Protocol Title	Combining Neuro-Imaging and Non-Invasive Brain Stimulation for Clinical Intervention in Opioid Use Disorder
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PROTOCOL COVER PAGE

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
6	**220211**	● **Added recruitment of buprenorphine subjects.** ● **Added mail ads as a source of recruitment** ● **Proposed adding review of medical records as a source of recruitment.**	**Yes**
5	210830	● 3.1: Corrected a typo. ● 11: Added recruitment sites and methods ● Expanded recruitment methods ○ Expanded sites to methadone clinics in Twin Cities area ○ Allowed for referral via clinical staff colleague ○ Expanded recruitment to community advertisements ○ Added recruitment tablet	No
4	210615	● 3.2, 5.2: Removed references to Rey subtests from cognitive battery as they are not needed for grant milestones. ● 4.0 Study Intervention(s)/Investigational Agent(s): Removed description of unused Starstim device system, updated description of Taskflow device system. ● Raised cap on recruitment in order to meet goal of 30 completed participants ○ 5.1, 10.0: FROM "up to 40" TO "up to 250" ● Lengthened treatment window to allow protocol to be more compatible with participants' busy schedules ○ 5.2: Separate Days 2, 8, and 14 into 2 visits each ○ 5.2: Change sentences to lengthen window of initial 14 visits from 30 days to two months ○ 5.2: Change sentences to lengthen treatment window 2 weeks for each of the 5 tDCS sessions ○ 5.3: Change anticipated study duration FROM 2.5 months TO 2.5-4 months.	Yes

		● Changed exclusion in order to more accurately represent the MAT population ○ 8.2: FROM "any stimulant use in the past 30 days)" ○ TO "stimulant use greater than 10 days in the 30 days prior to enrollment" ● Changed compensation distribution (but keep total amount the same): ○ 11.4: Increased tDCS visit compensation for each of the 10 tDCS visits FROM $10 TO $15 ○ 11.4: Decreased Follow-up 2 visit compensation FROM $100 TO $50	
3	200217	● Replaced all references of "WAIS-WISC" with "WAIS" for simplicity ● Abbreviations": Replaced reference to MINI Version 6 with MINI Version 7. ● 5.0: Specified that WAIS and D-KEFS will be administered on the digital platform Q-Interactive. ● 5.2: Replaced "reversal learning task" with "executive functioning tasks" ● Added locations for study visits ● Section 22: Clarified Multi-Site section ● Secton 9.1: Checked "None of the above" ● Added language to accommodate a flexible schedule of events ● Removed Rey Visual Memory Test ● Corrected minor errors and formatting errors	No
2	190806	● Added second tDCS device ● Modified task delivery platform description ● Changed length of time for tDCS delivery ● Changed cognitive training software ● Change total recruitment from "30" to "up to 40" ● Added notice of video and audio recording to consent form ● Added second tDCS device ● Changed cognitive training software	Yes

		• Added language to address tDCS voltage adjustments for subjects in the event of discomfort • Added language detailing protection of vulnerable populations • Remove reference to probation or parole • Change total recruitment from "30" to "up to 40"	
1	190301	Change procedures in protocol, including: Addition of 5 sessions for a total of 10 tDCS sessions, addition of a midpoint assessment and MRI after 5 tDCS sessions to assess interim safety and progress; change in compensation proportional to the additional study visits; addition of the Timeline Follow Back instruments to study assessments; addition of drug screens (urine/saliva) as often as weekly to ensure data quality and continued sobriety during study participation.	Yes

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ABBREVIATIONS/DEFINITIONS

- DLPFC - Dorsolateral Prefrontal Cortex
- NAcc - Nucleus accumbens
- FC - Functional connectivity
- OUD - Opioid use disorder
- fMRI - Functional magnetic resonance imaging
- tDCS - Transcranial direct current stimulation
- CMRR - Center for magnetic resonance research
- HCP - Human Connectome Project
- MOUD - Medications for opioid use disorder
- MINI - Mini International Neuropsychiatric Interview, Version 6
- TLFB - Timeline Follow Back

1.0 Objectives

1.1 Purpose: The overarching goal of this project is to expand the traditional expertise in non-invasive neuromodulation at the University of Minnesota towards developing novel paired-neuromodulation approaches using tDCS for new addiction treatments that support long-term abstinence. This study will allow us to investigate whether the pairing of DLPFC stimulation and cognitive training can enhance FC between DLPFC and NAcc. We have identified higher FC between DLPFC and NAcc in alcoholics that have successfully maintained abstinence for extended periods of time (7 years). This paired-neuromodulation approach can potentially be used as a therapeutic intervention to decrease substance use probability in addiction (e.g. opioid use disorder). The long term goal is to develop new addiction treatments that support long-term abstinence in opioid use disorder. The overall objective of this proposal is to enhance FC between DLPFC and NAcc as a therapeutic intervention to enhance cognition and reduce substance use rates in opioid use disorder.

2.0 Background

2.1 Significance of Research Question/Purpose: More effective interventions for opioid use disorder (OUD) are needed. With more than 115 individuals in the US dying daily from opioid overdose (HHS 2018), the opioid epidemic is a public health emergency. Despite effective medications for opioid use disorder, treatment discontinuation and substance use approaches 50% at one year. The fact that OUD is so difficult to treat may be reflective of extensive neuroplastic changes that induce and maintain the pathological addiction state. Existing treatment programs using medication and/or behavioral modification tools (e.g. 12-step) may not be sufficiently powerful to overcome the mechanisms maintaining this pathological state. We propose a neuroplasticity based intervention approach utilizing transcranial direct current stimulation (tDCS) and cognitive training with tasks selected to functionally target cognition and brain circuits that are impaired in opioid use disorder with the goal of reducing substance use.

