Basic Study Information

1. * **Title of study:**
AAT + tDCS to reduce cue-induced craving and smoking behavior

2. * **Short title:**
AAT+tDCS

3. * **Brief description:**
Smokers are highly reactive to smoking-related stimuli and report that this cue reactivity (CR) is a major obstacle to quitting. To date, no pharmacologic methods attenuate CR, and attempts to diminish it with traditional cue exposure treatment (CET) have not proven effective. The proposed study will test a highly novel cue-based smoking treatment adjunct combining an Approach/Avoidance Task (AAT) with brain stimulation via tDCS applied to the dorsolateral prefrontal cortex (dlPFC) during personalized multi-cue exposure; the goal of which is to discover an effective means of reducing cue reactivity and daily smoking, and increasing intent and confidence to quit, among high treatment-interest smokers.

4. * **What kind of study is this?**
Single-site study

5. * **Will an external IRB act as the IRB of record for this study?**
○ Yes ● **No**

6. * **Local principal investigator:**
Cynthia Conklin
* **Is this your first submission, as PI, to the Pitt IRB?**
○ Yes ● **No**

7. * **Does the local principal investigator have a financial interest related to this research?**
○ Yes ● **No**

8. **Attach the protocol:**
   - Sponsor/Multicenter/Investigator-initiated protocol
   - Coordinating Center supplement
   - Emergency Use Consent/ Protocol/ FDA Form 3926
   - Exempt Application form

Document	Category	Date Modified	Document History

There are no items to display

View: Pitt SF: Funding Sources (not integrated with Grants)

Funding Sources

1. * **Indicate all sources of support:**
   External funding

2. * **Identify each organization supplying funding for the study:**

Funding Source	Sponsor's Funding ID	Grants Office ID	Attachments	Pitt Awardee	Grant Recipient
National Institute on Drug Abuse	1 R21 DA053395-01		Grant Application R21 DA053395-01.pdf	yes	

Study Team Members

1. * **Identify each person involved in the design, conduct, or reporting of the research:**

Name	Roles	Department/School	Affiliation	Involved in Consent	Qualifications	Financial Interest
Brian Coffman	Co-investigator	U of Pgh | School of Medicine | Psychiatry	Pitt faculty	no	has a doctorate in Experimental Psychology with a concentration in Quantitative methods. He has considerable experience and has written several manu... view all	no
Cynthia Conklin	Principal Investigator	U of Pgh | School of Medicine | Psychiatry	Pitt faculty	yes	is an Associate Professor of Psychiatry with a doctorate in Clinical Psychology. She has considerable clinical and research expertise with conditioni... view all	no
Jordan Dawson	Secondary Study Coordinator	UPMC | Hospital Divisions | WPIC	UPP/UPMC staff	yes	Jordan is a Research Assistant at UPMC who will be explaining the consent with Dr. Tyagi and running participants through the study procedures.	no
Ronald Salkeld	Primary Study Coordinator	UPMC | Hospital Divisions | WPIC	UPP/UPMC staff	yes	Mr. Salkeld will be involved in recruiting, consenting, assessing study participants. He will run sessions, manage data and be responsible for the d... view all	no
Shachi Tyagi	Co-investigator	U of Pgh | School of Medicine | Medicine	Pitt faculty	yes	Dr. Tyagi's clinical training in medicine and geriatrics,	no

Name	Roles	Department/School	Affiliation	Involved in Consent	Qualifications	Financial Interest
					combined with her basic research experience in urology, has equipped her with the required ... view all	

2. **External team member information: (Address all study team members in item 1. above and leave this section blank)**

Name	Description
There are no items to display	

3. **Have you,** Cynthia Conklin**, verified that all members of the research team have the appropriate expertise, credentials, training, and if applicable, child clearances and/or hospital privileges to perform those research procedures that are their responsibility as outlined in the IRB application?**

* ● **Yes** ○ No

Study Scope

Check all that apply

1. * Will this study actively recruit any of the following populations?

- [ ] Adults with impaired decision-making capacity
- [ ] Children (under the applicable law of the jurisdiction in which the research will be conducted (<18 years for PA))
- [ ] Children who are Wards of the State
- [ ] Employees of the University of Pittsburgh/UPMC
- [ ] Medical Students of University of Pittsburgh as primary research group
- [ ] Students of the University of Pittsburgh
- [ ] Neonates of uncertain viability
- [ ] Non-viable neonates
- [ ] Non-English speakers
- [ ] Nursing home patients in the state of Pennsylvania
- [ ] Pregnant women
- [ ] Prisoners
- [x] N/A

2. * Will any Waivers be requested?

- [ ] Waiver/Alteration of Consent
- [ ] Waiver to Document Consent
- [ ] Waiver/Alteration of HIPAA
- [ ] Exception from consent for emergency research
- [x] N/A

3. * Will this study involve any of the following?

- [ ] Specimens
- [ ] Honest Broker to provide data/specimens
- [ ] Return of Results to Subjects or Others
- [ ] Fetal tissue
- [x] N/A

4. * Will Protected Health Information be collected?

- [ ] Pitt medical records
- [ ] UPMC medical records
- [ ] Other Institutions' medical records
- [x] N/A

5. * Other Requests?

- [ ] Deception (if not Exempt, also requires Waiver/Alteration of Consent)
- [ ] Emergency Use / Single Patient Expanded Access (using FDA Form 3926)
- [x] Placebo Arm
- [ ] Withdraw from usual care
- [ ] N/A

6. * Determining Scientific Review:
WPIC SRC - Western Psychiatric Institute and Clinic Scientific Review Committee (this option MUST be picked if from Department of Psychiatry)

7. * Has this study (or substantially similar study) been previously disapproved by the Pitt IRB or, to your knowledge, by any other IRB?

○ Yes ● **No**

Review the HRPO policy, if participating in research at the VA Pittsburgh Healthcare System or using funding from the VA

8. * **Does the study use an approved drug or biologic, use an unapproved drug or biologic, or use a food or dietary supplement to prevent, diagnose, cure, treat, or mitigate a disease or condition?**

○ Yes ● **No**

9. * **Does the study evaluate the safety or effectiveness of a device (includes in-vitro laboratory assays)?**

● **Yes** ○ No

10. * **Is this application being submitted to convert an approved study from OSIRIS to PittPRO?** (Tip Sheet)

○ Yes ● **No**

11. * **Does your research protocol involve the evaluation or use of procedures that emit ionizing radiation and, after reviewing this** HUSC guidance**, does your research protocol require HUSC review? (If yes, upload the** HUSC form **in the Local Supporting Documents section). If you are unsure of review requirement, select yes.**

○ Yes ● **No**

Research Sites

1. **Choose all sites that apply:**
   University of Pittsburgh
   UPMC

   * **Select the University of Pittsburgh sites where research will be conducted:**
   Main Campus – Pittsburgh

   List university owned off-campus research sites if applicable:

   * **Select the UPMC sites where research will be conducted:**
   Western Psychiatric Institute & Clinic

2. **Describe the availability of resources and the adequacy of the facilities to conduct this study:**
   Western Psychiatric Hospital (WPH) formerly Western Psychiatric Institute and Clinics (WPIC). A dual entity, WPH is the academic Department of Psychiatry within the University of Pittsburgh School of Medicine, and also a psychiatric hospital within the University of Pittsburgh Medical Center (UPMC). This dual status allows for optimal integration between the academic and clinical domain. WPH is recognized nationally and internationally as one of the premier research and treatment centers in the United States. The Department has over 200 primary faculty trained in a mix of disciplines including medicine, psychology, basic sciences, and social work, who are dedicated to the pursuit of excellence in research, training and provision of clinical care. Their efforts are supported by numerous emeritus, secondary, adjunct and volunteer faculty. The intellectual resources at WPH are enriched by close collaborative ties with numerous other Departments within the University of Pittsburgh including Psychology, Neuroscience, Neurology, Kinesiology/Sports Medicine and Radiology. The Department also maintains active collaborations with many other departments and research institutions in the U.S. and around the world. The Department of Psychiatry has been ranked first among all Departments of Psychiatry in the U.S. with regard to research funding from the National Institutes of Health (NIH) since the mid-1980s. The University of Pittsburgh ranks among the top ten universities nationwide in the level of funding from the National Institutes of Health (NIH) http://www.pitt.edu/research.html). Founded in 1787, it is one of the oldest institutions of higher education in the United States. As one of the nation's distinguished comprehensive universities, the resources of the University contribute to the intellectual, economic, and social enrichment of Pennsylvania and the nation. The University's mission is to provide high-quality undergraduate programs; offer superior graduate training; engage in research, artistic, and scholarly activities that advance learning through the extension of the frontiers of knowledge and creative endeavor; and cooperate with industrial and governmental institutions to transfer knowledge in science, technology, and health care. Due to its central location on the University of Pittsburgh campus, the Main WPH building is an easily accessed and familiar location for research participants. Most city bus lines stop within a block of this building, and campus shuttles stop directly in front of it. For individuals who choose to drive to research sessions, free parking is easily available in the building’s off-street garage.

