ClinicalTrials.gov Identifier: NCT02624284
Version 9: 5/10/17

PROTOCOL TITLE

1. Full Title: tDCS effects on resisting smoking: dose ranging study

STUDY SPONSORSHIP

Funding Sponsor: National Cancer Institute

PROTOCOL ABSTRACT

Behaviors such as tobacco use, unhealthy diet, and sedentary behavior have far-reaching health implications. These modifiable behaviors account for a substantial proportion of deaths from cancer, cardiovascular disease and diabetes, and take a significant economic toll. Yet, many unhealthy behaviors are very resistant to change, despite widespread knowledge of the risks. Although theories of behavior change have been advanced to explain the persistence of these behaviors, few consider the neurobehavioral underpinnings. These approaches also fail to address a fundamental aspect of behavior change – an individual's ability to exert sufficient self-control to overcome temptations for immediate gratification and/or to maintain attention to long-term goals. With advances in the neuroimaging field, we are learning where and how self-control over decisions and behaviors is executed in the brain. This work points to the central role of neural activity in the dorsolateral prefrontal cortices (DLPFC) in self-control processes that contribute to healthy choices. Further, emerging evidence shows that activity in the prefrontal cortices and cognitive control circuits can be modulated using a noninvasive and safe intervention: direct current transcranial stimulation (tDCS). Our pilot study demonstrated that a single session of 1mA tDCS increased the ability to resist smoking in a validated smoking lapse paradigm. The current study will use a between-subject design to investigate the dose/response relationship between tDCS (administered at 1mA, 2mA, or sham stimulation for three sessions) and ability to resist smoking.

OBJECTIVES

1. Overall Objectives

Aim 1: To assess the effects of three sessions of tDCS (1 mA, 2 mA vs. sham) on ability to resist smoking in healthy adult smokers.

Hypothesis: Active tDCS (compared to sham tDCS) will increase ability to resist smoking, and decrease ad-libitum smoking in the human laboratory setting; 2 mA tDCS will have more beneficial effects on these outcomes than 1 mA tDCS.

Aim 2: To assess the effects of tDCS on subjective measures.

Hypothesis: Active tDCS (compared to sham tDCS) will reduce smoking urges.

Aim 3: To assess the effects of tDCS on ability to maintain smoking abstinence during a 7-day monitored abstinence period.

Hypothesis: Active tDCS (compared to sham tDCS) will lead to greater number of days of biochemically verified abstinence during the monitored abstinence period.

BACKGROUND

There is a new opportunity to translate neuroscience-based interventions to promote healthy behavior change. With advances in the neuroimaging field, we have a growing understanding of the brain activity patterns that influence risky behaviors such as tobacco use and obesity. Research in our Center for Interdisciplinary Research on Nicotine Addiction (CIRNA) has shown that neural activity in the dorsolateral prefrontal cortices (DLPFC) contributes to working memory processes important in successful smoking cessation (Loughead, Ray et al. 2010,

Patterson, Jepson et al. 2010, Loughead, Wileyto et al. 2015). We have also identified patterns of resting state brain connectivity that contribute to cravings to smoke (Lerman, Gu et al. 2014). In order to develop more effective smoking cessation treatments, the next critical step is to evaluate whether modulating these brain processes can promote healthy behavior change.

A growing body of evidence supports the safety and potential utility of tDCS for improving executive cognitive function (Demirtas-Tatlidede, Vahabzadeh-Hagh et al. 2013). Initial data suggest that even a single session of tDCS targeted to DLPFC can improve memory, planning ability, functional brain connectivity, and neural efficiency during cognitive processing without any adverse side effects (Dockery, Hueckel-Weng et al. 2009, Meinzer, Lindenberg et al. 2013). Further, modulation of prefrontal activity using tDCS can alter choices between immediate smaller rewards versus larger later rewards (a measure of impulsive decision-making) (Figner, Knoch et al. 2010).

In our proof-of-concept study, we demonstrated that a single session of 1mA anodal tDCS administered to the left DLPFC increased the ability to resist smoking in a validated smoking lapse paradigm. This study will extend that research to test the effects of different doses of tDCS (1mA, 2mA, and sham) administered over three sessions on the ability to resist smoking in the same smoking lapse paradigm, and also whether tDCS increases the ability to remain abstinent during a 7-day monitored abstinence period (framed as a "practice quit attempt").

CHARACTERISTICS OF THE STUDY POPULATION

1. Target Population

400 healthy adult smokers between the ages of 18-60 will be enrolled/consented in order to have 180 participants complete the study. Smokers are those who report smoking at least 10 cigarettes per day.

2. Accrual

400 male or female participants will be enrolled to have 180 complete the study at the University of Pennsylvania Center for Interdisciplinary Research on Nicotine Addiction (CIRNA). Accounting conservatively for ~55% attrition between consenting and study completion, we estimate we will need to enroll 400 participants to have 180 participants complete the study. Participants will be screened over the telephone before completing an in-person Intake Visit to confirm final eligibility.

3. Key Inclusion Criteria

Eligible participants will be:

1. Healthy males and females who are between 18 and 60 years of age, report smoking at least 10 cigarettes per day for the past year and have a CO value of $\geq$ 10ppm at intake;
2. Planning to live in the area for at least the next 2 months;
3. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the combined consent and HIPAA form;
4. Able to communicate fluently in English (speaking, writing, and reading);
5. Smokers who answer yes on a question regarding motivation to quit smoking.

4. Key Exclusion Criteria

Subjects who present and/or self-report with the following criteria at any point during study participation will not be eligible to participate in the study:

Alcohol/Drugs:

1. History or current diagnosis or treatment for alcohol or drug abuse (as reported during phone screen);
2. Positive breath alcohol concentration test (BrAC $\geq$0.01) at any study visit.
    a. Participants testing positive for breath alcohol with a reading equal to or greater than .08 (the legal driving limit) or who are visibly impaired will be instructed not to drive themselves home after the appointment. If a participant needs to use a phone to call for a safe ride home, an office telephone will be made available to the participant.

