Effect of a Non-Invasive Brain Stimulation Technique on Smoking Cessation Behaviors

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PROTOCOL TITLE:

Effect of a Non-Invasive Brain Stimulation Technique on Smoking Cessation Behaviors

PRINCIPAL INVESTIGATOR:

Michael Kotlyar, PharmD
Associate Professor
Department of Experimental and Clinical Pharmacology
612-625-1160
kotly001@umn.edu

Co-Investigators

Y. Jazmin Camchong, PhD
Assistant Professor
Psychiatry
612-624-0134
camch002@umn.edu

Dorothy Hatsukami, PhD
Professor
Department of Psychiatry
612-626-2121
hatsu001@umn.edu

Kelvin Lim, MD
Professor
Department of Psychiatry
612-626-6772
kolim@umn.edu

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Version 3.0
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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
#1	11/28/17	Added weight measurement at Follow-Up visits	YES
# 2	5/16/18	Adding functional magnetic resonance imaging (fMRI)	YES

Table of Contents

After completing your protocol, right click on the Table of Contents below and select "Update Field." If prompted, select "Update entire table." This will automatically update the protocol sections and page numbers for you. Do this also each time you modify your protocol after initial approval.

ABBREVIATIONS/DEFINITIONS

- tDCS – transcranial direct current stimulation
- fMRI – functional magnetic resonance imaging
- FC – functional connectivity
- NAcc – nucleus accumbens
- DLPFC - dorsolateral prefrontal cortex
- MNWS – Minnesota Nicotine Withdrawal Scale
- QSU – Questionnaire of Smoking Urges
- CO – carbon monoxide

STUDY SUMMARY

Study Title	Effect of a Non-Invasive Brain Stimulation Technique on Smoking Cessation Behaviors
Study Design	Randomized Double-Blind Pilot Study
Primary Objective	To determine the feasibility of using tDCS (a non-invasive brain stimulation technique) as a treatment for smoking cessation
Research Intervention(s)/Investigational Agents	Transcranial direct current stimulation (tDCS)
IND/IDE # (if applicable)	n/a
Investigational Drug Services # (if applicable)	n/a
Study Population	medically stable smokers
Sample Size (number of participants)	20 to complete the study
Study Duration for Individual Participants	Approximately 6 weeks

1.0 Objectives

1.1 Aim 1: To determine the feasibility of using transcranial Direct Current Stimulation (tDCS) in a population of smokers interested in cessation

2.0 Background

2.1 *Significance of Research Question/Purpose:* The morbidity and mortality associated with smoking is well characterized, with the most recent Surgeon General's report estimating that approximately 480,000 deaths annually in the United States are attributable to smoking.[1] Although 70% of smokers indicate a desire to quit, the best current treatments result in less than 30% achieving long-term abstinence. New treatments for tobacco dependence are introduced rarely with only three medications currently approved for increasing smoking cessation rates (i.e. medicinal nicotine, varenicline, bupropion). Clearly, additional therapies are needed

2.2 *Preliminary / Existing Data:* Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique in which a weak electrical current (2mA or less) is applied to the scalp via anodal and cathodal electrode sponges, causing either increases or decreases in cortical excitability, respectively. Use of this technology has been studied for the treatment of several disorders (e.g. depression, Alzheimer's disease, Parkinson's disease) and has been suggested as a potential treatment modality for addiction. Drs. Camchong and Lim have identified, using functional magnetic resonance imaging (fMRI), brain biomarkers that support long-term abstinence from alcohol in those with alcohol use disorder. Specifically, cross-sectional and longitudinal findings suggest that higher functional connectivity (FC) between the nucleus accumbens (NAcc) and dorsolateral prefrontal cortex (DLPFC) is a potential brain biomarker that is associated with abstinence. Long-term abstinent alcoholics (7 years of abstinence) have higher resting FC between NAcc and DLPFC when compared to non-substance abusing healthy controls. Short-term abstinent alcoholics (11 weeks of abstinence) have intermediate FC (lower than long-term abstinent alcoholics and higher than controls).[2, 3] Further, lower FC between NAcc and DLPFC at 11 weeks of abstinence can be a predictor of subsequent relapse (with 74% accuracy).[4] Moreover, in a pilot longitudinal study examining resting FC of NAcc at 5 and 13 weeks of abstinence in individuals with substance use disorder, FC between NAcc and DLPFC decreased from 5 to 13 weeks of abstinence in subsequent relapsers, while it increased in subsequent abstainers.[5] One interpretation of this data is that long-term abstinence is supported by a compensatory mechanism that mediates proper executive function over reward (which is mediated by DLPFC-NAcc FC). This information provides a potential brain marker that could be an intervention target if methods can be identified that increase FC between DLPFC and NAcc.