Devices

1. * List each device in the study that will be evaluated for safety or effectiveness:

	Device	Purpose	Type
View	NeuroConn DC-Stimulator	An IDE application (G150197) was submitted to the FDA on August 14 (recieved by the FDA on September 9, 2015). The FDA has determined that the proposed study is a nonsignificant risk device study because it does not meet the definition of a significant risk (SR) device under §812.3(m) of the Investigational Device Exemption (IDE) regulation (21 CFR 812). The letter from the FDA is attached under the "other attachments section". Overall, there are no significant risks associated with tES as all risks are very unlikely and minimally serious. Several investigators have examined the safety aspects associated with transcranial direct current stimulation (tDCS). For example, Iyer et al. (2005), applied 1 and 2 mA anodal, cathodal, and sham DC stimulation to the left prefrontal cortex for 20 minutes while clinical EEG was recorded. Participants were encouraged to report any discomfort or subjective sensations while undergoing stimulation. These researchers observed no aversive EEG abnormalities resulting from DC stimulation, and no participants asked to stop the study or reported any significant discomfort. Differences in mood between sham and stimulation were assessed using the Visual Analog Mood Scale (VAMS) that measures subjective reports of anger, anxiety, confusion, energy, fright, happiness, sadness, tension, and tiredness. The investigators found no measurable effects of stimulation on participants' VAMS scores. Based on their findings, they conclude that limited exposure to direct current stimulation between 1 and 2 mA is a safe procedure in healthy participants. In another study conducted by Gandiga, Hummel, and Cohen (2006), tDCS and sham were compared in healthy volunteers and chronic stroke victims. Discomfort was measured using a 10 point scale, where 1 represented no discomfort and 10 represented extreme discomfort and pain. These researchers report transient and mild discomfort of sensations (12 on the 10 point scale) that weren't significant between sham and stimulation conditions, nor between healthy volunteers and stroke victims. Safety and tolerability of tES has also been examined in adults with schizophrenia (Brunellin et al., 2014), as well as childhood onset schizophrenia (Mattai et al., 2011). tES in these studies was wel ltolerated by participants, and no adverse events were reported. Recently, safety of other forms of tES have been thoroughly examined. Chaieb et al. (2014) examined assessed safety aspects of Sinusoidal transcranial alternating current stimulation (tACS) by measuring neuronspecific enolase (NSE) levels, examining electroencephalogram (EEG) traces and analyzing anatomical data by using magnetic resonance imaging (MRI). tACS was delivered at 5 kHz applied for 10 min at 1 mA intensity over the hand area of the primary motor cortex. No changes were detected in NSE levels, no structural alterations were observed in the anatomical scans and no pathological changes were found in the EEG recordings. Additionally, Zaghi et al. (2010) administered various behavioral and neuropsychological tests during tACS. tACS was not associated with any cognitive adverse effects and had no harmful effects on motor function (Purdue Pegboard Test, Finger Tapping Test). Moreover, tACS was not associated with pain, mood, or anxiety. DCSTIMULATOR has a Maximum Voltage Limitation of +/- 20V. The output circuit of the constant current source of the DCSTIMULATOR is equipped with an electrical fuse which limits the current to 5 mA. Therefore, in any faulty condition and during normal operation, the fuse will become open circuit if the current exceeds 5 mA by a significant amount. The higher the current exceeds 5 mA the faster it will become open circuit. This means that it is impossible for the participant to recieve a harmful level of current, even in cases of equipment malfunction. To avoid thermal discomfort and possible skin damage, the German authority (Bundesanstalt für Arzneimittel und Medizinprodukte) gives a limit of 0.1 mA/cm² for DC current applications. The largest current density we will use here is 0.08 mA/cm². We will monitor participant discomfort throughout the administration of tES. If at any point the participant reports perceived heat, tingling, or itching at the site of the electrodes as 8 or higher on a 10point scale, tES will be stopped immediately. The Co-I, Coffman, has administered tES to over 250 research participants in previous studies at the University of New Mexico, with only two adverse events, one of which was due to latex allergy, and the other was due to small electric shock caused by suboptimal equipment. Only the PI and trained research staff /Co-I's will administer tES here, and individuals with latex alergy will be excluded. The Neuroconn stimulator used here is robust, so we do not anticipate this to be a problem here. ++ Evidence of efficacy across past work, including some from our research team include the following: Past work has shown that brain stimulation with tDCS during CR further enhances cognitive training, as cognitive effects of tDCS are largely dependent upon the cognitive faculty being engaged at the time of stimulation (Bradnam, Stinear, Lewis, & Byblow, 2010). We found enhancement of alerting attention network function measured by the Attention Networks Test, a measure of proactive cognitive control, more than an hour after anodal tDCS directed at right inferior frontal gyrus (Falcone, Coffman, Clark, & Parasuraman, 2012). tDCS was paired with complex object detection training, which is thought to engage cognitive control networks in the brain. Further, tDCS directed at right frontal cortex has been used to increase reactive cognitive control in the stop-signal task (SST) as evidenced by reaction time and neurophysiological measures obtained with electroencephalography (EEG)(Jacobson, Ezra, Berger, & Lavidor, 2012). Thus, we plan to use CR + tDCS as a means of further enhancing cognitive control among smokers with schizophrenia. Three tDCS studies(Boggio et al., 2009; Fregni et al., 2008; Grundey et al., 2012) in healthy non-quitting smokers (randomized, active vs. sham 1-5 training days) targeting the dorsolateral prefrontal cortex (DLFPC) found dose dependent reductions in cue-induced craving and smoking behavior. tDCS has also been shown to significantly enhance the ability of smokers to resist the urge to smoke(Falcone et al., 2016). Our recent pilot study (N=6) found that weekly group sessions of 30 minutes of mindfulness + tDCS of the right IFG, followed by 60 minutes of mindfulness + counseling led to a significant 50% reduction in cigarettes per day at the end of treatment (d=0.50; Witkiewitz et al., 2015). However, CR will be used in this present study, not mindfulness, as it targets multiple aspects of cognition, and has shown greater efficacy to enhance cognitive deficits among patients with psychosis (d= >1(Hogarty et al., 2004) vs. d=.41 (Khoury, Lecomte, Gaudiano, & Paquin, 2013)respectively). --- Boggio, P. S., Liguori, P., Sultani, N., Rezende, L., Fecteau, S., & Fregni, F. (2009). Cumulative priming effects of cortical stimulation on smoking cue-induced craving. Neuroscience Letters, 463(1), 82–86. https://doi.org/10.1016/j.neulet.2009.07.041 Bradnam, L. V., Stinear, C. M., Lewis, G. N., & Byblow, W. D. (2010). Task-dependent modulation of inputs to proximal upper limb following transcranial direct current stimulation of primary motor cortex. Journal of Neurophysiology, 103(5), 2382–2389. Falcone, B., Coffman, B. A., Clark, V. P., & Parasuraman, R. (2012). Transcranial direct current stimulation augments perceptual sensitivity and 24-hour retention in a complex threat detection task. PloS One, 7(4), e34993. Falcone, M., Bernardo, L., Ashare, R. L., Hamilton, R., Faseyitan, O., McKee, S. A., … Lerman, C. (2016). Transcranial direct current brain stimulation increases ability to resist smoking. Brain Stimulation, 9(2), 191–196. Fregni, F., Liguori, P., Fecteau, S., Nitsche, M. A., Pascual-Leone, A., & Boggio, P. S. (2008). Cortical stimulation of the prefrontal cortex with transcranial direct current stimulation reduces cue-provoked smoking craving: a randomized, sham-controlled study. Journal of Clinical Psychiatry, 69(1), 32–40. Grundey, J., Thirugnanasambandam, N.,	Abbrevia

Device	Purpose	Type
	Kaminsky, K., Drees, A., Skwirba, A. C., Lang, N., … Nitsche, M. A. (2012). Neuroplasticity in cigarette smokers is altered under withdrawal and partially restituted by nicotine exposition. The Journal of Neuroscience, 32(12), 4156–4162. Hogarty, G. E., Flesher, S., Ulrich, R., Carter, M., Greenwald, D., Pogue-Geile, M., … others. (2004). Cognitive enhancement therapy for schizophrenia: effects of a 2-year randomized trial on cognition and behavior. Archives of General Psychiatry, 61(9), 866–876. Jacobson, L., Ezra, A., Berger, U., & Lavidor, M. (2012). Modulating oscillatory brain activity correlates of behavioral inhibition using transcranial direct current stimulation. Clinical Neurophysiology, 123(5), 979–984. Khoury, B., Lecomte, T., Gaudiano, B. A., & Paquin, K. (2013). Mindfulness interventions for psychosis: A meta-analysis. Schizophrenia Research, 150(1), 176–184. https://doi.org/10.1016/j.schres.2013.07.055 Witkiewitz K, Kirouac M, Frohe T, Armenta ML, McCallion E, Roos C, O'Sickey AJ, Brown D, Hunter M, Coffman BA, & Clark VP (2015). (2015). Mindfulness and Transcranial Direct Current Stimulation as an Intervention for Tobacco Dependence: A Pilot Study.	

2. **If applicable, identify each investigational device exemption (IDE) number:**

IDE Number	IDE Holder	Other Holder
There are no items to display		

3. **Attach files:** (attachments may include justification of risk determination, FDA correspondence and if the holder of the IDE is a University of Pittsburgh based, sponsor-investigator, attach both the FDA acknowledgement letter and approval letter)

	Document	Category	Date Modified	Document History
View	FDA Letter is same device.docx(0.02)	Device Attachment	4/22/2021	History
View	FDA_response_IDE_G150197_Version_0.01_Version_0.01.pdf(0.01)	Device Attachment	2/17/2021	History

4. * **Describe your plan to manage devices so that they will be used only on subjects and be used only by authorized investigators:**

tDCS will be administered by Drs. Conklin and Coffman and Research Coordinator Mr. Salkeld. Dr. Coffman has applied tDCS in previous research studies to a combined total of over 250 research subjects and Dr. Conklin and Mr. Salkeld have been trained by Dr. Coffman. The device will be stored in Dr. Conklin's personal office in a locked cabinet. Dr. Coffman will also train any additional research staff over the course of the 2-year study.

Click **Continue** as this page was intentionally left blank.

Recruitment Methods

* **Will you be recruiting individuals for participation in this study?**
● **Yes** ○ No

1. * **Describe who will be recruiting individuals for participation for this study:**
The research staff will be recruiting individuals for this research study.

2. * **Select all methods to be used for recruitment:**
Flyers/Posters or Brochures
Pitt+Me
Telephone scripts

3. * **Provide details on your recruitment methods:**
Pitt+Me will be utilized to recruit participants through the online portal. Eligible participants from Pitt+Me will then be contacted by research staff to undergo the telephone screen for further eligibility determination.

