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Lack of effect of transcranial direct current stimulation (tDCS) on short-term smoking cessation: Results of a randomized, sham-controlled clinical trial

Mary Falcone[a,*], Leah Bernardo[a], E. Paul Wileyto[b], Cheyenne Allenby[a], Anne Marie Burke[a], Roy Hamilton[c], Mario Cristancho[a], Rebecca L. Ashare[a], James Loughead[a], Caryn Lerman[a]

[a] Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA
[b] Dept of Biostatistics, Epidemiology & Informatics, University of Pennsylvania, Philadelphia, PA, USA
[c] Laboratory for Cognition and Neural Stimulation, University of Pennsylvania, Philadelphia, PA, USA

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) has been shown to improve measures of executive cognitive function and reduce cigarette consumption. Studies conducted to date have been small, and the results are mixed.

Methods: This randomized, double-blind, parallel arm clinical trial tested the effects of active anodal tDCS targeted to the left dorsolateral prefrontal cortex (versus sham) on 7-day smoking cessation in 106 treatment-seeking smokers. Participants received three sessions of sham (n = 35), 1 mA (n = 35), or 2 mA (n = 36) tDCS in the context of a validated smoking lapse paradigm then received brief smoking cessation counseling and completed a monitored quit attempt. The primary outcome was total number of days of abstinence confirmed via exhaled carbon monoxide.

Results: During the quit period, there were no effects of dose group on days of abstinence (sham, M (SD): 2.5 days (± 2.5); 1 mA: 2.5 days (± 2.5); 2 mA: 2.4 days (± 2.3); β = -0.08; p = 0.76) or on change in daily smoking rate (sham, M (SD): 12.6 CPD (± 4.8); 1 mA: -11.8 CPD (± 4.4); 2 mA: -11.7 CPD (± 5.3); β = 0.42, p = 0.49), nor were there effects of dose group on latency to smoke or number of cigarettes smoked during the smoking lapse paradigm. Side effects of tDCS were generally mild (< 5 out of 10), and participants were not able to distinguish between active and sham treatment.

Conclusions: These results do not support the efficacy of tDCS targeted to the left dorsolateral prefrontal cortex (DLPFC) for smoking cessation.

1. Introduction

Tobacco use is one of the leading causes of preventable death and illness worldwide (Global Burden of Disease Research Foundation Collaborators, 2016; World Health Organization (WHO, 2017), yet the majority of smokers who want to quit are unable to maintain abstinence even for a few days (Babb et al., 2017; Hughes et al., 2004). Many factors contribute to relapse, and existing treatments offer support for the most prominent factors such as withdrawal symptoms and cravings (Aubin et al., 2014; Piper et al., 2011; Shiffman et al., 2006). However, subtle deficits in executive cognitive function emerging during the first 24 h of abstinence may also contribute to relapse (Ashare et al., 2014; Loughead et al., 2015; McClernon et al., 2015). Such effects may reduce cognitive control over reward-driven or impulsive behaviors (such as smoking a cigarette) (Botvinick and Braver, 2014; Braver et al., 2014).

Functional magnetic resonance imaging (fMRI) studies have revealed a network of brain regions contributing to cognitive control; collectively, these regions are known as the executive control network (ECN) (Fox et al., 2005; Vincent et al., 2008). One region within this network is the dorsolateral prefrontal cortex (DLPFC), which has been implicated in working memory and attentional control (D'Esposito and Postle, 2014; Fassbender et al., 2004). During abstinence, smokers show alterations in connectivity between large scale networks including the ECN (Cole et al., 2010; Fedota et al., 2018; Lerman et al., 2014) as well as reductions in DLPFC activation that predict relapse above and beyond clinical and behavioral measures (Loughead et al., 2015; Wilcox et al., 2017). Therefore, treatments targeting DLPFC activation offer a novel therapeutic approach to smoking cessation (McClernon et al., 2015).

* Corresponding author at: Center for Interdisciplinary Research on Nicotine Addiction, 3535 Market Street, Suite 4100, University of Pennsylvania, Philadelphia, PA, 19104, USA.
E-mail address: mfalc@pennmedicine.upenn.edu (M. Falcone).