2.2 Preliminary Data: Combination of active tDCS and cognitive training increases frontal-striatal resting state functional connectivity (RSFC) and reduces time to relapse in alcohol use disorder. Our neuroimaging studies have identified a key frontal-striatal network associated with treatment outcome: low frontal-striatal RSFC predicts relapse (Camchong, Stenger, and Fein 2013b; Camchong, Endres, and Fein 2014) and high frontal-striatal RSFC supports long-term abstinence (Camchong, Stenger, and Fein 2013a, [c] 2013). These neuroimaging findings highlight the key role of frontal-striatal RSFC in supporting long-term abstinence. In our pilot randomized controlled study of participants with alcohol use disorder (n=11; Camchong PI) designed to enhance frontal-striatal RSFC and cognition, 6 subjects who received active tDCS (2mA anode over left DLPFC, cathode over right DLPFC) were compared to 5 subjects who received sham

tDCS. Intervention sessions were 46 minutes (13 min tDCS - 20 min off - 13 min tDCS), for five consecutive days (Trojak et al. 2016; Klauss et al. 2014). All participants underwent concurrent cognitive training (Reversal Learning task and BART) during the 46 minute session. Rest fMRI data was collected pre- and post-intervention. We found: significant Group (active vs sham tDCS) x Time interaction in prefrontal-nucleus accumbens (NAcc) RSFC ($F=7.105$, $p=0.026$; eta-square $\eta 2=0.441$), with prefrontal-NAcc RSFC increase in the active tDCS group but not the sham group (Figure 2). Findings suggest active tDCS during cognitive training can increase frontal-striatal RSFC in addiction. Eight-month follow-up showed that those receiving sham+cognitive training had a significantly shorter time to relapse ($M=19$ days, $SD=5.66$; 50% relapse rate) than those who received active tDCS + cognitive training ($M=110$ days, $SD=27.05$; 60% relapse rate) ($p=0.021$). While these are promising findings for alcohol use disorder, the safety, feasibility, and effect of this combined intervention (tDCS+cognitive training) has not been investigated in individuals with OUD.

2.3 Existing Literature: Opioid misuse is an epidemic in the United States. While medications for opioid use disorder (MOUD) are highly effective, approximately 40% of patients receiving them return to opioid use within the first year of treatment. Available treatments are not very effective with very high relapse rates. Chronic opioid use is associated with cognitive impairments that interfere with adaptive behavior needed for successful recovery (Terrett et al. 2017; Mercuri et al. 2016; Verdejo-García and Pérez-García 2007; Baldacchino, Balfour, and Matthews 2015). These cognitive impairments and their underlying neural substrates are promising targets for intervention that can augment MOUD and reduce substance use rates. Evidence suggests that cognitive training can improve cognition in individuals with opioid addiction, strengthen neural networks mediating cognition (Ramsay, Nienow, and MacDonald 2017; Haut, Lim, and MacDonald 2010; Zhang et al. 2015), and improve treatment outcome (Rezapour et al. 2017). However, cognitive training is effort intensive, has small effect sizes and may have limited durability. The primary objective of this study is to test whether transcranial direct current stimulation (tDCS) can be used to boost the effectiveness of cognitive training in enhancing NAcc-frontal functional connectivity and cognition in opioid addiction to improve MOUD treatment outcome. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that can modulate brain connectivity. DLPFC stimulation may increase input to NAcc to facilitate proper selection of goal-directed behavior and may also decrease craving in individuals with substance use disorder (Boggio et al. 2008).

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome: In a double-blind randomized design, up to 250 individuals with a current opioid use disorder (OUD) diagnosis, age 18-60 years, enrolled in a methadone or buprenorphine treatment program and

clinically stable will be recruited. We will recruit individuals who have been treatment with methadone or buprenorphine for at least 2 months. Patients will receive 10 sessions (2 5-day blocks of 46-minute daily tDCS intervention) of either (i) transcranial direct current stimulation (tDCS) to PFC or (ii) sham-tDCS. All subjects will perform cognitive training during tDCS intervention (active or sham) to prime the engagement of the NAcc-PFC brain circuit. Rest fMRI will be collected pre-intervention, after 5 sessions, and post-intervention. Follow-up interviews will be conducted 1- and 2-months after intervention completion to assess cognition, assess behavior, and query substance use. Dependent variables will be (i) change in NAcc-PFC FC across intervention imaging sessions, (ii) change in cognitive performance across intervention sessions, and (iii) substance use status 2 months after study participation. The Specific Aims are to determine if the intervention: (A1) is feasible and safe in individuals with OUD, (A2) induces circuit-based target engagement (an NIH funding requirement), (A3) induces cognitive performance changes, and (A4) is related to substance use status 2 months after study.

To evaluate feasibility (A1), withdrawal and retention policies are described in Section 12.0. To evaluate safety (A1), we will use the Treatment Side Effects Questionnaire to record intervention side effects. Based on our alcohol tDCS study and studies from other research groups, we hypothesize that the intervention will be feasible and safe.

To evaluate circuit-based target engagement (A2) we will compare brain activation change (from pre-intervention to post-intervention) between active tDCS and sham groups. We hypothesize that the active tDCS group will have a larger increase in brain circuit engagement than the sham group.

To evaluate cognitive performance changes (A3), we will compare cognitive performance change from pre-intervention to post-intervention) between active tDCS and sham groups. We hypothesize that the active tDCS group will have a larger improvement in cognitive performance than the sham group.

To evaluate substance use status during participation and 1- and 2-months later (A4), we will administer the Timeline Follow Back(Sobell and Sobell 1996) questionnaire, assess the number of days of opioid use, and amount at peak use at follow-up (1- and 2-months later). We will also collect saliva/urine samples as often as every week. Based on our alcohol pilot study and literature on the effect of tDCS in other addictions (Lupi et al. 2017; Batista et al. 2015), we hypothesize that the active tDCS group will have lower followup substance use rates and longer abstinence periods than the sham group.

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s): To determine generalization and durability of cognitive training, patients will be asked to complete the following tasks at pre-intervention, post-intervention, 1-month follow-up and 2-

month follow-up to examine generalization and durability effects of training: D-KEFS Trail Making Test, D-KEFS Verbal Fluency, D-KEFS Color Word, Digit-Span (WAIS-WISC), Digit Symbol (WAIS-WISC).