Interested respondents contact the office by telephone or are contacted by us from the information gained from Pitt+Me and are provided with a brief description of the study, including its purpose, research procedures, time involved to complete the study, and participant payments.

Telephone screen: We will ask a few short questions by telephone (screening tool attached) to determine whether the potential participant is a smoker and initially eligible to participate for the study and schedule the first visit. Forms for those who are not eligible will be shredded. No PHI will be collected if participant is found to be ineligible.

4. * **Describe all compensation/incentives offered to participants and timing of these offers:**
Participants will be compensated $20.00 per session, except for the two EEG visits, which they will be paid $50. At session 4 participants will be paid $20 plus $50 bonus for taking their pictures and continuing onto session 4. At session 10 (the last in person visit) they will receive $20.00 plus a $50 completion bonus. The participants will be paid $25.00 per visit for 2 follow-up visits that occur over the phone. Participants will also be reimbursed for public transit.

5. **Recruitment materials:** (attach all material to be seen or heard by subjects, including advertisements and scripts)

	Document	Category	Date Modified	Document History
View	AAT_tDCS study flyer updated phone.doc(0.03)	Recruitment Materials	3/2/2023	History
View	AAT_tDCS Craigslist Advertisement.docx(0.01)	Recruitment Materials	3/2/2023	History
View	Phone Screen(0.09)	Recruitment Materials	8/12/2022	History

Study Aims

1. * **Describe the purpose, specific aims, or objectives and state the hypotheses to be tested:**

Specific aims:

For decades addiction researchers have known that stimuli linked to smoking can evoke intense craving to smoke, but have failed to discover an effective means of reducing this persistent source of relapse risk.

Although nicotine replacement therapy reduces "abstinence-induced craving," brought on by nicotine withdrawal, it fails to decrease the intense craving evoked by exposure to smoking-related stimuli, or “cues." Smokers regularly report that cue-induced craving derails their quit attempts, and research shows that confrontation with one’s smoking cues in the natural environment increases the odds of lapsing and/or relapsing. However, past cue-exposure treatments (CET) to reduce cue reactivity (CR) consistently fail. Three clear CET methodological weakness likely drive that failure. First, CET traditionally includes only cues most closely linked to smoking, or proximal cues (e.g., lit cigarettes, lighters). We have repeatedly found that distal cues (i.e., people and environments) evoke more robust cue reactivity. A lit cigarette will make most smokers crave, but one’s smoking friends (people cue) or car on the way to work (environment cue) evoke much stronger craving and increase subsequent smoking. Reactivity is further enhanced when cues are combined. Yet, no CET has ever included these personal cues. Second, CET involves passive cue exposure. Smokers are repeatedly exposed to proximal cues while refraining from smoking until their CR diminishes. Although rooted in animal drug extinction studies, this method does not translate well to the cue-rich experience of human smokers or prepare them to encounter the panoply of smoking triggers in their daily lives. Thus, CET’s failure is not surprising, and it will continue to fail until personal cues are targeted and smokers are trained to actively reject their well engrained approach tendency to such cues. The Approach/Avoidance task (AAT), is an active behavioral method of cue re-training involving pushing away (rejecting) stimuli during exposure. This method engages the dorsolateral prefrontal cortex (PFC), a region of the brain linked to cognitive control over drug use decisions and motivations, making it an excellent candidate for our third CET improvement; namely brain stimulation to bolster cue re-training. Transcranial Direct Current Stimulation (tDCS) is a non-invasive means of increasing excitability in cortical brain regions. tDCS targeting the PFC has shown encouraging results in reducing smoking CR as a standalone treatment; however, studies of other disorders suggest greater efficacy when it is combined with a behavioral task that engages the same brain region being stimulated. Thus, combining PFC-targeted tDCS with AAT cue re-training, should provide a synergistically robust means of reducing smokers’ CR to personal smoking cues. We hypothesize that AAT and tDCS applied to the dlPFC will each attenuate smokers’ reactivity to personal combined smoking cues, indexed as cue-induced craving, smoking topography, and attentional bias (behavioral Stroop and neurophysiological EEG), and that the combination of AAT+tDCS will prove synergistically effective. We will also examine the impact of these methods on quit intention and confidence in quitting and reduction in cigarettes per day (cig/day) from pre-post training, and at 2 follow ups. We will explore sex and other individual differences as moderators of this new CET’s efficacy. Eighty high treatment-interest smokers will receive one of four training conditions: AAT+tDCS, AAT+sham tDCS, Active control (AC)+ tDCS, or AC+sham tDCS. Baseline assessment and re-test of reactivity variables will occur following 5 AAT/tDCS sessions of personal combined-cue exposure, with follow-up assessments of cig/day, intent and confidence to quit at 1 week and 1-month post-training.

Our specific goals are:

Aim 1: Determine the effectiveness of AAT and tDCS to attenuate cue-induced

craving and attentional bias to personal smoking stimuli. AAT, tDCS, and combined AAT + tDCS will each lead to greater
reductions in pre-post training cue-induced craving and improved behavioral (quicker reaction time) and neurophysiological (lower P300 ERP) measures of attentional bias for smoking cues over the control condition.
Aim 2: Determine the effectiveness of AAT and tDCS to reduce cue-provoked smoking behavior and daily smoking, and to increase intent and confidence to quit. AAT, tDCS, and combined AAT + tDCS will
each lead to greater pre-post-training reductions in smoking topography measures (latency to light & puff volume) assessed during cue exposure, as well as reduced cigs/day and increased confidence and intent to
quit from pre-training to post-training and 1-week & 1-month follow-up over the control condition.
Aim 3: Examine if changes in reactivity to smoking-related cues (Aim 1) are associated with posttraining reductions in smoking topography and/or cig/day and increases in intent and confidence to quit. (Aim 2). Reduced craving and attentional bias to smoking stimuli across all groups will be associated with reductions in smoking topography post-training, as well as post-training and follow-up changes in cigs/day and confidence and intent to quit Secondary Aim: Explore sex and other individual differences as moderators of outcome measures to explore who might benefit most from AAT and tDCS methods.
There have been few recent innovative approaches for alleviating cue-induced craving to smoke. AAT and tDCS are two promising methods to newly apply to this endeavor. Although this exploratory work is not fully powered to detect significant interaction effects of AAT and tDCS, we will examine the size of the interaction to inform potential efficacy trials of combined AAT + tDCS vs the individual therapies alone. The results here will thus guide a future RCT of novel CET methodology within a cessation trial aimed at helping more smokers stay quit.

2. * **Describe the relevant prior experience and gaps in current knowledge including preliminary data. Provide for the scientific or scholarly background for, rationale for, and significance of the research based on existing literature and how it will add to existing knowledge:**
SIGNIFICANCE
Obstacles to quitting smoking. Smoking accounts for upwards of 400,000 annual deaths in the U.S. alone.1 Most current smokers report a desire to quit, but cessation rates with any treatment rarely exceed 30%.
Cessation failure is often attributed to abstinence-induced craving during nicotine withdrawal. However, studies of nicotine replacement therapy (NRT) show that even when smokers are given nicotine at levels comparable to smoking, over 70% still relapse. Thus factors other than the pharmacological effects of nicotine clearly play a crucial role in smoking behavior. One such factor, frequently studied but not well understood, is reactivity to smoking cues. Considerable research demonstrates that stimuli present during smoking gain associative properties, which when later encountered in the absence of drug reinforcement (e.g., nicotine) induce robust urge to smoke (i.e. cue-induced craving). Recent cue reactivity (CR) studies show that cue-induced craving predicts immediate subsequent smoking, as well as speed and volume of actual smoking. Unlike abstinence based craving, cue-induced craving and smoking is not reduced with nicotine replacement and can continue long after physiological nicotine withdrawal abates. Moreover, smokers report that smoking-related cues are a vital aspect of their difficulty or inability to stay quit,15 making it even more unfortunate that, to date, no efficacious treatment exists to attenuate this unrelenting source of relapse risk.
New methods to reduce cue-induced reactivity. If reactivity to smoking-related cues is a factor driving craving and inhibiting a smoker's ability to stay quit, then, as many researcher purport, extinguishing CR through
repeated unreinforced exposure to smoking cues (i.e., cue exposure treatment; CET) should increase cessation success. However, traditional CET-based treatments have consistently failed to attenuate CR or increase smoking cessation rates. To improve CET, researchers have suggested that, given the link between cognition, craving, and relapse, cue-based treatments should focus on training

cognitive control to reduce cue reactivity. Moreover, empirical evaluation of past CET studies by us and others provide additional direction on promising ways to improve CET. Thus, we have identified three key reasons for past CET failure, as well as three techniques, exploiting new technology, to remedy CET.

1) Targeting just proximal cues is not adequate. Regardless of drug or cue presentation mode (e.g., pictorial, in vivo), the majority of CR studies and CETs have targeted smokers' reactivity to proximal cues, cues most closely linked to actual drug administration (e.g., cigarettes, lighter). However, our research clearly shows that distal stimuli present during smoking also gain associative control over craving. Specifically, the
actual environments and people in a smoker's life, through repeated pairing with smoking, can alone, in the absence of proximal cues, trigger strong cue-induced craving, and immediate smoking. When exposed to pictures of their personal smoking and nonsmoking environments, as well as standard smoking and nonsmoking environments, personalized smoking environments significantly enhanced smokers' self-reported craving over all other cue combinations. In another study, viewing personal smoking environments increased BOLD signal in multiple brain regions associated with craving to smoke, corresponding to higher self-report cue-induced craving ($F(2,180)=18.32$, $p<.0001$). Yet another study using pictures of smokers' friends and acquaintances around whom they do or do not smoke revealed both enhanced craving to pictures of smoking related people, and a significant inhibitory response on craving to people around whom they do not smoke. Most recently, we found that combining proximal and personal environment smoking cues, led to the greatest increase in cue-induced craving and smoking topography (indexed as latency to light, # of puffs, and puff volume during cue exposure). Thus, CET incorporating only proximal cues and standard, not personal, stimuli fails to capture the multitude of cues that bring about smokers' strongest cue-induced craving and actual smoking behavior. As noted by even the earliest researchers of extinction training, in order to adequately
reduce reactivity to cues, the cues targeted must be those that evoke the strongest reactivity. Our past work suggests that combining multiple personalized cue types lead to the greatest increases in cue-induced craving and smoking. These cues must be targeted in any treatment adjunct aimed at attenuating smokers' cue reactivity.

