Clinical Trials #: NCT03842137

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Title: tDCS to Decrease Opioid Relapse

MPIs: Ana Abrantes, PhD and Michael Stein, MD

BUTLER HOSPITAL CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

tDCS to Decrease Opioid Relapse

Sponsorship
This study is being paid for by the National Institute on Drug Abuse.

Research Project Summary
You are invited to participate in a study designed to understand how people do after buprenorphine or methadone treatment has started and whether a brain stimulation procedure called transcranial direct current stimulation (tDCS) affects craving for opioids. You have been invited to participate because you are currently in treatment for opioid use and are starting buprenorphine or methadone treatment. Your participation in the study will last approximately 2 weeks. Participation may be in-person, or by phone/video formats. It will require up to 7 visits to our research office, and approximately 10 hours of your time. At these visits, you will be asked interview questions by the research staff, have 5 sessions of transcranial direct current stimulation (tDCS), and complete 2 electroencephalography (EEG) sessions. You may also be asked to complete 2 functional magnetic resonance brain imaging (fMRI) scans. You will be compensated for your time (details below).

In order to decide whether or not you wish to be a part of this research study, you should know enough about its risks and benefits to make an informed judgment. This consent form gives you detailed information about the research study which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, risks associated with the procedures, possible benefits of participation, and possible alternatives. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form. This consent may contain words that you do not understand. Please ask the investigator or the study staff to explain any words or information that you do not clearly understand.

Description of Procedures
If you decide to participate, you will be asked to do a number of different activities as part of this study.

Assessment Interviews: You will be asked questions by the research staff either in-person or via a secured videoconference. These questions will be about you, your physical and mental health, your substance use, and your craving for opiates. These research questionnaires will begin today, and again in about 1-2 weeks. The assessments will be confidential and may be audio- or video-recorded. The recording is for training purposes, to ensure the staff are consistent in conducting the research assessment. We will tell you whenever we plan to use an audio-or video-recorder. By signing this consent form, you give us permission to audio- or video-record. You may refuse audio- or video-recording of interviews at any time and still participate in the study. Recordings will be destroyed at the end of the study. You will be asked to provide a urine sample to test for substance use at each study appointment. You will also be asked to sign a health information release form for the physician that prescribes your buprenorphine or methadone so that we may verify the date that you were prescribed the medication.

tDCS: You will have five sessions of tDCS -during which a very low level electrical current -stimulation is delivered to your head. These five sessions will take place over about one week. You will be randomly assigned (like the flip of a coin) to receive either active or fake (sham) tDCS. You will not know which condition you are assigned. At each session, you will have either the active or sham stimulation for approximately 20 minutes. In order to provide the active or sham stimulation, two wet sponges containing electrodes will be placed on your head. These sponges will be held in place by large rubber bands. During the tDCS period, these sponges and rubber bands will remain on your head. During each 20-minute period, you will also engage in an activity that's like a computer game.

fMRI: You may have two fMRI scans approximately one week apart. If you are asked to participate in fMRI scanning, we will either bring you to the fMRI facility at Brown University, about a mile away, or you will meet us there, where you will meet a staff member. While at the facility, you will have a Functional MRI (fMRI) scan which takes a picture of your brain working when you're asked to do certain things. At the beginning of this part of the scan, the research staff will describe the equipment and what you will be asked to do, and answer any questions you have. You will then put on earplugs, lie on the scanner table, and the table will slide you into the scanning area. On a computer screen in front of you, there will be several different computer games to complete, one of which will include seeing images of opioids on the screen. During the whole fMRI, which takes about an hour, you will be able to hear and to talk to the research staff, and you can stop the task at any time. You will have one scan this week, prior to beginning your tDCS sessions, and another about 7 days later. Each session, including travel to and from the scanning facility will take approximately 3 hours. You will be provided transportation (cab rides) for research procedures at Butler Hospital and at the fMRI scan facility, and back home after the appointments are completed.

EEG: In addition to the interview and questionnaires, you will also complete a computer task where you have to match letters to those on screen, lasting approximately 10 minutes. The task is designed to test working memory. During this task, you will have a recording of your brain waves through a noninvasive procedure called electroencephalography (EEG). Neurologists have used EEG for many years to evaluate the functioning of nerves ("neurons") in the brain and to diagnose various neurological conditions. The EEG recording in this research study, however, will not be used to diagnose any specific brain condition. For the EEG procedure, a trained technician will apply a special cap to your head. The cap contains little holes and special surfaces (electrodes) that make contact with the skin on your head to record electrical signals on your scalp. A special gel will be applied to your head through the holes in the cap to enhance the ability to detect the electrical signals from your scalp. Once the cap is on and the gel is applied, you will then sit quietly in a chair while the electrical activity of your brain is recorded. After several minutes of quietly sitting, you will complete the 10-minute computer task while the EEG is recording your brain activity. One EEG session will be completed this week, prior to beginning your tDCS sessions, and another about 7 days later.

Text Messaging

We would like to contact you by text message for the purposes listed below:

1. To schedule research-related appointments
2. To send reminders about appointments

How do Text Communications with CNE Researchers Work?

Text messages from the study staff will be sent from a phone that is dedicated for use in this research study. The phone will not be monitored for return messages constantly, but it will be checked periodically during regular office hours. You can respond to messages from researchers by sending them text messages, but there are only certain things you should communicate via text message.

Risks Related to Text Communication

You should be aware that there are risks associated with sending your health information via text. There is always a risk that the message could be intercepted or sent to the wrong number. Only the research team will have access to your text communications. We will only communicate by text to send you the information previously listed. We will not send text messages that contain urgent information. We will not send text messages to a group of recipients. If you share your mobile phone or messages with others, you risk losing privacy surrounding your health information and loss of privacy surrounding your participation in this study. You should make sure to protect your phone with a password if you send or receive text messages during participation in this study.

Cautions Related to Text~~-~~ Communication with Researchers

Text messages may not be received by researchers on a regular basis. It is possible that a message you send will go unnoticed, or will not be read by the research team for days or weeks. ***You should use the telephone to contact the research team for any urgent matters. Medical issues (symptoms, side effects, injuries, concerns about effects of study procedures, etc.) should NOT be communicated by text message.*** These should be directed to the research staff by telephone or in person. To discuss medical issues, please contact our office at 401-680-4160.

Can we contact you via text messaging? ☐YES_____(initial) OR ☐NO_____ (initial)

Email

We would like to contact you by e-mail for the purposes of sending you web-links, which will take you online to a secure database where you can complete various study assessment forms during participation in this research project.

How do e-mail communications with CNE researchers work?

You will receive an e-mail message from our research team sent to you from a secure Care New England-hosted research data system called "REDCap." The message will include a link for you to click. Clicking the link will securely connect you with REDCap, where you will see your study survey. You will respond by clicking on buttons you see on the screen. The e-mail messages you receive will not identify you by name, and the links to surveys you get through REDCap will be associated only with your e-mail address. Your e-mail address and any other information that personally identifies you will be removed from the final research database when the study is over.

