PROTOCOL TITLE:

Neurocircuit Strategy to Decrease Cocaine Cue Reactivity

PRINCIPAL INVESTIGATOR:

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1.0 Objectives / Specific Aims

A primary cause of relapse to cocaine use is the high motivation to seek drug produced by cocaine-associated cues. Cue-induced craving is associated with cue-induced elevated corticostriatal activity. Preclinical models demonstrate that decreasing activity in the medial prefrontal cortex (mPFC) and ventral striatum (i.e. nucleus accumbens core), henceforth the "corticostriatal circuit," can block cue-induced cocaine seeking. As an extension of these preclinical data, the scientific premise of Project 4 is that targeted inhibition of the corticostriatal circuit will dampen cue-induced cocaine craving in individuals with cocaine use disorder.

The overarching goal of this project is to evaluate the efficacy of continuous theta burst stimulation (cTBS) as a tool to restore corticostriatal circuitry function and dampen cocaine cue reactivity among treatment-engaged individuals. cTBS is a non-invasive brain stimulation tool that induces long-term depression (LTD) of neural excitability in the area stimulated and in monosynaptic targets. Recent data from our group demonstrates that a single dose of cTBS to the mPFC selectively decreases activity in the ventral striatum and craving. The efficacy of cTBS as a tool to modulate the striatum depends upon connectivity between the frontal cortex and the striatum. Specifically, the experiments described in this proposal will determine if LTD-like cTBS delivered over mPFC decreases cocaine cue reactivity in individuals with cocaine use disorder. We will evaluate our novel intervention through a double blinded (ACTIVE cTBS vs. SHAM;) study in 160 cocaine dependent individuals. The chance of being randomly assigned to any given group within one of the two treatment arms is 1:1. All individuals will undergo a screening visit (Visit 1; V1), and a baseline fMRI visit (Visit 2; V2) that will assess rsFC and drug cue-reactivity. Following Visit 2, individuals will be randomly assigned to one of 2 to receive either: 1) Active cTBS alone, or 2) Sham cTBS alone. Both groups of participants will undergo a second fMRI visit (Visit 3; V3) that will assess resting-state and drug cue-reactivity: once at the beginning of the session and again immediately following Active cTBS or Sham cTBS. Research staff will follow-up with participants via phone to assess current drug use and craving at 1-day, 1-week, 2-week and 3-weeks post-V3.

Aim – To evaluate mPFC cTBS as a tool to modulate corticostriatal rsFC and drug cue reactivity in treatment-seeking cocaine users. *Rationale:* Drug cues reliably activate the mPFC & striatum in multiple classes of substance users, including cocaine users. This contributes to craving and subsequent relapse. Through an LTD-like form of cTBS it is possible to decrease activity in the mPFC and the striatum and dampen self-reported craving in chronic cocaine users. *Hypothesis:* LTD-like cTBS to the mPFC of individuals with cocaine use disorder will decrease cocaine cue-reactivity BOLD response in corticostriatal nodes (i.e. mPFC, ventral striatum) and enhance corticostriatal rsFC.

2.0 Background

This project utilizes a multi-disciplinary approach with complementary design features to allow for the bidirectional translation of findings of treatment effects on neurobiology (animal) and neurocognition (human) on corticostriatal circuits. Findings will provide the foundation for identifying individual and combined neural mechanisms of action of cTBS and will inform the optimization of novel individually-guided cTBS for treating cocaine use disorder.

3.0 Intervention to be studied

Transcranial magnetic stimulation (TMS) is an FDA-approved, non-pharmacological intervention for Depresison, OCD, and Smoking Cessaion. It is a non-invasive form of brain stimulation that delivers magnetic pulses to the human brain to change brain excitability, and ultimately change behavior. TMS is not FDA-approve for cocaine use disorder, however PI Dr. Badran is a leading expert in brain stimulation and the MUSC IRB, as well as the FDA, have determined repetitive TMS to be a non-significant risk intervention. A specific form (parameter) of TMS known as continuous theta burst stimulation (cTBS) will be utilized as the intervention in this study.