2) New learning requires more than just unreinforced exposure. Most CETs involve passive exposure to cues while repeatedly refraining from smoking. However, active re-training may prove much more effective in reducing CR. The approach/avoidance task (AAT) specifically targets attentional biases toward visual stimuli. The AAT, by which smokers actively push away or pull in pictorial stimuli with a joystick, can reduce reactivity to smoking stimuli, specifically attentional bias, as well as daily smoking. This
approach/avoidance retraining method is based on cognitive embodiment theories, which have demonstrated the effects of motor actions on cognition. Arm movements during AAT activate motivational systems in the brain: Arm flexion (approach behavior) activates a reward motivation system, whereas arm extension (avoidance behavior) activates a motivational system involved in processing possible threats. Avoidance behaviors call for vigilance and controlled action. Because of this repeated association, avoidance behaviors may lead to greater recruitment of resources. Repeated exposure to smoking-related stimuli while smoking strengthens appetitive responses, which leads to the development of automatic approach tendencies, most often indexed as attentional
bias, to smoking-related cues. Smokers demonstrate a strong approach bias toward smoking stimuli that is not present in ex-smokers, a bias which has been implicated in the maintenance of smoking behavior and
likelihood of relapse. Neurologically, regulated avoidance responses during AAT (e.g., smokers avoiding smoking stimuli) leads to stronger activation in the dorsolateral prefrontal cortex (DLPFC) indexed as lower
deoxygenated hemoglobin (HHb).37 Thus, AAT re-training may alter implicit attitudes toward smoking by dynamically engaging DLPFC and increasing cognitive control during exposure to smoking-related cues.38

Further, although AAT has not been tested as a method of reducing cue-induced

craving, it has been shown reduce attentional bias to smoking stimuli and decrease daily smoking. Studies that included a follow-up
found sustained smoking reduction at 1-month and 3-months post-AAT training. Thus, multiple exposures that involve active re-training of motor responses to cues (executing an avoidance response by pushing smoking
stimuli away and an approach response by pulling in stimuli that inhibit craving) should activate the PFC and result in cognitive-control-mediated changes in CR (reduced craving and smoking). This more active and robust extinction training should better generalize to decision making when faced with personal smoking cues.

3) Non-invasive brain stimulation to bolster new learning. Transcranial Direct Current Stimulation (tDCS), is a safe, non-invasive method of brain stimulation that can enhance cortical excitability and help attenuate cue-induced craving. Animal studies show clear neurophysiological effects of tDCS, where anodal tDCS enhances and cathodal tDCS reduces neuronal excitability. Human pharmacological studies confirm these results. Thus, tDCS has become increasingly popular in clinical and neurocognitive research with known neurobiological targets, showing promising efficacy in reducing drug craving, auditory hallucinations in schizophrenia, depression, Parkinson's disease, stroke, and cognitive enhancement in healthy subjects. tDCS of the prefrontal cortex (PFC) reduces cue-induced craving and daily smoking by improving decision-making and cognitive control. Most important to note, although effective as a standalone treatment for reducing cue-induced craving, the effects of tDCS are greatly enhanced when stimulation is paired with tasks that engage the brain processes that underlie the targeted behavior. Thus, we purport that AAT during cue exposure, which engages the dlPFC, is a prime candidate for augmentation with PFC-targeted tDCS. Enhanced excitability in PFC during AAT should improve ability to dynamically recruit
cognitive control systems during avoidance behaviors, aiding in the retraining of smoking-related cue valence. Thus, effects of AAT+tDCS on CR to smoking cues and behavior should be synergistically more effective.

The decision to target PFC comes from its repeated implication as a key seat of cognitive control over craving, particularly cue-induced raving. Although several brain regions, notably the ventral striatum (VS),obitofrontal cortex (OFC), and anterior cingulate cortex (AAC) are
activated during exposure to drug cues, particularly during cost/value assessments, the PFC is hypothesized to combine these
valuations with other information, such as drug context/availability and prior outcomes. Imaging studies reveal that VS activation during cue exposure increases craving, and activation of the PFC during cue exposure downregulates the VS resulting in attenuation of craving Studies of PFC-targeted tDCS further support this link. In three studies of non-quitting smokers (randomized to active or sham for 1-5 days), stimulation of dorsolateral PFC (dlFPC) led to dose-dependent reductions in cue-induced craving and daily smoking (i.e. effectiveness increased with number of sessions, 30% fewer cigs/day). tDCS also enhances ability to resist the urge to smoke. In our recent study, weekly group sessions of 30min of Mindfulness + tDCS (targeting rPFC), followed by 60min of Mindfulness + counseling led to a significant 50% reduction in cig/day at the end of treatment (d=0.50), with individuals reporting greater control over craving after treatment. Given our focus on attenuating cue reactivity here, we will include AAT, not mindfulness. In AAT, avoidance behaviors have been shown to signal the recruitment of cognitive control centers in dlPFC, a likely component in its effectiveness. Thus, enhancement of dlPFC excitability with tDCS, and retraining approach/avoid biases to one's most salient personal smoking cues, are both promising methods that target PFC activation, and their combination may further enhance reductions in smokers' cue reactivity and other outcome measures. Of note: Studies have examined left or right dlPFC as a stimulation target, with one study comparing both, with no difference as a function of lateralization. We propose right side stimulation based on our past success targeting right PFC. tDCS, Attention, and Craving in alcohol and food: Aside from the smoking studies reviewed above, a few
studies on the impact of tDCS on attentional bias and craving for food and alcohol cues are worth noting. These studies found largely null results, albeit with methods

starkly different than those proposed here. Further, CR
varies by drug/substance of choice, with reactivity to alcohol and food cues being notably less robust and less affected by the same manipulations as smoking. One alcohol study, found no effect of 1 weekly tDCS session
for 4 weeks on attentional bias and craving in college drinkers, and three others, also using limited tDCS, showed no changes in attentional bias, but revealed craving reductions. One food study found null results after 1 tDCS + cognitive modification session to reduce chocolate craving. Smoking tDCS studies suggest that multiple sessions closely spaced increase efficacy, thus we propose 5 closely spaced sessions of tDCS during personal smoking cue exposure. No studies have used personal cues from participants lives, pre-post cue reactivity assessment of craving and behavior, or highly dependent individuals. No studies, including smoking, have examined combined tDCS + AAT. Thus, although the proposed work is high risk, past null findings across other substances using generic cues and focusing on attentional bias do not predict null effects here, rather extensive past work on each of our included components and strong theory behind combining tDCS + AAT suggest potential for high reward. Assessing the impact of novel CET on smoking-related outcome measures. Attentional Bias. Smokers demonstrate selective attention to smoking-related stimuli. and delayed reaction time (RT) during exposure to smoking cues. They are slower than controls to color-name smoking-related words in a modified Stroop task, which combines common words with intermittent presentation of smoking-related words. Smokers maintain their gaze on smoking stimuli longer than neutral stimuli, and show increased P300 response to smoking-related cues. The smoking-cue P300 is thought to reflect attentional and motivational state of smokers when cues prime smokers' urge to smoke. According to incentive-sensitization theory, these biases likely emerge from the motivational and attention-grabbing properties of smoking cues, which gain salience after repeated pairing with smoking. This causes sensitization of dopamine neurotransmission in the striatum increasing the salience of the stimuli long-term and resulting in greater allocation of attentional resources (attentional bias) and increases in
craving. Abstinent smokers with greater attentional bias to smoking stimuli are more likely to relapse, reducing this response may aid cessation. In our pilot studies, we assessed attentional bias behaviorally and using EEG,
in a forced-choice RT task and found a decreased RT difference between smoking and neutral stimuli of 60% ($p<0.05$) following tDCS. We also show that tDCS of right dlPFC using the same montage proposed here
(N=8) reduced the P300 difference between smoking and nonsmoking images compared to sham tDCS (N=8) in smokers with long-term/chronic schizophrenia (Figure 2). In the proposed study, we anticipate that AAT and
tDCS training will reduce approach bias indexed as decreased RT and P300 amplitude difference between smoking and neutral images from baseline to re-test during a modified smoking Stroop task. Cue-Induced Craving and Smoking. As noted above, smokers report that smoking cues are a major obstacle to quitting and multiple studies have demonstrated robust cue-induced craving,cue-induced smoking behavior, and a strong link between the two. Our procedures to personalize cues, present them in combination, and assess smokers' self-report and behavioral CR creates an ideal environment to develop and test novel CET methodology. Although the combination of AAT + tDCS has not been assessed for reduction of cue-induced reactivity (craving or smoking topography), research on these two procedures independently have
examined AAT effects on attentional bias and daily smoking, and tDCS effects on cue-provoked craving and daily smoking, with mixed but largely positive effects. Given that tDCS is known to be more effective when it is
used while engaging the neural processes targeted for change, we anticipate that combining AAT + tDCS during cue exposure may further enhance reduction in cue-induced craving and smoking topography (latency & puff volume) to combined personal smoking cues (proximal, environment, and people) as measured at baseline and re-testing after 5 sessions of training. Daily smoking (cigs/day) and Intent and Confidence to quit. Both AAT and tDCS have independently shown efficacy in reducing daily smoking among non-quitting smokers with high treatment

interest. We anticipate similar results here, as well as reductions in cue-induced craving and smoking topography. Given that tDCS should enhance AAT learning, we also anticipate that AAT+tDCS may further reduce in these measures. We will also examine potential increases in Intent and Confidence to quit, the former shown to increase with AAT training and both previously associated with quit initiation and ability to abstain. These three measures will be assessed pre-post training and, to examine more prolonged effects, at 1-week and 1-month post-training. Sex and individual differences. Although past cue reactivity, AAT, and tDCS work has not revealed sex differences across outcome variables, we will specifically recruit equal numbers of male and female smokers to determine if sex, as well as other individual differences (e.g., age, FTND, years smoking) moderate AAT/tDCS efficacy on our more comprehensive set of outcomes, and thereby offer new information about for whom our novel methods may work best as a smoking treatment.