Cognitive flexibility, the ability to change maladaptive behavior, depends on DLPFC input to NAcc. [6] DLPFC transmits reward representations to NAcc through glutamatergic projections that guide goal-directed behavior. [7] If DLPFC

fails to activate when required, as often observed in substance use disorder, target neurons in the NAcc core do not receive critical information needed to select the appropriate outcome, causing acquired maladaptive response patterns to persist (e.g. drug consumption).[6] Higher FC between DLPFC and NAcc may be achieved by stimulating DLPFC while subjects perform tasks that require cognitive flexibility, an aspect of executive functioning.

Transcranial direct current stimulation (tDCS) has shown in both healthy subjects and in patients (e.g. Parkinson's disease, stroke, and depression) to modulate synaptic strengthening and neurotransmitter-dependent plasticity underlying changes in behavior and learning.[8] It therefore has the potential to increase functional connectivity between NAcc and DLPFC when paired with a cognitive task engaging this pathway. As previously described, strengthening this pathway should facilitate proper selection of goal-directed behavior and decrease craving in those with substance use disorder.[9]

There is currently limited data regarding the efficacy of tDCS on smoking cessation and no data regarding the efficacy of combining tDCS with a concurrent task requiring cognitive flexibility. Although studies have assessed the effect of tDCS on smoking behavior, these have not combined stimulation with a task requiring cognitive flexibility nor have these studies assessed cessation outcomes. Instead, smoking cues were presented either immediately prior to, during or immediately after neurostimulation[10-14] with the outcomes assessed being either cue induced craving severity, number of cigarettes smoked during the days of stimulation or using laboratory based smoking choice paradigms. These studies have generally found small but positive effects in these measures. However by not combining tDCS with the cognitive flexibility task, these studies may not have been able to maximize the effects of this intervention.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome: As a pilot study, the main objective of this investigation is to determine the feasibility of using the proposed approach as a method by which to increase smoking cessation rates. The primary endpoint is therefore to determine if recruiting smokers into a study evaluating tDCS will be feasible and if the intervention is well tolerated by smokers.

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s): Secondary endpoints include measures associated with smoking cessation outcomes including time to smoking lapse, time to smoking relapse, number of cigarette smoked, severity of craving and severity of withdrawal symptom score. We will also assess impulsivity as tDCS may impact this measure. fMRI measures will be assessed in the sub-population of subjects enrolled after protocol revision # 3 is approved and after all preparations to enroll subjects into this portion of the study are complete.

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description: The tDCS will be performed with the Neuroelectrics Starstim NE (Neuroelectrics Barcelona, Spain). This device is located in the MnDRIVE Non-invasive Neuromodulation Laboratory (Room 247 at the Delaware Clinical

Research Unit of the CTSI).

4.2 Drug/Device Handling: To minimize risks of tDCS, study staff will be trained in and use standards of administration that have been shown as safe in numerous other studies using transcranial direct current stimulation. A recent review of the safety of tDCS found no reports of serious adverse effects or irreversible injury across over 33,200 session and 1,000 subjects with repeated sessions.[15] The length of administration of the current, size of electrode sponges used, and method of applying stimulation are no higher than those that have been demonstrated as safe.