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

Description: Transcranial Direct Current Stimulation (tDCS) - The tDCS will be performed with the TaskFlow Transcranial Electrical Stimulation device (TaskFlow-TES), IRB approved under different studies (STUDY00009059, STUDY00003506, STUDY00010333). The TaskFlow Transcranial Electrical Stimulation device (TaskFlow-TES) is a custom brain stimulation device developed in-house at the University of Minnesota. The performance of the Taskflow-TES device underwent laboratory bench testing to determine whether a programmed range of current levels (0.0 to 2.0 milliamps in 0.1 increments) was delivered by the device. The laboratory bench testing was conducted by a Biomedical Engineer, Dr. Mo Chen, Manager of the MnDRIVE Brain Conditions Noninvasive Neuromodulation Laboratory. For the tested range of 0.0 to 2.0 milliamperes, the deviation in delivered current was no more than 1%.
The FDA has deemed this device as a nonsignificant risk (NSR), however an NSR study is still subject to abbreviated investigational device exemption (IDE) requirements laid out in section 812.2(b) of the IED regulations (see FDA minimal risk letter). TaskFlow-TES is battery powered, communicates with the control computer via Bluetooth and monitors impedance and delivered current. To assess subject perceptions of the intervention, we will ask what treatment they believe they received each session.

Stimulation will consist of three periods: RampUp (30 sec), Constant (20 min), RampDown (30 sec). During the Ramp periods, 2 mA current will be delivered to both AF3 and AF4 with an ascending (RampUp) and descending ramp (RampDown) over 30 sec via two saline soaked electrode sponges (~ 25cm^2; current density = 0.08 mA/cm^2). Active tDCS: A 2-mA current will be administered via two circular carbon rubber core electrodes in saline-soaked surface sponges (25 cm2), placed in a neoprene headband with marked locations based on the 10-20 EEG system. The anodal stimulating electrode will be at location AF3, over left dorsolateral prefrontal cortex (DLPFC) and cathodal electrode at location AF4, over right DLPFC. Sham tDCS: For sham stimulation, the electrodes will be placed at the same positions as for active stimulation (F3 and F4), but current will be ramped down immediately after the initial 30 s ramp up period. Thus, participants will feel the initial itching sensation associated with tDCS but will receive no active current for the rest of the stimulation period. This method of sham stimulation has been shown to be reliable (Gandiga, Hummel, and Cohen 2006). To assess subject perceptions of the intervention, we will ask what treatment they believe they received each session. Executive Function Focused Cognitive Training Protocol. WM focused training occurs on a computer and consists of a variety of exercises selected to i) place demands on the executive and storage functions of working memory ii) adapt to challenge the participant's

current ability level, iii) provide ongoing feedback, and iv) present novel stimuli across verbal, visual and spatial modalities. Training tasks are developed in-house. Tasks for each subject are delivered from our AHC-IS server (cnc2.med.umn.edu). Responses of subjects and session audio and video are saved on our AHC-IS server for analysis of training performance and engagement. The aim of using multiple tasks that require WM functions is to engage thalamocortical connectivity in a number of different ways to promote generalization. In this scheme, experimenters will monitor each participant's training and customize the intervention to balance challenge and engagement. In addition, each week participants will perform 4-minute versions of a word and a spatial 3-back task that will remain the same across all weeks (but differ from the assessment versions) to allow us to track training improvements using a constant difficulty level.

Participant effort will be rated by experimenters at each session using the Work Behavior Inventory (Bryson, Bell, Lysaker, & Zito, 1997). Just before the end of each training session, subjects will complete a brief questionnaire that also asks about their perceived engagement in the training that day, as well as their mood, previous night's sleep, discomfort, and their perceived experimental condition. Finally, at the end of each session, the participant will select the final task from an array of fun games, which we have found promotes agency and improves attendance.

4.1 Drug/Device Handling: We will use transcranial direct current stimulation (tDCS) to stimulate dorsolateral prefrontal cortex (DLPFC). TDCS is a non-invasive brain stimulation technique that can modulate brain connectivity. TDCS involves applying a weak electrical current (2mA or less) to the scalp via anodal and cathodal electrode sponges, causing either increases or decreases in cortical excitability, respectively. Research has shown in both healthy subjects and patients (e.g. Alzheimer's disease, Parkinson's disease, stroke, and depression) that tDCS has the potential to modulate synaptic strengthening and neurotransmitter-dependent plasticity underlying changes in behavior and learning (Lang et al. 2005).

4.2 Biosafety: N/A

4.3 Stem Cells: N/A

5.0 Procedures Involved

5.1 Study Design:

This study is double-blind, within subject, within study staff, and sham-controlled. The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design includes: In a double-blind randomized design, up to 250 individuals with a

current opioid use disorder (OUD) diagnosis, age 18-60 years, enrolled in a methadone or buprenorphine treatment program and clinically stable will be recruited. Patients will receive 10 days (1 20-minute administration per day) of either (i) transcranial direct current stimulation (tDCS) to PFC or (ii) sham-tDCS. All subjects will perform cognitive training during tDCS intervention (active or sham) to prime the engagement of the NAcc-PFC brain circuit. Rest fMRI will be collected pre-intervention, at the midpoint of intervention, and post-intervention. The purpose for adding the midpoint MRI is to increase the statistical power of showing the trend of the experimental treatment's effectiveness over time. Follow-up interviews will be conducted 1- and 2-months after intervention completion to query substance use.

To examine generalization and durability effects of training, patients will be asked to complete the following tasks at pre-intervention, post-intervention, 1-month follow-up and 2-month follow-up: D-KEFS Trail Making Test, D-KEFS Verbal Fluency, D-KEFS Color Word, Digit-Span (WAIS-WISC), Intra-Extra Dimensional Set-Shift Task. Saliva/Urine tests checking for substance use will be administered at each follow-up timepoint.

5.2 Study Procedures:

Randomization: Random permuted blocks (subgroups of 4) will be used to ensure equal group assignment (active or sham tDCS) at predefined equally spaced points in the sequence of patient assignment. Blinding: Participants will not be informed on their assigned protocol. During consent, they will be informed that there is a 50% chance of receiving active tDCS or sham tDCS every visit for five study visits.