INNOVATION.

The proposed study will be the first active and sham-controlled test of AATand tDCS during personalized multi-cue exposure to attenuate several indices of smoking-related cue reactivity and behavior. Several aspects of this exploratory/developmental study are highly innovative. 1) AAT: Although recommended, AAT effects on cue-induced craving have surprisingly not been formally studied. Past AAT smoking cue studies reveal promising effects for AAT on measures of daily smoking and attentional bias, but have not examined cue-induced craving. Likewise, no AAT studies have included neuropsychological measurement of attentional bias (EEG) or changes in cue-induced smoking topography (latency to light, puff volume). 2) tDCS: tDCS applied to the dlPFC can reduce reactivity to proximal smoking cues (cigarettes, lighters) and can reduce daily smoking in non-quitting smokers. This will be the first assessment of dlPCF-targeted tDCS effects on smoking attentional bias (Stroop and EEG), craving to personal cues, and cue-induced smoking topography. 3) Combining AAT + tDCS: No studies have examined combined AAT+tDCS on smoking CR, attentional measures or smoking behavior. Given that tDCS is known to be more effective when used while engaging the faculty targeted for change we anticipate combined AAT+ tDCS targeting dlPFC will have a synergistic effect on our comprehensive index of reactivity measures to combined personal smoking cues, as well as daily smoking and intent and confidence to quit. Our 2 x 2 design allows us to examine AAT and tDCS independently across multiple new outcome variables, as well as the combined impact of these two methods. 4) Multiple Personal Cues Exposure: CET should be most effective when cues evoke smokers' strongest reactivity and capture key elements of the original contexts of learning. The proposed study will be the first to incorporate all cue types (people, places and objects) during CET to target numerous specific stimuli that trigger each smoker's strongest urges to smoke. Multiple exposures to real world cue re-creations should enhance the generalizability of training outside of sessions, a purported shortcoming of past CETs, and allow us to capture smokers' most salient cues without the inherent difficulties of conducting real world exposures.

Study Design

1. **Total number of subjects to be enrolled at this site (enter -1 for chart reviews, banking, registries):**
   160

2. **Describe and explain the study design:**
   Study Design and Procedures. Eighty (male=40, female=40) high treatment-interest daily smokers age 26-55 will be recruited from the local Pittsburgh community. As noted, past work has not revealed sex differences in CR, AAT, or tDCS training outcomes with smokers, but we will examine sex differences here. Participants will be screened via telephone interview, and again in person, for multiple measures including level of quit interest, assessed by asking subjects if they intend to quit smoking in the next 1, 3, 6, 12 months, longer, or never. Using a 2 x 2 design we will examine AAT (AAT, active control [AC]) X tDCS (active, sham) to reduce cue-induced craving and smoking topography, and attenuate behavioral and neurophysiological measures of attentional bias to combined personal smoking cues. We will also determine the impact of this novel CET methodology on daily smoking, intent and confidence to quit, and explore sex and other individual differences in the efficacy. Eligible participants will come to the laboratory and complete informed consent and further screening, including vision screening for sensory deficits that may affect cue reactivity and/or EEG testing, re-assessment of treatment interest and completion of forms. Participants will also undergo the semi-structured interview to identify the places of which to take pictures, and complete camera practice. After initial screening, participants will be randomized to one of the 4 groups (stratified by sex & age). Dropouts will be replaced but examined by AAT/tDCS group to assess tolerability. Groups include: 1) AAT + active (2.0 mA) tDCS, 2) AAT + sham (0.01 mA), 3) active control (AC) + active tDCS, or 4) AC + sham. Participants will participate in AAT/tDCS intervention sessions for 5 days over 3 weeks, but the over all study will be 10 visits total similar to our tDCS/schizophrenia study (DA0417742), and that by Mattai et al. Cue-induced craving, smoking topography, and attentional bias (reaction time & ERPs), as well as cigs/day intent to quit90 and confidence in quitting91 will be assessed at Week 1 Baseline sessions 1 & 2 and Re-test sessions 9 & 10 during Week 3. Cigs/day, intent and confidence to quit will be re-assessed during follow-up phone calls 1-week and 1-month post-training

3. **Describe the primary and secondary study endpoints:**
   Primary:

   1.Cue Reactivity to personal cues, baseline to post treatment. Attenuation of reactivity to smoking-related cues will be a primary outcome variables for this study. The measures include self-reported cue induced craving, smoking topography measures of latency to light and puff volume, as well as attentional bias measures of reaction time and ERPs to smoking stimuli.
   2. Daily Smoking, baseline to post-training and follow up. To examine the impact of AAT + tDCS on daily smoking we will assess each participant's pre- and post-training daily smoking, indexed as cigs/day.We will then re-assess average cigs/per day via follow-up phone call assessments at 2 time points (1-week and 1-month post training).
   3. Intent and confidence to quit, Baseline to Post-treatment and follow-up. Participant ratings of Intent to Quit and Confidence to quit will be assessed at baseline and end of treatment to determine if AAT/ tDCS training has a measurable impact on these smoking cessation related measures. To examine prolonged effects of AAT / tDCS, they we be re-assessed at 1-week and 1-month post-training via follow-up phone call assessments.
   Secondary:
   Sex and Individual Differences, Baseline to Post-training and follow up. Secondary

analyses will probe whether sex and other individual difference variables (e.g.,FTND, age) moderate the effect of experimental group on cue-induced craving and attentional bias, smoking topography, daily cig/day and intent & confidence to quit.

4. **Provide a description of the following study timelines:**

Duration of an individual subject's active participation:
Approx 2 months
Duration anticipated to enroll all subjects:
Approx 19 months
Estimated date for the investigator to complete this study (complete primary analyses):
4/28/2023

5. **List the inclusion criteria:**
Inclusion Criteria:
-Between the ages of 22 & 65
-Ability to provide written informed consent
-Smoke ≥ 5 cigarettes per day
-Expired breath CO ≥ 5 ppm at screening
-Ability to attend 10 sessions over a 3-week period, and complete 2 follow-up phone assessments

6. **List the exclusion criteria:**
Exclusion Criteria:
-Implanted cardiac or brain medical devices
-History of epilepsy or current seizure disorder
-History of brain surgery or skull fracture
-History of a head trauma (losing consciousness >10 min and/or problems with speech or movement because of head injury)
-Latex allergy
-Scalp irritation
-History of diabetes that caused loss of consciousness (>10 min) or weakness in your arms or legs
-History of ECT (electroconvulsive therapy) in the last 5 years
-Current use of dextromethorphan
-Diagnosed with or undergone treatment for alcohol or substance dependence past 3 months
-Uncorrected vision deficit
-Colorblindness
-Use of tobacco products other than commercially available cigarettes

7. **Will children or any gender, racial or ethnic subgroups be explicitly excluded from participation?**
● **Yes** ○ No

* **Identify the subgroups and provide a justification:**
Children, individuals defined as under the age of 18, will not be included as it is illegal to sell cigarettes to minors in Pennsylvania. The safety and efficacy of tDCS has not been tested in pediatric smokers, and standard doses have not been established.

8. **Describe the power analysis used and cite your method of statistical analysis. If a power analysis is not possible, thoroughly justify the sample size required for the study, including appropriate literature citation (alternatively provide page reference in attached protocol):**
Statistical design and power
This study uses a 2 x 2 AAT (AAT, active control[AC]) x tDCS (tDCS, sham tDCS) design to assess prepost training changes in cue-induced craving and smoking

topography (latency to light and puff volume during cue exposure) and attentional bias (reaction time and ERPs) to smoking-related cues, as well as daily smoking (cigarettes per day) and confidence and intent to quit. The primary analyses (Aims 1 and 2) will be evaluated via repeated measures multivariate analysis of covariance (RM-ANCOVA) and will test the main effects of AAT, tDCS, and their interaction on measures of craving, reaction time, P300 amplitude, controlling for baseline levels as covariates (Aim 1). This process will be repeated for Aim 2, where MANCOVA will test effects on latency to smoke, total puff volume, and cigs/day. An additional 2x2x3 repeated measures (RM-) MANCOVA will test group differences in cig/day and intent & confidence to quit
across time points (post-training, 1-week, and 1-month). For Aim 3, regression analysis will be used to examine if attenuation of cue-induced craving and attentional bias measures predict reductions in smoking
topography and daily smoking and elevations in intention to quit and confidence to quit, while controlling for baseline levels of these variables. Exploratory analyses will probe whether sex and other individual differences (e.g., age, FTND) moderate the effects of AAT/tDCS training on all outcome variables.
Power is based on n=20 high treatment-interest smokers per group, with 4 experimental groups. Drop outs
in this experimental study will be replaced. We will examine differential group dropout to assess tolerability of methods. Limited past work leads us to constrain our power analysis to AAT and/or tDCS for each variable, but we expect the synergistic effects of combined AAT + tDCS to be even greater, making these power analyses conservative. However, this exploratory work is not fully powered to detect significant interaction effects. Aim 1. Craving and Attentional bias. Assuming a Cohen's d effect size (ES) of 1.02- 1.57 based on prior literature, a multivariate α = .05, and an R2 of .3 from other covariates in the model, we expect to have greater than 0.99 power to detect main effects of tDCS on cue-induced craving. Boggio et al.41 found an ES of d=1.13 for reduction in cue-induced craving via tDCS. Our pilot P300 EEG data from our current study in smokers with schizophrenia shows ES of d=1.3. AAT work indicates post-training
attentional approach bias reductions to smoking cues of d=1.2629, thus we expect greater than .80 power to detect changes in attentional bias. Aim 2. Smoking topography and cig/day. Based on our past cue studies, smoking topography to multiple cues are of similar magnitude to cue-induced craving (d=.90). Further, past tDCS studies of daily smoking outcome show an ES of 0.58100. Thus, with a multivariate of α=.05, 20 subjects per group, and an R2 of .3, we expect greater than 0.84 power to detect an effect of tDCS on smoking behavior in both the MANCOVA assessing immediate effects on smoking behavior and the RM-MANCOVA assessing longitudinal effects on cig/day and intent & confidence to quit. Again, tDCS
+ AAT should enhance effects. Aim 3. Smoking prediction. Assuming α=0.17 (conservative adjustment for 3 outcome variables) and controlling for other variables contributing an R2 of .3, we will have power greater than .99 to detect an R2 of 0.2422 or larger, in the model predicting smoking topography and cig/day from cue-induced craving and attentional bias change scores.