Medication:

Current use or recent discontinuation (within the last 14 days at the time of Intake) of:

1. Smoking cessation medication (e.g., Zyban, Wellbutrin, Wellbutrin SR, Chantix);
2. Anti-psychotic medications;
3. Nicotine replacement therapy (NRT);
4. GABAergic medications;
5. Glutamatergic medications;
6. Any medication that could compromise participant safety as determined by the Principal Investigator and/or Study Physician.

Daily use of:

7. Opiate-containing medications for chronic pain;
8. Benzodiazepines.

Medical/Neuropsychiatric:

1. Women who are pregnant, planning a pregnancy, and/or breast feeding. All female subjects will complete a urine pregnancy test at the intake visit and preceding all brain stimulation sessions (4 urine pregnancy tests in total). Women who self-report a condition which renders them unable to become pregnant (i.e., hysterectomy, surgical sterility, menopause, etc) will not be required to complete the pregnancy tests;
2. History of epilepsy or a seizure disorder;
3. History of stroke;
4. Self-reported history of brain or spinal tumor;
5. Self-reported history or current diagnosis of psychosis, including schizophrenia, mania, bipolar disorder, major depression (subjects with a history of major depression but in remission for past 6 months are eligible).

tDCS-related:

1. Self-report of metallic objects in the face or head **other than** dental apparatus (e.g. braces, fillings, and implants);
2. Self-report of pacemakers or implantable cardioverter-defibrillator (ICD).
3. Self-report of any skull fracture or opening.

   Note: In contrast to Transcranial Magnetic Stimulation (TMS), there is no known risk of seizures with tDCS. However, the individuals with self-reported history of epilepsy, a seizure disorder, or any seizure in the last 6 months will be excluded. Similarly, although there is no known risk of tDCS to the fetus, the issue has not been fully addressed. Consequently, pregnant women will be excluded. All women of childbearing age (that is, not post-menopausal, surgically sterile, or otherwise unable to become pregnant) will complete a pregnancy test prior to each tDCS session.

General Exclusion:

1. Any medical condition, illness, disorder, or concomitant medication that could compromise participant safety or treatment, as determined by the Principal Investigator;
2. Low or borderline intellectual functioning – determined by a score of less than 85 on the Shipley Institute of Living Scale (SILS) (administered at Intake Visit). The SILS correlates with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Estimated IQ Test;
3. Inability to provide informed consent or complete any of the study tasks as determined by the Principal Investigator.

5. Vulnerable Populations

Children (under age 18), pregnant women or prisoners are not included in this research study.

6. Populations vulnerable to undue influence or coercion

Educationally or economically disadvantaged persons are included but not solely targeted for recruitment. Cognitively impaired persons are not included in the current study. Because of our recruitment efforts for this study, it is possible that University of Pennsylvania employees and students may be invited to participate. Status of participation in the current study will be independent of the participant's work or school activities.

7. Subject Recruitment

Participants may be recruited from television, radio, Craigslist.org/Internet advertisements, experiments@penn, newspaper, iConnect, flyers, University of Pennsylvania Human Resources (HR) communication vehicles (e.g. Penn Current, myHR Newsletters, hr.upenn.edu, etc.), and/or from our database of previous participants who have agreed to be re-contacted for future studies. Participants initially eligible during a telephone screening will attend an Intake Visit at our center during which the purpose and procedures of this study will be described to them and final eligibility will be confirmed.

