demonstrated to be reliable for this purpose.[5,6]

METHOD

Study Subjects

Subjects were recruited by local advertising on Web sites, and in flyers, and notices distributed throughout local universities. The inclusion criteria were to be between 18 and 55 years old and currently smoking 15 or more cigarettes per day for at least 1 year. Subjects were excluded if they had any neuropsychiatric disorder or current or past history of alcohol or other drug abuse, were taking any psychiatric medication, were pregnant, were in the process of stopping smoking, or were unable to complete the study questionnaires. Twenty-four subjects (mean ± SD age = 24.8 ± 7.6 years, 11 female) were enrolled in this study.

This study was performed at the University of Mackenzie (Sao Paulo, Brazil). The subjects gave written informed consent for the study, and approval was obtained from the local research ethics committee. The study was carried out in conformance with the principles of the Declaration of Helsinki. The study ran from January 2006 to October 2006.

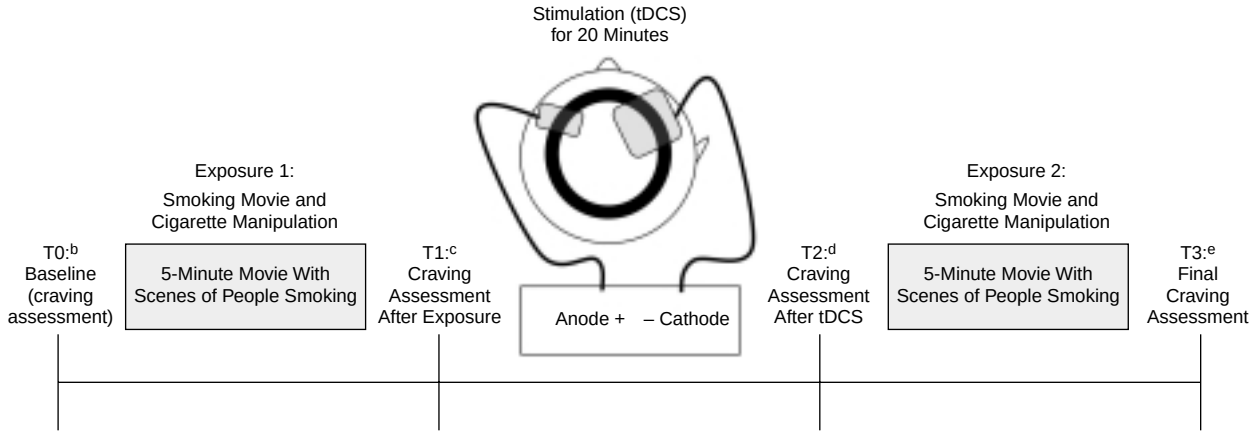
Study Protocol

This study was a randomized, double-blind, sham-controlled crossover study in which subjects received 3 different types of brain stimulation with tDCS: sham tDCS, anodal tDCS of the left DLPFC, and anodal tDCS of the right DLPFC, with 48 hours' intersession interval to avoid carryover effects. Furthermore, the order of stimulation was randomized and counterbalanced across subjects using a Latin square design. We used a Latin square of order 3 (sham tDCS, left anodal tDCS, and right anodal tDCS) × 3 (subject 1, 2, and 3) array, repeated 8 times to accommodate the 24 subjects of this study. Each cell of the array contained 1 type of treatment, in such a way that each treatment occurred once in each row and once in each column. Participants and the investigators, except the investigators who applied tDCS, were blinded to the treatment arm.

All experiments were carried out by the same researchers at the same time of the day. At the baseline, demographic and smoking-habits profile data were collected. Subjects were instructed to keep their regular smoking habit but not to smoke for 1 hour and 30 minutes before the experiment. Although 1 hour and 30 minutes might be considered a rather short period to induce craving; we chose this interval for 2 reasons: (1) to increase compliance, as this time period would be a realistic interval between 2 cigarettes (given the smoking pattern of our population) and (2) to investigate (although there was a risk of a floor effect due to submaximum craving in this case) whether tDCS decreases craving associated with a regular smoking habit (i.e., immediately before the next cigarette). The experimental design is summarized below. (See Figure 1.)

