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Transcranial Direct Current Brain Stimulation Increases Ability to Resist Smoking

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Abstract

Background—The ability to exert self-control over temptation is a fundamental component of smoking behavior change. Transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) has been shown to modulate cognitive control circuits. Although prior studies show that stimulation reduces cigarette craving and self-reported smoking, effects on ability to resist smoking have not been investigated directly.

Objectives—We assessed effects of a single 20-minute session of 1.0 mA anodal stimulation over the left DLPFC with cathodal stimulation over the right supra-orbital area (vs. sham stimulation) on ability to resist smoking in a validated smoking lapse paradigm.

Methods—Twenty-five participants completed two tDCS sessions (active and sham stimulation) in a within-subject, double-blind, randomized and counterbalanced order with a two-week washout period. Following overnight abstinence, participants received tDCS in the presence of smoking related cues; they had the option to smoke at any time or receive \$1 for every 5 minutes they abstained. After 50 minutes, they participated in a one hour *ad libitum* smoking session. Primary and secondary outcomes were time to first cigarette and cigarette consumption, respectively.

Results—In multiple regression models, active tDCS (compared to sham) significantly increased latency to smoke ($p = 0.02$) and decreased the total number of cigarettes smoked ($p = 0.014$) during the session.

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Conclusion—These findings suggest that acute anodal stimulation over the left DLPFC (with cathodal stimulation over the right supra-orbital area) can improve ability to resist smoking, supporting the therapeutic potential of tDCS for smoking cessation treatment.

Keywords

tDCS; nicotine addiction; smoking relapse

Introduction

Tobacco use accounts for over six million deaths each year worldwide [1] and takes a significant economic toll [1, 2]. Even with the best treatments available, most people revert to their former smoking practices [3]. While currently available treatments may address symptoms of nicotine withdrawal or alter the reinforcing effects of nicotine, they do not address the disruptive brain processes that may undermine attempts to quit smoking [4].

Abstinence from smoking produces cognitive impairments and altered brain functions that can make it more difficult to resist temptations to smoke (e.g., smoking cessation) [5]. For example, working memory performance and associated neural activity in the dorsolateral prefrontal cortices (DLPFC) are downregulated during nicotine withdrawal, compared to smoking satiety [6-9]. Reductions in working memory-related DLPFC activity predict smoking relapse above and beyond clinical and performance measures, with 81% accuracy [10]. The DLPFC is at the core of the brain's cognitive control network which supports behavioral self-control [11-14], suggesting that targeting DLPFC functions may be a therapeutic strategy to support smoking behavior change.

Emerging evidence shows that activity in the DLPFC and cognitive control circuits can be modulated using a noninvasive and safe intervention: direct current transcranial stimulation (tDCS) [15-17]. Active anodal tDCS administered to the DLPFC has been shown to increase task-related activity in the DLPFC during a risk sensitivity task, and to increase resting state functional connectivity in the attention network [18, 19]. In smokers, tDCS has been shown to reduce smoking cue-induced craving and self-reported cigarette intake [20-22]. However, these studies examined minimally-abstinent (1.5 hrs or less) smokers. Another study found that active tDCS versus sham reduced negative affect but not cigarette craving in smokers after overnight abstinence [23], but this study did not examine subsequent smoking behavior.

Given the relevance of DLPFC activity for smoking relapse, we tested the hypothesis that anodal tDCS over the left DLPFC (with cathodal stimulation over the right supra-orbital area) after overnight abstinence will increase ability to resist temptations to smoke. This preliminary study employed a within-subject crossover design to compare active versus sham stimulation, such that each participant served as his/her own control, and utilized a validated smoking lapse paradigm that is sensitive to the effects of efficacious smoking treatments [24, 25]. We predicted that active stimulation (versus sham) would increase latency to first cigarette and decrease the total number of cigarettes smoked during the session.

Materials and Methods

Participants

All procedures were approved by the University of Pennsylvania Institutional Review Board and carried out in accordance with the Declaration of Helsinki. Healthy adults between the ages of 18 and 60 who reported smoking at least 10 cigarettes per day (CPD) for the past year and were not planning to quit smoking in the next 3 months were recruited through mass media. All participants provided written informed consent and completed an in-person eligibility screen including a urine drug screen, a breath alcohol test, and an expired breath carbon monoxide (CO) reading to confirm smoking status; women completed a urine pregnancy test. Individuals who self-reported a history of DSM-IV Axis I psychiatric or substance disorders (except nicotine dependence) and those taking psychotropic medications were excluded. Additional exclusion criteria included: current use of chewing tobacco, snuff, or smoking cessation products; pregnancy, planned pregnancy or breastfeeding; history of brain injury or seizures; presence of metal (other than dental apparatus) in the face or head; low or borderline intelligence (estimated IQ <90 on Shipley Institute of Living Scale [26]); and any impairment that would prevent task performance.