Risks related to e-mail communication

You should be aware that there are risks associated with sending your health information via e-mail. There is always a risk that the message could be intercepted or sent to the wrong e-mail address. E-mail messages from research staff may contain health information that identifies you. Information sent by e-mail could allow others to identify you along with your medical health conditions and psychiatric diagnosis (if applicable). Only the research team will have access to your e-mail communications. We will only communicate by e-mail to send you the information listed above. We will not send e-mail messages that contain urgent information or results of medical tests or diagnostic procedures. We will not send messages that direct you to get medical care.

Using this secure e-mail system will help reduce the chance that you will experience loss of confidentiality when using e-mail. If you share a home computer with other family members and do not want them to know you are participating in this study, make sure you provide an e-mail address that only you can access. Your employer or school will have access to any e-mail communications sent or received on a work or school computer. Additionally, when using any public computer you should be careful to protect your username and password, and make sure you log-out before getting up from the computer.

Cautions related to e-mail with researchers

Study participants are required to send any e-mail messages they write to the research team through this secure system. ***E-mails may not be received by researchers on a regular basis. It is possible that a message you send will go unnoticed, or will not be read by the research team for days or weeks. You should use the telephone to contact the research team for any urgent matters. Medical issues (symptoms, side effects, injuries, questions about medications, concerns about effects of study procedures, etc.) should NOT be communicated by e-mail***. These should be directed to the research staff by telephone or in person. To discuss medical issues, please contact our office at 401-680-4160.

Can we contact you via email? ☐YES_____(initial) OR ☐NO_____ (initial)

Risks and Inconveniences

1) Questionnaires

You may refuse to answer any questions that make you feel uncomfortable and you can stop the interview at any time. Most people do not experience any discomfort during these assessments, but others may find answering these questions upsetting and uncomfortable. We will make every effort to minimize any discomfort you may feel during this process. Interviews will be conducted in a private area in the hospital or via a secured videoconference. You can pause the interview at any time if you need a short break.

All information obtained will be kept confidential. Your responses to the questions will not be linked to any information that can identify you as an individual. Your information will be available only to our research staff.

2) tDCS

tDCS has a risk of skin irritation and temporary redness on your scalp where the sponges and electrodes are placed. Local skin burns are also possible; however, these would be considered extremely rare given the type of tDCS used in this study. Hypomania (feelings of elevated mood or too much energy), has also been reported in a small percent of people who received daily tDCS for depression. In one study where daily tDCS was used for depression with or without antidepressant medication, as many as 5-6% of people developed hypomania. In most cases, the hypomania went away after stopping tDCS or by making adjustments to medications. However, the overall risk of hypomania occurring with tDCS is still unclear. Other effects such as temporary headache, nausea, and fatigue are sometimes reported with tDCS. It is possible that tDCS may have other unforeseen side effects. We will monitor you closely but if you experience discomfort, please tell us immediately. A physician will be on-call during all tDCS procedures. We will also check in with you regularly during your weekly visits about any side effects you may be experiencing.

3) fMRI

There are few risks associated with the fMRI procedure, although some people report feeling nervous inside the loud scanning machine or uncomfortable in small spaces (claustrophobia). MRI may not be safe if you have metal implanted in your body that could interact with the magnetic field in the scanner. Please tell us if you have any metallic tattoos or implanted no removable metal on or in your body. You may experience some frustration from the computer tasks you complete while you are in the fMRI facility. Also, you may experience distress or cravings when you see the images of opioids during the fMRI. At the end of the fMRI session, we will provide you with strategies for managing any remaining distress or cravings.

You will be asked to sign a separate consent form which describes the fMRI risks in more details.

Any medical treatment or procedure may have unforeseen side effects. You should know that the prediction of effects from a treatment or procedure for any individual cannot be done with certainty, and unexpected potentially harmful effects occasionally occur with the administration of any type of treatment. If you have questions about investigational procedures or treatments, or if you experience any disturbing side effects during participation in this study, inform study personnel. In the event of any unexpected, potentially harmful effects of any treatment or procedure administered in this study, we will monitor your condition closely and institute appropriate treatment. If significant new knowledge is obtained through the course of the research which may impact your willingness to continue participation, you will be informed of this knowledge.

4) EEG

EEG recording is considered "noninvasive" and is therefore considered to be generally safe. There are minor inconveniences associated with EEG, such as having residual paste in your hair or on your scalp

after the procedure. The paste can be removed with soap and water but we do not have a facility for you to shower or thoroughly wash your head in the area where the EEG recordings take place. It is possible you will feel some minor discomfort from having your head in contact with the EEG cap. Allergic reaction or skin irritation from the neoprene material in the EEG cap or from the EEG gel is very rare.

Women Please Note:
The effects of tDCS, as used in this study, during pregnancy are unknown. An fMRI scan may be harmful to a developing fetus. Therefore, you may be tested for pregnancy at the time of your admission to the study. Prior to your beginning the study, we will discuss with you in more detail the importance of avoiding pregnancy. We will specifically ask you to let us know if you change your mind and decide to become pregnant during the study.

Benefits
You may benefit by feeling a reduction in your cravings for opiates. However, we cannot guarantee that you will benefit. The main benefits of this study are to help researchers and clinicians develop a better understanding of craving and substance use after starting buprenorphine or methadone.

Economic Considerations
You will receive $75 for the baseline interview, $5025 for each of the 5 tDCS sessions, $75 for each EEG recording session, and $75 for the final interview. If you are asked to participate in fMRI scanning, you will be paid $75 for each fMRI scan. All payments will be in the form of a gift card to a local store or supermarket.

Depending on the amount of payment you might receive for your participation in this study, you might have to provide your name, address, and taxpayer ID or Social Security number to the Butler/CNE Research Accounting Department. In order to receive payment of $300 or more for participation in this research, you will have to complete and sign a W-9 form. If you are paid $600 or more in any calendar year for research participation, the IRS will be notified of the total amount you were paid, in accordance with federal regulations. You should ask the researcher for more information if you have questions about this process.

In Case of Injury
We will offer you services in Care New England facilities as needed to treat any injury that results directly from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for any injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed on the last page of this consent form.

Alternative Treatments/Alternative to Participation
There are no known effective alternative treatments to manage craving or reduce drug use for persons who have recently begun buprenorphine or methadone and are receiving standard medical management.

Financial Disclosure
None

Voluntary Participation
You are free to decide whether or not to participate in this study, and you are free to withdraw from the study at any time. A decision not to participate or to withdraw from the study will not adversely affect your current or future interactions with Butler Hospital or Care New England. Your participation in the study may be terminated by the researchers without regard to your consent; in that case, you are entitled to an explanation of the circumstances leading to that decision.