1. Baseline evaluation: subjects were instructed to complete 1 visual analog scale (VAS) with 16 items evaluating mood and another VAS measuring smoking craving that consisted of 5 items[1]: "I have a desire for a cigarette right now"; "If it were possible, I would smoke now"; "All I want right now is a cigarette"; "I have an urge for a cigarette"; "I crave a cigarette right now."[23] Each item was rated using a scale that ranged from 0 (not at all) to 100 (the strongest feeling possible).
2. Cue-provoked craving: subjects were then exposed to smoking cues that included cigarette manipulation and watching a video showing scenes of people smoking to provoke craving. For the cigarette manipulation cue, subjects were instructed to open a pack of their favored brand of cigarette, pick up a cigarette, place it in their mouths, pick up a lighter, and pretend to light and smoke the cigarette. These procedures were standardized to be performed in 30 seconds. Subjects were then asked to put the cigarette away and were shown a movie of 5 minutes' duration presenting people smoking in a pleasant way. (Six different equivalent movies were randomized across subjects, as

Figure 1. Exposure, Intervention, and Assessments Throughout the Treatment[a]



[a]Craving was evaluated at T0, T1, T2, and T3.
[b]T0 corresponds to baseline assessment: pre-tDCS, pre–first cue exposure.
[c]T1 corresponds to pre-tDCS, post–first cue exposure.
[d]T2 corresponds to post-tDCS, pre–second cue exposure.
[e]T3 corresponds to post-tDCS, post–second cue exposure.
Abbreviation: tDCS = transcranial direct current stimulation.

the subjects were exposed to a different movie before and after the 3 types of treatment).
3. Subjects were assessed again regarding their smoking craving.
4. Subjects underwent tDCS treatment for 20 minutes. (As detailed below, this time period corresponds to the interval between T1 and T2.)
5. The procedure of the pretreatment was repeated: initial craving evaluation, smoking cues to provoke craving, and new assessment of craving and mood using VAS scales.

It is worthy of note that our urge-elicitation strategy might have produced craving processing that differs slightly from other types of naturally occurring craving. For instance, evidence shows that exposure to drug cues with drug availability may produce a more intense craving than would occur without drug availability.[24] Because we could not offer cigarettes after smoking cues exposure, craving in our study should be viewed as a craving without drug availability, and although this lack of drug availability might be a potential inherent limitation of our study, our method of eliciting craving was effective (as shown in the results section) and also has been used successfully in a similar study.[14] Indeed, lack of availability has not eliminated cue-induced craving across several other cue studies in which smokers were not allowed to smoke immediately after cue presentation.[5,23]

Instruments of Evaluation

As aforementioned, we used a VAS to measure craving and mood changes. To characterize the study population regarding smoking habits, we used the modified scale of Fagerstrom, the Fagerstrom Test for Nicotine Dependence (FTND).[25] Mood was assessed (at baseline—T0—and at the end of the study—T3), as mood was a potential confounder in this study, because stimulation of DLPFC has been shown to be an effective treatment for major depression, and thus can change mood.[26,27] We used a VAS that ranged from 0 to 10 to assess 16 different domains of mood. We assessed adverse effects at the end of each section, asking subjects about the most common adverse effects after tDCS (such as headache, scalp burning, tingling, and dizziness). Common adverse effects of tDCS are based on our experience and previous studies. (See Nitsche et al.[16] and Iyer et al.[28])

Transcranial Direct Current Stimulation

Direct current was transferred by a saline-soaked pair of surface sponge electrodes and delivered by a specially developed, battery-driven, constant current stimulator with a maximum output of 10 mA. (For more technical details, please contact Sergio A. Boggio at sboggio@colband.com.br.) We used electrodes of 2 different sizes: for the anode electrode,[15] we used a sponge of 35 cm^2; for the cathode electrode, we used a larger electrode of 100 cm^2. It has been shown that this large electrode induces fewer effects on cortical activity (M.A.N., unpublished data, 2005). This electrode montage was set to perform a functional monopolar anodal stimulation of the DLPFC without relevantly shifting excitability of the contralateral DLPFC by the cathodal, reference electrode.