4.3 IND/IDE. In studies using tDCS, approval of the device in research has generally been granted without an investigational device exemption due to meeting criteria for non-significant risk (NSR). A recent review of regulatory considerations for the clinical and research use of tDCS concluded that in the United States, "IRB's ubiquitously (at a minimum overwhelmingly) designate tDCS trials NSR (see adverse event discussion above), thus not requiring a formal IDE application to the FDA." [16]

4.4 Biosafety: N/A

5.0 Procedures Involved

5.1 Study Design: This study is a randomized double-blind pilot study in which subjects will receive either active or sham tDCS

5.2 Study Procedures: The following procedures will occur during the study

5.2.1 *Screening visit:* Initial eligibility will be assessed via a phone interview. Those likely to qualify will be scheduled for a screening visit at which written informed consent will be obtained and eligibility confirmed. Medical, psychiatric and smoking history will be obtained via subject report with smoking status biochemically confirmed (via an exhaled carbon monoxide (CO) concentration of $\geq$ 8 ppm or a urinary nicotine test strip = 6). Baseline levels of a variety of measures such as severity of smoking urges, severity of withdrawal symptoms, extent of nicotine dependence and how subjects evaluate their current cigarettes will be assessed via questionnaires. Height and weight will be measured. Those who qualify will be scheduled for a week during which they will come in daily for 5 consecutive days to receive tDCS treatments (active or sham) and will be asked to maintain a daily tobacco use diary in order to assess baseline levels of smoking. Subjects enrolled after revision # 3 has been approved and all preparations to enroll subjects into the scanning portion of the study are complete will be asked to come in for two additional visits to collect fMRI data: one visit before tDCS treatments begin, and a second visit after all tDCS treatments are completed.

5.2.2 MRI scanning visits (2 visits, 1 visit occurring during the week prior to and the other visit occurring during the week following the tDCS visits): Participants will undergo an MRI scan (3T), which takes about 75 to 80 minutes. MRI involves taking pictures of the participant's brain, from which the properties of certain brain tissues can be measured. These scans are strictly for research

purposes and therefore will not receive a clinical or medical interpretation. For the scan, the participant will be asked to lie down quietly on a bed, and the bed will slide into the scanner. Once the participant is inside the scanner, the imaging will begin. During the scan, the participant will be asked to lie quietly in the scanner with their eyes closed and may also be asked to perform a cognitive task (e.g., reversal learning task). The MRI scan will be performed at the University of Minnesota's Center for Magnet Resonance Research.

5.2.3 *tDCS Visits (5 visits on consecutive days):* At each of these visits, subjects will receive active or sham tDCS. The length of stimulation and the current used is consistent with the parameters previously found in clinical studies of alcohol dependence to reduce relapse.[17] Specifically, subjects will receive two 13 minute 2-mA sessions to the left DLPFC at each visit with a rest interval (no stimulation) of 20 minutes in between. [17, 18] While receiving stimulation, subjects will perform cognitive training tasks drawn from the commercially-available Brain HQ suite of tasks. Over each 46 minute period (i.e., the two 13 minute tDCS session separated by 20 minutes in between), each of 7 tasks will be performed for approximately 6 minutes. These tasks are designed to be adaptive based on participants' performance and therefore are more engaging than non-adaptive tasks. Multiple peer-reviewed medical and science journal articles have been published on Brain HQ exercises and assessments in varied clinical populations. Its commercial availability also makes Brain HQ amenable to potential future large scale deployment. Table 1 summarizes the Brain HQ tasks that will be utilized

Table 1: Brain HQ Executive Function Tasks

Task	Modality	Domain	Description
Freeze Frame	Visual	Behavioral Inhibition	Must decide if pictures match one presented at start of task. Respond ONLY when pictures DO NOT match.
Mixed Signals	Visual & Auditory	Behavioral inhibition	Listen to a number, letter of color while looking at a set of numbers letters or colors. Decide if the two stimuli match quickly as possible.
Divided Attention	Visual	Behavioral inhibition; Set shifting	Decide if two objects match depending on rule (color vs. shape).
Mind Bender	Visual	Set shifting	Must respond based on two competing rules depending on the type of stimuli
Card Shark	Visual	Working Memory	Visual n-Back
Auditory Ace	Auditory	Working Memory	Auditory n-back task
Juggle Factor	Visual	Working Memory	Presented with a sequence of numbers that are placed within moving circles; Must reconstruct the sequence in the right order & locations.