Potential Risks of TMS are minor, however include:

1). Potential risk of a seizure: The major risk using repetitive TMS subjects is the possibility of inducing a seizure. We have now studied and given rTMS to more than several hundred subjects over past 15 years. None of these patients has developed a seizure. We will exclude patients with a prior history of seizures.

2). Potential for scalp discomfort and headaches: Some people report mild discomfort when the magnetic pulses are applied over the scalp. A small number of people (~5%) report headache following TMS. However, the headaches are temporary and manageable with common over-the-counter pain remedies.

3). Potential hearing loss: The discharge of the rTMS coil generates a high-energy click that may cause cochlear damage. Foam earplugs can protect against these changes and will be worn by the subjects and the researchers present during TMS sessions.

The research team is highly experienced in administering TMS and Dr. Badran has been administering TMS for over 10 yeas in thousands of sessions. Furthermore, the team will properly pre-screen participants to ensure safety and minimize risk.

4.0 Study Endpoints

Change in fMRI brain response.

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion Criteria

1. Age 18-65
2. English fluency
4. Meet criteria for cocaine use disorder (CUD), as determined by DSM-V criteria, using the Structured Clinical Interview for DSM-V.
5. Enrolled in an intensive outpatient treatment program (MUSC Center for Drug and Alcohol Programs Intensive Outpatient Program (CDAP-IOP), currently engaged in treatment for substance related problems, or interested in seeking treatment for substance related problems.
6. Able to read and understand questionnaires and informed consent
7. Lives within 50 miles of the study site.
8. Is not at elevated risk of seizure (i.e., does not have a history of seizures, is not currently prescribed medications known to lower seizure threshold)
9. Does not have metal objects in the head/neck.
10. Does not have a history of traumatic brain injury, including a head injury that resulted in hospitalization, loss of consciousness for more than 10 minutes, or having ever been informed that they have an epidural, subdural, or subarachnoid hemorrhage.
11. Does not have a history of claustrophobia leading to significant clinical anxiety symptoms.

Exclusion Criteria

1. Past head injury or primary neurological disorder associated with MRI abnormalities, including dementia, MCI, brain tumors, epilepsy, Parkinson's disease, or demyelinating diseases
2. Any physical or intellectual disability affecting completion of assessments
3. Any contraindication to MRI
4. Current or past psychosis
5. ECT in last 6 months
6. Among females, pregnancy at screening will be exclusionary. Females of child bearing potential must agree to undergo a pregnancy test 72 hours prior to the fMRI scanning session and regularly before and during the medication trial. They must further agree to notify the study physician or PA if they become pregnant during the study.
7. Clinical Institute Withdrawal Assessment (CIWA-Ar) scale will be used to assess alcohol withdrawal. Individuals with CIWA > 8 will be excluded.

8. Individuals with unstable medical illness (e.g., hypertension, diabetes, myocardial infarction)
9. Has current suicidal ideation or homicidal ideation.
10. Has the need for maintenance or acute treatment with any psychoactive medication including anti-seizure medications and medications for ADHD
11. Suffers from chronic migraines
12. Any physical or intellectual disability affecting completion of assessments

We will not be enrolling vulnerable populations, specifically pregnant women, children, prisoners, or institutionalized individuals. We also will not enroll subjects incapable of providing their own consent. Should a potential subject present where there is a concern about their ability to understand study procedures and provide meaningful consent, their cognitive status and understanding of the study will be evaluated by Dr. Gray (Co-I). If there is any concern that the individual may be impaired, they will not be eligible for participation and not enrolled in the study. The rationale will be provided to the individual as well as his or her family members. Referrals for further evaluation, including urgent or emergent evaluation, will be made as needed and clinically warranted.

6.0 Number of Subjects

Total enrollment number is 160. We plan to acquire full data sets from 144 individuals (24/group) to allow for a 10% rate of data loss due to motion artifacts in the MRI scanner. This will require 160 individuals to be invited to the consent/screening visit.