Procedures

Participants in this within-subject cross-over investigation completed two identical laboratory sessions (one session involving active stimulation and the other involving sham stimulation) scheduled at least two weeks apart to minimize carryover effects. Session order was double-blind, randomized and counterbalanced. Sessions started at approximately 9am (+/- 1 hr) after overnight abstinence (~12 hours). Participants provided an expired CO reading at the start of the session which was required to be <10ppm (or at least a 50% reduction from the reading obtained at the eligibility screen) in order to confirm compliance with the abstinence requirement. Following confirmation of eligibility, participants completed the Questionnaire on Smoking Urges – brief version (QSU-B; [27]) and then received 20 minutes of active or sham stimulation during a laboratory smoking lapse paradigm.

Smoking lapse paradigm

The smoking lapse paradigm was based on that designed by McKee & colleagues [24] and adapted for co-administration of tDCS. Participants were escorted to a 10 × 10 room equipped with industrial grade exhaust fans approved for exhaust of cigarette smoke, a comfortable couch, a coffee table, and a portable smoking topography unit (Clinical Research Smoking Systems, Plowshare Technologies/Borgwaldt, Baltimore, MD). A pack of cigarettes of the participant's preferred brand was placed in view on the table along with a lighter and ashtray. Prior to initiating tDCS, participants were instructed that over the next 50 minutes they should try not to smoke. Participants could choose to start smoking at any time, but for each 5 minute period that they were able to delay, they would earn \$1.00 (up to a maximum of \$10; [24]). Once they decided to smoke, they could smoke as little or as much as they wished through the smoking topography device. Participants were permitted to read books or magazines but were asked to refrain from using smartphones or other electronic devices. Once instructions were delivered, tDCS commenced. The tDCS

equipment remained in place until the end of the 50 minute resist period to avoid influencing the participant's smoking behavior; however, stimulation was delivered only for the first 20 minutes. Participants remained in the smoking room for the full 50 minutes, regardless of when they decided to smoke, so that all participants would begin the subsequent *ad libitum* period at the same time relative to tDCS administration (30 minutes post-stimulation). Time to first cigarette (latency to smoke) and total number of cigarettes smoked were recorded electronically via the smoking topography device.

After the 50 minute resist period ended, the tDCS equipment was removed and participants were given new instructions for a 60 minute *ad libitum* smoking period. During this period, participants were given eight cigarettes of their preferred brand and informed that they had a \$4.00 “tab” with the researchers. Participants were instructed to smoke as much or as little as they wished through the smoking topography device, but that for each cigarette lit, they would “lose \$0.50 from their \$4.00 tab.” Participants received any money left in the tab at the end of the session. Self-reported smoking behavior (number of cigarettes smoked) for the 24 hours following the tDCS session was assessed using a timeline follow-back method during a follow-up call the next day.

tDCS procedures

A Magstim Eldith 1 Channel DC Stimulator Plus was used to apply a constant direct current via two 5cm × 5cm electrodes covered in saline-soaked sponges. Electrode placement was determined using the international 10-20 system developed for EEG [28]; the anodal electrode was placed over the F3 area for stimulation over the left DLPFC and the cathode was placed over the right supra-orbital area. During the active condition, current was ramped up to 1.0 mA over 30s, maintained for 19 minutes and ramped down over 30s (total stimulation period 20 min). During the sham condition, the current was ramped up to 1.0 mA over 30s and immediately ramped down at the beginning and end of the 20 minute period. This process mimics the skin sensations experienced during active stimulation; most participants cannot distinguish between real and sham tDCS using this procedure [29].

Measures

Outcomes—The primary outcome was latency to smoke (in minutes) and the secondary outcome was total number of cigarettes smoked during the resist and *ad libitum* periods. Latency to smoke was set to 110 minutes if a participant did not smoke during either period (i.e. the combined duration of the abstinence period plus the *ad libitum* smoking period). As exploratory measures, we examined smoking topography (total puff volume) and self-reported smoking behavior for the 24 hours following the tDCS session. Total puff volume was set to zero if a participant did not smoke during either period.