STUDY DESIGN

1. Phase

Not applicable

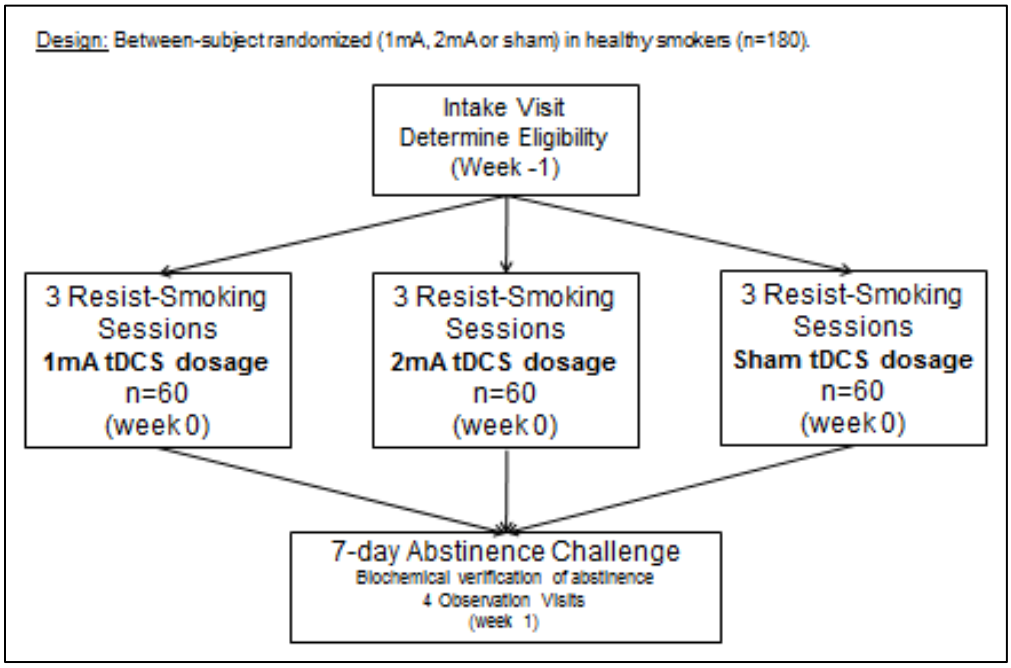
2. Design

This trial will use a between-subject single blind design in which participants will be randomized to one of three tDCS dosage groups (1mA, 2mA or sham) and will receive three 20 minute sessions of the same dosage over the course of 1 week before completing a 7 day quit attempt. Eligible participants will complete an **Intake Visit (week -1)** for final eligibility determination, and complete baseline measures (if eligible). Participants will then be randomly assigned to one of the three dosage groups (1mA, 2mA or sham) and will attend **three identical tDCS resist-smoking sessions (study days 1, 3, & 5)** during which they will receive 20 minutes of their assigned tDCS dosage and complete a resist smoking paradigm. During the resist smoking sessions, participants will receive a session of their assigned dosage of tDCS for 20 minutes while being exposed to in vivo smoking cues (their cigarette pack, cigarettes, an ashtray). Participants will not be informed of their dosage condition. During and after the tDCS session, participants will have the opportunity to smoke in the approved smoking lab. We will measure time to first cigarette and subsequent ad-libitum smoking during the resist smoking paradigm. Following Session 3 participants will receive a 20 minute coaching session from a trained smoking cessation counselor to help them prepare for a **7-day quit attempt.** During the 7-day quit attempt participants will be asked to attend **4 monitoring visits (study days 6, 8, 10 & 12**) to confirm smoking status.

3. Study Duration

Enrollment began in October 2015. Based on the accrual projections described previously, we anticipate enrollment lasting through March 2018 (~25 months). Each participant will be required to be in the study for approx. ~3-4 weeks.

Figure 1.



DRUGS OR DEVICES

Transcranial direct current stimulation (tDCS) and sham stimulation.

STUDY PROCEDURES

1. Procedures

Telephone Screening: Potential participants will be screened by an experienced research technician to determine initial study eligibility. If the subject meets preliminary telephone eligibility criteria he/she will be invited to attend a 3 hour Intake visit.

Visit Reminders: Participants will receive study visit reminders 24 – 48 hours prior to their scheduled study visits via phone call, email or text (participants who provide a cell phone number for contact).

Intake (week -1): (Visit duration: ~3 hours). Participants will:

1. Hear a study description where all study procedures will be reviewed. Participant questions will be answered. Following this presentation, the combined informed consent and HIPAA form will be completed;
2. Women of childbearing potential will be provided with a urine pregnancy screen and will be instructed to perform the screening independently Participants will be instructed that women who think they are pregnant are advised not to participate in the study;
3. Perform a BrAC assessment to control for alcohol consumption. Participants with a BrAC greater than or equal to 0.01 at Intake Visit will be ineligible;
4. Perform a carbon monoxide (CO) breath assessment to confirm (CO≥10 ppm) tobacco exposure;
5. Complete a brief medical history form with a trained staff member;
6. Complete Shipley Institute of Living Scale (SILS) IQ test. Participants earning less than an estimated WAIS-R IQ score of 85 will be ineligible;
7. Complete demographics and smoking history (smoking rate, nicotine dependence, Cigarette Brand Form, brief QSU), G-FCQ-S, ETOH, and cognitive tasks (see Measures table);
8. Provide one 2ml saliva sample for DNA collection and genotyping (Oragene™) and a 5ml saliva sample for nicotine metabolite assay. These saliva samples are voluntary for study participation.

tDCS Sessions: (Visit duration ~3 hours). The stimulation protocol is adapted from IRB protocol 809185 (Transcranial Direct Current Stimulation Investigations of Cognition and Action), which was employed in The Laboratory for Cognition and Neural Stimulation (LCNS) and protocols 820231, 819023 & 820371 at CIRNA.

Participants will complete stimulation sessions on Days 1, 3, & 5 **(week 1).** Participants will receive a call instructing them to stop smoking ~18 hours before their tDCS Session 1, tDCS Session 2, and tDCS Session 3 appointment start times (resulting in ~18 hours of smoking abstinence at the start of these visits).

Participants will complete the following prior to the tDCS period:

1. Women of childbearing potential will be provided with a urine pregnancy screen and will be instructed to perform the screening independently. Participants will be instructed that women who think they are pregnant are advised not to participate in the study;
2. BrAC assessment. See breath alcohol concentration under screening/covariates for exclusionary criteria;
3. Carbon monoxide (CO) Breath sample (must be <10 ppm or 50% of intake CO level at Session 1 to participate).
4. Paper and pencil questionnaires (brief QSU-B, G-FCQ-S, smoking TLFB).

tDCS Training Procedures: Prior to each tDCS period an investigator or trained research assistant will review the procedures, goals, risks, and potential benefits of the study and confirm that no change has occurred affecting study inclusion and exclusion criteria. The tDCS sessions will be conducted by a trained technician using the neuroConn DC-Stimulator Plus system. Participants will receive sham or active tDCS using the parameters described below. The participant will be blind to condition (sham vs. active and dosage).

Active tDCS: A neuroConn DC-Stimulator Plus will apply a constant direct current (1.0 mA to 2.0 mA via 5x7 electrode) to the left dorsal lateral prefrontal cortex. Each participant will receive anodal stimulation for a period of 20 minutes. For anodal stimulation over the left DLPFC, the anodal electrode will be placed over the left F3 and the cathodal electrode over the right supraorbital area (international EEG 10/20 system).