7.0 Setting

All visits will take place on MUSC's campus at 30 Bee St at the Health Neuroscience Center and the Center for Biomedical Imaging.

8.0 Recruitment Methods

Subjects for this study will be primarily recruited from the MUSC Center for Drug and Alcohol Intensive Outpatient Program (CDAP). Subjects interested in seeking treatment for substance related problems will also be recruited from advertisements consisting of flyers posted on the MUSC campus and the surrounding Charleston community, craigslist postings, posts on social media (i.e., Facebook, Instagram, and Twitter) and Trialfacts, as well as referrals for treatment to CDAP. Trialfacts will create compliant advertisements used in its recruitment strategy. Trialfacts creates a mobile and tablet friendly study web page, which is the central destination for all interested participants. Trialfacts promotes the study to its database of 60,000+ volunteers interested in participating in clinical trials. Trialfacts accesses highly targeted participant populations by searching online through social media, i.e. Facebook, Instagram, YouTube, Reddit, Quora, Craigslist, and Google searches. Trialfacts creates and manages an automated pre-screening questionnaire that participants complete to determine their eligibility. When a participant is deemed eligible based on their responses made in the pre-screening questionnaire, Trialfacts will notify the study staff immediately by sending an email with a password protected PDF attachment containing the participant's contact information. Once a participant passes the pre-screening, he/she will have the option of scheduling a time for a phone call with one of our research personnel. A separate email notification will then be sent when a participant books a time to receive a call from the study staff to schedule an in-person screening visit. All other information from potential participants' responses will be stored in a deidentified referral spreadsheet in a secure, encrypted Google Drive folder with restricted access to the study staff only. The first point of contact between the research team and potential participants will be at the first INTAKE visit day 1 (orientation) of the CDAP program or by telephone or email contact initiated by the subject. The research staff will talk to the individuals about the rationale for this research, explain the study, and encourage interested and comfortable individuals to sign up to participate. The exclusion criteria of this research study are designed to minimize risks to participants. Medical and psychiatric evaluations are extensive at the beginning of the trial, and these evaluations may be conducted at unscheduled times when clinically indicated for safety. Individuals who meet the eligibility criteria and sign up will be contacted for a screening visit (Study V1), which will be followed by an experimental visit 1 (Study V2) that will include a MRI. At experimental visit 2 (Study V3) individuals

will have an MRI before and after cTBS. Individuals will be followed up with by telephone 1 day, 1 week, 2 weeks and 3 weeks after their final visit (V3). An informed consent form which details the study requirements, risks, and benefits will be given to the potential research subject to read and sign.

9.0 Consent Process

We will obtain formal written consent from all new participants enrolled in this project. Following policies of the MUSC Institutional Review Board, written informed consent will be obtained and documented by the study's Research Coordinator before any study-related procedures are performed. Informed consent will be obtained in a private research office. A study coordinator will review study procedures and the consent form with each potential participant. Each individual may take as much time as they like to read the consent document and decide if they do or do not wish to participate. A decision not to participate will not affect their participation in other studies at MUSC, nor will it affect their access to health care at MUSC. Dr. Badran and research staff will review all screening material and determine study eligibility for each person.

10.0 Study Design / Methods

Overview of study protocol. The overarching goal of Project 4 within the COCA is to evaluate the efficacy of brain stimultion on addiction pathophysiology in corticostriatal circuitry, and to bidirectionally translate our findings with the preclinical COCA projects that are discovering molecular and physiological mechanisms of cue-induced drug seeking in animal models. Extending prior studies by our team and leveraging the intellectual resources of the COCA faculty, we will investigate the impact of active and sham cTBS on corticostriatal rsFC, drug cue reactivity and craving. This will be achieved through a double blind, active sham- and placebo-controlled study in cocaine users from the community or that have enrolled in an intensive outpatient treatment program (MUSC Center for Drug and Alcohol Programs Intensive Outpatient Program (CDAP-IOP). Participants will be randomized to receive 3600 pulses of either active or sham cTBS alone without administration of any study medication. The study will require 3 visits while they are enrolled in the study. The cTBS sessions last 5 minutes and will occur immediately before their intensive outpatient visits. Clinical Assessments (see Assessments below) and neuroimaging data will be acquired at 2 timepoints: Baseline (V2) and immediately after cTBS (V3).