Confidentiality
Personal identifiers will be removed from any identifiable private information about you (and/or your biospecimens) in the final research dataset created by this study. The de-identified information or biospecimens may be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you (or the legally authorized representative). You will not be personally identified in any reports or publications that may result from this study. The confidentiality of the information you provide to us will be maintained in accordance with state and federal laws. If you tell us something that makes us believe that you or others have been or may be physically harmed, we may report that information to the appropriate agencies.

Clinically relevant research results, including individual research results, will not be disclosed to you. To keep your information safe, we will store all information in locked file cabinets and on password protected secure computer servers. To the extent possible, we store identifying information (such as your name or address) separately from study data (such as questionnaires that you complete). In addition to keeping research data, we will place a note with a brief description of study involvement and procedures (including tDCS procedures) in a Butler Hospital medical record. You will not be identified on audio- or video-recordings and they will be stored on a secure server which is password protected and only accessible to research staff. All identifying information, except what is part of your medical record at Butler, will be destroyed 6 years after the completion of the study. If you tell us something that makes us believe that you or others have been or may be physically harmed, we may report that information to the appropriate agencies.

General information about this study has been or will be submitted to the federal clinical trial registry databank, which can be accessed on the Internet at www.ClinicalTrials.gov.

This research is covered by a Certificate of Confidentiality. Unless you give special written permission, the researchers and Butler Hospital cannot give out any information about you that could potentially identify you or be used as evidence in a legal case (including any federal, state, or local civil, criminal, administrative, or legislative case).

The only situations where researchers would share your information with others are:
(1) when a specific law (federal, state, or local) requires that potentially harmful things be reported to the authorities (such as reporting child abuse, elder abuse or spread of communicable diseases);
(2) when you have given permission (consent) for the information to be shared in order to help your medical treatment; or
(3) when your information will be used for other scientific research, as allowed by federal regulations protecting research subjects.

Authorization for use/disclosure of Health Information that Identifies you for a Research Study
If you sign this document, you give permission to Drs. Abrantes and Stein (Study Directors) at Butler Hospital to use your health information that identifies you, for the purpose of conducting the research study described above.

Your health information related to this study may also be shared with and used by individuals outside of Butler Hospital, including:

- The Brown fMRI facility staff.
- Other healthcare and public safety professionals, if we are concerned that you are at risk of hurting yourself or others.

The health information that we may use or share with others for research purposes includes any information that you give us as part of your study participation, information in your ADP medical chart, and results of any assessments that we do as part of the study that is relevant to the above individuals. We will not collect or share more information than is necessary.

Your health information may also be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, and conducting public health surveillance, investigations, or interventions. The U.S. Food and Drug Administration (FDA) may inspect all study records to ensure that the study is being conducted in accordance with FDA regulations.

Butler Hospital is required by law to protect your health information. Individuals outside of Butler that receive your health information may not be required by Federal privacy laws (such as the HIPAA Privacy Rule) to protect it, so we cannot guarantee that they will not share it without your permission.

Please note that:

- You do not have to sign this consent form, but if you do not, you may not participate in or receive research-related treatment in this study.
- Butler Hospital may not withhold treatment or refuse to treat you, based on whether you sign this consent form.
- You may change your mind and revoke (take back) this consent and authorization at any time. If you no longer want to give us permission to use your health information for this research study, you must contact the Principal Investigators, Dr. Ana Abrantes or Dr. Michael Stein, and you will be instructed to provide a written statement.
- Even if you revoke (take back) this consent and authorization, Butler researchers may still use or share health information about you that they already have obtained, when doing so is necessary to maintain the integrity or reliability of the current research.
- You generally will not have access to your personal health information related to this research until the study is completed. At the conclusion of the research and at your request, you will have access to your health information that Butler Hospital maintains in a designated record set, according to the Notice of Privacy Practices provided to you by Butler Hospital. The designated record set includes medical information or billing records used by doctors or other health care providers at Butler Hospital to make decisions about individuals.
- Your health information will be provided to you or to your physician if it is necessary for your care.
- If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

This Authorization will expire when all the activities associated with this research study have concluded.

Questions

Taking part in this study is entirely voluntary. We urge you to discuss any questions about this study with our staff members, either in-person or by audio/video platforms. You should take as much time as you

need to make your decision. If you decide to participate, you must sign this form to show that you want to take part.

Authorization:
I have read this form and decided that I, _____
(print name of participant)
will participate in the project described above. Its general purposes, the nature of my involvement, and possible hazards and inconveniences have been explained to my satisfaction. I have received a copy of this consent form.

_____ _____
Signature Date

_____ _____
Signature of Principal Investigator Date

~or~

_____ _____
Signature of Person Obtaining Consent Date

Telephone Number of Principal Investigator or Person Obtaining Consent_____

If you have further questions about this project or about research-related injuries, please contact Ana Abrantes 401-455-6440. If you have questions about your rights as a research subject, please contact Paul F. Malloy, Ph.D., Vice Chair, Butler Hospital Institutional Review Board, at 401-455-6355.

THIS FORM IS NOT VALID UNLESS THE FOLLOWING BOX HAS BEEN COMPLETED BY THE IRB OFFICE

THIS FORM IS VALID UNTIL

DATE:

IRBNET ID#

BUTLER IRB REFERENCE#

BY (ADMINISTRATOR):

Grant Number: UH3DA047793

Title: tDCS to Decrease Opioid Relapse

MPIs: Ana Abrantes, PhD and Michael Stein, MD

Medical Monitor: Dr. Michael Stein

2. Summary of the Protocol:

2.a, 2.b Brief Description of the Protocol, Primary and Secondary Outcome Measures

This study has two phases. In phase one (UG3), we propose to use functional magnetic resonance imaging (FMRI) and electroencephalographic (EEG) to quantify changes in brain function and reported craving before and after administration of five sessions of transcranial direct current stimulation (tDCS) targeting the right dorsolateral prefrontal cortex (DLPFC). Opioid dependent participants (n=60) who recently initiated buprenorphine or methadone will be randomized to tDCS+Cognitive Control Network (CCN) priming stimulation vs. sham tDCS+CCN priming. Participants in their first month of prescribed buprenorphine or methadone will be assessed using FMRI and EEG, once prior to tDCS and again one week later after completion of 5 sessions of tDCS+CCN priming. With a focus on the craving outcome, we will use two task-based FMRI paradigms that challenge networks associated with craving (CR) and cognitive control (CCN), and will examine these and the salience network using resting state functional connectivity. We examine an additional validation measure of the effect of tDCS on the DLPFC – an oscillatory target -- EEG frontal theta power during working memory(WM). In this UG3 phase, FMRI and EEG will be expected to provide 1) validation of expected network and oscillatory changes from tDCS-targeting and 2) an effect size for DLPFC vs sham stimulation. Go/no go criteria for the UG3 phase will be demonstration of greater FMRI change in any node of the CR *or* CCN networks *or* enhanced frontal theta power during a WM task AND greater change (at least 10% difference between conditions, controlling for baseline craving) in subjective craving measured during a cue reactivity task *or* outside the FMRI following the tDCS+CCN priming intervention compared to sham tDCS+CCN priming.