Sham tDCS: During sham tDCS, a 1.0 mA to 2.0 mA current will be delivered for approximately 30 seconds before being extinguished over a course of seconds. Again, the anodal electrode will be placed over the left F3 and the cathodal electrode over the right supraorbital area. Most participants cannot distinguish between real and sham tDCS (Gandiga, Hummel et al. 2006).

tDCS Safety: Although neuroConn DC-Stimulator Plus is not FDA-approved, the tDCS procedures described above have been considered to pose a minimal risk by the University of Pennsylvania IRB (protocol 809185 in normal controls, 811842 in stroke patients, 814366 in patients with neglect, 818662 in patients with Primary Progressive Aphasia, 819023 in normal controls and healthy smokers, and 820231 in healthy smokers). A literature search on the topic of tDCS in healthy individuals, smokers, stroke patients, dementia, and neurologic diseases indicates a lack of adverse events or significant risks in these populations (for detailed discussion of safety see RISK/BENEFIT ASSESSMENT below). Although adverse effects are considered unlikely to occur, a physician will always be within a 5 minute transit time of the subject during any tDCS application.

Craving and Smoking Assessment: Following the protocol developed and validated by Sherry McKee at Yale University (McKee 2009), the smoking lapse paradigm will be conducted as follows:

1. Participants will be placed in a CIRNA laboratory 10 x 10 room equipped with industrial grade exhaust fans designed and approved for exhaust of cigarette smoking; a comfortable chair; and viewing windows to observe participants.
2. Eight cigarettes of their preferred brand will be placed in view on a table in the lab room along with a lighter and ashtray. Prior to initiating the tDCS session, they will be informed that over the next 50 minutes "you can start smoking at any time, but for each 5 minute period that you are able to delay, you earn $1.00 for a maximum of $10.00." They will also be told "once you decide to smoke, you may smoke as little or as much of these cigarettes as you wish." They will be instructed that there is a set time for discharge to avoid them ending the resist period early, thinking they will be discharged early. Once instructions have been delivered the 20 minute tDCS session will begin. The tDCS headgear will remain in place until the end of the 50 minute resist period to avoid influencing the participant's smoking behavior; however, the stimulation will only be delivered for the first 20 minutes. Smoking sessions will be video recorded to capture smoking behavior (i.e. time to first cigarette, number of cigarettes smoked). These video recordings will be destroyed after they have been transcribed.
3. After 50 minutes (regardless of whether the participant decided to smoke during the resist period), the 60 minute ad-lib smoking session will commence. During this period, participants will receive $4.00 at the beginning of the session and will be instructed to "smoke as much or as little as you wish." They will be further instructed that for each cigarette lit, they would "lose $0.50 from their $4.00 tab." The primary outcomes will be latency to first cigarette and number of cigarettes smoked during the resist and ad-lib periods.
4. At the end of the ad-lib period, all participants will be asked to smoke one cigarette in order to standardize smoke exposure for subsequent tasks.
5. Participants will complete paper and pencil assessments of craving and a tDCS side effects questionnaire.

At the end of Session 3, smokers will receive a 20-minute in person coaching session and be instructed to try to remain abstinent from 10 P.M. that evening until after the final Monitoring Visit (7 days of monitored abstinence), with small monetary incentives for abstinence and biochemical verification. All participants will be discharged ~4 hours after their appointment start time.

Monitoring Visits: (Visit duration ~20 minutes). During the monitored abstinence period, participants will complete 4 Monitoring Visits (days 6, 8, 10, and 12). Participants will be given instructions to remain abstinent from smoking from 10 P.M. the evening of Day 5 until after they complete their final Monitoring Visit on Day 12. On Days 6, 8, 10, and 12, all participants will be asked to come to the CIRNA for brief visits to complete the following:

- Complete CO, smoking rate (TLFB), and concomitant medication assessment.
    - To increase abstinence motivation, participants will receive $15/day (in cash) for each day of self-reported abstinence that is biochemically-confirmed. On Day 6, a CO reading of less than 10ppm or less than 50% of CO breath sample taken at the Intake session will be sufficient as

biochemically-confirmed abstinence. On Days 8, 10, and 12, a CO reading less than 8 ppm will be considered as biochemically-confirmed abstinence.

- Complete measures of smoking urges (Table 1).

Table 1. Measures and Time Points

Activity	Intake	tDCS Sessions 1-3	Monitoring Visits 1-4
Weeks	-1	0	1
Urine Pregnancy Screen	x	x	
BrAC	x	x	
Time Line Follow Back (TLFB), CO	x	x	x
Demographics	x		
ETOH History	x		
Height	x		
Weight	x		
Medical History Form	x		
Shipley Institute of Living Scale (IQ)	x		
Saliva for DNA (Oragene™)	x		
Saliva sample (for nicotine metabolites)	x		
Smoking Behavior (FTND & Cigarette Brand	x		
Treatment/Training			
tDCS (1mA, 2mA or sham)		x	
Side effects		x	
Intermediate Outcomes			
Urges/Cravings (QSU-B)	x	x	x
Post-Test Questionnaire		x*	
Primary Outcomes			
Ability to Resist Smoking		x	
Number of Puffs, Cigarettes		x	
Days of biochemically confirmed abstinence			x

*after session 3 only

1. Screening/Covariates:

Urine Pregnancy Test (females only): At the Intake and Session 1-3 visits (4 urine pregnancy screens total), participants will be supplied with a simple, CLIA-waived urine pregnancy screen and informed that pregnant women are not advised to participate in this research study. Participants will then be instructed to administer the pregnancy test independently and will inform study staff if they would like to continue participation after they have administered the pregnancy screen. Participants will be informed that there is no penalty for discontinuing participation at this point in the visit and that they will still receive travel reimbursement for the visit.

Breath Alcohol Concentration: The BrAC assessment will be administered at all study visits. The breath alcohol monitor is a handheld device that uses a disposable mouthpiece and reports the concentration of alcohol in exhaled breath. Any reading > 0.000 indicates alcohol consumption within the last 14 hours. Participants with a BrAC greater than or equal to 0.01 at the Intake Visit will be ineligible. Participants who have a BrAC reading greater than or equal to 0.01 at either tDCS visit may be ineligible to continue with the visit and will only be rescheduled/allowed to proceed with the study at the discretion of the Principal Investigator.