Primary hypotheses: Real mPFC cTBS will cause a larger decrease in cocaine cue-evoked functional connectivity than sham cTBS. The relationship between baseline rsFC and changes in rsFC will also be investigated as factors that mediate the effects of cTBS cocaine cue reactivity in the striatum and craving.

Participants. We plan to acquire full data sets from 144 individuals (24/group) to allow for a 10% rate of data loss due to motion artifacts in the MRI scanner. This will require 160 individuals to be invited the Consent/Screening Visit (V1)(see Targeted Enrollment Plan, Inclusion of Women & Minorities). This is based on a 66% eligibility rate from V1 (screening) to V2, followed by a 90% retention rate from V2 to V3. These enrollment and retention rates are based on prior studies by Dr. Hanlon in cocaine users which have used the MUSC Intensive Outpatient Program as a recruitment source (R01DA036617, R21DA041610). Treatment-seeking cocaine-dependent men and women, 18- 65 years old will be enrolled through the MUSC intensive outpatient substance abuse treatment program (see below) or their own initiated contact from study recruitment advertisements and randomized to receive either real or sham cTBS (stratified by gender). Randomization is appropriate for this sample [14] and therefore used to assign participants to experimental arms.

MUSC Intensive Outpatient Treatment Program. (More details of this program are found in *Resources*). Briefly, the program consists of 20 total treatment days (4 hours/day), spread across 4-5 weeks. Participants attend daily individual and group therapy sessions with staff certified in Cognitive Behavioral Therapy, contingency management, motivational interviewing and other established addiction treatment practices. Approximately 8-10 cocaine dependent individuals enroll in the Intensive Outpatient Program each month (60% male, 84% between the ages of 21-45, 10% of whom are court-ordered). The retention

rate for cocaine dependent individuals is 72% for the 4-week outpatient program, with 60% attending 1 month and 44% attending 2-month Accountability/Continuity visits. Participants will not be exclusively recruited from this treatment program – they will also be recruited from the community as we intend to enroll any adult that meets inclusion criteria.

Power analyses for study Aim 1—effects of cTBS on corticostriatal rsFC and cue-reactivity—were based on pilot data from a sham-controlled crossover study in which interleaved TMS/MRI was used to assess functional connectivity in cocaine users immediately before and after they received real or sham mPFC cTBS (see Significance). In these preliminary data in 12 cocaine users, real cTBS resulted in a larger effect on BOLD signal in the medial prefrontal cortex (eigenvalues real cTBS 0.62±0.24 vs. sham cTBS 0.33±0.44; Cohen's d=0.72). Subjects will be assessed at 2 time points (m) with an anticipated interclass correlation coefficient (ICC) of 0.8 for the within subjects measures. The design effect accounts for multiple correlated observations within each subject, is estimated to be 1.8 (DE= [1+(2-1)0.8];[15]. To allow for a 10% rate of data loss due to motion artifacts in the MRI scanner we have planned to enroll 160 individuals.

Overview of Experimental Procedures.

Visit 1 Procedures: Informed Consent, screening and Assessments. Participants will be introduced to the study procedures and asked to sign an informed consent approved by the Medical University of South Carolina Institutional Review Board, prior to official enrollment in the study. Following informed consent, a series of assessments designed to evaluate cocaine dependence and use, psychiatric conditions, and mood will be given to the participants. These include a health and physical examine conducted with the study physician or physician's assistant, urine pregnancy test for females, a urine drug screen, CIWA-Ar, standard MUSC clinical intake evaluation screen for clinical substance dependence research which includes medical history (used by the PI), MINI International Neuropsychiatric Interview [17], TLFB for cocaine, alcohol, and marijuana [18], Center for Epidemiologic Studies Depression Scale (CES-D), State-Trait Anxiety Inventory [19], Profile of Mood States [20], cocaine craving inventory [21], Fagerström Test of Nicotine Dependence [22] & Modified Cigarette Evaluation Questionnaire [23], alcohol use inventory (AUDIT)[24], computer based tests of behavioral value. Though these are not primary outcomes, the results will be used in post-hoc analyses of the data. Surveys will be filled out by the patient on tablet computers and data entry done directly via Redcap Software to prevent data loss.