Baseline measures and covariates—Nicotine dependence was assessed at the eligibility session using the Fagerström Test for Nicotine Dependence (FTND, [30]). Pre-stimulation breath CO was obtained at each tDCS session to confirm compliance with the overnight abstinence requirement. Smoking urges (QSU-B) were assessed prior to stimulation [27], but were not assessed as an outcome measure due to potential confounding based on whether or not the participant smoked during the session.

Treatment-related measures—Side effects of tDCS and blinding success were assessed using a questionnaire [31]. Participants were asked to rate to what extent they experienced 10 potential side effects of tDCS during and after stimulation (headache, difficulty concentrating, acute mood changes, changes in visual perception, tingling, itching, burning, pain, fatigue, and nervousness), plus visual sensation at the start or end of stimulation, on a scale from 0 (not at all) to 10 (to a high degree). Participants were also asked to guess at which session they had received active stimulation and which session involved sham stimulation. Because we included this question, the questionnaire was administered only at the end of the second session to avoid drawing attention to the difference and influencing future sessions.

Analysis

Descriptive statistics were obtained for all variables. Effects of stimulation on the smoking behavior outcomes were modeled using regression with subject-level random effects, and estimated using maximum likelihood techniques (Stata xt-reg; Stata Corporation, College Station, TX, USA) with linear mixed effects models. Pre-session craving for negative reinforcement (QSU-B Factor 2) and FTND score were included as covariates in the multiple regression models based on prior associations with latency to smoke and number of cigarettes smoked in the smoking lapse paradigm [24, 32]; session order (active first vs. sham first) was also included as a covariate. Session order by stimulation interaction effects, age, and sex were tested but allowed to drop from the model if non-significant. We used an adjusted alpha of $p < 0.025$ to correct for testing the two primary outcome measures.

Results

Descriptive Data

Twenty-eight subjects completed session 1. One subject withdrew from the study prior to session 2 and two were ineligible at session 2 due to non-compliance with the abstinence requirement, leaving 25 subjects included in the analysis. The sample was predominantly male ($n = 15$, 60%) and African-American ($n = 16$, 64%); most had completed at least some college or beyond ($n = 14$, 56%). The mean age was 42.1 years (SD 11.2), the mean cigarettes per day was 15.2 (SD 4.4), mean expired CO at the eligibility screen was 19.1ppm (SD 5.9), and the mean FTND score was 5.4 (SD 1.9).

Expired CO readings at the start of the tDCS sessions were significantly reduced compared to the eligibility screen ($p < 0.0001$) indicating compliance with the abstinence requirement. Participants reported abstaining from cigarettes for a mean of 12.6 hrs (range: 11-16 hrs). Expired CO and pre-stimulation smoking urges did not differ between active and sham sessions ($p > 0.1$), which is expected because the same abstinence requirements were used for both sessions.

Outcome Data

In the multiple regression models, active stimulation significantly increased latency to smoke [mean time to first cigarette: 56.2 min (SD 43.1) during the sham session and 64.8 min (SD 43.5) during the active session; $\beta = 9.6$, 95% Confidence Interval (CI) 1.5 to 17.7, p

= 0.02]. Active stimulation also significantly decreased the total number of cigarettes smoked during the session [mean total cigarettes smoked: 1.44 (SD 1.3) during the sham session and 1.20 (SD 1.2) during active session; $\beta = -0.27$, 95% CI -0.49 to -0.06 , $p = 0.014$; Figure 1]. Nicotine dependence (FTND score) was negatively associated with latency to smoke ($\beta = -10.9$, $p = 0.003$) and positively associated with total number of cigarettes smoked ($\beta = 0.26$, $p = 0.02$). Urge to smoke for negative reinforcement (QSU-B Factor 2) was positively associated with total number of cigarettes smoked ($\beta = 0.05$, $p = 0.03$) but not with latency to smoke ($p = 0.06$). There was also a trend toward decreased total puff volume during the active session compared to sham which did not reach significance ($p = 0.07$). There was no effect of stimulation on self-reported number of cigarettes smoked in the 24 hours following the tDCS session ($p > 0.8$). Age, sex, and session order were not significantly associated with any of the outcomes ($ps > 0.05$) and there were no stimulation by session order interaction effects ($ps > 0.4$).

tDCS Side Effects and Blinding

The most commonly reported side effect of stimulation was tingling at the site of the electrode (reported by 92% of participants), followed by itching (80%), burning sensation (64%), fatigue (56%), nervousness (48%), difficulty concentrating (48%), mood change (44%), pain (36%), headache (36%), and visual sensation at the start or end of stimulation (24%). Side effects were generally mild (mean rating < 5 out of 10) except for tingling (mean rating 6.0, SD 2.9) and itching (mean rating 5.0, SD 3.4). Because we recorded side effects only at the end of the second session, we could not assess whether side effects differed for active compared to sham stimulation. Participants were not able to correctly identify active stimulation versus sham at a rate significantly greater than chance (64% correct, one sample binomial test $p > 0.1$), indicating successful blinding to stimulation type.