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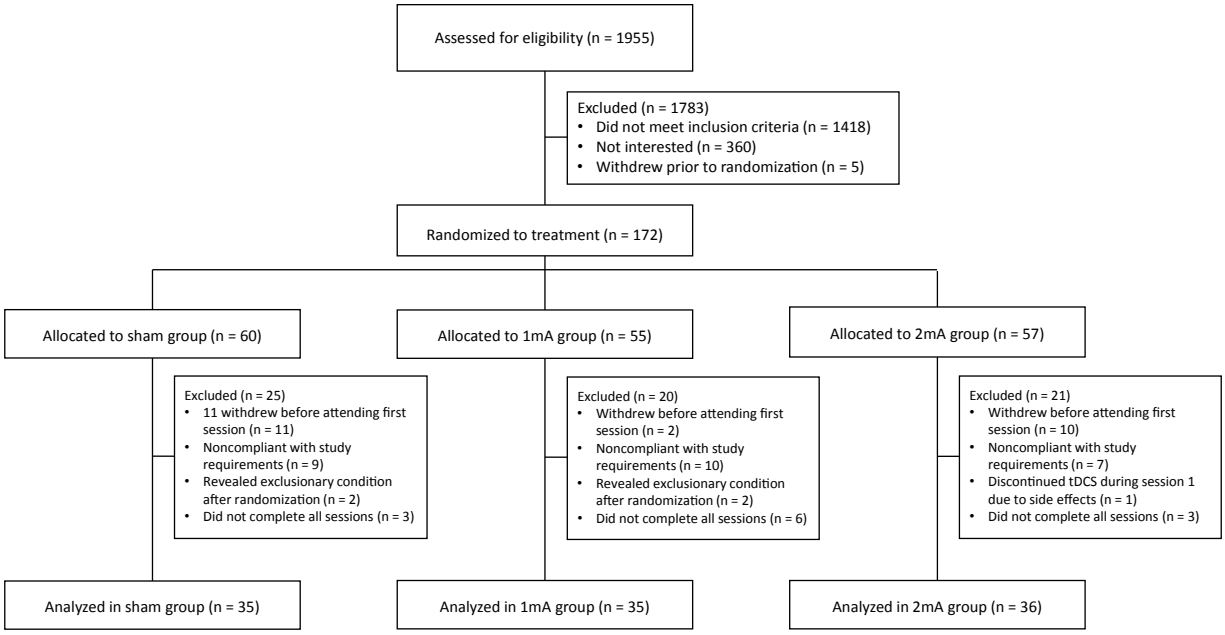

Fig. 1. CONSORT Participant Flow Diagram. Compared to participants who completed the study, participants who withdrew after randomization but before receiving stimulation (n = 23) were younger [mean (SD) 39.2 (12.3) years for those who withdrew vs. 45.3 years for study completers] and more likely to be white (52% of those who withdrew vs. 24% of study completers). Compared to study completers, participants who withdrew after receiving at least one stimulation session (n = 12) were more likely to be white (58% of those who withdrew vs. 24% of study completers) and were heavier smokers at baseline (mean 21.4 CPD vs. 15.3 CPD among study completers). There were no other differences in baseline demographics or smoking history between study completers and participants who withdrew.

Recently, there has been a surge of interest in non-invasive methods to stimulate brain activity for the treatment of addiction (Coles et al., 2018). One such method is transcranial direct current stimulation (tDCS), a technique in which light electrical currents (1–2 mA) are applied to the scalp over targeted regions of the brain. Initial studies suggest that active anodal tDCS targeted to the right or left DLPFC can reduce cravings to smoke (Fregni et al., 2008; Yang et al., 2017) as well as latency to smoke in the laboratory (Falcone et al., 2016) and daily smoking rates (Boggio et al., 2009; Fecteau et al., 2014; Vitor de Souza Brangioni et al., 2018). However, other studies found no changes in craving (Kroczek et al., 2016; Pripfl and Lamm, 2015; Smith et al., 2015; Xu et al., 2013) or found that reductions in craving did not transfer to changes in smoking behavior (Mondino et al., 2018). Variation in reported outcomes may be related to small sample sizes (n ≈ 10–40 subjects per trial), differences in baseline smoking rates (studies with non-significant outcomes may include more light or non-daily smokers than those which reported significant effects), or differences in treatment protocols (i.e., intensity, duration, and number of sessions). Further research is necessary in order to identify optimal treatment conditions.

This parallel arm randomized double-blind clinical trial evaluated the effects of three anodal tDCS treatments (sham/placebo, 1 mA, or 2 mA dose) targeted to the left DLPFC on short-term smoking cessation. Our primary outcome was the number of days of abstinence during a 7-day monitored abstinence period, a brief cessation model shown to be highly predictive of 6-month smoking cessation rates (Ashare et al., 2013). Secondary outcomes were latency to smoke and total number of cigarettes smoked during a laboratory smoking lapse paradigm completed during the stimulation sessions (Falcone et al., 2016). We predicted a positive dose response effect of tDCS (2 mA > 1 mA > sham) on the total number of days of abstinence during the quit period and on the ability to resist smoking during the laboratory sessions.