Research Activities

1. * **Provide a detailed description of all research activities (including screening and follow-up procedures) that will be performed for the purpose of this research study. This description of activities should be complete and of sufficient detail to permit an assessment of associated risks.**
The PI, Co-I's and Research Coordinators will be responsible for carrying out all the research activities.
Visit 1: During this visit we will explain the study and all its procedures with the potential participant. If he/she agrees to participate and signs the consent we will move forward with visit 1 procedures. A carbon monoxide (CO) level will be measured by giving a breath sample using our breath CO monitor. If the participants CO level is below 8 ppm they will not be able to continue with the study and will be paid for today's visit and excused from the study.
The participant will complete the following forms:

•Smoking History: This form will ask questions about the participant and their smoking history and will also assess the participant's level of nicotine dependence.
•Quit Interest: This is a questionnaire for evaluating the participant's interest in quitting smoking.
•Intent to Quit: This measures the participant's degree of intention to quit smoking.
•Confidence in Quitting: This questionnaire assesses the participant's confidence in quitting smoking.

Next, we will identify personal smoking and non-smoking cues of places. The participant will go through a brief interview during which we will identify places in which they regularly smoke or do not smoke. We will lend them a camera and teach them how to take pictures before the next visit. The participant will take pictures of their top 4 places that are 'smoking cues' and 4 places 'non-smoking cues' from various angles. We ask that they don't take pictures of people (passers-by or any other friends/family in the pictures) or personal identifiers (license plates, street names, etc.) to protect privacy. The participant will bring the camera containing the pictures back with them to the second session during which time they will be checked to make sure they took the correct pictures identified and that they will work for the presentation program used in the study. If they do not the participant will be instructed to take more pictures to bring with them at the next scheduled visit. Participants will be advised that they must not send any images that are considered distasteful, obscene, implicate legal action.

The participant will return the lent camera containing the pictures when they come back for the next study visit. We will also have the participant complete a brief vision test during this visit. They will stand 10 feet from an eye chart, identify and read out loud the line they can see most comfortably.
•The participant will be randomly assigned to one of four groups:
1. AAT + tDCS
2. AAT + sham tDCS
3. AC + tDCS
4. AC + sham tDCS
The components of these groups are defined as:
•Approach/Avoidance Task (AAT): The participant will use a joystick to push and pull images in different directions on a computer screen.
•Transcranial Direct Current Stimulation (tDCS): is used to slightly change the way the brain works for a short time. One wet, thin sponge is placed on the participants head and another wet thin sponge is placed on their arm and connected to electrodes which will deliver a very weak electrical current. Before stimulation, their head and arm will be checked for any redness, irritation, or recent shaving of the head. If any of these are seen, we will exclude them from the study. Some participants may feel a slight painless tingling as the current begins, but the tingling should go away after a short time. tDCS will be given at 2.0 mA and stimulate the

dorsolateral PFC (dlFPC) the sham tDCS will be given at 0.01 mA. We will ask the participant at the beginning of and throughout the stimulation to report how much tingling they are feeling on a scale of 1 being “not at all” and 10 being “extreme”. If at any point they are experiencing extreme discomfort, we will end the stimulation.
•Active Control (AC): The participant will assess the orientation of a picture and indicate it with a key press.
•Sham tDCS: Two wet, thin sponges are placed on the participants head and arm and the sponges will be connected to electrodes just as the actual tDCS but they will not deliver any electrical current.

Visits 2 and 9: During this visit the participant will have an attentional bias assessment while undergoing an electroencephalography (EEG).
•Attentional-Bias: You will be seated in front of a computer with a four-button color response box. Four different word lists of 15 words each will be presented in a random order with no repeats. For each trial, a cross appears in the center of the screen followed by one word from the list in one of four colors. You will press the button that matches the color in which the word appears.
•EEG: The EEG allows us to measure electrical activity of the participants brain. A cap containing sensors will be placed on their head. In addition, sensors will be placed behind the ears, and on the tip of the nose. Gel will be inserted into the cap to connect the sensors to the scalp. The participant will not feel any sensations from these electrodes. While wearing the cap, they will complete the attentional bias training. Afterwards, we will clean as much of the gel from their scalp as possible.
•Cue-reactivity: Cue reactivity involves viewing pictures of the participants personal smoking-related and non-smoking-related pictures and rating how they felt while viewing those pictures. The pictures and the ratings are presented on a computer and some pictures will be projected on the wall.

Visits 3 and 10: During these visits the participant will complete cue-reactivity to their personal smoking and non-smoking cues and smoke cigarettes using a special cigarette holder that will measure how they smoke their cigarette. The participant will be given special instructions on how to light the cigarette and place it into the holder before they smoke. They will be seated comfortably in front of a large computer monitor and view 12 picture trials. Each picture trial will be followed by post-trial ratings. After all the picture trials, a screen will appear informing them that when pictures begin to appear again they may smoke (using the cigarette holder) as much or little as they like, or not smoke at all, it is up to them and watch the pictures. At any point while viewing these pictures they may start or stop smoking.

Visits 4-8: During these visits the participant will go through cue-reactivity while either doing AAT while receiving tDCS (Group 1), doing AAT while receiving sham tDCS (Group 2), doing AC while receiving tDCS (Group 3), or doing AC while receiving sham tDCS (Group 4). The participant will not specifically know which group they are in.

Follow-up: We will call the participants at 1-week and 1-month after visit 10 and ask them how many cigarettes per day they are smoking and ask them the intent and confidence to quit questionnaires.

2. Upload a copy of all materials used to collect data about subjects: (Attach all surveys, interview/focus group scripts, and data collection forms except for case report forms, SCID or KSADS):

	Document	Category	Date Modified	Document History
View	Environment Listing Sheet(2)	Data Collection	3/2/2023	History
View	AAT_tDCS Study Calendar Handout.docx(0.02)	Data Collection	5/23/2022	History
View	BIDR-IM.doc(0.01)	Data Collection	5/17/2022	History

	Document	Category	Date Modified	Document History
View	Smoking Environment Places Interview Sheet.doc(0.01)	Data Collection	5/17/2022	History
View	Non Smoking Environment Places Interview Sheet.doc(0.01)	Data Collection	5/17/2022	History
View	Smoking History Form(0.01)	Data Collection	3/15/2021	History
View	Intent Ladder(0.01)	Data Collection	3/15/2021	History
View	Intent to Quit(0.01)	Data Collection	3/15/2021	History

3. * **Will blood samples be obtained for research purposes?**

○ Yes ● **No**

Consent Process

Enter N/A in response to the following questions if a Waiver of Consent is requested for all research activities or if no subjects are being enrolled.

1. * **Indicate where the consent process will take place and at what point consent will be obtained:**
Informed consent will take place at Session 1 in Dr. Conklin's laboratory on the 16th floor of the Department of Psychiatry at Western Psychiatric Hospital after the subject has been telephone screened. The informed consent process is a concerted effort between Dr. Tyagi and either Dr. Conklin, and/or the research coordinator. The potential participant is addressed in a private room and the most current IRB-approved informed consent form is reviewed point by point with either Dr. Conklin, and/or the research coordinator. All aspects of the study are explained, including but not limited to the nature of the study, its purpose and associated procedures, the expected duration, and the potential risks of participation. In addition, the subject is informed about the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. The opportunity for questions is given at various times. Following this explanation, we will zoom video or phone call (phone call will only occur if Dr. Tyagi isn't currently available to zoom call) with our licensed physician co-investigator, Dr. Tyagi, (whose office is in Montefiore Hospital) at which point the participant will be able to have any further questions or concerns about the study and the device used addressed by Dr. Tyagi. Once all questions are satisfactorily addressed, the participant signs the consent form and we will scan the signed consent form to Dr. Tyagi. Dr. Tyagi will print, sign and then scan the consent with both signatures back to us. We will print the signed consent form to file and the participant will be given a copy, as well. Once both the participant and Dr. Tyagi have signed the consent form and we receive the scanned copy back from Dr. Tyagi we will begin research procedures. No research activities will begin until both the subject and the licensed physician Co-I signed the consent form. This entire process will be documented in the participant's research chart.

2. * **Describe the steps that will be taken to minimize coercion and undue influence, including assurance that there is sufficient time for subjects to make an informed decision:**
The consent process will include a short summary of the study commitment, an in-depth explanation and breakdown of each visit, the purpose of the study, the risks involved and our duty to the research participants, as detailed in the attached consent form. The voluntary nature of the study will be emphasized.

3. **For studies that involve multiple visits, describe the process to ensure ongoing consent:**
At the beginning of each visit the participant will be asked if they have any new questions or concerns regarding the study and their participation and also be told about any new information about the study to ensure they are completely informed and want to continue in the study. Subjects active at the time of approval of MOD 003 will be reconsented.