The tDCS device, which was developed by our group, has a special feature that makes it particularly reliable for

double-blind trials. We noted in our previous trials[26,29] that patients try to look at the tDCS display during stimulation, and we encountered situations in which we had to hide the device from patients receiving sham treatment. Therefore, we 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 visual display indicating the parameters of stimulation throughout the procedure. As aforementioned, participants received 3 different types of treatment:

1. Anodal stimulation of the left DLPFC: the anode electrode (35 cm^2) was placed over F3 (EEG 10/20 system) and the cathode electrode (100 cm^2) over F4.
2. Anodal stimulation of right DLPFC: the anode electrode (35 cm^2) was placed over F4 (EEG 10/20 system) and the cathode electrode (100 cm^2) over F3.
3. Sham stimulation of DLPFC: for sham stimulation, the electrodes were placed at the same positions as for the active stimulation; however, the stimulator was turned off after 30 seconds of stimulation. (We used the electrodes' position of treatment 1 in half of the subjects and of treatment 2 in the other half of the subjects.) Therefore, the subjects felt the initial itching sensation but received no current for the rest of the stimulation period. A recent study showed that this method of sham stimulation is reliable.[30]

The main area of treatment was the DLPFC, as transcranial magnetic stimulation studies have shown that modulation of this area results in a decrease in smoking[13] and also food craving,[31] and neuroimaging studies have shown that this area is significantly modulated during smoking craving.[5,6] Another reason for choosing the DLPFC as the site of stimulation is that the effects of tDCS are concentrated in the cortical convexity and thus DLPFC activity can be modified by tDCS.

A constant current of 2 mA intensity was applied for 20 minutes. Stimulation with 2 mA (for a single session) has been shown to be safe in healthy volunteers.[28]

Statistical Analysis

Analyses were done with SAS statistical software, version 9.1 (SAS Institute Inc., Cary, N.C.). We used a mixed linear model to analyze craving changes throughout the trial. We modeled craving change (as indexed by a VAS) using the covariates of time, condition, and interaction between condition and time. For the outcome measure, we averaged the 5 craving-indexing items to produce a mean craving intensity score for each time point. We used a longitudinal study design that included a random factor for individual subjects within and across treatments.

We initially performed this model including all time points (T0, T1, T2, and T3) and all the conditions (left DLPFC, right DLPFC, and sham stimulation) and then performed separate models to study the differences across the slopes representing the different types of treatment, using Bonferroni correction for multiple comparisons. We therefore defined the time points (see Figure 1) as: (1) T0 = baseline assessment: before tDCS before first cue exposure; (2) T1 = before tDCS, after first cue exposure; (3) T2 = after tDCS, before second cue exposure; (4) T3 = after tDCS, after second cue exposure.

We compared the slopes of the 3 interventions using different time periods, such as:

- Slope T0–T1: assessment of craving after initial exposure to craving stimuli;
- Slope T0–T2: assessment of effects of tDCS immediately after stimulation, before the second smoking cues exposure;
- Slope T0–T3: assessment of effects of tDCS at baseline vs. assessment after the second smoking cues exposure (entire treatment);
- Slope T1–T3: assessment of effects of tDCS on cue-elicited craving.

For the other end points, such as mood changes, we used a repeated-measures analysis of variance in which the dependent variable was one of these end points and the independent variables were condition (sham and active tDCS), time of treatment (pretreatment and posttreatment), and interaction condition versus time. When appropriate, post hoc comparisons were performed using Bonferroni correction.

Using the Pearson correlation test, we assessed, in an exploratory way (without correcting p values for multiple comparisons), whether there was a correlation between craving reduction (as indexed by VAS scales) and the variables age, duration of smoking, number of cigarettes smoked per day, age at onset of smoking, and FTND score.

There was 1 dropout after 1 session of tDCS (sham tDCS), and the few missing data were considered missing at random. Statistical significance refers to a 2-tailed p value $< .05$.