At the beginning of each tDCS visit, participants will be assessed for number of cigarettes smoked 24 hours prior to the session, the time since last cigarette and exhaled CO levels. A cigarette evaluation scale will be completed at each visit. Additionally, adverse events, smoking urges and nicotine withdrawal symptom severity will be assessed before and after each session using several questionnaires. At the first tDCS session, urine will be collected to be analyzed at a later time for markers of cigarette smoking (e.g., cotinine concentrations). Prior to the first and after the last tDCS session, participants will also complete an impulsiveness questionnaire as this parameter is thought to be affected by tDCS, a

questionnaire assessing nicotine dependence as well as a questionnaire assessing motivation and self-efficacy to quit smoking.[19] Total participation time at each visit is not expected to exceed 2 hours per day.

At these visits, participants will be provided a smoking cessation treatment manual (Clearing the Air) and begin preparation for the quit date, which will be at the end of the 5th visit. The standardized content of the brief (10 min) behavioral treatment session provided to participants will include discussing benefits of quitting, ways to prepare the environment to minimize smoking cues (e.g., removing ashtrays), and methods to reduce craving and withdrawal symptoms (e.g., deep breathing). Participants will also keep track of situations associated with smoking and begin to develop a plan to deal with these situations.

This tDCS device to be used in this study is located in the MnDRIVE Non-invasive Neuromodulation Laboratory. There is currently no evidence of serious side-effects.[15] Mild side-effects that typically resolve upon discontinuing tDC include light itching under the electrode at the beginning of administration, headache, fatigue, and nausea. The subject may choose to discontinue stimulation at any time during the session if experiencing excessive discomfort or side effects. Although seizures are not a known risk of tDCS intervention,[20] anyone with a history or a risk for seizures will be excluded from the study. No other risks related to tDCS are anticipated.

5.2.4 *Post Cessation Visits (4 visits):* Follow-up visits will occur at each of 4 weekly visits. At each visit, smoking diaries will be collected and exhaled CO will be measured. Urine will be collected at the week 1, 2 and 4 visits. Weight will be measured at week 1, 2, 3 and 4 visits. Questionnaire assessing craving and withdrawal symptoms severity will be assessed as will the effects that participants report from smoking (via the cigarette evaluation scale[21]).

5.3 Individually Identifiable Health Information: All information is collected directly from subjects (i.e., medical records will not be requested) and this is not a treatment study. The data being collected therefore does not meet the definition of PHI.

5.4 Use of radiation*: N/A*

5.5 Use of Center for Magnetic Resonance Research*:* This study has been reviewed by the CMRR (Project Application Review System application # 5101)

6.0 Data and Specimen Banking

6.1 Storage and Access: Urine will be collected from subjects at the Day 1 and Weeks 1,2 and 4 visits. The samples will be stored in freezers located in labs used by faculty in the ECP department (currently these freezers are located on the 5th floor of 717 Delaware Ave). Samples will be stored until later batch analysis can be completed.

7.0 Sharing of Results with Participants

7.1 Study results will not be shared with participants.

8.0 Study Duration

- The anticipated duration for an individual participant's participation in the study is approximately 6 weeks (depending in part on length of time between the screening visit and first tDCS visit).
- Data collection is expected to be complete within 1 year of starting the study.

9.0 Study Population

9.1 Inclusion Criteria: To be eligible subjects must:

a) Be between the ages of 18 and 64

b) Smoke (on average) at least 5 cigarette per day

c) Be motivated to quit smoking

9.2 Exclusion Criteria: Subjects will be excluded if they:

a) Regularly use tobacco products other than cigarettes (> 9 times per month)

b) Have any major medical or psychiatric condition that is unstable and renders them unable to participate in the study.

c) Have any medical condition with neurological sequelae (e.g., stroke, seizures).

d) History of loss of consciousness of greater than 30 minutes duration or loss of consciousness with neurological sequelae

e) Have any medical condition or use any medication that would either increase risk of subjects participating in this study (e.g., medications that lower the seizure threshold) or that would impact measures of interest (e.g. smoking cessation medications).

f) Have any contraindications for MRI scanning (e.g., metal implants, pacemakers or any other implanted electrical device, injury with metal, braces, non-removable body piercings, pregnancy)

g) Are pregnant or planning to become pregnant during the study

h) Have any contraindications to tDCS (e.g., current use of pacemaker, intracranial electrodes or implanted defibrillator).