Participants who consent to the study and meet study criteria as per the screening evaluation will be asked to participate in up to 17 study visits over a period of up to two months. This time period includes 10 tDCS sessions over a period of up to 5 weeks.

Participants will also be asked to be available for in-person 1- and 2-month follow-up visits after intervention completion to query substance use and complete cognitive tasks. All sessions will be coordinated with participants' visits to the clinic to minimize burden.

VISIT ONE/Screening Visit: After the participant has agreed to be in the study and signed the consent, the participant will be interviewed by a research staff member from the University of Minnesota and asked questions about the participant's health history and clinical symptoms. Females who could potentially be pregnant will be tested for pregnancy and, if positive, will not be allowed to participate. If testing is refused, participation will not be allowed. If eligible, the participant will complete the Timeline Follow Back (TLFB) and other paper questionnaires reporting opioid use and craving levels. Participants will complete baseline measures for: D-KEFS Trail Making Test, D-KEFS Verbal Fluency, D-KEFS

Color Word, Digit-Span (WAIS-WISC). The participant will then be asked to complete a series of questionnaires that assess behavior, personality and substance use. Day 1 assessments will take about 2 hours total. After consent and after the participant acknowledges full understanding of the intervention, the participant will be randomly assigned (with 50% chance) to receive either active tDCS or sham tDCS while the participant performs the reversal learning task (see description of intervention under day 3).

VISIT 2-3/PRE-INTERVENTION: The participant will undergo a pre-intervention assessment, lasting about 2 hours. During the assessment, participants will complete a series of questionnaires that assess opioid use and craving levels, behavior, personality and substance use.

The participant will also undergo a pre-intervention MRI, lasting about 2 hours. The MRI involves taking pictures of the participant's brain, from which the properties of certain brain tissues can be measured. While sometimes MRI scans are done for clinical purposes, the scans the participant will receive are being done for research purposes. Since these scans are not designed for clinical or medical reading, the participant's scans 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, it will start to take the pictures. During the scan, the participant will simply lie quietly in the scanner with eyes closed while the scanner takes images of the participant's brain. The MRI scan will be performed at the University of Minnesota's Center for Magnetic Resonance Research.

The assessment visit may be performed before, same-day, or after the MRI visit for ease of accommodating the schedule of the scanner or participant.

VISITS 4-8: Will involve cognitive training tasks concurrently with tDCS, with tDCS for the first 20 minutes (46 minutes total per day). We will first explain to the participant what the training tasks entail and detail tDCS procedures. TDCS side-effects questionnaire will be administered daily before and after intervention.

During tDCS intervention (active) the participant will be seated in a reclining chair while the participant perform the reversal learning task. Total participation time for visits 4-8 will be about 1 hour each day, or about 5 hours over a period of 2 weeks.

VISITS 9-10/MIDPOINT: At the midpoint assessments and MRI, the participant will be administered the same cognitive assessments, and substance use questionnaires as Visit Two. Craving will be re-assessed and follow-up MRI scan with same procedures as Visit Three will be collected. Total participation time for Visits 9-10 will be about 4 hours.

The assessment visit may be performed before, same-day, or after the MRI visit for ease of accommodating the schedule of the scanner or participant.

VISITS 11-15: Will involve cognitive training tasks concurrently with tDCS, with tDCS for the first 20 minutes (46 minutes total per day). We will first remind the participant what the tasks entail and detail tDCS procedures. TDCS side-effects questionnaire will be administered daily before and after intervention.

During tDCS intervention (active or sham) the participant will be seated in a reclining chair while the participant perform the reversal learning task. Total participation time for days 3-7 will be about 1 hour each day, or about 5 hours over a period of 2 weeks.

VISITS 16-17/POST-INTERVENTION: At the post-intervention assessments and MRI, the participant will be administered the same clinical assessments, cognitive assessments, and substance use questionnaires as Visits 9-10. Craving will be re-assessed and follow-up MRI scan with same procedures as baseline will be collected. Total participation time for Visits 16-17 will be about 4 hours.

The assessment visit may be performed before, same-day, or after the MRI visit for ease of accommodating the schedule of the scanner or participant.

IN PERSON FOLLOW-UP: The participant will be asked to return 1- and 2-months after intervention to fill out the same clinical, cognitive and substance use questionnaires that were administered on Visits 2, 9, and 16. Follow-up visits will be about 1.5 hours each. Subjects will undergo saliva/urine tests evaluating recent drug/alcohol use.

At follow-up timepoints, we will contact subjects two weeks prior to the next follow-up to coordinate scheduling with sufficient time so that data is collected as close to the target as possible.

Retention: To maximize participant retention we will have all consented participants fill out a “contact” document in which they will provide at least two telephone numbers to be reached and one home address. We will ask participants to provide the phone number of a good friend or relative who will know their whereabouts to help us re-contacting the participant if needed. Before follow-up appointments, we will call participants over the phone to confirm their attendance and we will send reminder cards through regular mail. If participants give their consent, we will also send a text to their contact phone number.

5.3 Study Duration:

- The anticipated duration an individual participant’s participation in the study is 2.5-4 months since recruitment.

- The duration anticipated to enroll all study participants: Anticipated end date Summer 2022.
- The duration anticipated to complete all study procedures and data analysis: Anticipated end date Fall 2023.

5.4 Individually Identifiable Health Information: We have submitted the University's Privacy Office online application for data privacy and security review. We will print and upload the application with this protocol.

5.5 Use of radiation*:* N/A

5.6 Use of Center for Magnetic Resonance Research*:* This study will be approved by the CMRR (PARS) Project Application Review System.