RESULTS

Table 1 shows the demographic information for study subjects. Twenty-four subjects participated in this study, and 23 completed the entire study (3 different sessions of treatment); 1 subject did not complete the study—performing only the first session (sham tDCS)—due to school work that precluded him from returning to the other stimulation sessions. These subjects smoked a mean ± SD of 18.5 ± 4.5 cigarettes per day and presented

Table 1. Characteristics of Participants Who Smoked 15 or More Cigarettes Per Day for at Least 1 Year (N = 24)

Characteristic	Value
Age, mean (SD), y	24.8 (7.6)
Gender (M/F)	13/11
Cigarettes/d, mean (SD)	18.5 (4.5)
Age at onset of smoking, mean (SD), y	15.5 (3.2)
Duration of daily smoking, mean (SD), y	9.3 (8.5)
FTND score, mean (SD)	5.0 (1.8)

Abbreviation: FTND = Fagerstrom Test for Nicotine Dependence.

Table 2. Adverse Effects

	Intervention			
Adverse Effect	Sham tDCS[a]	Left DLPFC tDCS[a]	Right DLPFC tDCS[a]	p Value[b]
Drowsiness	2	0	1	.93
Itching	5	6	8	
Headache	2	3	2	
Scalp burning	3	5	4	
Concentration problems	1	0	1	
Mood changes	1	1	0	
Tingling	0	1	0	

[a]Number of subjects presenting with the respective adverse effect after each condition of stimulation.
[b]Fisher exact test: adverse effects in each condition were collapsed, and then the difference across conditions of stimulation was analyzed.
Abbreviations: DLPFC = dorsolateral prefrontal cortex, tDCS = transcranial direct current stimulation.

a mean ± SD FTND score of 4.96 ± 1.81, suggesting that they have medium dependence. (This scale ranges from 0 to 10.) They started smoking at a mean ± SD age of 15.5 ± 3.2 years and had smoked for a mean ± SD duration of 9.3 ± 8.5 years.

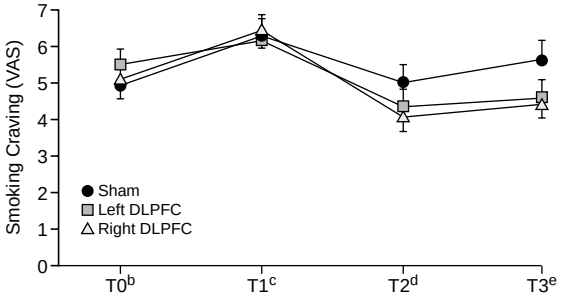
Subjects tolerated tDCS well. The adverse effects were mild and similar across the 3 conditions of stimulation (p = .93). The most frequent adverse effects were scalp burning, headache, and local itching; see Table 2 for more details.

Smoking Craving Assessment

We initially performed an assessment including all time points and all conditions. This model showed a significant interaction time vs. treatment (F = 7.56; df = 1,214; p = .0065), suggesting a significant change in craving throughout the experiment and across the different types of treatment. (See Figure 2.) Because the interaction term was significant, we then explored the different slopes (post hoc tests) as detailed below:

Slope T0–T1: craving evaluation. This comparison analyzed the efficacy of our stimuli for inducing craving, as it compared craving at baseline and after exposure but before tDCS. As expected, the 3 conditions behaved similarly in this analysis—the interaction term (F = 1.56; df = 2,69; p = .21) and main effect of condition (F = 0.26; df = 2,69; p = .77) were not significant, but there was a highly significant effect of time (F = 45.1; df = 1,69; p < .0001). Our paradigm significantly increased craving by an average of 22.6%.

Figure 2. Craving Levels (as indexed by VAS) Changes Across Time (T0, T1, T2, and T3) During the 3 Different Interventions: Anodal tDCS of Left DLPFC, Anodal tDCS of Right DLPFC, and Sham tDCS[a,b]



[a]Each time point represents mean craving.
[b]Error bars represent standard error of mean.
Abbreviations: DLPFC = dorsolateral prefrontal cortex, tDCS = transcranial direct current stimulation, VAS = visual analog scale.