4. * **Steps to be taken to ensure the subjects' understanding:**
A brief explanation of the study will be given on the telephone screening call.
Dr. Tyagi will review and answer any additional questions the subject may have after the Co-I's/research coordinator's explanation to ensure her understanding. The participant will be given as much time as needed to think about participating.

5. * **Are you requesting an exception to the IRB policy related to the informed consent process:**

○ Yes ● **No**

Consent Forms

1. **Consent Forms:**

	Document	Category	Date Modified	Document History
View	Consent Form(0.15)	Consent Form	9/19/2023	History

Refer to the following templates and instructional documents:

- Guidance - Consent Wording
- Template - Consent Document - Short Form
- HRP-090 - SOP - Informed Consent Process for Research
- HRP-091 - SOP - Written Documentation of Consent

Electronic Data Management

1. * **Will only anonymous data be collected (select NO if identifiers will be recorded at anytime during the conduct of the study)?**
   ○ Yes ● No

Select all identifiers to be collected during any phase of the research including screening:

Name:	☑	**Internet Protocol (IP) Address:**	☐
E-mail address:	☑	**Web Universal Resource Locators (URLs):**	☐
Social security #:	☐	**Social security # (for Vincent payment only):**	☑
Phone/Fax #:	☑	**Full face photo images or comparable images:**	☐
Account #:	☐	**Health plan beneficiary #:**	☐
Medical record #:	☐	**Device identifiers/serial numbers:**	☐
Certificate/license #:	☐	**Vehicle identifiers/serial #/license plate #:**	☐
		Biometric identifiers, finger and voice prints:	☐

* **a: Will you be collecting any of the following location data: geographic subdivisions smaller than a State such as street address, city, county, precinct, zip, geocodes, etc.?** ● Yes ○ No

* **b: Will you be collecting any date information such as birth date, death, admission, discharge, date of surgery/service?** ● Yes ○ No

c: List any other unique identifying numbers, characteristics or codes related to an individual that are to be collected:

d: Will you be collecting any data subject to the General Data Protection Regulation (GDPR)? ○ Yes ● No

* **e: Provide a justification for recording Social Security numbers including why it's required, where it's stored, how it's protected and who will have access:** For vincent payment purposes only

* **For ALL identifiable data collected, will you be coding the data by removing the identifiers and assigning a unique study ID/code to protect the identity of the participant?** ● Yes ○ No

* **Will the data be HIPAA de-identified?** ○ Yes ● No

* **Briefly describe your plan to store coded data separately from the identifiable data:** On enrollment, each participant is assigned a research code number that is used to label all research data collected on the participant. The research team secures the link between the participants' identity and the assigned research code number. The link is secured in a password and firewall protected electronic database

2. **During this study, will restricted data as defined by the University's Data Risk Classification matrix (https://www.technology.pitt.edu/security/data-risk-classification-and-compliance) be processed, stored, or transmitted?**
   ● Yes ○ No

3. * **During this study, will sensitive data (https://www.hrpo.pitt.edu/electronic-data-security) be collected where disclosure of identifying information could have adverse consequences for subjects or damage their financial standing, employability, insurability, educational advancement, reputation or place them at risk for criminal or civil liability?**
   ● Yes ○ No

4. * **Select all locations where data will be stored or archived(including e.g., personal / employer laptop or desktop): If you have access to University owned or controlled resources, facilities, or repositories, such as computer servers, please choose that option to comply with the Research Data Management Interim Policy R1 14.**

Please note that to address Research Security Requirements, University data must be stored in University owned, controlled, or approved repositories, such as Pitt OneDrive. If UPMC or external electronic repositories must be used, they must be approved by Pitt IT.

	Storage Device	Description	Identifiable Data	Sensitive Data	De-Identified/Anonymous Data
View	UPMC owned desktop, laptop or other device		no	no	yes
View	UPMC: Departmental or Hospital Server		yes	yes	yes
View	UPMC: OneDrive /Sharepoint		no	no	yes

5. * **Select all technologies being used to collect data or interact with subjects: Technologies selected in this section may require a Vendor Security Risk Assessment, which can be requested here.**

Web-based site, survey, or other tool

Other

6. * **Web Based Technologies – identify all web based technologies to be used to collect data during any phase of the research:**

	name	Identifiable
View	Pitt Redcap Version	

7. * **Other Technologies:**

name	Identifiable
Digital Camera	no

Data Safety and Monitoring

1. * **Describe your plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor:**
DATA SAFETY AND MONITORING PLAN
The Principal Investigator, Drs. Conklin, and the Co-I Dr. Coffman will ensure that there are no changes in the risk/benefit ratio throughout the duration of the proposed studies. Investigators and study personnel will meet weekly to discuss the progress of the study. Minutes of these meetings will be maintained in the study binder. At each meeting, the study goals will be discussed and any changes needed to the IRB application will be made.

Real-time safety monitoring. Our safety monitoring plan involves monitoring of adverse events at each lab visit during the study. Drs. Conklin and Coffman will be available at all times by phone/pager during all sessions if adverse events need to be addressed, as will Sr Research Coordinator Ron Salkeld. In addition, subjects will be able to call if they experience adverse events while away from the lab, a procedure we have employed in past studies. The PIs and Co-Is will monitor the research literature tDCS to identify new findings regarding the overall safety and use with participants. However, no new risks are anticipated, as the overall risks associated with transcranial direct current stimulation (tDCS) are considered minimal or no significant risk.

Data Security. All computers in which data is input and/or maintained have firewalls, strong password protection, and authorized access to data built in against breaches of confidentiality. We will emphasize patient confidentiality throughout the study. Consent forms, and other identifying data will be separated from case-report forms. Nevertheless, potential breaches will be reviewed with study participants in the consent form, which will be reviewed in-person and will involve informing potential participants of the potential for breaches in data security, and of the procedures that are taken to minimize this possibility. All subject data folders will be maintained in locked filing cabinets in the PI's locked laboratory. Access will be given only to the study investigator and study staff supervised by the investigators. All staff will be trained on data input and maintenance, as well as confidentiality.

Study review meetings. At monthly meetings, the research team will review the interests of study participants, assess the safety and utility of study procedures, and monitor the overall conduct of the study. Quarterly reports will be compiled by the Research Project Coordinator, under supervision of the PIs, and will be reviewed by the study team regarding subject accrual (including adherence to protocol regarding demographics and inclusion/exclusion criteria), adverse events, compliance with treatment, attrition, breaches of confidentiality, and participant progress.
1. Measurement and Reports of Subjects to Accrual and Adherence to Inclusion/Exclusion Criteria. These will be reported quarterly as indicated. This will insure that subjects meet eligibility criteria and that ethnic diversity goals are being met.
2. Measurement and Reporting of Adverse Events. Any adverse events that are reported will be examined by both the PI and the study team. Any serious adverse event will be reported to the IRB and NIH within 24 hours.
3. Measurement and Reporting of Participant Compliance with Treatment Protocol. Data on compliance to the protocol will be collected and reviewed quarterly by the team. The review will include an evaluation of attendance records of participants and compliance records of staff regarding subject recruitment and study procedures. In addition, the proposed research will be reviewed and approved by the Institutional Review Board of the University of Pittsburgh. Also, the Principal Investigators will continually evaluate the progress of the study at weekly meetings with study staff. The study procedures addressed at these meetings also will include:

a. Subject safety and confidentiality issues
b. Participant recruitment, accrual and retention
c. Data quality and integrity issues. If over the course of the study there is concern about changes in the risk-benefit ratio, interim analyses will be conducted to determine if the study should proceed as originally designed.

2. * **Describe your plan for sharing data and/or specimens:**
Individuals from the NIH/NIDA will have access to these records as they are the funding source and we may share de-identified research data in the future with secondary researchers who also have an interest in this research.

3. **If any research data is collected, stored, or shared in a paper format, address what precautions will be used to maintain the confidentiality of the data:**
Data will be kept in locked filing cabinets in a secure suite. On enrollment, each participant is assigned a research code number that is used to label all research data collected on the participant. The research team secures the link between the participants' identity and the assigned research code number.

Risk and Benefits

1. * Enter all reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to subjects' participation in the research:

View

Research Activity	**Questionnaires**
Common Risks	**Some people may find the interview and questionnaires uncomfortable. All interviews and questionnaires will be completed by trained personnel. The subject will be given breaks as needed and will be reminded that he/she doesn't have to answer questions he/she chooses not to and she may stop at any time.**
Infrequent Risks	***No Value Entered***
Other Risks	***No Value Entered***

View

Research Activity	**tDCS**
Common Risks	***No Value Entered***
Infrequent Risks	**The risk associated with transcranial electrical stimulation is minimal. There is a small risk of skin irritation which is minimized by using saline water as the conductive medium, and through the monitoring of participant discomfort throughout the procedure. tDCS is seen as a non-invasive medical procedure, and the commonly reported side-effects in active vs. sham treatments are itching (39.3% vs 32.9%), tingling (22.2% vs 18.3%), headache (14.8% vs 16.2%), burning sensation (8.7% vs 10%), and discomfort (10.4% vs 13.4%).107 Redness at the electrode site has also been reported.**
Other Risks	***No Value Entered***

View

Research Activity	**Cue-Reactivity**
Common Risks	**Some of the stimuli used have been shown to significantly increase urge to smoke. The discomfort of increased urge to smoke is anticipated to dissipate fairly quickly, and over the course of the treatment may lead to less robust responses.**
Infrequent Risks	***No Value Entered***
Other Risks	***No Value Entered***

View

Research Activity	**Collection and storage of private information**
Common Risks	***No Value Entered***
Infrequent Risks	**There is a rare possibility of a breach of confidentiality, but we have safeguards in place to minimize that. All records related to your involvement in this research study will be stored in a locked file cabinet and all electronic records are password and firewall protected. Your identity on these records will be indicated by a case number rather than by your name, although we may use your initials on certain forms.**
Other Risks	***No Value Entered***

2. * Describe the steps that will be taken to prevent or to minimize risks:

The Neucoconn DC Stimulator Plus used in this study will be routinely tested (monthly) to ensure that the current and voltage delivered by the device are as expected based on the settings applied. We will test these parameters using a standard multimeter (Fluke), and electronic logs of these tests will be maintained by the PI. Potential risk of skin irritation from transcranial DC stimulation is minimized by using saline water as the conductive medium, through the monitoring of participant discomfort throughout the procedure, and by discontinuation of the procedure if significant discomfort is experienced by the participant. Confidentiality and loss of Privacy. Information on research participants will be protected for confidentiality similar to medical records, and will be kept separate from the research binders in locked metal cabinets and for authorized access only. No

identifiable data will be made available while compiling the study report or when preparing the eventual results for a journal article. If the cue reactivity or questionnaires cause the participant discomfort they do not have to answer the questions and may stop the study at any time.