6.0 Data and Specimen Banking

6.1 Storage and Access: Only research staff will have access to subject information. Data contained on paper records and computer files will not include names or other identifying information of subjects. Records containing identifying information will be stored in a private research office in a locked file cabinet and be accessible only by the principal investigator and the study coordinator. The study coordinator or the principal investigator will review and remind research staff of this guideline on a regular basis. Paper and electronic records will be kept for 3 years or longer. Paper records not under use will be stored in locked file cabinets in a private research space. Any identifying information on magnetic or optical media will be stored in a similar manner or be password protected. The password for accessing this information will be available to only select staff that need access to the information to conduct their research duties. All other data will not contain identifying information. All other data will be stored on encrypted magnetic or optical media that is secured or on computer systems accessible only by research staff and computer system administrators via password. There is a slight possibility that data (without identifiers) will be requested by reviewers and other scientists when study data is presented to the scientific community

6.2 Data: All diagnostic and other sensitive data will be kept in a locked file and be available only to authorized investigators involved in this study. Identifiers will include name, birthdate, address, and telephone numbers. The PI will keep the data file containing the link between subject number and identity. This will be kept in a password-protected computer file and also in printed form in a locked file cabinet. Research staff will have access to the identifiers only after a subject has agreed to participate in the study. They will use this information only for making contact to schedule visits, etc.

6.3 Release/Sharing: The data collected may represent a unique resource for some investigators. Following HHS/CDC (Department of Health and Human Services/Centers for Disease Control and Prevention) policy, we will make the de-identified data available to interested investigators who contact us for access to the data. As the proposed work is a clinical trial, the most appropriate database for our collected data appears to be clinicaltrials.gov. The investigator, co-investigator, and research staff will permit trial-related monitoring, audits, IRB/IEC(s) review and regulatory inspection(s) by providing direct access to source data/documentation.

7.0 Sharing of Results with Participants

No results are shared with participants.

8.0 Study Population

8.1 Inclusion Criteria: Participants will have a current diagnosis of OUD, be age 18-60 years, be enrolled in a methadone or buprenorphine treatment program in Hennepin Healthcare and be clinically stable. We will recruit individuals who have been in treatment with methadone or buprenorphine for at least 2 months. Inclusion criteria: (i) ability to provide written consent and comply with study procedures; (ii) meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) diagnostic criteria for OUD. Subjects may have current comorbid drug use, but their primary substance use disorder diagnosis needs to be based on opioid use. Subjects must have the intention to remain in the methadone or buprenorphine treatment program until the end of the intervention portion of the study. Vulnerable populations will not be included.

8.2 Exclusion Criteria: Any medical condition or treatment with neurological sequelae (i.e. stroke, tumor, loss of consciousness>30 min, HIV); (ii) a head injury resulting in a skull fracture or a loss of consciousness exceeding 30 minutes (i.e., moderate or severe TBI); (iii) any contraindications for tDCS or MRI scanning (tDCS contraindication: actively receiving treatment for seizures or epilepsy; MRI contraindications; metal implants, pacemakers or any other implanted electrical device, injury with metal, braces, dental implants, non-removable body piercings, pregnancy, breathing or moving disorder); (iv) current active psychosis or mania; (v) presence of a condition that would render study measures difficult or impossible to administer or interpret (e.g. current mania, active psychosis); (vi) age outside the range of 18 to 60; (vii) primary current substance use disorder diagnosis on a substance other than opioid except for caffeine or nicotine; (viii) have current significant stimulant use (stimulant use greater than 10 days in the 30 days prior to enrollment) (ix) history of ECT or cortical energy exposure within the past 12 months, including participation in any other neuromodulation studies, (x) prisoners. Nicotine use will be recorded.

The study staff person will thoroughly describe the study and read the consent form. Then the patient will be given time to read the consent form and ask questions of study staff. If the patient agrees they will sign the consent with the study staff person looking on. Part of the consent involves asking questions of the patient via the UBACC form and having him or her record their responses to ensure they understand the study and that they can terminate participation at any point. To protect vulnerable populations, if the patient does not seem to fully understand the nature of the study (including procedures, risks, confidentiality, voluntary nature), they will not be included in the study. They are also informed that study staff may terminate study participation at any point if they are concerned about the patient's welfare or behavior.

8.3 Screening: Individuals will be screened using an IRB approved screening questionnaire that asks about demographics, type of substance use, clinical and psychiatric history, and MRI compatibility. If they do qualify for the study, they are asked if they are still interested in participating, and informed consent process starts. After informed consent, individuals will complete a screening questionnaire for contraindications of MRI scanning. Any affirmative responses on the questionnaire will result in an interview regarding the possible contraindication. CMRR staff will need to approve any affirmative response before a participant can undergo MRI scanning. Female subjects in child-bearing years will be informed that their consent to participate indicates that they are willing to complete a urine pregnancy test to demonstrate that they are not pregnant.

9.0 Vulnerable Populations

9.1 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 an 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

9.2 Additional Safeguards:

- Study will recruit individuals (18-60 years old) who have been in treatment with methadone or buprenorphine for at least 2 months. Recruited individuals will meet DSM-V criteria for opioid use disorder (OUD; a psychiatric disorder). Potential participants will self-identify based on response to a flyer posted on IRB approved boards within the treatment program.
- Opioid use disorder is considered a psychiatric disorder, capacity to consent will be evaluated thoroughly by research staff as detailed below. Potential participants may have a lifetime psychiatric diagnosis (e.g. Anxiety or depression, not psychosis) that is under stable treatment or medication.
- Part of the consent involves asking questions of the subject and having him or her record their responses to ensure they understand the study and that they can terminate participation at any point. Participants are explained the study in detail before giving informed consent and evaluated on their capacity to consent with a form that contains the following items:

-Participant was given time to review the consent form
-The Consent document was explained, discussed, and reviewed
-Study explanation and discussion was completed (check all that apply)
-The participant's comprehension was assessed to ensure that he/she understands the research and the risks and benefits involved in the study
-Participant's questions were answered satisfactorily and concerns were addressed
-Upon completion of conversation, participant did not have any additional questions or concerns
-The participant has agreed to participate in the study, and has signed and dated the most current,
-IRB-approved consent form prior to the start of any study procedures.
-Written consent was obtained with most recent IRB approved consent form
-Participant was given a copy of the consent form
-The original signed and dated consent form was placed in the research record or participant study binder

- To protect vulnerable populations, if the patient does not seem to fully understand the nature of the study (including procedures, risks, confidentiality, voluntary nature), they will not be included in the study.

They are also informed that study staff may terminate study participation at any point if they are concerned about the patient's welfare or behavior.