Slope T0–T2: baseline vs. immediately after the end of tDCS. We compared the effects of tDCS on craving before the second exposure to smoking cues, comparing baseline values to those immediately after stimulation but before the second smoking cues exposure. Interestingly, after sham stimulation, subjects returned to similar baseline levels (there was only a small nonsignificant difference of 0.01% in craving levels) but decreased significantly after treatment with left (decrease of 20.1%) and right (decrease of 21.4%) DLPFC stimulation. These 3 slopes differed significantly from each other (F = 5.28; df = 2,69; p = .007). Both active treatments resulted in identical slopes (p = .85) but were significantly different from sham stimulation (sham vs. left DLPFC stimulation, p = .01; sham vs. right DLPFC stimulation, p = .007).

Slope T0–T3: baseline vs. last assessment. We then compared the effects of tDCS on craving using VAS scales between baseline and the last evaluation (after tDCS treatment and smoking cues). The results showed that, at the last evaluation, sham tDCS increased craving (by 13.4%) but active stimulation decreased it (by 13.4% after left DLPFC stimulation and by 13.6% after right DLPFC stimulation) as compared to baseline. The slopes from the active conditions were significantly different from that of sham stimulation (sham vs. left DLPFC stimulation, p = .003; sham vs. right DLPFC stimulation, p = .016).

Slope T1–T3: cue-elicited craving. In order to evaluate whether tDCS could reduce cue-elicited smoking craving specifically, we compared VAS scales immediately after the first cue provoking craving (before tDCS) with VAS scales after the second cue provoking craving (post-tDCS). This analysis revealed a significant interaction

Table 3. Results of Mood Evaluation[a,b]

		Intervention						
		Sham tDCS		Left DLPFC tDCS		Right DLPFC tDCS		
Mood	Time	Mean	SD	Mean	SD	Mean	SD	p Value*
Calm/restless	pre	4.80	2.66	3.87	2.72	3.67	2.63	.45
	post	3.89	2.79	3.73	2.92	3.75	2.47	
Alert/drowsy	pre	3.92	2.37	3.43	2.21	3.98	2.78	.93
	post	3.94	2.51	3.68	2.07	4.24	2.11	
Apathetic/dynamic	pre	7.09	1.92	7.48	2.09	6.76	2.55	.64
	post	7.06	1.91	7.20	2.12	6.98	1.88	
Confused/lucid	pre	7.19	2.24	7.41	2.81	6.83	2.52	.86
	post	7.13	1.98	7.19	2.46	6.49	2.00	
Strong/weak	pre	3.06	2.49	2.75	2.32	3.47	2.16	.93
	post	2.84	1.62	2.59	2.20	3.45	1.94	
Sharp/blunt	pre	3.58	2.12	3.19	2.19	3.28	2.26	.51
	post	3.47	1.68	2.74	1.80	3.57	2.12	
Satisfied/unfulfilled	pre	3.52	2.47	2.89	2.43	3.66	2.50	.45
	post	3.53	2.04	2.83	2.53	3.65	2.06	
Worried/unconcerned	pre	5.63	3.07	6.24	2.97	6.21	2.77	.54
	post	6.35	2.57	6.22	2.89	6.95	1.70	
Fast mind/slow mind	pre	6.29	2.11	6.85	1.69	6.52	1.66	.21
	post	6.97	1.72	6.52	2.57	6.78	1.84	
Tense/relaxed	pre	5.89	2.60	6.57	2.57	5.50	2.82	.48
	post	6.35	2.86	6.46	3.20	6.18	2.67	
Attentive/neglectful	pre	2.83	1.74	3.12	1.78	3.49	2.17	.28
	post	3.49	2.53	2.97	2.26	3.05	2.05	
Inept/competent	pre	7.71	1.17	7.84	1.45	6.99	1.72	.78
	post	7.65	1.57	7.68	2.10	7.11	1.84	
Happy/sad	pre	3.07	2.47	2.57	2.03	2.77	1.98	.86
	post	2.88	1.98	2.44	2.06	3.69	2.42	
Hostile/friendly	pre	7.13	2.40	7.53	2.07	6.49	2.53	.25
	post	7.16	2.59	7.06	2.61	7.03	2.36	
Interested/indifferent	pre	2.29	1.94	1.88	1.65	2.38	2.30	.61
	post	2.15	1.51	1.67	1.30	2.71	2.12	
Quiet/sociable	pre	7.15	2.64	7.81	2.05	8.13	1.92	.28
	post	7.22	2.23	8.05	2.34	7.57	2.46	