Visit 2 Procedures (MRI 1, Medication initiation). Participants will undergo a baseline MRI scanning session and the following sequences will be collected:

- *T1 MPRAGE* (5 min). High-resolution structural scans will be obtained using an inversion recovery GeneRalized Autocalibrating Partial Parallel Acquisition (GRAPPA) sequence, 192 slices, voxel size: 1.0 x 1.0 x 1.0 mm, field of view: 256 mm, section thickness:1.0 mm with no gap, giving an in-plane resolution of 256. This sequence will be used for anatomic overlays of the functional data and spatial normalization to a standard atlas, TMS coil positioning, and subsequent voxel-based morphometry. *Field Map* (1 min) Field Map calculations allow for offline correction of imaging distortion during post-processing. Field map configurations will include: flip angle (FA)= 60 degrees, field of view (FOV) = 192 mm; voxel size = 2.0 x 2.0 x 2.0 mm, 72 contiguous slices 2.0 mm thick.

- *Resting-State Functional Connectivity (24 min).* The resting-state scan consists of four 6-minute runs. The first two runs will occur just prior to the cocaine cue reactivity task and the last two resting-state runs will occur immediately after the cocaine cue reactivity task. All participants will be asked to keep their eyes open and to not fall asleep. Participant's wakefulness during resting-state scans through the use of a) respiratory and heart rate signal and b) eye movement monitoring, in order to ensure participants are not sleeping. *Data processing.* Resting-state functional connectivity (rsFC) will be assessed using the in-house scripts with MATLAB and FSL. First, experimental design variables, pre-processed functional images filtered with a 0.01 to 0.08 Hz band-pass filter, and segmented images will be uploaded into the toolbox. 5-mm radius spheres will be created around a priori regions of interest (ROIs) (nucleus accumbens,

mPFC). Individuals' WM and CSF templates, heart-rate (HR), respiration rate and movement parameters will be included as covariates. rZ scores for each person will be generated and entered into statistical models.

- *Functional MRI Cocaine Cue Reactivity Task (24 min)*. This task has been used in 4 original research publications by our group and reliably activates orbitofrontal and medial prefrontal regions [26-28]. They will receive two 12m runs of the task (randomized, counterbalanced order within groups). During both runs they will be instructed to 'allow' themselves to crave (passive limbic engagement). When the task begins participants are shown pseudorandomly interspersed blocks of images: 1) cocaine images (COC), 2) neutral images (NEU), and 3) pleasant images (PLE), all NEU and PLE images will be chromatically matched to the COC images. Stimuli are presented in six blocks across two runs, with each block lasting 3 min and 43 sec per image type (two blocks each of COC, NEU, PLE). Each block is followed by a 6-s washout period, allowing the hemodynamic response from the previous block to decline before the next is presented. Scanning parameters: Multislice gradient-echo echo planar imaging (TR=2000, TE=36 msec, field of view of 207 mm, voxel size 2.0 x 2.0 x 2.0 mm, 69 slices, 2 mm thickness, no skip).