Discussion

This study is the first to demonstrate a significant effect of active anodal tDCS over the left DLPFC (with cathodal stimulation over the right supra-orbital area) on ability to resist smoking in the presence of in vivo smoking cues. Smokers in this within-subject cross-over study were able to delay smoking for an average of ~9 minutes longer when they received active stimulation compared to when they received sham stimulation. Active stimulation also reduced the total amount of cigarettes smoked by about a quarter of a cigarette, an approximately 17% reduction in cigarette intake during the two-hour laboratory session.

Although increasing latency to smoke by ~9 minutes may appear to be a small improvement, the ability to delay smoking for a short time might allow smokers to wait out acute urges which are typically of limited duration [33-35]. Although further research is necessary to examine whether the effects of acute tDCS on smoking behavior are persistent, a reduction of one-fourth of a cigarette every 2 hours could potentially translate into a reduction in daily smoking of 2 cigarettes over a 16 hour waking period. In a clinical trial examining the effects of nicotine replacement therapy and motivational advice in smokers unmotivated to quit, Carpenter and colleagues [36] found that every 1% reduction in daily cigarettes smoked over six weeks increased the odds of making a quit attempt by 2% and of achieving

abstinence at 24 weeks by 3%, which suggests that even a small reduction in intake may be clinically relevant. Although we did not see an effect of stimulation on self-reported smoking quantity in the 24 hours following the session, smokers in this study were not currently interested in quitting and were not instructed to attempt to reduce their smoking after the session. The effects of stimulation on smoking behavior during the laboratory session, when smokers were actively attempting to resist smoking, are promising.

The smoking paradigm utilized in this study was adapted from a validated smoking lapse paradigm which has been shown to be sensitive to identifying treatments known to be efficacious for smoking cessation [24]. However, the effect sizes in the current study are smaller than the effects previously noted for the smoking cessation medications varenicline and bupropion in this paradigm. Following administration to steady state, these efficacious smoking cessation medications were shown to increase latency to smoke by approximately 20 minutes and number of cigarettes smoked by about half, but only among highly dependent smokers (those who report smoking within five minutes of waking; [24]). The number of participants in our sample who reported smoking within five minutes of waking was too small ($n = 4$) to test for an interaction effect; however, the effects of a single acute dose of active tDCS were observed in the full sample and were not restricted to highly dependent smokers.

Our findings add to literature reports of overall reductions in daily cigarette intake during multi-day treatment periods involving daily sessions of active anodal stimulation over the left or right DLPFC or other frontal regions [20, 22, 37]. These studies reported that daily cigarette consumption was approximately 30% lower during the active stimulation period compared to the sham period, which is slightly greater than the reduction in intake noted during our laboratory study. This difference may be due to the extended treatment period (five daily sessions versus a single acute session), differences in tDCS dosage (2.0 mA versus 1.0 mA in the current study), or placement of the cathodal electrode (over the right DLPFC compared to over the supra-orbital area in the current study). Some studies have also demonstrated an acute effect of active anodal stimulation over the left or right DLPFC on cue-induced craving for cigarettes [20-22], although another study reported no effect of anodal stimulation of the left DLPFC on cue-induced craving following overnight abstinence [23]. Although our participants were exposed to cigarette cues during the smoking lapse paradigm, we did not include craving as an outcome measure due to the fact that post-session craving levels would be confounded by the participant's decision to smoke or not smoke during the lapse paradigm.

An interesting feature of the smoking lapse paradigm is its manipulation of reward: first, the paradigm offers money as an alternative reward for smokers who successfully resist smoking; and second, the two periods (resist and *ad libitum*) utilize different approaches to reward. During the resist period, the monetary reward is presented as a positive reinforcer; smokers can earn \$1 for every five minutes they resist smoking. During the *ad libitum* period, the monetary reward is a negative reinforcer; smokers are told that they have potential earnings of \$4, but that they will lose \$0.50 from this total for every cigarette they smoke [24]. Prior work has demonstrated that tDCS effects may be reward-dependent; for example, Fecteau and colleagues found that active stimulation over the DLPFC increased

the likelihood that smokers would reject offers of cigarettes during an Ultimatum game, but had no effect on the frequency with which they rejected offers of money [20]. Additional research employing variations of the smoking lapse paradigm may be useful to evaluate whether the effects of tDCS on smoking behavior are sensitive to the nature or presentation of alternative rewards.