Demographics: Standard surveys will collect demographics (e.g., age, education, race, and gender).

Medical: Height and weight will be measured and recorded. All participants will complete a medical history form with a trained staff member to review for all contraindications listed previously.

Shipley Institute of Living Scale: All participants will complete the Shipley Institute of Living Scale (SILS) at the Intake Visit. The scale consists of two subtests: a 40-item vocabulary test and a 20-item test of abstract thinking. The total administration time is 20 minutes (10 minutes per subtest). A trained member of the study staff will score

the test. The SILS correlates with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Estimated IQ Test; those participants earning less than an estimated WAIS-R IQ of 85 will be ineligible. The SILS is considered a highly reliable assessment tool, with a good total score internal consistency (Cronbach's alpha=.92).

Saliva for DNA for Exploratory Genetic Studies: The 2ml saliva sample via the Oragene™ collection kit will be used to explore associations of genes relevant to smoking craving and ability to resist smoking. Because all genetic analyses are exploratory, participants will not be informed of their genetic test results. All samples and results will be kept confidential and secure. The saliva Oragene™ sample will be collected at the Intake Visit.

Saliva for Nicotine Metabolites: A 5ml saliva sample will be collected at the Intake Visit to assess nicotine metabolites.

ETOH History: ETOH history will be administered at the Intake Visit and will ask subjects about their alcohol consumption over the past 7 days.

Smoking Behavior: Participants will complete the 6-item Fagerstrom test for nicotine dependence (FTND; Heatherton et al. 1991) and a smoking history assessment include age at first cigarette, age at regular (daily) smoking, current smoking rate and cigarette brand information. Number of cigarettes smoked in past 24 hours and time of last cigarette will be recorded at each visit and carbon monoxide (CO) levels (analyzed by Vitalograph) will be assessed as a biochemical verification of smoking exposure. The well-validated timeline follow back method (TLFB) will be used to assess baseline smoking rate at intake and the number of cigarettes smoked prior to each session.

Post Study Questionnaire: Side effects of tDCS will be assessed at the end of Session 3 using the Post-Study Questionnaire. Using a 10 point Likert-like scale, participants will be asked to indicate to what extent they experienced symptoms during or after tDCS administration (from "Not at all" to "a high degree"). This form will also ask participants to guess whether they received real stimulation or sham stimulation to allow us to assess the efficacy of the blinding procedures.

Outcomes:
Smoking Urges/Cravings: The 10-item brief QSU (QSU-B) questionnaire will be used to assess smoking urges (Cox, Tiffany et al. 2001). The QSU-B contains 2 subscales (anticipation of reward, relief from negative affect). Craving has also been related to long-term cessation outcome in many, but not all, clinical studies (Killen and Fortmann 1997). The QSU-B with a "Right Now" frame of reference will be administered at all study visits.

Resisting Smoking: Once the participant has received the resist period instructions the study staff will leave the laboratory smoking room and observe the participant's behavior through a one-way observation window. Time to first cigarette will be recorded.

Ad-libitum Smoking: Once the participant has begun the ad-libitum smoking period, number of puffs taken and number of cigarettes smoked will be recorded for the remainder of the 60 minute period.

Monitored Abstinence: Number of days of biochemically verified abstinence during the monitoring period will be recorded.

STUDY ANALYSIS PLAN

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 $\chi 2$ tests were used to examine baseline differences in demographics between dose groups. Analysis of laboratory outcomes utilized multiple regression modeling (Stata; StataCorp LLC, College Station, TX, USA) to examine effects of dose group on pre-session craving as well as latency to smoke and total number of cigarettes smoked during the smoking lapse paradigm on day 5. 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). Similar models were used 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.

We conducted a futility analysis based on conditional power (futility = conditional power <20%) using results from the mixed model with dose of 1mA and 2mA 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).

2. Confidentiality

Confidentiality of the data generated in this study shall be maintained in the following ways:

- Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.
- Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.
- Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.
- Whenever feasible, identifiers will be removed from study-related information
- Any study communications made by e-mail will use ID numbers only and never include names or any other personal information
- Audio and/or video recordings will be transcribed and then destroyed to eliminate audible/visual identification of subjects.
- Biological samples will be de-identified, labeled with a study ID number, and stored in our private bank. The sample bank is accessible to study staff only, and is located within our Center at 3535 Market St.

Confidentiality of the data generated in this study shall be maintained in the following ways. First, all participant information/files will be kept in a secure filing cabinet that is accessible only to authorized study personnel. Second, all databases containing participant information will be password protected, and again, accessible only to authorized study personnel. Third, any study communications made by e-mail will use ID numbers only and never include names or any other personal information. Fourth, in all data sets we will use ID numbers only. A separate data set subject map table linking names with ID numbers will be accessible only by authorized personnel.

Since self-report and biological data will be collected and stored as part of this study, it is possible that subject privacy or confidentiality can be threatened. To address this concern, the data management system has set up several safeguards to prevent unauthorized access to study data. In the subject map table, an automatically generated index number is assigned to a subject's study identification number. A linked subject identification table is created to store subject name, address, and telephone contact information. This table uses the automatically generated index number rather than the study identification number. The master subject map and subject identification information are maintained in separate locations. Using this method, no identifying subject information is directly linked to bio-samples or results. Any publication of data will not identify participants by name or with an identifier that could be used to reveal identity.

All biological samples will be labeled with study ID only. All subject data that can be linked to the study ID will be stored in the secure data management system, which has limited, password-required access. Additionally, biological samples will be stored in our private sample bank which is locked at all times and is accessible only to the research team.

The aforementioned precautions and procedures will be applied to protecting subject privacy and the protected health information detailed in Section 4 below.