In the present study, we elected to keep aspects of the tDCS protocol consistent with prior studies. That is, we will place the anode over the right DLPFC (F4 on the EEG 10-20 system) and the cathode over the left DLPFC (F3) using 25cm^2 sponges at an intensity of 2mA. Stimulation will be delivered via two saline-soaked surface sponge electrodes and a battery-driven, constant current stimulator (NeuroConn DC Stimulator Plus). This device includes a study mode, in which subject-specific codes are entered to deliver active or sham stimulation, keeping the administrator blinded. Sham stimulation will use a method in which stimulation will be ramped up and back down over a 30-second period at the beginning and end of sham tDCS. This approach has been found to be an effective sham condition in previous studies using tDCS at 2mA with no difference between sham and active tDCS groups in guessing their group assignment. Each participant will receive 20-minutes of either active or sham tDCS +CCN priming during each of the five sessions. During the final 15 minutes of each stimulation session, once a participant is settled, s/he will engage in standardized tests from the NIH Toolbox that engage the CCN (i.e. CCN priming): Flanker Inhibitory Control and Attention Test, List Sorting Working Memory Test, and Dimensional Change Card Sort Test).

The optimal frequency, duration and number of tDCS sessions to maximize effects on craving, or any other construct in this young field, remain obscure. We chose to deliver 5 sessions of tDCS because this number has been used in prior successful tDCS craving interventions and must be balanced against adherence concerns. While we are hopeful that participants will complete 5 consecutive days of tDCS, the interruption of weekends and the transition from the ADP setting (where the tDCS protocol will start) where days are structured, to the community setting, raises the possibility of missed tDCS sessions and therefore we will allow these 5 sessions to occur over 10 days if necessary, as has been described in prior studies, tracking both average number of sessions received and period of treatment for analyses. The sham tDCS condition is included in our design to separate the effects of ongoing opioid treatment from the effect of active tDCS on craving. We decided not to include a third no-tDCS arm, as this would omit any nonspecific treatment effects (match for attention, expectation) of entering a neurostimulation treatment protocol. This protocol will provide a basis for future studies of tDCS stimulation parameters (frequency, duration, number) that could optimize adherence and treatment effects of drug use outcomes.

In phase two (UH3), we will perform a larger RCT using the same treatment protocol in 100 opioid dependent participants who recently initiated buprenorphine or methadone. Participants will be randomized to receive five sessions of tDCS+CCN priming stimulation vs. sham tDCS+CCN priming. Phase two will address long-term (3-month) neurobehavioral outcomes, including opioid relapse, craving, and sustained fMRI changes during a paradigm that challenges networks associated with craving (CR) and cognitive control (CCN). During the 12 weeks of opioid maintenance treatment, we will examine our primary clinical outcome, relapse (opioid use on >4 days per month and having an opioid positive urine screen), as well as days of opioid use.

2.c Inclusion/Exclusion Criteria:

UG3/UH3 Inclusion Criteria: (a) current opioid dependence, (b) between 21-50 years of age, (c) recent initiation of buprenorphine or methadone (<30 days)

Exclusion Criteria: (a) diagnosis of organic brain disorder, bipolar disorder, schizophrenia, schizo-affective, schizophreniform, or paranoid disorder, (b) current suicidality, (c) evidence of neurocognitive dysfunction, (d) contraindications for tDCS (e.g seizure disorder), (e) probation/parole requirements or an upcoming move that might interfere with protocol participation, (f) planning to terminate buprenorphine or methadone in less than 3 months, and (g) scalp lesions near the tDCS electrode sites.

Exclusion Criteria related to FMRI scanning are: (a) history of neurological disorder (e.g., epilepsy, stroke, brain injury with loss of consciousness>10 min), (b) impaired uncorrected vision, and (c) MRI contraindications (e.g., claustrophobia, specific metallic implants and injuries, and pregnancy).

tDCS-related considerations: Careful consideration will be given when determining whether tDCS is safe for potential participants. Additional exclusion criteria related to tDCS include: metal implanted in the cranial cavity, pacemaker, poor cognitive functioning (i.e., Alzheimer's disease or dementia), history of neurological disorder (e.g., epilepsy or other seizure disorder), or other significant or chronic medical conditions that affect the brain (e.g., Parkinson's disease, Huntington's disease, multiple sclerosis, traumatic brain injury). Dr. Stein will have the final decision regarding whether a participant is medically stable enough to engage in this trial.

2.d Power Calculation and Sample Size:

In the UG3 phase of this project, we plan to enroll 60 participants. With an expected attrition rate of 20% (data loss over two sessions due to poor performance or movement artifact—a conservative estimate that is a larger loss than in our ongoing FIRST study), our final sample size will be 48, or 24 per group. This number provides 82% power for the expected effect size of .75, chosen based on prior tDCS studies and our belief that a large effect size should be required to continue to the UH3. In the UH3 phase, we again anticipate a 20% attrition rate over the 5 tDCS sessions and initial two FMRI scans. If the third scan (at 4 weeks) is missed, we expect this will be due to treatment drop-out or relapse. With 100 participants enrolled, we will have a final sample of 80 patients which provides a power of .8 to detect a group difference in relapse between relapse and sham of 15% vs 39% at 3 months follow-up.

Effect size estimates for baseline differences in FMRI signal based upon subsequent lapse are not available; however we have taken steps to maximize our ability to detect group differences, if present. First, we will use ROI methods, which focus our analyses on more functionally homogenous brain regions related to each task. Therefore, we predict larger and less variable effect sizes. Second, we have chosen FMRI paradigms with which we have already obtained reliable and valid response patterns. Third, the constructs that we propose to assess in FMRI paradigms are significantly related to relapse in behavioral studies.