2. Materials and methods

2.1. 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 who expressed an intent to quit or reduce smoking in the next 3 months were recruited through mass media between November 2015 and March 2018 in the greater Philadelphia area. We recruited participants who reported that they intended to quit smoking in the next 3 months in order to identify likely treatment-seeking smokers, who have been shown to respond differently to smoking cessation treatments than non-treatment seekers (Perkins and Lerman, 2014). Self-reported intent to quit or reduce smoking is a strong predictor of subsequent quit attempts (Hyland et al., 2006; Vangeli et al., 2011; Perkins and Lerman, 2014). All participants provided written informed consent and completed an in-person eligibility screen including a breath alcohol test and a carbon monoxide (CO) breath assessment to confirm tobacco exposure; participants with a positive breath alcohol test or an exhaled CO < 10 ppm were excluded (SRNT Subcommittee on Biochemical Verification, 2002). Female participants completed a urine pregnancy test. Participants who self-reported a history of DSM-IV Axis I psychiatric or substance use disorders (except nicotine dependence) or the use of psychotropic medications were excluded. Additional exclusion criteria included current or recent use (past two weeks at eligibility assessment) of smoking cessation medications; pregnancy, breastfeeding, or planning a pregnancy; history of stroke, seizure disorder, brain injury or tumor; skull fracture or opening; pacemakers or metallic objects in the face or head (other than dental apparatus); low or borderline intellectual functioning (estimated IQ < 85 on Shipley Institute of Living Scale); and any impairment that would prevent task performance. Fig. 1 shows the CONSORT flow diagram for the study.

2.2. Procedures

This study used a between-subject, randomized and double-blind design. Participants were assigned to one of three tDCS dosage groups (1 mA, 2 mA, or sham) in a 1:1:1 allocation ratio using simple randomization with replacement. Randomization was handled by the data management team: following confirmation of eligibility, a research assistant entered participant information into a study database which automatically assigned them to the next available randomization slot stratified by nicotine dependence [Fagerström Test for Nicotine Dependence (FTND) > 5 vs. FTND ≤ 5]. A collection of five-digit codes was associated with each dose group and were given to the tDCS technician for use during the sessions (see Section 2.4 for details). Procedures for each group were identical: all participants completed three stimulation sessions over the course of one week (days 1, 3, 5) followed by a 7-day monitored abstinence period (framed as a 'practice quit attempt') consisting of 4 in-person visits (days 6, 8, 10, 12) to confirm smoking status.

Participants were abstinent for 18 h prior to each stimulation session. Abstinence was biochemically confirmed by exhaled CO reading at the start of the session. At Session 1, exhaled CO was required to be less than 10 ppm or at least a 50% reduction from the reading at their eligibility screen. At subsequent sessions, participants were instructed to remain abstinent for 18 h and exhaled CO was assessed, but due to the potential for unanticipated effects of tDCS on smoking behavior participants were not withdrawn from the study if they did not meet the cutoff. Following the CO assessment, participants rated their cravings to smoke using the Questionnaire on Smoking Urges (Cox et al., 2001) and then received 20 min of their assigned tDCS dosage during a laboratory smoking lapse paradigm.

2.3. Smoking lapse paradigm

The smoking lapse paradigm was identical to that used in our prior study based on the design by McKee and colleagues (McKee et al., 2012) and adapted for tDCS co-administration (Falcone et al., 2016). This paradigm is designed to model lapse behavior during abstinence, where the decision to choose an immediate reward (smoking a cigarette) over a delayed reward (improved health outcomes) can lead to smoking relapse. The paradigm targets two critical features of lapse behavior: the ability to resist smoking during abstinence and choices regarding subsequent smoking following a lapse (McKee et al., 2012). Monetary rewards are used as an alternative reinforcer to model the tradeoffs between immediate and delayed rewards. Participants were escorted to a 10 × 10 room equipped with industrial grade exhaust fans approved for exhaust of cigarette smoke, a comfortable couch, coffee table, and magazines. A pack of the participant's preferred brand of cigarettes was placed in view on the table in addition to a lighter and an ashtray. For the entirety of the session participants were asked to not use their phone, fall asleep, or eat, but they were permitted to read and drink water. Prior to tDCS administration, participants were instructed that during the next 50 min (the "resist" period) they would have the opportunity to smoke or to earn money by not smoking. For every 5 min that they were able to resist smoking, they would receive $1, up to a maximum of $10. At any point they were able to give in and smoke, but they would only receive the money earned up until that point. The tDCS administration took place during the first 20 min (see "tDCS procedures" below for more details); however, the tDCS equipment remained in place for the entire 50-minute resist period. We viewed the instruction to "try to resist smoking" as a "task" which would engage the executive control network targeted by the stimulation.

Following the resist period, the tDCS equipment was removed, and participants began an *ad libitum* smoking period that lasted 60 min. At this time 8 cigarettes were placed in front of the participant, and they were instructed that they had a $4 tab with the researchers. They could smoke as many or as few of the cigarettes as they would like, but for every cigarette smoked $0.50 was removed from the tab, and at the end of the 60 min the participant received any remaining balance. Participant smoking behavior was monitored during the session, and each cigarette smoked was video recorded on a Panasonic HC-V279 camera for validation. The outcomes for this paradigm are time to first cigarette and total number of cigarettes smoked; these measures are sensitive to the effects of efficacious smoking cessation medications such as varenicline and bupropion (McKee et al., 2012).