*From a 2-way analysis of variance (interaction term treatment vs. time).
[a]Pre indicates craving levels at T0.
[b]Post indicates craving levels at T2.
Abbreviations: DLPFC = dorsolateral prefrontal cortex, tDCS = transcranial direct current stimulation.

term (time effect, $F = 4.95$; $df = 1,72$; $p = .029$). The slopes from the active conditions were significantly different from that of sham stimulation (sham vs. left DLPFC stimulation, $p = .043$; sham vs. right DLPFC stimulation, $p = .020$).

Order and gender effect. Although we randomized and counterbalanced the order of stimulation, we evaluated whether there was an order effect. In addition, we evaluated the gender effect. We included the terms *order* and *gender* in the model and showed that neither term was significant ($F = 1.58$; $df = 1,214$; $p = .21$; and $F = 0.5$; $df = 1,104$; $p = .48$; respectively).

Mood Scales

We evaluated mood using a scale that contains 16 items. This analysis (comparing results at baseline [T0] with those after the end of treatment [T3]) disclosed that none of the items was significantly associated with treatment, time of evaluation or interaction treatment vs. time, showing that mood changes did not confound our results. (See Table 3 for details.)

Correlations

Correlation of craving changes with age, number of cigarettes per day, years of smoking, age at onset of smoking, and total FTND score showed that age and years of smoking were negatively correlated to craving changes (between T0 and T2) after left ($r = –.48$, $p = .02$ and $r = –0.57$, $p = .003$, respectively) and right ($r = –0.62$, $p = .001$ and $r = –0.58$, $p = .003$, respectively) DLPFC stimulation, indicating that older subjects with longer duration of smoking had fewer changes in craving after active stimulation.

DISCUSSION

The results of our study demonstrate that (1) the cue-exposure paradigm was effective in increasing craving (T0 vs. T1); (2) tDCS reduced general craving during a short period of smoking abstinence (T0 vs. T2); and (3) tDCS also reduced cue-elicited craving (T1 vs. T3). Furthermore, there were no significant mood changes after any type of tDCS treatment; thus, mood changes did

not confound our results. Finally, the results showed that tDCS was well tolerated. The adverse effects were mild and equally distributed across the 3 conditions of stimulation.

Mechanisms of tDCS Effects on Craving Reduction

Transcranial direct current stimulation is a technically simple tool of noninvasive brain stimulation that is based on a continuous current that flows between 2 electrodes applied to the scalp. This current induces a shift of membrane polarity, resulting in a change of cortical excitability that outlasts the period of stimulation and depends on the current direction.[16] Several animal studies have shown that anodal stimulation increases neuronal firing and that cathodal stimulation results in reversed effects.[18] In humans, similar results have been obtained: anodal stimulation of the motor and visual cortices increases cortical excitability, and cathodal stimulation decreases it.[15,17,32] Furthermore, the effects of 13 minutes of tDCS on cortical excitability can last up to 90 minutes after the end of the stimulation,[17] most probably due to changes of *N*-methyl-D-aspartic acid–receptor efficacy.[16] Transcranial DC stimulation, as used in current protocols, is safe in humans as shown by neuropsychological testing,[28,33] electroencephalogram assessment,[28] a neuroimaging study,[34] and brain metabolites evaluation.[17]

The results of this study show that tDCS of DLPFC reduces 2 different types of craving, cue-elicited craving and general craving, during a short period of smoking abstinence. Because this study did not assess other parameters, such as brain activity as indexed by neuroimaging tools, we can only speculate about the mechanisms of action based on previous studies.