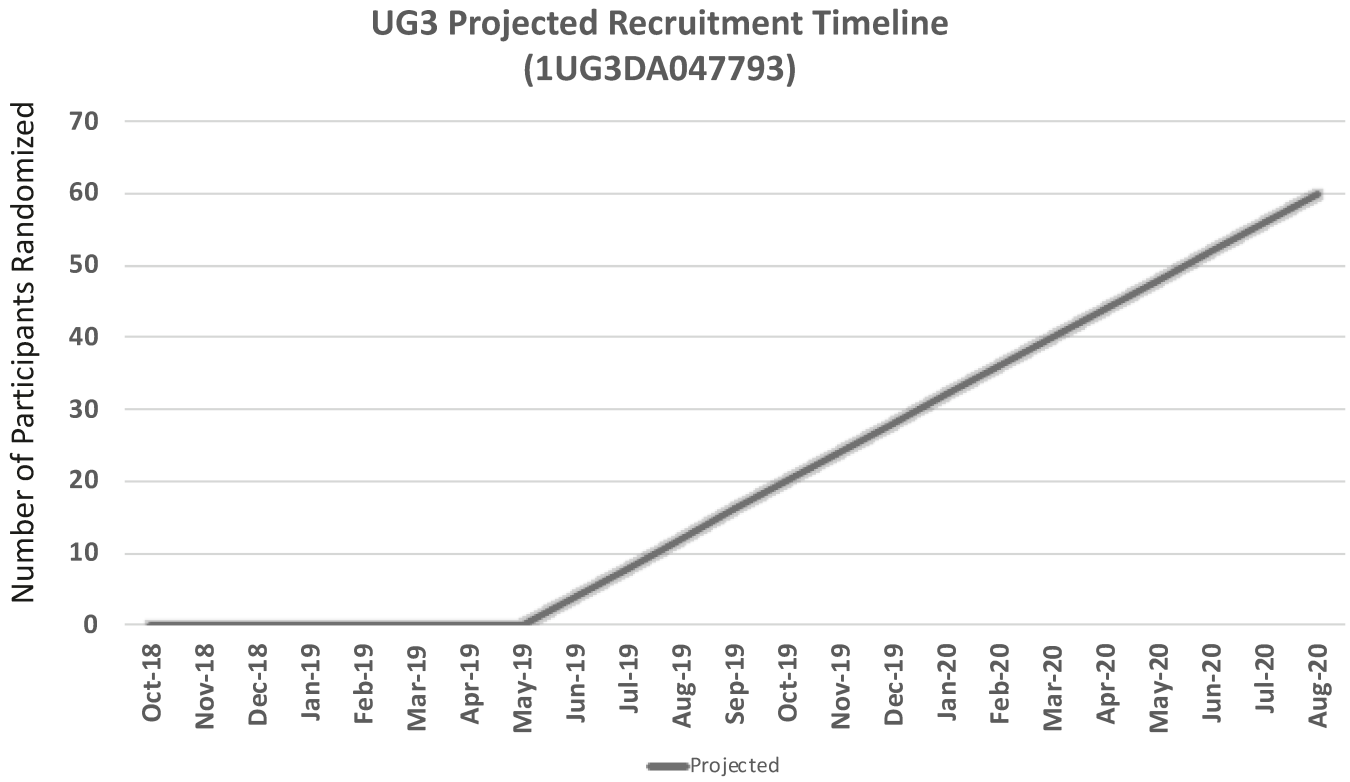
3. Trial Management:

3.a List of Participating enrolling clinics or data collection centers

1. Butler Hospital Alcohol and Drug Partial Hospital Program (ADP)
2. Butler Hospital Alcohol and Drug Inpatient Detoxification Program (ADI)
3. Community Advertisements

3.b Projected Timetable

After staff hiring and training, FMRI programming, and establishing EEG procedures, participant recruitment will begin in month 8 of the UG3 (see below for projected recruitment Timeline). If we proceed to a UH3, we will recruit 100 participants from months 1-29 with the final assessment at month 32. This will leave months 33-36 for data analyses and final manuscript preparation.



3.c Target Population Distribution

In order to increase the percentage of minority subjects in the study, we will over-sample for these groups in our recruitment procedures to obtain a sample that is at least 10% African American and 20% Latino.

Women will be included in this study. We anticipate that the sample will be approximately 40% female based on our experience with previous intervention studies with buprenorphine patients.

4. Data Management and Analysis

4.a, 4.b Data Acquisition and Transition and Data Entry Methods

Drs. Stein and Abrantes will have primary responsibility for the day-to-day monitoring of the quality of operations in all data collection. All data collected by the research team are considered part of the subject's confidential record. There are several sources of data. In most cases, data from assessments will be directly entered into the research database. Research assistants will also code all data from research interviews that is not directly entered. This coded data will be entered into the research database. Audiorecordings of interviews with participants will be uploaded and stored on a secure server in a digital format. A study ID will be used to identify the recordings. Otherwise they are not connected with the primary study database in any way.

All data will be collected for research purposes only and all records will be stored in locked files (physical or on computer) in locked rooms accessible only to research staff. Data gathered from people are screened but who do not meet inclusion criteria or decide not to participate will be stripped of personal identifiers or links and only demographic characteristics and the reason for study exclusion will be kept. Paper forms with personal identifiers (such as consent forms or contact information) will be stored in a locked file that does not contain subject code numbers. All other data will be stored in files locked in a separate location with only code numbers identifying subjects, no personal identifiers. A cross-index of code numbers and participant names will be kept in a separate, password-protected computer file that is available only to research staff (for collecting follow-ups), the PIs, and mandated auditing agencies during audits.

All de-identified research data will be entered into REDCap. REDCap is a secure, web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails, and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). Participants may complete surveys in the laboratory or anywhere they can access a web browser, including on their Internet-connected smartphone or tablet. The system was developed by a multi-institutional consortium and was initiated at Vanderbilt University. The CNE RedCap is hosted on a CNE-based server. Network transmissions (data entry, survey submission, web browsing, etc.) in REDCap are protected via Secure Sockets Layer (SSL) encryption. Access to REDCap can be restricted at different levels (e.g., research assistant, PI, and Co-Investigators). Exported data from REDCap will be stored on the Behavioral Medicine and Addiction Research's secure password-protected server.

Final Storage of Paper Data. Only the participants' study identification number will appear on any of the final paper data collection instruments. Once data have been entered and passed audit verification, paper copies of data will be housed at a facility that specializes in the storage of medical/research information. Only the subject's study identification number will be present on the forms. Any indication of the subject's name will be removed from the questionnaires prior to archiving. The destruction date of these paper files will be at least 7 years from the termination of the study and will be authorized by the Principal Investigator of the research study.

4.c Data Analysis Plan

Neuroimaging. In the UG3, three sets of analyses will be conducted to examine task-based responses to 1) the CR (craving) and 2) n-Back (CCN) challenges, and 3) tonic changes in network coherence at rest.

1) CR: Two 2x2 mixed ANOVAs will be used to determine whether mean response to cues during CR decline across nodes of the craving network (VS, amygdala, VMPFC), including salience network (AI, ACC) and increases in the CCN (MFG, IPL). Significant pre-post main effects and group x treatment interactions are predicted in each. Those who received tDCS+CCN priming are expected to exhibit greater change. Follow up analyses of individual nodes within each network and whole-brain voxel-wise contrasts will be conducted to inform phase 2 analyses.

2) n-Back: Two 2x2 mixed ANOVAs will be used to determine whether mean response to the n-Back challenge increases across nodes of the CCN (MFG, IPL) and the salience network (ACC and AI). Significant pre-post main effects and group x treatment interactions are predicted in each. Those who received tDCS are expected to exhibit greater change. Follow up analyses of individual nodes within each network and whole-brain voxel-wise contrasts will be conducted to inform phase 2 analyses.

3) Resting state: Two 2x2 mixed ANOVAs will be used to determine whether mean network coherence (functional connectivity) decreases across nodes of the craving network (VS, amygdala, VMPFC), including the salience network (AI, ACC) and increases in the CCN (MFG, IPL). Significant pre-post main effects and group x treatment interactions are predicted

in each. Those who received tDCS are expected to exhibit greater change. Parallel exploratory analyses will be conducted to examine resting state functional connectivity of the salience network and DMN.