2.4. tDCS procedures

A trained technician administered tDCS using a neuroConn DC-Stimulator Plus system. The device was employed in study mode, which facilitates blinding of both the participant and technician. This mode allows the assignment of a collection of five-digit codes to each treatment group; the randomization procedure applied by the data management team supplies a code for the tDCS technician to input into the device. Current was administered via 5 cm x 5 cm electrodes covered with saline-soaked sponges. The anodal electrode was placed over the left dorsolateral prefrontal cortex (F3 in the international 10–20 system for EEG), and the cathodal electrode was placed over the right supraorbital area (FP2 in the 10–20 system). In the two active tDCS conditions, current was ramped up to the target dose (1 mA or 2 mA) over 30 s, held constant for 19 min, and then ramped down over 30 s (total stimulation time 20 min). In the sham tDCS condition, current was initially ramped up to 2 mA over 30 s and immediately ramped down to 0 mA. This procedure was repeated at the end of the 20 min session. These brief ramped up and down periods were delivered to aid the blinding so that participants would experience scalp sensations typical of active tDCS (Gandiga et al., 2006), but this brief stimulation is unlikely to cause changes in cortical excitability (Keeser et al., 2011; Lang et al., 2004; Nitsche et al., 2003; Nitsche et al., 2003; Stagg et al., 2013).

2.5. Seven-day monitored quit period

In accordance with a validated 7-day quit paradigm (Perkins et al., 2010, 2008), participants received a 20-minute in-person counseling session following session 3 of tDCS to prepare them for their quit attempt. They were instructed to try to remain abstinent from 10 P M that evening until after the last monitoring visit (for a total of 7 days). During this period, participants had 4 monitoring visits (days 6, 8, 10, and 12), during which they reported on their smoking behavior using a time line follow-back procedure, provided an exhaled CO reading to biochemically confirm reported abstinence, and rated their cravings to smoke (Cox et al., 2001). As in 7-day quit studies (Perkins and Lerman, 2014; Perkins et al., 2013b), participants received a $15 cash bonus for each day of biochemically-verified abstinence. At the first monitoring visit (day 6), a CO reading of less than 10 ppm (or at least a 50% reduction from the reading at their eligibility screen) was required to confirm abstinence (Sandberg et al., 2011), and at the remaining three visits (days 8, 10, 12) a CO reading of less than 5 ppm was required to confirm abstinence (Perkins et al., 2013a, b). The primary outcome was total number of days of biochemically verified abstinence (Perkins and Lerman, 2014; Perkins et al., 2010, 2008). As a secondary outcome, we examined the change in mean number of cigarettes smoked per day during the quit period compared to baseline smoking rate, based on self-report (quit period minus baseline). In accordance with standard practice for smoking cessation trials, participants who did not attend the monitoring visits were assumed to be smoking but were excluded from the analysis of mean cigarettes per day as missing data.

2.6. Analysis

A planned interim analysis was conducted upon reaching a sample size of n = 35 per dose group. Descriptive statistics were obtained for

all variables. ANOVA and χ^2 tests were used to examine baseline differences in demographics between dose groups. The primary analysis utilized multiple regression modeling (Stata; StataCorp LLC, College Station, TX, USA) to estimate the effects of dose group on total number of days of biochemically-verified abstinence during the monitored abstinence period; age, sex, race, and nicotine dependence (FTND score) were included as covariates. Secondary analyses used similar models to examine effects of dose group on change in mean CPD (quit period minus baseline) and dose by session interaction effects on latency to smoke and total number of cigarettes smoked during the smoking lapse paradigm. Age, sex, race, nicotine dependence, and pre-session craving for negative affect relief (QSU-B Factor 2) were included as covariates in the models of the smoking lapse paradigm outcomes based on prior associations with latency to smoke using this paradigm (Falcone et al., 2016; McKee et al., 2012; Roche et al., 2014). Although post-session craving was confounded by whether or not the participant chose to smoke during the laboratory session, as an exploratory analysis we examined effects of dose group on change in pre-session craving (session 3 minus session 1). This analysis utilized multiple regression and controlled for the same covariates listed above.

3. Results

3.1. Descriptive data

One hundred and six subjects completed all three tDCS sessions. The sample was predominantly male (n = 68, 64%) and African-American (n = 77, 73%); most had completed at least some college or beyond (n = 68, 64%). The mean age was 45.3 years (SD 9.9), the mean CPD was 16.3 (SD 5.8), the mean expired CO at the eligibility screen was 16.6 ppm (SD 6.5), and the mean FTND score was 5.2 (SD 1.6). There were no differences in demographics or baseline smoking behavior between dose groups (p > 0.4 for all; Table 1). The majority of participants (69%) reported at least one prior quit attempt in their lifetime, and the average duration of the longest prior quit period was 9.8 months (range: 2 days to 10 years); however, all participants had been daily smokers of at least 10 CPD for the past year.