3. **Financial risks - will the subject or insurer be charged for any research required procedures?**
   ○ Yes ● **No**

4. **Describe the steps that will be taken to protect subjects' privacy:**
   All research procedures will be completed in a private room and with only the research staff present.

5. **What steps will be taken in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the study:**
   The PI's would consult with the subject and refer to the appropriate physician for follow-up.

6. **Describe the potential benefit that individual subjects may experience from taking part in the research or indicate if there is no direct benefit. Do not include benefits to society or others:**
   There isn't a direct benefit to the participant for participating in this study; however, it's possible they may find the study procedures helpful to their urge to smoke.

7. **Do you anticipate any circumstances under which subjects might be withdrawn from the research without their consent?**
   ● **Yes** ○ No

   * **Describe the circumstances and any procedures for orderly termination:**
   It is possible that the subject may be removed from the research study by the researchers if he/she is unable to perform any of the required tasks or does not show up for scheduled study visits. He/She will always be paid for a session she attended prior to being formally withdrawn from the study.

8. **Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection and data already collected:**
   Research data will be kept and reviewed for an indefinite period of time. Research information collected before excusal or withdrawal from the study will continue to be used and disclosed by the investigators for the purposes described above.

Placebo Arm

1. * **Is there a commonly used diagnostic/treatment approach that is currently recognized as being effective for the proposed subjects' disease or condition, and that will be withheld from subjects assigned to the placebo arm of this research study:**
   N/A - the proposed subjects are normal, healthy volunteers

2. **Describe the commonly used diagnostic/treatment approaches that will be withheld from subjects assigned to the placebo arm of this research study:**

3. **Is enrollment into this study limited to individuals in whom the commonly used diagnostic/treatment approaches are known to be ineffective or intolerable?**

4. **Provide a scientific justification for the placebo-control arm of this research study:**
   This is a balanced 2 x 2 design to examine the impact of two new methods to reduce cue reactivity to personal smoking cues. The placebo arm allows us to examine the individual and combined impact of the two techniques and compare them with a time and contact control. The effectiveness of the techniques being examined, independently or in combination, as methods to reduce cue reactivity to personal smoking cues has yet to be examined, so a placebo comparison is warranted.

5. **How long will subjects participate in the placebo arm? Justify why this duration is necessary:**
   They will be in the placebo arm for the duration of the study 10 sessions. There are also follow-up phone calls at 1 week and 1 month post-training. This allows the placebo arm to serve as a control for subject time and contact.

6. **How frequently will the subject's condition or disease be monitored and compare that to the frequency of monitoring associated with standard care for this disease/condition?**

7. **What specific endpoints will result in discontinuing a subject's participation due to worsening of the subject's disease or condition?**

8. **What is the risk to subjects who receive no active treatment for their disease or condition while in the placebo arm?**
   There is no notable risk, their smoking behavior and craving is expected to remain stable, whereas we anticipate possible reductions in these measures in the other arms of the study.

9. **Describe the planned involvement of a 'contact person' who interacts with the subject on a regular basis and who will notify the investigators immediately of any problems related to the subject's disease or condition:**

   Note: The involvement of the contact person must also be addressed in the consent form

Conflict of Interest

Institutional Financial Interests

1. * **To the best of your knowledge, has the University of Pittsburgh optioned or licensed technology that will be tested or evaluated in this research?**
   ○ Yes ● **No**

Ancillary Reviews

1. **Ancillary reviews or notifications selected below are required based on previous answers to questions. If a selection is incorrect, return to the appropriate page and adjust the answers to questions on that page:**

- [ ] Conflict of Interest (**COI**)
- [ ] Clinical and Translational Research Center (**CTRC**)
- [ ] Data Security
- [ ] Honest Broker
- [ ] UPMC Investigational Drug Service
- [ ] Pitt Medical School Review
- [x] Pitt+Me
- [ ] IND & IDE Support(**IIS**)
- [ ] Radioactive Drug Research Committee (**RDRC**)(study involves the evaluation or use of procedures that emit ionizing radiation)
- [ ] ORP Business **Manager** (required for industry sponsored studies)
- [ ] Religious Directives
- [x] Scientific Review
- [ ] Health Record Research Request (**R3**) (required if using UPMC clinical data and authorization for other UPMC data sources for research)
- [x] UPMC Office of Sponsored Programs and Research **Support** (using UPMC facilities and/or UPMC patients during the conduct of the study)

2. **Additional ancillary reviews the PI may choose to include as needed for the research:**

- [ ] Human Stem Cell Oversight (**hSCRO**)
- [ ] Institutional Biosafety Committee (**IBC**)(study involves deliberate transfer of recombinant or synthetic nucleic acid molecules)

Good Clinical Practice (GCP) Training

1. * **Regardless of funding source, is this study a clinical trial (**as defined by the NIH**)?**
   ● **Yes** ○ No

ClinicalTrials.gov Information

Visit the University of Pittsburgh Office for ClinicalTrials.gov website or contact ctgov@pitt.edu for further information.

2. * **Was this study registered, or will it be registered, on ClinicalTrials.gov?**
   ● **Yes** ○ No

3. * **Is the University of Pittsburgh or UPMC the Sponsor Organization for this study record?**
   ● **Yes** ○ No

   * **Who will be the Responsible Party for this study record?**

   Principal Investigator of this IRB application

Supporting Documents

1. **Attach any additional supporting documents not previously uploaded. Name the documents as you want them to appear in the approval letter:**

Document	Category	Date Modified	Document History
There are no items to display			

Add Storage Information

1. * **Select a Storage Type:**
   UPMC owned desktop, laptop or other device

2. **Description:**

3. * **Will identifiable data be stored in this location?**
   ○ Yes ● **No**

4. * **Will sensitive data be stored in this location?**
   ○ Yes ● **No**

5. **Will de-Identified or anonymous data be stored in this location?**
   ● **Yes** ○ No

6. * **Is anti-virus software installed and up to date on all devices and are the operating systems kept up-to-date on all devices?**
   ● **Yes** ○ No

7. **Provide additional information as needed:**

Add Storage Information

1. * **Select a Storage Type:**
   UPMC: Departmental or Hospital Server

2. **Description:**

3. * **Will identifiable data be stored in this location?**
   ● **Yes** ○ No

4. * **Will sensitive data be stored in this location?**
   ● **Yes** ○ No

5. **Will de-Identified or anonymous data be stored in this location?**
   ● **Yes** ○ No

6. **Provide additional information as needed:**

Add Storage Information

1. * **Select a Storage Type:**
   UPMC: OneDrive /Sharepoint

2. **Description:**

3. * **Will identifiable data be stored in this location?**
   ○ Yes ● **No**

4. * **Will sensitive data be stored in this location?**
   ○ Yes ● **No**

5. **Will de-Identified or anonymous data be stored in this location?**
   ● **Yes** ○ No

6. **Provide additional information as needed:**

7. **Will access to the files or folders be restricted to only those research team members involved in the study(e.g., Specific people are granted access)?**
   ○ Yes ○ No

Risk

1. * **Research Activity:**
   Questionnaires

2. **Common Risks:**
   Some people may find the interview and questionnaires uncomfortable. All interviews and questionnaires will be completed by trained personnel. The subject will be given breaks as needed and will be reminded that he/she doesn't have to answer questions he/she chooses not to and she may stop at any time.

3. **Infrequent Risks:**

4. **Other Risks:**

Risk

1. * **Research Activity:**
   tDCS

2. **Common Risks:**

3. **Infrequent Risks:**
   The risk associated with transcranial electrical stimulation is minimal. There is a small risk of skin irritation which is minimized by using saline water as the conductive medium, and through the monitoring of participant discomfort throughout the procedure. tDCS is seen as a non-invasive medical procedure, and the commonly reported side-effects in active vs. sham treatments are itching (39.3% vs 32.9%), tingling (22.2% vs 18.3%), headache (14.8% vs 16.2%), burning sensation (8.7% vs 10%), and discomfort (10.4% vs 13.4%).107 Redness at the electrode site has also been reported.

4. **Other Risks:**

Risk

1. * **Research Activity:**
   Cue-Reactivity

2. **Common Risks:**
   Some of the stimuli used have been shown to significantly increase urge to smoke. The discomfort of increased urge to smoke is anticipated to dissipate fairly quickly, and over the course of the treatment may lead to less robust responses.

3. **Infrequent Risks:**

4. **Other Risks:**

Risk

1. * **Research Activity:**
   Collection and storage of private information

2. **Common Risks:**

3. **Infrequent Risks:**
   There is a rare possibility of a breach of confidentiality, but we have safeguards in place to minimize that. All records related to your involvement in this research study will be stored in a locked file cabinet and all electronic records are password and firewall protected. Your identity on these records will be indicated by a case number rather than by your name, although we may use your initials on certain forms.

4. **Other Risks:**