- Importance of knowledge to be gained: There are increasing data supporting specific cognitive and brain functional connectivity abnormalities in opioid use disorder. An understanding of whether these specific abnormalities can be modulated with cognitive training and non-invasive brain stimulation interventions will hold significant promise in designing new targeted interventions that can reduce vulnerability to relapse and improve treatment outcome.
- Protection Against Risk. Trained research staff will be instructed to keep the content of the records confidential. During the initial consent process subjects will be told that they have the right to refuse to answer questions; however, this may affect whether they continue in the study. At all points in the study subjects will be warned at the beginning of procedures which involve the disclosure of personal and sensitive information. These warnings will occur in the introductory comments of interviews or in the instructions of questionnaires and surveys.
- Importance of Knowledge Gained. The knowledge derived from this research will allow us to gather crucial evidence supporting the therapeutic use of interventions targeting both cognitive and underlying neural mechanisms that support abstinence. The knowledge gained from this study may eventually help guide further research in the area and future studies to improve addiction treatment programs.
- Recruitment will conform to HIPAA requirements regarding protection of private health information.
- To protect vulnerable populations, if the patient does not seem to fully understand the nature of the study (including procedures, risks, confidentiality, voluntary nature), they will not be included in the study. They are also informed that study staff may terminate study participation at any point if they are concerned about the patient's welfare or behavior.
- After detailed informed consent, participants' capacity is further evaluated with the UCSD Brief Assessment of Capacity to Consent (UBACC).
- No neonates, prisoners, individuals who have not attained legal age for consent.

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented: Up to 250

11.0 Local Recruitment Methods

11.1 Recruitment Process:

(1) Patients enrolled in a methadone or buprenorphine treatment program in the Twin Cities Area (such as Hennepin Healthcare and VA Medical Center) will learn about the study through an IRB-approved brochure or flyer posted on a board . Participants will also learn about the study via word of

mouth at their treatment program. Participants will self-identify and call research staff to learn more.

(2) Clinical staff colleagues will inform patients about the study via a recruitment card or brochure if he or she believes it would be beneficial to the patient. These participants will call research staff to learn more if interested.

(3) Study staff will post advertisements online and paper flyers in community publications. Participants will self-identify and call research staff to learn more.

(4) Patients enrolled in a methadone or buprenorphine treatment site who agree to do study recruitment (such as Hennepin Healthcare) will learn about the study via a displayed tablet paired with the words "Research Opportunity". If a patient is interested in learning more about participation in the study, they are directed to complete the opt-in REDCap form on the tablet. Research staff will review the survey and call the participant back with an eligibility decision or more information.

(5) Patients enrolled in a methadone or buprenorphine treatment site will be sent mail ads for the study.

If a patient is interested in participating in the study, they are instructed to call research staff. During this first contact call, patients are given general information about the study and if patients want to learn more about the study and to find out if they qualify to be in it, a phone appointment or in-person appointment is set up to meet research staff at a specific date and time. At this appointment, research staff will give the patient detailed information about the study. If participants are still interested in participating in the study after learning all details of the study, research staff will ask them if they would like to answer confidential questions to determine if they qualify to be in the study.

If participants do not qualify to be in the study, research staff will thank them for their time and tell them the general reasons why they do not qualify to be in the study. If participants do qualify to be in the study, research staff will let them know that they do qualify to be in the study and ask them if they are still interested to be in the study. If so, research staff will proceed with enrollment (e.g. consent, HIPAA, etc.).

A trained and IRB-approved study staff person will carry out the consent process. The subject will be given time to read the consent form and to ask questions. If the subject agrees they will sign the consent form with the study staff person looking on. Part of the consent involves asking questions of the subject and having him or her record their responses to ensure they understand the study and that they can terminate participation at any point. They are also informed that study staff may terminate study participation at any point if they are concerned about the subject's welfare or behavior.

11.2 Identification of Potential Participants: Individuals with opioid use disorder (OUD) will be recruited via the methods described in 11.1. We will monitor recruitment progress and expand outreach goals to other clinics if we are not meeting project targets. Clinic staff will not be involved in the intervention.

Participants will not be recruited based on information contained in private/protected records.

- No private/protected records will be used.
- Potential participants will self-identify and express their interest after learning about the study on IRB approved materials in the treatment program, word of mouth, community referral, or referral via clinical staff colleague.
- MEDICAL records will be used to send recruitment letters, in a manner as approved by the partner treatment site (e.g. MHealth Fairview)
- HIPAA form states that the participant does agree to have research staff communicate with treatment program staff that they are participating in research.

11.3 Recruitment Materials: Participants will see a flyer posted (uploaded to Ethos) in poster boards within the treatment program. If interested, participants call phone number in flyer to set up an in-person informational/screening appointment.

11.4 Payment: Participant compensation will be provided according to the schedule below:

- Screening/Visit 1: $10 for screening evaluation; $25 for completing baseline questionnaires
- Visits 2-3: $25 for completion of pre-intervention assessments; $25 for completion of MRI scan
- Visits 4-8: $15 for tDCS interventions (up to $75)
- Visit 9-10: $25 for completion of midpoint assessments; $25 for completion of MRI scan
- Visits 11-15: $15 for tDCS interventions (up to $75)
- Visits 16-17: $25 for completion of post-intervention assessments; $25 for completion of MRI scan
- Follow-up visit 1: $50
- Follow-up visit 2: $50

The total amount a participant could receive if he/she completes all study visits and activities is $435.

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances: Participants will be able to discontinue study participation at any time. The participants may choose to discontinue stimulation at any time during the session if experiencing excessive discomfort or side effects. Criteria for discontinuation related to intervention: i) sores at the tDCS administration site; ii) headaches that impair global functioning. If subjects choose to stop their participation, they will be released from the study. To protect vulnerable populations, if a patient that was deemed capable of providing consent goes through unforeseeable situations that may affect their capacity to consent, their capacity will be reassessed, and if not deemed capable, they will be withdrawn from the study. Participants are also informed that study staff may terminate study participation at any point if they are concerned about the patient's welfare or behavior.

12.2 Withdrawal Procedures: 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.

If participants withdraw from procedures, all their data collected until the withdrawal data will be retained. No new data will be collected from any private/protected record.