Expired CO readings at the start of the tDCS sessions were significantly reduced compared to the eligibility screen [Session 1, M (SD): 4.3 ppm (2.1); Session 2: 5.4 ppm (3.3); Session 3: 5.1 ppm (3.3); p < 0.0001 for all], which indicates compliance with the abstinence requirement. Participants reported abstaining from cigarettes for a mean of 18.1 h. (range: 7–25 hrs.) prior to all sessions; this did not differ by session or dose group (p-values > 0.1).

Table 1
Demographics by Dose Group.

Measure	Sham group (n = 35)	1 mA group (n = 35)	2 mA group (n = 36)	p-value
Age, m (SD)	44.7 (11.2)	45.6 (9.4)	45.4 (9.2)	0.93
Sex, n (%) female	15 (43%)	13 (37%)	10 (28%)	0.41
Race, n (%)	24 (69%)	25 (71%)	28 (80%)	0.66
African American	0 (0%)	1 (3%)	0 (0%)	
American Indian/	0 (0%)	0 (0%)	1 (3%)	
Alaskan Native	10 (29%)	8 (23%)	7 (19%)	
Asian	1 (3%)	1 (3%)	0 (0%)	
White				
More than one race				
Education	13 (37%)	10 (29%)	15 (42%)	0.51
High school or less	22 (63%)	25 (71%)	21 (58%)	
Some college/college grad				
CPD, m (SD)	15.4 (4.8)	16.9 (6.3)	16.5 (6.1)	0.53
CO at eligibility (ppm), m (SD)	17.8 (6.9)	16.1 (6.6)	16.1 (6.1)	0.45
FTND score, m (SD)	5.3 (1.5)	5.1 (1.6)	5.1 (1.8)	0.84

3.2. Primary outcome

Results of the multiple regression model showed no association between dose group and total number of days of CO-verified abstinence during the quit period (sham, M (SD): 2.5 days (± 2.5); 1 mA: 2.5 days (± 2.5); 2 mA: 2.4 days (± 2.3); β = -0.08; p = 0.76, Fig. 2A).

3.3. Secondary outcomes

In the multiple regression model, there was no association between dose group and change in mean CPD from baseline to quit period [sham, M (SD): 12.6 CPD (± 4.8); 1 mA: -11.8 CPD (± 4.4); 2 mA: -11.7 CPD (± 5.3); β = 0.42, p = 0.49; Fig. 2B]. There were no main effects of dose group or session and no significant dose group by session interaction effects on either latency to smoke or total number of cigarettes smoked during the sessions (p > 0.1 for all; Fig. 2C-D). Age was positively associated with latency to smoke (β = 0.74, p = 0.008) and negatively associated with total number of cigarettes smoked across all sessions (β = -0.02, p = 0.02). There were significant associations between sex and lapse paradigm outcomes: women showed greater latency to smoke (β = 14.3, p = 0.013) and smoked fewer total cigarettes during the sessions (β = -0.56, p = 0.003). Urge to smoke for negative reinforcement (QSU-B Factor 2) was negatively associated with latency to smoke (β = -0.97, p < 0.001) and positively associated with total number of cigarettes smoked (β = 0.02, p = 0.015) across all sessions. Neither race nor nicotine dependence were associated with either of the secondary outcomes (p-values > 0.05). In the exploratory analysis, there was no effect of dose group on change in pre-session craving (p = 0.3; Fig. 2E).

3.4. tDCS side effects and blinding

Side effects of tDCS were generally mild (< 5 out of 10) and (with one exception) did not differ between dose groups (p-values > 0.05; Table 2). The exception was for reports of itching at Session 3; participants in the 1 mA group experienced greater itching at the site of the electrodes during stimulation compared to other groups (p = 0.02). At the end of each session, participants were asked to guess whether they received active or sham stimulation. Approximately 85% of participants believed they received real stimulation at each session, and this did not differ by session or dose group (p-values > 0.5).

3.5. Conditional power analysis

We conducted a futility analysis based on conditional power (futility = conditional power < 20%) using results from the mixed model with dose of 1 mA and 2 mA lumped. Conditional power was calculated using PASS v15 (Power and Sample Size, NCSS Software, Kaysville, UT). Conditional power is the probability of rejecting the null hypothesis given the data already revealed; data that have not been revealed yet are assumed to follow the original assumed effect size. We used the z-score for the comparison of sham with lumped active treatment (z = 0.04, p = 0.96, effect size = 0.01) combined with the original design effect size of d = 0.45. Conditional power was 0.13, indicating that the study should be abandoned for futility (Proschan et al., 2006).