Exposure to smoking cues induces a significant craving response, and tDCS was effective in reducing this increase in craving in this study. Previous studies investigating neural responses to cues in nicotine abusers demonstrated that the anterior cingulate, amygdala, insula, and orbitofrontal and dorsolateral prefrontal cortices are associated with craving.[6] Indeed, one of the most important areas participating in the cue-associated anticipation and planning of drug use involves the DLPFC, an area involved in planning and memory.[6] In a study in which smoking craving was induced by a video, cigarette smokers responded to smoking stimuli with increased craving and activation in bilateral dorsolateral prefrontal cortices and other areas such as the anterior cingulate and medial and orbital prefrontal cortices.[5] The data of our study are in conformity with these previous findings, as modulation of either left or right DLPFC activity reduces craving.

Specifically, our data suggest that a transient excitability enhancement of either the left or right dorsolateral prefrontal cortex also reduces general smoking craving. McBride et al.[5] proposed that the DLPFC "integrates information about internal state (craving, withdrawal), motivation, expectancy, and cues, and uses this information in the regulation and planning of drug-seeking or drug-avoiding behavior."[5(p7)] Based on this assumption, we conjecture that our treatment might have decreased craving by the following mechanism: anodal tDCS, which increases local cortical excitability, increased activity in the DLPFC and thus reinforced drug-avoiding behavior or, alternatively, disrupted this specific network of drug craving by a local disruption (although tDCS has not been shown to have local disruptive effects on cortical activity) or by activation of other interconnected neural networks. Another potential mechanism proposed by Eichhammer et al.[14] is that stimulation of the DLPFC might mimic craving-related processes and thus reduce the necessity to start reward-related behavior. This effect might be achieved by the modulation of dopaminergic systems or other neurotransmitters that are associated with the mesolimbic dopaminergic reward system. The dopaminergic system seems to play a critical role in the reinforcing effects of nicotine.[35] Although data are still lacking regarding the modulation of dopamine levels after stimulation with tDCS, in a recent study, Nitsche et al.[36] showed that sulpiride, a D_2-receptor blocker, abolished the induction of tDCS effects nearly completely, suggesting a role of dopamine in the after-effects of tDCS. Although rTMS has other mechanisms of action—rTMS induces brief pulses of electric current of a relatively high intensity, whereas tDCS induces a continuous electric current of low intensity—stimulation of the prefrontal cortex with excitability-enhancing high-frequency rTMS has also been shown to induce dopamine release in animal[37] and human[38] studies. Despite the differences between these 2 techniques of brain stimulation, they might induce similar effects in the dopaminergic system.

Two less likely hypotheses have been proposed. The first is that stimulation of either right or left DLPFC ruptures the balance between the right and left DLPFC activity that might be necessary for craving states. A balanced bilateral activation of DLPFC is shown by neuroimaging studies.[6] The second is that modulation of the DLPFC modulates other areas associated with craving, such as the orbitofrontal cortex,[39,40] which also has extensive connections to other brain areas, such as the striatum and amygdala, integrating the cortical and subcortical processing of motivational behavior and rewarding. This hypothesis is also supported by recent data showing that tDCS results in widespread changes in regional brain activity.[41] Finally, it should be noted that modulation of the same area (DLPFC) is responsible for reducing cue-elicited and general craving; suggesting that similar neural networks are involved in the processing of these 2 types of craving.

An interesting additional finding is the significant negative correlation between age and number of smoking years with craving reduction. It has been shown that

neural responses to cues depend on the user's level of dependence; therefore, longer smoking duration might be associated with a differential brain response to smoking cues that, as a result, might be more difficult to reverse with a single session of tDCS.

Previous Studies

To the best of our knowledge, our study is the first one to use tDCS in the investigation of smoking craving reduction; however, we can compare the results of our study to others[13,14,31,42] using rTMS to reduce smoking and other types of craving. Both techniques induce similar excitability modulations of the cerebral cortex—i.e., reducing or increasing excitability beyond the period of stimulation—although through different mechanisms of action.