Participants who withdraw from the study after having received tDCS will be asked if they can be contacted by telephone to ascertain substance use status. We will attempt to contact participants 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 substance use status.

12.3 Termination Procedures: If at any point research staff is concerned about participant's welfare or behavior, they will notify the participant that their participation in the study needs to terminate because of safety reasons. The participant will be paid for their time as per 11.4 until their last active participation day. Data collected until the termination date will be used and considered incomplete.

13.0 Risks to Participants

13.1 Foreseeable Risks:

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 side effects. Although seizures are not a known risk of tDCS intervention (Fregni et al. 2006), anyone with a history or a risk for seizures will be excluded from the study. No other risks related to tDCS are anticipated. To minimize risks regarding tDCS, study staff will be using standards of administration that have been shown as safe in numerous other studies using transcranial direct current stimulation. The length of administration of the current, size of electrode sponges used, and method of applying stimulation are the same as methods of administration that have been demonstrated as safe.

The other potential risks pertain to the maintenance of confidentiality. Participants will be probed for personal information during the interviewing process. As noted in the consent form, participants will be told that all diagnostic and other sensitive raw data will be kept in a locked file and available only to authorized investigators involved in this study. To minimize confidentiality risks, as noted in the consent form, all diagnostic and other sensitive raw data will be kept in a locked file and be available only to authorized investigators involved in this study.

MRI risks. Individuals will complete a screening questionnaire for contraindications of MRI scanning. Any affirmative responses on the questionnaire will result in an interview regarding the possible contraindication. An attempt will be made to secure any records of the nature of the possible contraindication and this information will be reviewed by the PI and 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. If approved for scanning by professionals, all risks to the subject will be conveyed to him or her so they can deliberate as to whether or not they want to complete the procedure. Any concerns from the review committee will be conveyed to the participant at that time. If the subject has certain problematic iron or steel implants in their body that cannot be removed, the subject may not have the scan and will be excluded from the study.

There are no known risks to humans due to the static magnetic field. Subjects, operators, and guests are carefully screened prior to entering the magnetic environment, and frequently reminded of the potential danger of introducing magnetic objects to the controlled area. Subjects are carefully screened and 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.

13.2 Reproduction Risks: Since the MRI risks to fetuses are unknown, pregnant women are excluded from the study. Female subjects in child-bearing years will be informed that their consent to participate indicates that they are willing to complete a urine pregnancy test to demonstrate that they are not pregnant.

13.3 Risks to Others: N/A

14.0 Potential Benefits to Participants

14.1 Potential Benefits: No benefit is guaranteed for the subject from being in this study, yet some individuals may feel rewarded by contributing to science.

15.0 Statistical Considerations

15.1 Data Analysis Plan: Compare brain FC between groups: Sham vs Active tDCS. Compare FC within groups to examine time effects: before and after intervention. Look for interaction effects (group x time).

15.2 Power Analysis: The study in reference is a pilot study for which a power analysis is not applicable.

15.3 Statistical Analysis: A mixed model analysis of variance will be conducted with between-group measures (sham vs active tDCS) and within-group measures (FC and craving reports before and after cognitive training and tDCS intervention). This mixed model analysis will examine main- and interaction-effects. To examine the long-term effects of cognitive training and tDCS, we will conduct a repeated measures analysis using longitudinal data collected at 1- and 2-month follow-up timepoints after intervention completion. A Log-rank (Mantel-Cox) Test (used in (Klauss et al. 2014) will be conducted to establish the efficacy of cognitive training and active tDCS vs. cognitive training and sham tDCS in the time domain.

15.4 Data Integrity: The principal investigator and co-investigator will monitor data quality for this study. They will ensure that data are generated, documented (recorded), and reported - in compliance with this protocol, with Good Clinical Practice, and any other applicable regulatory requirements.

16.0 Confidentiality

16.1 Data Security: Trained research staff will be instructed to keep the content of the records confidential. During the initial consent process subjects will be told that they have the right to refuse to answer questions; however, this may affect whether they continue in the study. At all points in the study subjects will be warned at the beginning of procedures which involve the disclosure of personal and sensitive information. These warnings will occur in the introductory comments of interviews or in the instructions of questionnaires and surveys.

Only research staff will have access to subject information. Data contained on paper records and computer files will not include names or other identifying information of subjects. Records containing identifying information will be stored in a private research office in a locked file cabinet and be accessible only by the principal investigator and the study coordinator. The study coordinator or the principal investigator will review and remind research staff of this guideline on a regular basis. Paper and electronic records will be kept for 3 years or longer. Paper records not under use will be stored in locked file cabinets in a private research space. Any identifying information on magnetic or optical media will be stored in a similar manner or be password protected. The password for accessing this information will be available to only select staff that need access to the information to conduct their research duties. All other data will not contain identifying information. All other data will be stored on encrypted magnetic or optical media that is secured or on computer systems accessible only by research staff and computer system administrators via password.

No copy of the consent form or other research study information will be placed in the participants' medical, employment, or educational records.

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

17.1 Data Integrity Monitoring. The study will be monitored by CTSI in accordance with its institutionally approved monitoring plan.

17.2 Data Safety Monitoring: It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

18.0 Provisions to Protect the Privacy Interests of Participants

18.1 Protecting Privacy: The study consent form will describe in detail any intrusive, uncomfortable, or unfamiliar questions, procedures, or interactions with researchers or study personnel that the participant will be asked to complete. Furthermore, the study consent form will communicate that it is the participant's right to opt-out of any study procedures or the study as a whole or withdraw from the study at any time and this information will be reiterated and revisited periodically throughout the study in advance of intrusive, uncomfortable, or unfamiliar questions procedures or interactions. Participants will not be compelled or pressured to provide information or specimens or study data that they do not wish to provide.

Access to Participants: Participants will be fully informed of the ways in which their data will/may be used during the informed consent process. The research team has been trained in conducting these conversations and the participants are also assessed for their understanding of consent prior to signing the consent form or initiating any study procedures.