4. Discussion

In the largest study of the effects of tDCS on smoking behavior reported to date, we found no evidence for effects of three sessions of tDCS on the ability to remain abstinent during a 7-day short-term quit period. Furthermore, we also found no evidence for acute effects of tDCS on change in number of cigarettes per day from baseline or on the ability to resist smoking during a validated smoking lapse paradigm. The conditional power analysis performed after the interim analysis

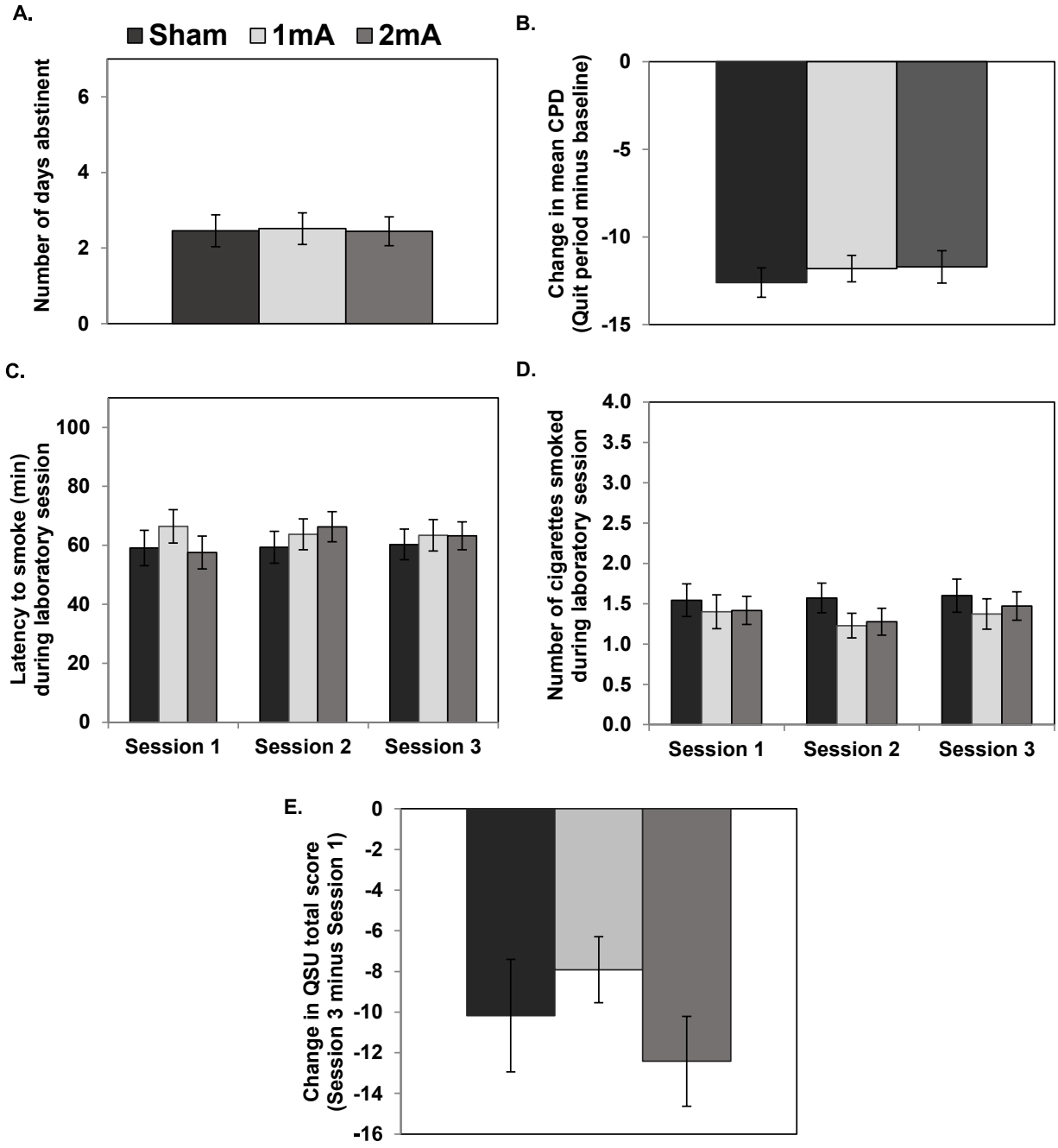

Fig. 2. Smoking Outcomes by Dose Group. There were no significant effects of tDCS on A) the total number of days of abstinence during the quit period, or B) change in average number of cigarettes smoked per day during the quit period compared to baseline; ps > 0.4). There were no significant session by dose group interaction effects on C) overall latency to smoke during the laboratory period, or D) total cigarettes smoked during the laboratory sessions (ps > 0.1). E) There was no significant effect of dose group on change in pre-session craving to smoke (p = 0.3).

suggested that the study be terminated early. These findings do not support further development of this particular tDCS paradigm as an adjunctive treatment for smoking cessation.