Two studies have shown that rTMS reduces the subjective urge to smoke[13] and subsequent cigarette consumption[14] in dependent smokers. In an initial pilot study, Johann et al.[13] showed that craving was significantly reduced to 48% of prestimulation craving levels after active high-frequency, excitability-enhancing rTMS, as opposed to 68% in the sham condition. The same group performed another study[14] evaluating the effects of rTMS on cigarette consumption and craving. In this trial, 14 patients received either sham or active rTMS (20 Hz, 1000 pulses per session, 2 sessions of each condition). The number of cigarettes smoked during an ad libitum smoking period and craving (as assessed by a VAS) were evaluated. The authors showed a significant reduction in the number of cigarettes smoked after active rTMS as compared to sham stimulation; however, craving levels did not change in this study. Two factors pointed out by the authors of this study might explain the lack of effects of rTMS on craving in this study: (1) methodological issues such as the evaluation of craving (craving was evaluated 30 minutes after stimulation, and smoking cues were not used) and (2) the sample size of this study was too small to detect significant differences (it was almost half of our sample size). In addition, the authors of the current study speculate that tDCS might be superior to rTMS in reducing craving; indeed, in the motor cortex, tDCS induces a larger effect on cortical excitability when compared to rTMS. (See the studies of Nitsche et al.[17] and Romero et al.[43])

Brain stimulation using rTMS has also been used to reduce craving in subjects with food and cocaine craving. A preliminary study[31] investigated the effects of high-frequency (10 Hz) rTMS of the left DLPFC to decrease food craving in 28 women with frequent cravings for food. The results of this study showed that food craving during exposure to foods remained constant in the active treatment group but increased in the sham treatment group. Another study[43] in patients in treatment for cocaine abuse during acute abstinence showed that active high-frequency rTMS of the right, but not left, DLPFC decreased craving levels significantly. All this evidence together suggests that noninvasive brain stimulation might be an efficacious method for reducing not only smoking but also other types of craving.

It is noteworthy that there were no significant mood changes in this study despite the fact that DLPFC was stimulated. At a first glance, this seems contradictory to our previous pilot study,[26] in which we showed that anodal tDCS over left DLPFC induces mood improvement. However, this previous study was performed in depressed patients (and 5 sessions of tDCS were applied). Thus, the impact of tDCS on the DLPFC on mood in healthy subjects might differ. In fact, a previous study[44] in healthy subjects has shown that rTMS of the DLPFC induces contrary effects (as compared to depressed patients) such as that high-frequency rTMS of the left DLPFC induces mood worsening. Interestingly, although not significant, excitability-enhancing anodal tDCS of the right DLPFC induced a trend for mood improvement in our study.

Clinical Implications

Although we showed that direct current stimulation of the prefrontal cortex reduces smoking craving, the results of this study do not imply necessarily that direct current stimulation might be effective in helping smoking cessation. It should be pointed out that the reduction of craving was only temporary, as we only applied a single session of tDCS (for each condition). To induce longer lasting effects, several sessions of tDCS need to be applied. It has been demonstrated recently that repeated tDCS induces prolonged aftereffects of tDCS on clinical symptoms.[20] Thus, the next step of the investigation of the role of tDCS in smoking craving is the study of consecutive sessions of tDCS to explore whether craving reduction might translate to smoking cessation.

Limitations

One might argue that, because there was no neutral cue condition, it was difficult to interpret whether tDCS reduced cue-specific craving or whether the effects were a result of a general attenuation in craving. However, this latter explanation is less likely, as we observed a significant increase in craving (a mean increase of 22.6%) after our method for inducing craving, and we used 2 different methods to induce craving that have been successfully demonstrated to induce craving in other studies.[5,23] Indeed, a previous study investigating the effects of a similar smoking cue (a cigarette in an ashtray) showed that this method of inducing smoking craving is effective when compared with a neutral cue (a glass of water).[23] Similarly, McBride et al. [5] showed that smoking videos significantly increase subjective reports of craving as compared with control videos.

CONCLUSION

Our study demonstrates that anodal tDCS of the DLPFC can suppress cue-provoked smoking craving. This finding extends the results of a previous study[13] using rTMS to inhibit craving and therefore opens the way for the exploration of noninvasive brain stimulation for smoking cessation.

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