19.0 Compensation for Research-Related Injury

19.1 Compensation for Research-Related Injury: There is no compensation in the event of research-related injury. The consent form states: "In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or the participant's insurance company. If you think that you have suffered a research-related injury, please let us know right away."

19.2 Contract Language: N/A

20.0 Consent Process

20.1 Consent Process (when consent will be obtained): Screening and consent will take place in a private room in Hennepin Healthcare.

The study research staff will thoroughly describe the study and read the consent form. Then the patient will be given time to read the consent form and ask questions of study staff. If the patient agrees, they will sign the consent with the study staff person looking on. Part of the consent involves asking questions of the patient and having him or her record their responses to ensure they understand the study and that they can terminate participation at any point. To protect vulnerable populations, if the patient does not seem to fully understand the nature of the study (including procedures, risks, confidentiality, voluntary nature), they will not be included in the study. They are also informed that study staff may terminate study participation at any point if they are concerned about the patient's welfare or behavior.

The study staff person will thoroughly describe the study and read the consent form. Then the patient will be given time to read the consent form and ask questions of study staff. If the patient agrees they will sign the consent with the study staff person looking on. Part of the consent involves asking questions of the patient and having him or her record their responses to ensure they understand the study and that they can terminate participation at any point. To protect vulnerable populations, if the patient does not seem to fully understand the nature of the study (including procedures, risks, confidentiality, voluntary nature), they will not be included in the study. They are also informed that study staff may terminate study participation at any point if they are concerned about the patient's welfare or behavior.

To protect vulnerable populations, if the patient does not seem to fully understand the nature of the study (including procedures, risks, confidentiality, voluntary nature), they will not be included in the study. They are also informed that study staff may terminate study participation at any point if they are concerned about the patient's welfare or behavior.

To ensure ongoing consent: After consent is provided and at each intervention day, participants are monitored for any concerns they have about the intervention with the Treatment Side Effect Questionnaire. Participants who agree to continue in the study will sign this questionnaire daily.

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

20.3 Non-English Speaking Participants: N/A

20.4 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): N/A

20.5 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: We will record informed consent process in the "Documentation of the Informed Consent Process" to ensure full understanding of study procedures and voluntary nature.

20.6 Adults Unable to Consent: N/A

- Permission:
- Assent:
- Dissent:

21.0 Setting

21.1 Research Sites:

- Participants will be recruited from a methadone or buprenorphine treatment program in Hennepin Healthcare.
  - No Hennepin Healthcare staff will be involved in the intervention.
- Screening, consent, interview, assessments and tDCS intervention will take place at Hennepin Healthcare.
- Brain scans will be conducted at the Center for Magnetic Resonance Research (CMRR) at the University of Minnesota.
  - If participants can transport themselves to CMRR, we will meet them at CMRR. If participants need assistance with transportation, we will provide it, with Uber/Lyft/Taxi.

21.2 International Research: N/A

22.0 Multi-Site Research: N/A

22.1 Study-Wide Number of Participants:

22.2 Study-Wide Recruitment Methods:

22.3 Study-Wide Recruitment Materials:

22.4 Communication Among Sites:

22.5 Communication to Sites:

23.0 Resources Available

23.1 Resources Available: To collect complete follow-up data for participants with opioid use disorder.

Facilities:

Laboratory of Neuropsychiatric Imaging (LNPI; led by Dr. Lim). Drs. Lim and Camchong are part of the LNPI, a multidisciplinary research group that studies the biological underpinnings of neuropsychiatric disorders by combining imaging techniques with neurocognitive assessments and genetics. Dr. Lim and Dr.

Camchong's offices and research team are located in Suite 516 within the 717 Delaware Research Building (717 Delaware St. SE, Minneapolis, MN). The facility is a fully equipped and secure research laboratory supported by the UMN Medical with private offices and conference rooms, full computer and telecommunication systems and support, secure entrance and file storage, private research testing rooms, a reception desk and waiting area for research subjects, and physical space to house multiple research staff and support graduate student research efforts. All of these resources are currently and will continue to be available to the investigators.

Center for Magnetic Resonance Research (CMRR). The CMRR is located on the UMN campus. This imaging center was established in 1991 as a result of the rapidly growing and successful in vivo magnetic resonance imaging (MRI). CMRR is an interdepartmental and interdisciplinary research laboratory that provides state-of-the-art instrumentation, expertise, and infrastructure to carry out biomedical research utilizing the unique capabilities provided by high field MRI and MRS methodology. The central aim of the research conducted in CMRR is to non-invasively obtain functional, physiological, and biochemical information in intact biological systems, and use this capability to probe biological processes in health and disease. The CMRR is currently equipped with nine high field magnets for humans with magnetic field strength of 3 Tesla and greater, with the most notable being a 10.5 Tesla/89cm. MRI data (resting, task-evoked and high-resolution structural scans) will be collected using a 32-channel head coil on a Siemens Prisma FIT 3T scanner (Siemens Medical Solutions, Erlangen, Germany). The Prisma was inspired by the success of the Connectome 3T systems, in particular the one-of-a-kind modified Siemens Skyra system that was built specifically for the WU-Minn Human Connectome Project (HCP) consortium (Connectome Skyra). The HCP is from the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research. The consortium led by Washington University, University of Minnesota, and Oxford University (the WU-Minn HCP consortium) is comprehensively mapping human brain circuitry in a target number of 1200 healthy adults using cutting-edge methods of non-invasive neuroimaging. The unique features of the Prisma system are based on an integrated system that combines a high strength gradient system with capability of 80 mT/m @ 200 T/m/s (FDA approved mode, but capable of 100 mT/m in research mode)), an advanced RF receiver system that provide better signal-to-noise performance, 64 channel receive capability. Accelerated data collection provides improved signal in resting state networks (Griffanti et al. 2014). HCP has developed and supports multiband acquisition sequences for the Prisma, which accelerate data acquisition by a factor of up to 12. These fMRI sequences use MB factor of 8, allowing us to collect 32 slices in 1/8 TR, which is 8 simultaneous slices in one TR.

Kelvin O. Lim, MD will be available in case of unanticipated issues.

All research staff will undergo protocol training. Only trained research staff will obtain consent.

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