9.3 Screening: At the screening visit, subjects will complete a serious of questionnaires including those that ask about medical history, smoking history and motivation to quit smoking. All inclusion / exclusion will be based on self-report except for smoking status which will be confirmed via an exhaled carbon monoxide (CO) concentration of $\geq$ 8 ppm or a urinary nicotine test strip reading of 6. Non-pregnant status will be confirmed via a urine pregnancy test.

10.0 Vulnerable Populations

10.1 Vulnerable Populations:

☐ Children
☐ Pregnant women/Fetuses/Neonates
☐ Prisoners
☐ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
☐ Serious health condition for which there are no satisfactory standard treatments
☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
☐ Undervalued or disenfranchised social group
☐ Members of the military
☐ Non-English speakers
☐ Those unable to read (illiterate)
☐ Employees of the researcher
☐ Students of the researcher
☒ None of the above

11.0 Local Number of Participants

11.1 Local Number of Participants to be Consented: We plan on recruiting subjects until approximately 20 have completed the study. We expect that as many as 50 subjects will undergo the consent process. Some of those that attend the screening visit will likely not meet inclusion / exclusion criteria whereas others will not be interested in participating.

12.0 Local Recruitment Methods

12.1 Recruitment Process: Advertisements for the study will be placed in various print and on-line sources and via flyers. Interested participants will call the phone number listed. Study staff will explain the study to potential study subjects. Individuals that indicate an interest in participating in the study will then be screened by telephone to see if they are likely to qualify for the study. Additionally subjects that in previous studies agreed to be contacted regarding other research opportunities may be called – in this case, subjects

will be informed why they are being called with the telephone screening process being the same as for subjects who contacted us after seeing the study advertised.

12.2 Recruitment Materials: Flyers and advertisements placed in local publications or on on-line resources (for example, Craigslist) will be used to recruit participants.

12.3 Payment: Subjects will receive $20 for each visit that they complete (e.g. screening visit, MRI scans, 5 visits at which tDCS will be administered, 4 follow-up visits). Subjects who attend all study visits and comply with all study related procedures will receive a $60 bonus. Subjects can therefore receive up to $300 for completing the entire study. Payment will be provided at the end of each visit in the form of a pre-paid debit card.

13.0 Withdrawal of Participants

13.1 Withdrawal Circumstances: Participants will be withdrawn from the study if they report any side effects of greater than moderate severity or that raise any safety concerns. Subjects may also be withdrawn from the study if they fail to follow study procedures (e.g., show up to scheduled study visits). Additionally, subjects will be told that participation is voluntary and that they may discontinue participation at any time for any reasons.

13.2 Withdrawal Procedures: Subjects who withdraw from the study after having received tDCS will be asked if they can be contacted by telephone to ascertain smoking status. We will attempt to contact subjects by telephone who do not show up to scheduled visit to ascertain if they wish to continue to participate in the study (and if not, why not) and to determine smoking status.

14.0 Risks to Participants

14.1 Foreseeable Risks: The device to be used in this study is a transcranial direct current stimulator - tDCS. tDCS is considered to be a safe brain stimulation technique that rarely results in adverse events. There is currently no evidence of serious side-effects. Mild side-effects that typically resolve upon discontinuing tDCS include light itching under the electrode at the beginning of administration, headache, fatigue, and nausea. The subject may choose to discontinue stimulation at any time during the session if experiencing excessive discomfort or sideeffects. Although seizures are not a known risk of tDCS intervention,[20] anyone with a history or a risk for seizures will be excluded from the study. No other risks related to tDCS are anticipated.

MRI risks: Individuals will complete a screening questionnaire for contraindications of MRI scanning which will be reviewed by CMRR staff at the University of Minnesota. A determination will be made regarding the level of risk to the subject and whether they are approved for scanning.

There are no known risks to humans due to the static magnetic field. Subjects, operators, and guests are screened prior to entering the magnetic environment,

and frequently reminded of the potential danger of introducing magnetic objects to the controlled area. Subjects are excluded from the study if they have any implanted devices. Subjects are always accompanied when near the magnet, and reminded to move slowly and carefully as they enter and leave the magnet.