In the UH3, neuroimaging analyses will generally parallel those described for UG3. We will use a 2x3 ANOVA (three time points) to test the hypothesis that tDCS+CCN priming will be superior to sham tDCS+CCN priming on both subjective and fMRI measures of craving and cognitive control at the end of 5 sessions and at 3-months post tDCS. This same analytical method will be used to test the effect of intervention on days of drug use at the end of 5 sessions and at 3-months. We will use the Pearson χ^2-test of independence to compare tDCS+CCN priming to sham tDCS+CCN priming on relapse at 3-months.

FMRI data analyses

Whole-brain echoplanar FMRI will be conducted using a Siemen's TIM Trio 3.0 T scanner (TR/TE 2500/28ms, FOV=192^2 mm, matrix=64^2, 3mm axial slices). Volumes acquired will be 228 for the 2-Back, 384 for CR, and 120 during the rest-only imaging run. This procedure yields BOLD signal values across time for each voxel. A whole-brain, high-resolution (FOV=240^2, matrix=256^2) MPRAGE series will be conducted in 1mm sagittal slice thickness for anatomical reference. All FMRI processing and statistical analyses will be conducted using AFNI software. Data from subjects who exhibit invalid response patterns will be excluded. Processing includes concatenation of imaging runs, movement correction, slice-time correction, band pass frequency filtering, removal of linear drift, and application of a 6mm Gaussian kernel. For active tasks (n-Back and CR), GLM will be used to quantify task-related effects per voxel. Task-related response will be calculated compared to the appropriate active control tasks. The time course of the challenge of interest (2-Back blocks or opiate cues [CR]) and active control tasks (0-Back blocks or neutral images presentations [CR]) will be separately convolved with a gamma function and used as predictors. These procedures generate individual activation maps of task-related effects per voxel. These individual datasets will be used as dependent measures in tests of our hypotheses using ROI analyses following quality control checks and stereotactic standardization.

A priori task-based FMRI ROI analyses will be our primary method for quantifying changes in the craving, salience and cognitive control networks and subsequent hypothesis testing, while analyses involving the functionally defined ROIs will serve to validate our a priori findings. Mean task-related effect will be determined for each ROI of each individual for each condition of each task by averaging all voxels of each ROI. Results of these quantifications will be used as dependent measures in hypothesis testing. In primary analyses, mean effects will be examined across all nodes of each network, followed by analyses of each network node. Functional connectivity analyses will be performed on all networks during crosshair fixation (resting). We will use the seed region method. Briefly, BOLD signal will be averaged from four 3mm3 seed voxels at the center of mass of each ROI of each network (see Table 1) and extracted for each of the time points acquired. These reference series files will be used as predictors in one voxel-wise GLM analyses per ROI to identify the strength of the relationship between each brain voxel and the average of the seed region over time. Each a priori region will serve as a seed region once for its particular network. After Fischer's transformation from r-values to z-values, the resulting mean voxel-wise values will be averaged in each target node (i.e., ROI not serving as the seed) following each GLM. For CR, these target ROI averages will then be averaged across two seed region iterations (i.e., excluding the seed region; this step is not needed for the 2 ROI salience networks). The resulting means for the nodes of each network will be averaged across ROIs (3 for craving, 2 for salience, 3 for CCN) to derive a network coherence metric. Substance use type (heroin, prescription pills) will be included as a covariate in statistical models.

EEG analyses.

EEG Data Processing. Semi-automatic preprocessing for artifact detection will be performed using the FASTER algorithm (Nolan, Whelan, & Reilly, 2010). This EEGLAB toolbox uses Welch methods and removes muscle, heart, motion, ocular artifacts, and other noise using a multiple step procedure consisting of a) bandpass and notch filtering, b) Independent Component Analysis (ICA), c) rejection and/or interpolation of bad channels/epochs. The final step of preprocessing includes visual inspection of the data rejecting any remaining artifactual epochs. Windows of 1400 ms (1100 -2500 ms after stimulus onset) will be included in analysis. Theta band (4 -8 Hz) power in frontal (Afz, Fz) electrodes will be averaged across both n-back levels.

Working Memory and EEG Summary Indices. Working memory performance at each assessment will be represented by d' to capture executive skills without influence by demographic variables, psychiatric status, or intelligence quotient (Haatveit et al., 2010). For each participant, and within each n- condition, values for d' will thus be calculated by dividing the difference of Z (false alarms) and Z ("hits") by the root mean square of 2; d' captures the participant's ability to discriminate between the two stimulus types (i.e., the 2-back target letters and the non-target letters). Difference in theta power between 0-back and 2-back conditions (∆theta) will also be calculated at EEG/n-back assessment. Comparison of pre- versus post-treatment ∆theta will test the primary hypothesis that opioid dependent participants who received the active tDCS intervention will show greater increases in theta power after 5 intervention sessions than sham tDCS recipients. Estimation of power spectrum density (PSD) values in the beta band (13-30 Hz) will be computed and averaged from channels in four regions (frontal, central, temporal, and occipital-parietal) for analysis in relation to craving scores.

EEG outcome measures analyses**.** We will conduct a repeated-measures ANCOVA with a within-subject factor of time (baseline and end-of-stimulation (EOS)), between-subject factor of intervention condition (active tDCS and sham) and covariates to test if there is a statistically significant difference in in the EEG outcome (∆theta) across treatment groups. Pearson correlations will be used to examine beta PSD values in relation to craving scores. A separate ANCOVA with the same factors will be used to explore treatment group differences in resting state EEG beta PSD values. Covariates for both analyses will include the baseline measure of the evaluated outcome, as well as baseline variables found to vary significantly ($p < 0.05$) by intervention arm, or which significantly ($p < 0.05$) predict attrition at EOS. Post-hoc t-tests will be used to probe anticipated significant interactions.

5. Quality Assurance

All research personnel, will have formal training in research with human subjects (e.g., CITI training, NIH Human Subjects training). Drs. Abrantes, Stein, and Carpenter will provide training to and supervise research assistants. Research assistants will also have training in Good Clinical Practice.

Drs. Stein and Abrantes will be responsible for quality control of this study. They will review recruitment and retention reports, and AE reports on a weekly basis. The MPIs (or their designee) will inspect BL documents (consent forms, release of information) for completeness within a week after they are signed. The MPIs (or their designee) will also conduct protocol and data quality monitoring twice a year using a checklist. This monitoring will include reviewing other study records to ensure completeness.