The absence of a tDCS effect on latency to smoke and number of cigarettes smoked during the laboratory sessions contradicts a previous report using this laboratory paradigm (Falcone et al., 2016). However, the prior trial utilized a within-subject design with one session each of active and sham stimulation (separated by a two-week washout period to minimize carryover effects). Although the study was double-blind, and participants in that study were not able to identify the sessions in which they received active and sham stimulation at rates higher than chance, they were debriefed at the end of the study and asked to make a retrospective judgement. It may be that the sensations produced by sham stimulation are different than those produced by active stimulation and that this biases immediate expectations regarding treatment and smoking behavior (Falcone et al., 2016). The current study utilized a between-subject design, and participant beliefs were assessed at the end of each session. Participants were not able to correctly guess which type of stimulation they had received; approximately 85% of participants in all treatment groups believed they had received active stimulation, suggesting effective blinding in the current study.

A few other studies utilizing a between-subject design in smokers observed significant benefits of tDCS on craving and smoking behavior (Boggio et al., 2009; Vitor de Souza Brangioni et al., 2018). Boggio et al. (2009) reported a significant and cumulative reduction in craving in participants receiving active tDCS (compared to sham) over the course

Table 2
Side Effects of tDCS at Session 3.

Effect	Sham group (n = 35)	1 mA group (n = 35)	2 mA group (n = 36)	p-value
Tingling	2.7 (2.3)	3.9 (3.2)	3.4 (3.0)	0.23
Itching	2.7 (2.6)	4.6 (3.4)	3.1 (2.9)	**0.02**
Burning	1.9 (2.5)	2.0 (2.8)	2.8 (3.2)	0.31
Pain	0.8 (1.7)	0.9 (2.0)	1.2 (2.2)	0.72
Fatigue	1.5 (2.6)	2.1 (3.0)	1.7 (3.0)	0.70
Nervousness	1.3 (2.5)	0.4 (1.1)	0.5 (1.3)	0.08
Headache	0.6 (1.3)	0.6 (1.5)	0.3 (0.9)	0.52
Difficulty Concentrating	0.9 (1.9)	1.2 (2.0)	0.9 (2.2)	0.80
Mood Change	0.7 (1.8)	0.5 (1.0)	0.7 (1.7)	0.82
Change in Vision	0.8 (1.9)	0.5 (1.2)	0.5 (1.4)	0.68
Visual Sensation (lights)	5	6	8	0.68

Values shown are mean (SD) except for Visual Sensation (lights), which is n.

of five treatment sessions and a significant reduction in the number of cigarettes smoked during the treatment period in the active condition (although participants were not actively attempting to quit or reduce their smoking). Others have similarly observed reductions in smoking quantity despite no specific instructions to reduce smoking (Fecteau et al., 2014). Vitor de Souza Brangioni et al. (2018) observed a significant reduction in daily smoking quantity four weeks after treatment in the active treatment group compared to sham in smokers who were attempting to quit. Although measurement of daily smoking quantity during the treatment period in our current study would be confounded by our requirement for participants to remain abstinent for 18 h prior to each session, we did not observe effects of tDCS on smoking quantity during the 7-day quit period. One possible reason for the difference in outcomes is that participants in the prior studies received a total of five tDCS sessions (compared to three sessions in our current study). It is possible that more sessions are necessary in order to observe a persistent effect. However, other studies have observed no effect of five sessions of active 2 mA tDCS (versus sham) on craving or cigarette consumption in smokers with schizophrenia who were not instructed to alter their smoking behavior (Smith et al., 2015) and no effect of 10 sessions of 2 mA tDCS on cigarette consumption in healthy smokers who were highly motivated to quit (but not specifically instructed to do so) (Mondino et al., 2018). Within-subject designs also show mixed results: although several studies report decreased craving following active tDCS compared to sham (Fecteau et al., 2014; Fregni et al., 2008; Yang et al., 2017), others show no changes (Pripfl and Lamm, 2015; Xu et al., 2013). Studies of tDCS effects on smoking behavior have varied in baseline smoking rates among participants; it is possible that the variability in outcomes may relate to differences in tDCS effects among lighter versus heavier smokers. Although the number of heavier smokers (≥20 CPD) in our sample was too small to test for an interaction effect, it may be useful for future studies to examine whether baseline smoking quantity influences tDCS effects or whether tDCS influences puffing topography (e.g., puff latency, puff volume, or length of remaining cigarette).