The risk of tissue damage by energy emitted by the MRI device is controlled by compliance with FDA guidelines for commercial MRI devices. Safety devices are in place so that the magnet will cease to operate should any parameters begin to exceed their preset safety limits. The risk of peripheral nerve stimulation by dB/dt is limited by safety devices. The noise levels generated by each scan are monitored to ensure adherence to guidelines. In addition, subjects are provided with earplugs and secondary protection (foam covering or headphones) to increase comfort during the scan..

14.2 Reproduction Risks: There is limited data regarding the risks of tDCS to an embryo or fetus although since tDCS is a localized brain stimulation treatment, it is unlikely to have reproductive risks.[22] The risks of MRI to fetuses are unknown. We will therefore exclude women who are pregnant or are planning to become pregnant during the study.

14.3 Risks to Others: There are no anticipated risks to others.

15.0 Potential Benefits to Participants

15.1 Potential Benefits: As this is not a treatment study, there is no direct benefit to individual participants.

16.0 Data Management

Data Analysis Plan: Data collected in this pilot study will be used as preliminary data and proof of concept to facilitate the design of and estimate power for subsequent larger grants. Descriptive statistics will conducted and effect sizes will be estimated. Linear mixed models will be used to examine time, group (sham vs. active) and group by time effects for various continuous outcome measures (e.g. craving). Survival analyses will be used to examine group differences on time to relapse to smoking.

16.1 Power Analysis: As this is a pilot study, no power analysis was done.

16.2 Data Integrity: In order to ensure that data entry is correct, data collected on paper questionnaires will be entered twice with the two entries compared and any discrepancies resolved.

17.0 Confidentiality

17.1 Data Security: To ensure confidentiality, all subjects will be assigned a study identification code to be used on all data collection forms except those for which use of personal identifiers is mandatory (e.g., informed consent form). Forms that link the name of the participant and the subject identification code will be kept in a locked cabinet or office or in an electronic file stored on password

protected secure computer servers maintained by the University. Visits will be conducted at the CTSI, therefore there will be a record of the subject's participation in the CTSI records although a copy of the consent form will not be placed in the participants' medical records.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

The CTSI monitoring group will be asked to monitor this study using their standard procedures.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy: During the consent process, subjects will be told that they can discontinue participation at any time for any reason. Furthermore, they are free to not answer any questions asked on the questionnaires. However since certain information is needed to assess eligibility or to assess measures of interest, declining to answer certain questions may lead to a subject not being eligible to participate or to continue with the study.

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury: No compensation is available in the event of research related injury.

21.0 Consent Process

21.1 Consent Process (when consent will be obtained): Informed consent will be obtained at the screening visit. Subjects will have the opportunity to read the consent document and ask any questions that they have. A member of the study staff will then ask the subject questions to make sure that they understand the study procedures. No study procedures will be administered until the subject has signed the consent form.

21.2 Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

21.3 Non-English Speaking Participants: N/A

21.4 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): Individuals under the age of 18 will be excluded from the study. Subjects will be asked to present ID at the screening visit to confirm that they are over the age of 18.

21.5 Cognitively Impaired Adults or adults with fluctuating or diminished capacity to consent: We are not planning on enrolling subjects with fluctuating or diminished capacity to consent. Subjects that appear during the consent process

to have impaired capacity to consent will be excluded from the study.

21.6 Adults Unable to Consent: N/A

22.0 Setting

22.1 Research Sites: Potential subjects will be recruited via the use of flyers and advertisements placed in local publications or on on-line resources (for example, Craigslist). Additionally subjects that in previous studies agreed to be contacted regarding other research opportunities may be called. Study visits will occur in the Delaware Clinical Research Unit (formerly part of the Clinical and Translational Research Institutes (CTSI) facilities). Scans will be conducted at the Center for Magnetic Resonance Research (CMRR).

23.0 Multi-Site Research: N/A

24.0 Resources Available

This study is being supported by a grant from the Academic Health Center Seed Grant Program. The tDCS device being utilized in this study is located in the MnDRIVE Non-invasive Neuromodulation Laboratory (Room 247 at the Delaware Clinical Research Unit of the CTSI). The personnel assisting with this study (e.g., study coordinators) work with the research groups of the investigators. Based on previous studies, we believe that that there are adequate smokers in the community interested in participating in research studies in order to meet recruitment goals. However, as a feasibility study, the ability to recruit smokers is one of the outcomes of interest.

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