6. Regulatory Issues

6.a, 6.c Reporting of SAEs, Non-Medication Trials

Drs. Abrantes and Stein will be responsible for overseeing the daily safety of all participants. There are several ways in which they will become aware of adverse events. First, research staff will ask participants about serious adverse events (as defined by Office of Human Research Protections (OHRP); e.g., inpatient hospitalization) at each research contact point (UG3: baseline, week 2 assessment, 5 tDCS appointments, 2 FMRI; UH3: baseline,

week 2, 4, 6, 8, 12 assessments, 5 tDCS appointments, 3 FMRI). For monitoring expected adverse effects of tDCS, we use the SAFTEE at each session that includes changes in physical health status. Deaths are reported by significant others when we try to locate participants who missed appointments. Butler Hospital has a psychiatric emergency room available 24 hours a day. All research procedures will be supervised by Drs. Stein and Abrantes who will be on call 24-hours a day.

Second, all study staff will be trained in the OHRP definitions of adverse events that are also unanticipated problems; serious adverse events; or unanticipated problems that are not adverse events. All study staff are required to report any event that might meet one of these criteria to one of the PIs immediately both verbally and in writing. When necessary, a report of a serious adverse event will result in one of the PIs contacting the participant to further assess the event.

Drs. Stein and Abrantes will meet weekly with research assistants to review staff experiences with participants. Based on the sources of information detailed above as well as direct patient contact and/or consultation with the scientific team, Drs. Stein and Abrantes will determine if the event is: a) a serious adverse event that is also an unanticipated problem; b) an unanticipated problem that is not an adverse event. The Butler Hospital IRB require that fatalities related to the study be reported within 24 hours, all other serious adverse events related to the study be reported within 5 business/7 calendar days, and other serious adverse events related to the study be reported at the continuing review (at least annually).

6.d Reporting of IRB Actions to NIDA

All SAEs will be reported to NIDA within 72 hours of the MPIs becoming aware.

6.e Report of changes of amendments to the protocol

Changes to the proposal must be approved by NIDA prior to implementation

6.f Trial stopping rules

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) any new information becomes available during the trial that necessitates stopping the trial; or

6.g Disclosure of Conflict of Interest

Ana Abrantes: None
Michael Stein: None
Linda Carpenter: None
Lawrence Sweet: None

7. Trial Safety

7.a Potential Risks and Benefits for Participants

Potential Coercion.

Risks. It is possible that individuals may feel coerced into participating.

Minimization. Issues related to coercion can arise from the payments that participants can earn from assessment participation. The payments made amount to approximately $20 per hour as compensation for assessment and travel time. This rate is consistent with local standards for research.

Risks due to tDCS.

Risks. There is some inherent risk with application of tDCS, mainly risk of skin irritation and, as in a small number of case reports, local skin burns where the electrodes are placed. Such cases have typically been seen only after repeated daily stimulation to the same region (Palm et al., 2008), or after unintentional abrasion of the skin with alcohol swabs prior to

stimulation (Loo et al., 2011). Though a possible risk, skin burns are rare. In a recent review of clinical research with tDCS, Brunoni and colleagues (2012) noted that "tDCS has been tested in thousands of subjects world-wide with no evidence of toxic effects to date." The most common side effects include mild local sensations at the electrode sites, including tingling or itching, and moderate fatigue, and headache. In research experience totaling 567 tDCS sessions, Poreisz and colleagues (2007) reported that no participants requested tDCS be stopped or required any medical intervention during or after stimulation. Notably, adverse effects did not differ between healthy individuals and patients. Safety testing of tDCS has found high tolerability and no reports of discomfort by participants when stimulating for 20 minutes at either 1 or 2mA for 20 minutes (Iyer et al., 2005). There have also been a small number of case reports of hypomania induction during tDCS for depression interventions, in both individuals with bipolar and unipolar depression (Arul-Anandam, Loo, Mitchell, 2010; Galvez et la., 2011; Baccaro et al., 2010). Most recently, Brunoni, et al (2013) reported during a factorial design testing tDCS and the antidepressant sertraline, 7 of 120 participants developed mania or hypomania, with 5 of the 7 cases occurring in the combined tDCS+sertraline group. As the participants in that study were all drug-free prior to study entry, it is unknown whether this was due to starting an antidepressant medication, tDCS, or the combination.

Minimization. To minimize risks due to tDCS, all participants will be carefully screened prior to tDCS for contraindications to tDCS. Those with a history of mood symptoms suggesting risk for hypomania or bipolar disorder will be excluded. Use of an electrically isolated power source (i.e., battery-powered DC stimulation device) also protects against delivery of more intense currents than intended. Participants with lesions or open wounds on the scalp will be excluded. Participants will be closely observed for signs of skin burns, discomfort, or other stress. During stimulation sessions, participants will be closely monitored to ensure the electrode sponges stay moist with saline (to enhance conductivity) and in good contact with the scalp in order to help prevent burns. Participants will have the option of discontinuing the study at any time and will be explicitly instructed to inform the tDCS administrator immediately if they experience any discomfort. The tDCS administrator will inform the supervising physician about any participant who has significant discomfort or a skin lesion that emerges after tDCS delivery. A Butler Neuromodulation Research Facility covering physician is available during all procedures to evaluate any participant or research staff identifying a concern related to study procedures. If there is any doubt about the mental or physical status of an individual before or after testing, the supervising physician will evaluate the participant and make a recommendation for cancelling the research procedure and /or arranging follow-up care, as indicated. Telephone or in-person follow-up will be arranged as needed and will not be considered a protocol deviation. Any participant that has experienced adverse effects will be evaluated, treated as necessary, and withdrawn from the study if deemed necessary.

All tDCS will be administered by a trained member of the research staff who is supervised and credentialed by Dr. Carpenter. Butler Neuromodulation Research Facility fees include access to a covering physician with neuromodulation training who is versed in the procedures of the study and is available to supervise or consult on tDCS administration in this study. This physician will be immediately available for management of emergent events. Prior to administering tDCS in this protocol, all staff involved in administration of tDCS will be required to undergo training and demonstrate competence in the safe delivery of tDCS. Certification in Basic Cardiac Life Support, HIPAA, and Good Clinical Practices training are also required for use of the Butler Neuromodulation Research Facility. There are multiple components of training required of investigators and staff in order to be able to administer tDCS, including initial didactic training to introduce concepts critical to tDCS, direct observation of tDCS procedures, practice of the various steps of setting up/administering tDCS on non-patient volunteers, including role-plays of scenarios of when the covering physician should be consulted to further address adverse events related to the study protocol, and demonstration of competency in all aspects of relevant subject assessment and in administration of the entire

tDCS procedure under direct observation of a qualified tDCS administrator. Competence in specific aspects of the procedure comprising best practice standards for tDCS will be documented and updated every 2 years. Subject feedback will be solicited to further aid training and refine the skills of research staff delivering tDCS in this protocol.