4. Subject Privacy/Protected Health Information

The following protected health information (PHI) may be collected as part of this study:

1. Name
2. Street address, city, county, zip code
3. All elements of dates (except year) for dates directly related to an individual and all ages over 89
4. Date of birth
5. Social Security Number
6. Telephone number
7. Email address
8. Results from all questionnaires, tests, and procedures
9. Saliva sample for nicotine metabolite and genetic analysis
10. Any other unique identifying number, characteristic, or code
11. Video recordings of smoking sessions including the participant's face

Potential participants will be contacted over the phone after responding to recruitment advertisements. Participants will undergo an initial phone screening where preliminary eligibility for the research study will be determined. Only if a participant is initially eligible, will they attend an in-person Intake Visit to confirm eligibility. All data collected over the phone and during in-person visits will be collected by research staff that have completed the CITI Protection of Human Subjects Research Training as well as HIPAA Compliance Training. Information will never be recorded with identifiers other than study ID. A separate list of names with ID numbers will be accessible only by authorized personnel. All records will be kept in locked filing cabinets to maintain confidentiality. Results will not be communicated to other personnel or to the subjects. All analyses will be conducted on de-identified data. Data will be accessible to the Study Investigators, Study Physician, study staff, UPenn IRB, Office of Clinical Research, authorized UPenn staff (e.g. accounting and billing matters, provide treatment, etc.) and the Food and Drug Administration. Video recordings of participants will not include other identifying information other than their face, such as name. Recordings will be kept on password protected computers accessible to study specific staff only. Recordings will be destroyed one year after study completion after data has been reviewed and verified.

5. Tissue Specimens

Saliva: A 2ml saliva sample will be collected for DNA extraction using the Oragene™ kit at the Intake Visit for genetic analyses. An additional saliva sample (~ 5ml) will be collected at the Intake Visit to analyze nicotine metabolites.

Urine: Urine (~30ml) will be collected at the Intake Visit to conduct a urine pregnancy screen (females only). A urine pregnancy screen (females only) will be required at all study visits.

6. Genetic Testing

All genetic information (as with all study information) will be kept strictly confidential using the procedures outlined in Section 3, above. Results will not be revealed to study participants.

RISK/BENEFIT ASSESSMENT

1. Potential Study Risks

The potential risks to participants, and their likelihood and seriousness, are described below. Participants can choose, as an alternative, to not enroll in this study. Overall, there is minimal risk for serious adverse reactions as a consequence of enrolling in this study. Adverse reactions will be assessed and reported as required by Federal law and UPenn regulations.

tDCS: The animal literature regarding the safety of direct current stimulation of the brain was reviewed by Agnew and McCreery (Agnew and McCreery 1987) and McCreery and others (McCreery, Agnew et al. 1990). Based on these reviews, as well as their own work with humans, Nitsche and colleagues (Nitsche, Liebetanz et al. 2003) published a comprehensive review of the safety of tDCS. Citing animal research, they argue that the major variables relevant to safety in humans are current density and total charge. Current density is calculated as the current strength/electrode size. Assuming electrode sizes of 25 cm^2 (the standard electrode size with the neuroConn Channel-DC Stimulator Plus unit), the current density that would be generated by a 1 mA current is .04 C/cm^2; the current density generated by a 2.0 mA current is .08 mA/cm^2. McCreery and colleagues (McCreery, Agnew et al. 1990) demonstrated that current densities below 25 mA/cm^2 were not associated with evidence of tissue damage. The maximum current density that we propose to employ is 1/312 the level that was

considered to be safe in animals; additionally, this current density is similar to that employed by other investigators in the field.

Total charge in this context refers to the total amount of current that passes through the skin in the course of the study. It is noteworthy that the current delivered to the brain is estimated to be approximately 50% that delivered to the skin. Total charge is calculated as the current strength/electrode size x stimulation duration. McCreery and colleagues (McCreery, Agnew et al. 1990) reported that the lowest total charge at which tissue damage was recorded in animals was 216 C/cm^2. Assuming the maximum current that we propose to employ (2.0 mA) for the maximum duration that we propose to employ (20 minutes), the total charge to which our participants would be subjected is 0.096 C/cm^2, an amount that is 1/2250 of the minimum total charge that generated detectable changes in animals. The safety of tDCS has been addressed in a number of manuscripts. As described by Nitsche et al (2003), studies have demonstrated that using current densities of up to 0.02875 mA/cm^2 and total charges of up to 0.022 C/cm^2, there is no heating under the electrode, no increase in neuron-specific enolase (a marker of neuronal injury), no changes in diffusion weighted or contrast-enhanced MRI and no abnormalities on EEG. Additionally, Nitsche and colleagues (Nitsche, Niehaus et al. 2004) reported that tDCS protocols that were shown to produce effects lasting for an hour were not associated with abnormalities on T1, T2 or diffusion-weighted MRI performed 30 and 60 minutes after stimulation.

A second study exploring the safety of the technique was reported by Iyer and colleagues (Iyer, Mattu et al. 2005). These investigators report experience with 103 subjects from age 19-70 (mean 37.5 ±12.9); half of the participants received sham treatment. In this study, a current density of 40 microA/cm^2 for 20 minutes was administered to approximately 36 participants and a current density of 80 microA/cm^2 was used for 15 participants. One electrode was placed over the left frontal region and the other over the right supraorbital region. EEG was recorded in 9 participants. No participant asked to stop the protocol and no participant reported significant pain. Some participants noted mild tingling at the electrode site. Minor redness was noted under the electrode site in two men who had recently shaved their heads. Cognitive function was assessed before and after stimulation. With 80 microA/cm^2 current density a significant improvement in verbal fluency was observed with anodal stimulation but not in the sham or cathodal stimulation groups. A battery of neuropsychological tasks was administered to screen for adverse effects. No adverse effects were found for any measure of cognitive performance.