Furthermore, although our intended target was anodal stimulation of the left DLPFC, tDCS can result in widespread changes in brain activation outside of the targeted region (Stagg et al., 2013). The tDCS montage consists of both an anode and a cathode, and the flow of current is influenced by both. Our hypothesis was that anodal stimulation of the left DLPFC would increase the ability to resist smoking by enhancing executive control; we chose the montage used in this study (anodal electrode over F3, cathodal over contralateral supraorbital area) based on studies showing beneficial effects for executive function (Andrews et al., 2011; Teo et al., 2011; Vanderhasselt et al., 2013) and smoking behavior (Falcone et al., 2016; Vitor de Souza Brangioni et al., 2018). However, fMRI studies using this montage have shown widespread changes in activation and functional connectivity beyond the DLPFC (Keeser et al., 2011; Stagg et al., 2013). In addition, some studies which have demonstrated beneficial effects of anodal stimulation of the left DLPFC for smoking behavior have varied in the placement of the cathodal electrode; for example, some have used a larger cathodal electrode to reduce the current density in underlying regions (Boggio et al., 2009; Mondino et al., 2018), others placed the cathode over the right DLPFC for bilateral stimulation (Fregni et al., 2008), and others used a reversed bilateral (anodal right, cathodal left) montage (Fecteau et al., 2014). Further research is necessary in order to understand the effects of tDCS montage on stimulation of the targeted region and nearby regions (Bikson et al., 2018; Tremblay et al., 2014). Collectively, these results highlight the need for a better understanding of factors contributing to tDCS outcomes in order to optimize treatment approach.

Although our findings do not support further development of tDCS as a treatment for smoking cessation, other brain stimulation modalities have shown promise for nicotine addiction and other substance use disorders (Coles et al., 2018; Hanlon et al., 2018). Repetitive transcranial magnetic stimulation (TMS) is a modality in which magnetic fields are used to induce temporary electrical currents in targeted cortical regions (Hallett, 2007). The majority of studies examining TMS in smokers found that stimulation of the DLPFC reduced cravings and/or cigarette consumption (Coles et al., 2018), with one exception (Li et al., 2017). Across substances, reduction in craving following stimulation of the DLPFC is a common finding; however, translating those reductions to changes in behavior is less consistent (Coles et al., 2018; Hanlon et al., 2018; Wing et al., 2013).

4.1. Strengths and limitations

Strengths of this study include the large sample size, the inclusion of treatment-seeking smokers (who may respond differently to treatment compared to non-treatment seekers) (Perkins et al., 2008), and biochemical confirmation of abstinence during the 7-day quit attempt. Abstinence during the first week of a quit attempt has been shown to significantly predict cessation at 6 months post-target quit date (Ashare et al., 2013). Abstinence rates observed during the quit attempt are similar to those observed in validation studies of the 7-day quit paradigm (Perkins and Lerman, 2014); the failure of tDCS to increase days of abstinence in this trial therefore does not support a clinical benefit.

Potential limitations of the study include the timing of tDCS administration and the concurrent task chosen to engage the relevant neural circuits during stimulation. Participants in our study received tDCS at the start of the smoking lapse paradigm when they were 18 h abstinent. Prior studies have shown that nicotine withdrawal may impair tDCS-induced neuroplasticity (Grundey et al., 2012), which may have limited the potential persistent effects in our study. We chose to administer tDCS while participants were abstinent because we viewed the task of "resisting the urge to smoke while abstinent" as a training task that would engage the neural circuits targeted by tDCS, and abstinence was therefore a necessary condition. However, future research utilizing a different training task, such as a response inhibition task (Houben et al., 2011) which can be administered while smokers are not in withdrawal, may have a greater chance of observing persistent effects. It is also possible that a 3-day treatment protocol may not be sufficient to induce the required neuroplasticity to elicit tangible and durable effects on cravings and cigarette consumption. Longer protocols, similar to those used to study the antidepressant effects of tDCS, may be required (Loo et al., 2018). Our study sample consisted of a high proportion (~73%) of African-American smokers, which reflects the demographics of our location in west Philadelphia, Pennsylvania. Although this proportion is higher than observed in the general population of smokers in the United States (Jamal et al., 2018), race was not significantly associated with any of the outcomes, and the study was underpowered to test whether race moderates the impact of tDCS.

5. Conclusions

Recent research into non-invasive brain stimulation techniques such as tDCS has shown highly variable results for effects on smoking behavior. Our findings suggest that three sessions of anodal tDCS targeted to the left DLPFC are not sufficient to induce persistent effects on smoking behavior in treatment-seeking smokers. Further research aimed at understanding and optimizing factors contributing to tDCS outcomes would be beneficial for the field, as would studies of alternative forms of neuromodulation.

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Contributors

Dr. Lerman conceived of and led the project. Drs. Falcone, Ashare, and Loughead contributed to the study design and selection of measures. Dr. Cristancho served as study physician. Dr. Hamilton developed the tDCS procedures and supervised the training of the tDCS technicians. Ms. Bernardo and Ms. Burke contributed to study design and served as study coordinators. Drs. Falcone and Wileyto and Ms. Allenby developed and conducted the analytical approach. All authors contributed to the development of the manuscript and approved the final version.

Conflict of interest

None.

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