Visit 3 Procedures (MRI 2, cTBS, MRI 3). Following three full days of study medication for the pretreatment arm or at least 24 hrs for the no pretreatment arm, participants will return to the lab and undergo MRI and cTBS procedures as outlined below:

- *T1 MPRAGE, Field Map, Resting-State Functional Connectivity, and Cocaine Cue Reactivity task (MRI 2):* These scans will be repeated exactly as done in Visit 2.
- *Continuous Theta Burst Stimulation to the mPFC (5 min).* The cTBS treatment lasts 5 minutes and will be given before the group therapy session. Detailed descriptions of the real and active sham cTBS paradigm have been reported elsewhere [8-9]. After the MRI scans participants will be escorted into the Brain Stimulation room (30 feet away) where the TMS procedure will be performed. TMS will be administered using a neuronavigational targeting approach via the Brainsight imaging system (Rogue Industries). This method allows for the integration of participant's individual structural brain images and synchronizes these images in the real-life 3-D setting using infrared cameras and sensors that enable the TMS operator to precisely administer magnetic fields to an individual's precise brain target with sub-5mm accuracy. Furthermore, functional brain targets may be incorporated in the structural imagery in order to create a network-based personalized treatment approach. This system is safe and does not add any further risk to the participant - it simply requires the participant to wear a headband containing infrared sensors to be tracked in real-time by the camera. No pictures or video will be recorded by the camera, simply the reflections of the infrared laser that return to the camera after coming in contact with sensors which detect movement in the 3-D space. We will then determine the participant's resting motor threshold (RMT, the minimal amount of stimulation required over the hand area of the primary motor cortex to induce contraction of the APB muscle of the hand 50% of the time) via the standardized PEST procedure [29]. During each TMS session, we will take a non-identifiable photo of the participants' forehead (eyes covered with an index card) to ensure the coil is correctly placed each time they return to the lab. The procedures for acquiring the motor threshold, performing cortical localization, standardized procedures, blinding, establishing standardized paradigms and training regimens for all staff, as well as safety and ring the experimental procedures are consistent with our prior publications [8-9, 27,30-32]. We will also publish a Standard Operating Procedure document and video file as supplementary material with any publications that arise from this project. For continuous theta burst stimulation, participants will receive stimulation over the left frontal pole (FP1) (each train: 3 pulse bursts presented at 5Hz, 15 pulses/sec, 600 pulses/train, 60 sec intertrain interval; 110% RMT, MagPro) using a figure 8 coil (Coil Cool-B65 A/P). This protocol has been shown to attenuate BOLD activation in the mPFC and striatum in cocaine dependent individuals in the past [8-9].

Briefly, two trains of either real or sham LTD-like cTBS will be applied over the left frontal pole (EEG 10-20 system: FP1) (1 train: 120 sec, 3 pulse bursts presented at 5Hz, 15 pulses/sec, 1800 pulses/train, 60 sec intertrain interval; 110% RMT, MagPro) using a figure-of- 8 coil (Coil Cool-B65 A/P). During the real and sham cTBS treatment sessions the amplifier output will be escalated (over 30 seconds) from 80% to 110% RMT to enhance tolerability. The MagVenture MagPro system has an integrated, active sham that

passes current through two surface electrodes placed on the scalp. The electrodes will be placed on the left frontalis muscle for all sessions. A patient ID card will randomize participants to receive either real or sham stimulation. This system maintains blinding by a gyroscope in the coil which indicates to the clinical staff whether the coil should be rotated up or down for this participant once the card is entered into the machine. One side of the coil is active, the other is sham. The integrity of the double-blind procedure will be assessed by asking the patients and study personnel rate their confidence regarding their assignment to real or sham TMS (scale 1-10). Immediately after the cTBS session:

- *Confidence in Active or Sham cTBS Assignment (1min).* Participants will complete a form indicating their confidence (scale 1-10) in whether they are receiving active or sham treatment, and will be prompted to audio record a reason (audio recordings are then transcribed to text, in order to avoid handwriting recognition challenges). Pooled accuracy from prior work in our collaborator's laboratory was 47.6% suggesting that individuals were not aware of the stimulation being received.

- *T1 MPRAGE, Field Map, Resting-State Functional Connectivity, Functional MRI Cocaine Cue Reactivity Task (MRI 3):* These scans will be repeated exactly as mentioned above for V2 (MRI 1).