Finally, Poreisz and colleagues (Poreisz, Boros et al. 2007) reported on their extensive experience (567 sessions) with tDCS to multiple brain regions in 102 healthy participants and patients. None of the participants asked for a session to be terminated or required any medical assistance. For this study all participants completed a questionnaire inquiring about potential adverse effects. The questionnaire included assessment of headache, difficulties in concentrating, mood changes, visual perceptual changes and uncomfortable sensations (e.g., tingling, burning). Responders included healthy participants (75.5%), migraineuers (8.8%), post-stroke patients (5.9%) and patients with tinnitus (9.8%). A mild tingling sensation was the most common symptom, occurring in 71% of participants; the mean rating of the tingling was 1.74 ± 0.84 on a 1-5 scale. Moderate fatigue was noted in 35% of participants during but not after the stimulation; the mean rating was 2.17 ±1.11. Itching under the electrode was reported by 30%; the mean rating was 1.6 ± 0.72. Burning was reported by 22% and pain by 16% but, once again, both were regarded as quite mild (1.59 ± 0.91 and 1.41 ± 0.71, respectively).

There have been no significant side effects noted in any study involving tDCS to date. That is to say that in the approximately 300+ studies that have been published to date there have been no reported seizures, loss of consciousness or persistent neurologic signs or symptoms. Moreover, there have been 15 studies in which tDCS has been administered to stroke patients, again with no significant side effects. These data are in accord with our collaborator laboratory's observations. In the approximately 200 sessions Dr. Hamilton’s laboratory has performed with normal healthy participants there have been no significant side effects. In short, all existing evidence indicates risks posed by tDCS are non-significant. In the unlikely event that either the participant or the person administering tDCS has significant concerns, the participant will be escorted to the Emergency Room if a physician involved with the study cannot be contacted immediately. A physician involved with the study will then contact the participant within 24 hours to follow up.

All personnel using tDCS will be properly trained in the research protocol to ensure safe handling of the equipment. The training protocol includes hands-on training, written examination, mandatory observation of tDCS delivery and mandatory administration of tDCS under observation by a trained staff member.

Nicotine Withdrawal: Many individuals who stop smoking exhibit a pattern of symptoms related to withdrawal from tobacco use. These symptoms include: sadness and anxiety, irritability, anger, difficulty concentrating, appetite change and weight gain, insomnia, and decreased heart rate. Eliminating the risk for these would not be possible, although in most cases these events are short-lived and have low intensity. The study personnel will be trained to recognize these symptoms and educate the participants about them (e.g., duration, methods for reducing them).

Email Communications: In this research study participants may prefer to receive appointment reminders via email or submit questions related to study logistics. Email is not a secure means of communication. Email messages travel across the Internet passing through multiple computers before reaching their final destination. It is not possible to know whether an email a participant sends will be viewed along the way. Additionally, if sent messages are not deleted, an email provider may have an archive of everything that is sent. If someone gets access to an email account (for example, a participant's family member), they could see archived messages. There are many other ways in which emails are not secure—these are only selected examples. To manage this risk the informed consent form will include specific language to educate research participants on the privacy risks involved in email communications. Participants will also be explicitly instructed to only use email communications for routine matters and never for personal or confidential messages or questions.

Video Recordings: Video recordings will be made of participant smoking sessions during Sessions 1-3 for the purpose of verifying number of cigarettes smoked during a session and latency to smoke. Video recordings of participants will not include other identifying information other than their face, such as name. Recordings will be kept on password protected computers accessible to study specific staff only. Recordings will be destroyed one year after study completion after data has reviewed and verified.

Genetic Testing: All genetic information (as with all study information) will be kept strictly confidential using the procedures outlined in section 3 (Confidentiality), above. Results will not be revealed to study participants.

Threats to Privacy/Confidentiality: See description in Section 3 (Confidentiality) and 4 (Subject Privacy/Protected Health Information) above.

2. Potential Study Benefits

By participating in this research study participants may have the opportunity to improve their ability to resist smoking via tDCS training. This benefit is not guaranteed.

3. Alternatives to Participation

The alternative to participating in the research study is to decide not to enroll in this particular research study.

4. Data and Safety Monitoring

During the course of the study, data and safety monitoring will be performed on an ongoing basis by the Principal Investigator, project staff, and the IRB. The project staff are responsible for collecting and recording all clinical data. This includes ensuring that all source documents exist for the data on the case report forms, ensuring all fields are completed appropriately, and all corrections are done according to Good Clinical Practice (GCP's). Any inconsistencies/deviations will be documented. Project staff will perform regular chart reviews to verify data integrity. Project staff will meet on a regular basis to reconcile data queries. The IRB will review the trial on an on-going basis.

5. Management of Information for Multi-center Research where a Penn Investigator is the Lead Investigator of a multi- center study, or Penn is the lead site in a multi-site study.

Not applicable.

6. Risk/Benefit Assessment

Research staff will monitor participants closely during the tDCS sessions. Thus, the risk to benefit ratio for this project is perceived to be low and justifies its implementation.

INFORMED CONSENT

1. Consent Process

Participants will complete an initial eligibility assessment by phone, reducing the likelihood that participants attend an Intake Visit only to learn that they are ineligible. The phone screen poses no more than minimal risk and involves no procedures for which written consent is normally required outside of the research context. All participants who are contacted for the phone screen will have responded to an advertisement for the research study, and have therefore requested the initial phone screening call. Those interested/eligible at phone screen will be scheduled for an in-person Intake Visit (Week -1). At this Intake Visit, participants will review the informed consent document with study staff and will view a visual presentation as part of the consent process. Interested participants will then provide written study consent and HIPAA documents (combined) before completing additional survey measures and undergoing any study related activities. Participants will receive a copy of the combined consent/HIPAA form. Hard copies of Intake Visit data and a copy of the signed combined consent/HIPAA forms will be stored in a subject's study folder. The original signed combined consents/HIPAA will be centrally stored in Regulatory Consent Binders.