Non-invasive brain stimulation with tDCS has been investigated as a potential treatment for addiction and obesity, two conditions which share similar features such as craving, compulsive behavior, and impaired decision-making capability [38, 39]. A recent meta-analysis of studies utilizing tDCS or repetitive transcranial magnetic stimulation (rTMS) found that stimulation of the DLPFC reduced craving for nicotine, alcohol, and marijuana in addicted individuals, and reduced craving for food in subjects who normally experienced strong food cravings [40]. It has been suggested that stimulation of the DLPFC may alter smoking behavior and substance use by modulating cognitive control circuits involved in decision-making behavior and regulation of craving [20-22, 41]. Another study found that tDCS targeting other fronto-parietal regions involved in cognitive control also reduced cigarette consumption [37]. Modulation of these circuits may help to suppress craving or reduce risk-seeking behavior by enhancing executive function, which contributes to improved control over impulsive, reward-motivated behaviors [20, 38-40, 42].

Studies of tDCS effects on cognitive function have proposed that achieving optimal benefits may require co-administration of a training task designed to engage the desired function (i.e., working memory is enhanced when tDCS is co-administered with a working memory task such as the n-back; [43, 44]). In the present study, we considered the instruction to “try to resist smoking” to be a task engaging the cognitive control circuit. Supporting this decision are neuroimaging studies which have shown that resisting cigarette cue-induced craving is associated with greater activation in parts of the attention and decision-making networks including the prefrontal cortex [45, 46]. Some participants did actively engage in this task, as demonstrated by comments recorded during a post-session thought-listing task (i.e., “I was thinking about smoking cigarettes but didn’t want to give in to the temptation”; “I was determined not to smoke”; etc.). However, some participants chose to “give in” and smoke during the 20-minute tDCS administration period. Therefore, it could be argued that the training task was not standardized across all participants; some participants may in fact have engaged in “training” the very behavior they were instructed to avoid (i.e., smoking). Utilization of a standardized training task such as a response inhibition task to engage the cognitive control circuit during tDCS might strengthen the results. Furthermore, nicotine withdrawal has been shown to reduce tDCS-induced neural plasticity, and acute administration of nicotine reverses this effect [47]; however, it is not known whether re-introduction of nicotine during a withdrawal state (as seen in participants who smoked during stimulation) might influence the effects of stimulation on the ability to resist subsequent smoking. Although this would not have affected our primary outcome of latency to smoke, future studies could explore the effects of nicotine intake during tDCS on subsequent smoking behavior.

Strengths of our study include the use of a validated laboratory model of smoking lapse with direct observation of smoking behavior and the within-subject crossover design which

allowed each participant to serve as his/her own control. Limitations include the use of a single acute dose of tDCS and the short observation period. Further research is necessary to investigate whether the effects observed here are persistent over time, may be enhanced with multiple tDCS sessions, or may benefit from a standardized task to engage cognitive control circuits during stimulation. Furthermore, future studies may evaluate treatment-seeking smokers since they may respond differently than non-treatment-seekers in medication and cessation paradigms [48]. However, our findings that active anodal tDCS over the left DLPFC with cathodal tDCS over the right supra-orbital area increased latency to smoke and decreased cigarette consumption in a validated model of smoking lapse suggests that tDCS may offer promise as a novel treatment for smoking cessation.

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Highlights

- We examine effects of acute brain stimulation in a validated smoking lapse paradigm.
- Active anodal tDCS over left DLPFC vs. sham stimulation increased latency to smoke.
- Active tDCS (vs. sham) decreased the total number of cigarettes smoked.
- Acute tDCS over the left DLPFC shows promise for smoking cessation treatment.

Figure 1. Effects of tDCS on smoking behavior

Latency to smoke and total number of cigarettes smoked in each session (sham vs. active stimulation); error bars are standard error of the mean. In the multiple regression models, active stimulation significantly increased latency to smoke ($\beta = 9.6$, 95% Confidence Interval (CI) 1.5 to 17.7, $p = 0.02$) and decreased the number of cigarettes consumed during the session ($\beta = -0.27$, 95% CI -0.49 to -0.06 , $p = 0.014$).