In order to assess for and monitor presence and tolerability of adverse effects, we will use a modified version of a tDCS Side Effects Questionnaire informed by Brunoni and colleagues[11]. This is a 10-item measure that assess such effects as headache, neck pain, scalp pain, skin redness, sleepiness, difficulty concentrating, and acute mood changes. The measure will be administered after each tDCS session. For each item, participants are asked to report how bothersome each symptom on the form has been with response options "None," "Mild," "Moderate," or "Severe." For any item rated "severe," or any item which appears to significantly increase in severity over the course of the session, the evaluator will notify the covering physician immediately and the covering physician will provide further evaluation as medically necessary. tDCS administrators are encouraged to contact the covering physician about any additional tDCS related concerns and this will not be considered a protocol deviation. Reported side-effects endorsed will be reviewed during weekly meetings of study staff. Follow-up or further evaluation will occur as necessary.

In addition, in order to monitor participant safety during the intervention period, we will also have participants complete self-report measures to assess for increased manic or hypomanic symptoms (from the Altman Self-Rating Mania Scale (ASRM)). The ASRM will be administered at baseline and prior to the first and last session of tDCS (sessions 1 and 5). Scores ≥ 6 will be considered clinically significant and will require evaluation by a study clinician. Further, we will assess significant changes in affect such as anxiety/activation/anergia/sedation from the PANAS scale at the baseline and week 2 follow-up assessment. Lastly, changes in frequency and dosage of any medication will be monitored at every participant contact time point. The study physician will monitor affective symptom changes and make determinations as to whether the participant should discontinue the intervention and receive additional mental health treatment.

Risks due to FMRI.

Risks. The primary FMRI contraindications are claustrophobia, metal implants, and pregnancy. Some individuals may experience discomfort from loud noises inside the scanner.

Minimization. FMRI contraindications, such as claustrophobia or metal implants, will be assessed at the time of study screening and again on the day of the scan by research staff. The MR technician, who is trained by the Brown University FMRI facility staff in safety procedures, will also screen for these concerns immediately prior to the scan and will be responsible for participant safety during the scan. A pregnancy test will be required prior to study inclusion for all females who report the possibility of being pregnant.

Risks due to cue-reactivity task.

Risks. There is a risk that participants will find the exposure to opioid-related images (e.g., needles, pills) during the cue-reactivity task distressing, due to the task's intended goal of eliciting craving.

Minimization**.** We have developed a standardized protocol for minimizing distress related to the cue-reactivity task that will be administered to all participants at the end of the fMRI imaging session. First, participants will be given a tailored, pre-generated list of their personal motivations for opioid abstinence. Second, participants will be given a handout with a list of various coping strategies (e.g., go to a meeting, call a friend/sponsor, deep breathing, mindfulness exercises, etc.). Third, based on the empirical support for playing Tetris as a craving reduction strategy (Skorka-Brown, et al., 2015), they will play a game of Tetris on a study iPad for 5 minutes. Fourth, they will be encouraged to use that day's usual, prescribed buprenorphine or methadone dose. Lastly, Drs. Abrantes and Stein will be available to talk to any participant who continues to feel any distress following these minimization procedures.

Emotional Discomfort due to assessments and/or intervention procedures

Risks. During the assessments we will ask participants about their thoughts, feelings, behaviors, and symptoms. It is possible that asking participants about this information may increase distress or discomfort. In addition, participants may become bored or tired during the EEG assessments and tDCS+CCN sessions.

Minimization. To minimize the risk of distress arising from the assessment procedure, only study staff that has been adequately trained in the assessment battery will complete all assessments, and senior study staff will supervise all assessment procedures. Individuals will also be advised that they may choose not to answer any question which they find upsetting. Further, during EEG and tDCS+CCN sessions, participants will be reminded they can stop the procedure at any time, if they get tired. All study procedures will be explained to the participants with an emphasis on the voluntary nature of the study. Furthermore, staff members will be trained to respect participants' wishes regarding their participation in the study or certain aspects of the study's procedure. There is minimal, if any, additional risk in having EEG data recorded; EEG is a safe and painless noninvasive technique that is routinely used in clinical medicine.

Benefits

Participants may benefit by feeling a reduction in their cravings for opiates. However, we cannot guarantee that they will benefit. The main benefits of this study are to help researchers and clinicians develop a better understanding of craving and substance use after starting opioid treatment.

7.b. Collection and reporting of AEs and SAEs

See 6.a

7.c Management of SAEs and other study risks

See 6.a and 7.a.

8. Trial Efficacy

8.a Plans for interim Analysis of efficacy data

Go/no go criteria for the UG3 phase will be demonstration of greater FMRI change in any node of the CR *or* CCN networks *or* enhanced frontal theta power during a WM task AND greater change in subjective craving measured during a cue reactivity task *or* outside the FMRI following the tDCS+CCN priming intervention compared to sham tDCS+CCN priming.

9. DSM Plan Administration

9.a Responsibility for data and safety monitoring

The Data Safety Monitoring Board will be comprised of 2 individuals independent from this research project. No member of the board will be a collaborator with the MPI on any other studies or have co-published with the MPIs in the past 3 years. They will be qualified to review the patient safety data generated by this study.

They will review rates of adverse events to determine any changes in participant risk and will make appropriate recommendations for changes in protocol, which will be submitted to the Butler Hospital IRB and NIDA for review.

9.b Frequency of DSM

Study progress and safety will be reviewed by the MPIs monthly (and more frequently if needed). Semi-annually, a progress report will be generated for the DSMB's review. The full DSMB will be convened twice per year to review the semi-annual report and discuss data and participant safety.

9.c. Content of DSM Report

The DSM report will include a brief description of the aim of the trial, baseline and demographic information, recruitment and retention, regulatory issues or data quality issues that have arisen, and AE/SAEs. The DSM report will be sent to the NIDA Program Officer annually.

The study team will specifically generate the following for the DSM report:

Interim CONSORT document (number screened, number consented, reasons not eligible, status of all participants enrolled in the study, number completed the study vs. withdrawn)

Actual vs. expected enrollment numbers

Gender, age, race, and ethnicity of enrolled participants

List and description of deaths, unanticipated problems, and SAEs

Summary table of AEs

List of protocol deviations, if any

Ongoing quality assurance and quality control procedures and findings.

The DSMB will determine whether 1) AE rates are with pre-study assumptions, 2) whether continuation of the study is justified, and 3) conditions under which the study would be prematurely terminated.

10. DSM Board Plan

10.a Members and Affiliation

Noah S. Philip, M.D. – Director of Neuropsychiatric Modulation at the Providence Veterans Affairs Medical Center; Associate Professor of Psychiatry and Human Behavior at the Alpert Medical School of Brown University.

Edward V. Nunes, M.D. – Deputy Director of Intervention Studies at the New York State Psychiatric Institute; Professor of Psychiatry at Columbia University Medical Center.

10.b Frequency of Meetings

See 9.b

10. c Conflict of Interest

Pending

10.d. Protection of Confidentiality

Only de-identified data will be presented in DSMB reports.

10.e Monitoring Activities

See 9.a

10.f Communication plan to IRB, NIDA, and FDA

DSMB reports will be submitted to both the Butler Hospital IRB and NIDA.

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