2. Waiver of Authorization.

Not applicable

RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION

2. Staff Training

The Principal Investigator and the Project Managers will oversee the development of protocols for laboratory related tasks and training of staff in these protocols. The Principal Investigator and/or the Project Managers will be responsible for the development of procedures pertaining to all other study visits and implementing and monitoring ongoing staff training procedures accordingly. An initial, intensive training period will be implemented followed by periodic in-service trainings that will be coordinated by the Project Managers. They will also oversee study progress as part of regular study meetings. All research staff will undergo training on research practices involving human subjects, including the protection of subject confidentiality, and will maintain current certification in patient oriented research. Moreover, all research staff are required to undergo a training course in the safe administration of tDCS.

3. Study Facilities

This project will be conducted at and through the Center for Interdisciplinary Research on Nicotine Addiction (CIRNA) at the University of Pennsylvania. The CIRNA has numerous similar protocols and well-developed procedures for staff training, data collection and storage, and study completion. The facilities available for this project include a large conference room, individual consulting rooms with computer/internet access, storage rooms, office space for study personnel, and data management facilities.

The tDCS neuroConn DC-Stimulator Plus units were purchased from Jali Medical, Inc., and are stored at our Center in a locked filing cabinet in the locked office of one of the Study Managers. All tDCS administration will be conducted by trained personnel. The training protocol includes hands-on training, written examination, mandatory observation of tDCS delivery and mandatory administration of tDCS under observation by a trained staff member.

The stimulation protocols are programmed into the unit and are not alterable by the research staff administering the stimulation. The programs have been adapted from prior protocols employed in The Laboratory for Cognition and Neural Stimulation (LCNS) and CIRNA.

References

Agnew, W. F. and D. B. McCreery (1987). "Considerations for safety in the use of extracranial stimulation for motor evoked potentials." Neurosurgery **20**(1): 143-147.
Cox, L. S., S. T. Tiffany and A. G. Christen (2001). "Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings." Nicotine Tob Res **3**(1): 7-16.
Demirtas-Tatlidede, A., A. M. Vahabzadeh-Hagh and A. Pascual-Leone (2013). "Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders?" Neuropharmacology **64**: 566-578.
Dockery, C. A., R. Hueckel-Weng, N. Birbaumer and C. Plewnia (2009). "Enhancement of planning ability by transcranial direct current stimulation." J Neurosci **29**(22): 7271-7277.
Figner, B., D. Knoch, E. J. Johnson, A. R. Krosch, S. H. Lisanby, E. Fehr and E. U. Weber (2010). "Lateral prefrontal cortex and self-control in intertemporal choice." Nat Neurosci **13**(5): 538-539.
Gandiga, P. C., F. C. Hummel and L. G. Cohen (2006). "Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation." Clin Neurophysiol **117**(4): 845-850.
Iyer, M. B., U. Mattu, J. Grafman, M. Lomarev, S. Sato and E. M. Wassermann (2005). "Safety and cognitive effect of frontal DC brain polarization in healthy individuals." Neurology **64**(5): 872-875.
Killen, J. D. and S. P. Fortmann (1997). "Craving is associated with smoking relapse: findings from three prospective studies." Exp Clin Psychopharmacol **5**(2): 137-142.
Lerman, C., H. Gu, J. Loughead, K. Ruparel, Y. Yang and E. A. Stein (2014). "Large-scale brain network coupling predicts acute nicotine abstinence effects on craving and cognitive function." JAMA Psychiatry **71**(5): 523-530.
Loughead, J., R. Ray, E. P. Wileyto, K. Ruparel, P. Sanborn, S. Siegel, R. C. Gur and C. Lerman (2010). "Effects of the alpha4beta2 partial agonist varenicline on brain activity and working memory in abstinent smokers." Biol Psychiatry **67**(8): 715-721.
Loughead, J., E. P. Wileyto, K. Ruparel, M. Falcone, R. Hopson, R. Gur and C. Lerman (2015). "Working memory-related neural activity predicts future smoking relapse." Neuropsychopharmacology **40**(6): 1311-1320.
McCreery, D. B., W. F. Agnew, T. G. Yuen and L. Bullara (1990). "Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation." IEEE Trans Biomed Eng **37**(10): 996-1001.
McKee, S. A. (2009). "Developing human laboratory models of smoking lapse behavior for medication screening." Addict Biol **14**(1): 99-107.
Meinzer, M., R. Lindenberg, D. Antonenko, T. Flaisch and A. Floel (2013). "Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes." J Neurosci **33**(30): 12470-12478.
Nitsche, M. A., D. Liebetanz, N. Lang, A. Antal, F. Tergau and W. Paulus (2003). "Safety criteria for transcranial direct current stimulation (tDCS) in humans." Clin Neurophysiol **114**(11): 2220-2222; author reply 2222-2223.
Nitsche, M. A., L. Niehaus, K. T. Hoffmann, S. Hengst, D. Liebetanz, W. Paulus and B. U. Meyer (2004). "MRI study of human brain exposed to weak direct current stimulation of the frontal cortex." Clin Neurophysiol **115**(10): 2419-2423.
Patterson, F., C. Jepson, J. Loughead, K. Perkins, A. A. Strasser, S. Siegel, J. Frey, R. Gur and C. Lerman (2010). "Working memory deficits predict short-term smoking resumption following brief abstinence." Drug Alcohol Depend **106**(1): 61-64.
Poreisz, C., K. Boros, A. Antal and W. Paulus (2007). "Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients." Brain Res Bull **72**(4-6): 208-214.