- *Behavioral Assessments.* In order to produce a clinically meaningful effect of TBS on behavioral measures such as drug craving, mood, or usage multiple days (and likely multiple weeks of TBS treatment are required). Therefore, brain based dependent measures are the primary outcomes of the study (as they are sensitive to a single day of real versus sham TBS [39]. For the purpose of being thorough however, we will acquire measurements of cocaine craving (Numerical rating scale 1-10) before, 10, 20, 30 minutes after TBS, as well the demand and value of cocaine as a reinforcer using a delayed discounting task and hypothetical purchasing task (before TBS as well as at the conclusion of the TBS visit).

- *Participant compensation.* Participants will be compensated up to $250 for completion of all study procedures. Participants will receive $25 at the screening visit, $80 for the baseline experimental visit and $80 for the second fMRI scanning session. Participants will receive $10 for each follow up phone call, up to $40 for 1 day, 1 week, 2 weeks and 3 weeks after their last visit. Participants will also receive a $25 bonus for completion of all study visits, follow ups. Compensation will be made for each session completed and will not be contingent upon completion of the entire study. During the informed consent procedure, participants will be notified that they can withdraw from the study at any time under no penalty. Payment will be made for each session completed and will not be contingent upon completion of the entire study. During the informed consent procedure, participants will be notified that they can withdraw from the study at any time under no penalty.

- *DSM Board Plan:* The PIs and Co-I (Kevin M. Gray, M.D.) will have overall responsibility for safety and data monitoring on a day-to-day basis. The DSMB, as noted below, will provide guidance and input on a scheduled and as-needed basis. As previously mentioned, the DSM Board will meet every 5-7 months with the PI to discuss the information listed in "Content of ME/DSM report". This content of this meeting will be formalized in a report which will be circulated by email and digitally approved by the PI and ME/DSMB. The approved report will be sent to the MUSC IRB, and to the NIH.

11.0 Specimen Collection and Banking

Urine samples will be collected for pregnancy testing and drug screening purposes. There will be no identifiers except for a code number on the samples. Urine samples may be stored for point of care for pregnancy testing. A digital key to the code numbers will be maintained in password protected database on the MUSC network. The study PI (Dr. Badran) will have access to the password.

12.0 Data Management

Prior to formal statistical analysis, summary statistics for all variables will be obtained and spaghetti plots will be generated. All behavioral outcome measures will be based on standardized composite scores from

the literature. We will also use data reduction techniques (such as factor analysis or principle component analysis) to confirm the applicability of the composite scores in our population. In the interests of eventually translating these mechanistic data to a larger clinical trial, we will perform a preliminary Intent-to-Treat analysis on each of the 6 groups to estimate effect sizes for a subsequent power analysis. Analyses will be performed for each phase separately. Image pre-processing will be conducted with FSL v. 5.0: (FMRIB Analysis Group, Oxford, UK) [33] realignment to the first volume, smoothing with an anisotropic 8-mm Gaussian kernel, high-pass filtering, resampling to 2-mm isotropic voxels, and stereotactic registration to the Montreal Neurological Institute 152-subject average template. Subjects with >3 mm movement (total mean frame displacement across the entire task) will be excluded from analysis.

Specific Aim 1 (cTBS): Evaluate mPFC cTBS as a tool to modulate corticostriatal rsFC and drug cue-reactivity in treatment-seeking cocaine users.
Rationale: Drug cues reliably activate the mPFC & ventral striatum in multiple classes of substance users, including cocaine users. Through an LTD-like form of TBS it is possible to decrease activity in the mPFC and the ventral striatum in chronic cocaine users and alcohol users [9]. *Primary dependent measure:* Change in cue-evoked brain activity and rsFC in corticostriatal circuitry after real but not sham cTBS. *Hypothesis:* LTD-like cTBS to the MPFC of individuals with cocaine use disorder will decrease cocaine cue-reactivity BOLD response in corticostriatal nodes (i.e. mPFC, ventral striatum) and strengthen rsFC between these key nodes.
Methods and analysis: Using a standardized cocaine cue-reactivity paradigm we will quantify the percent BOLD signal change in the mPFC and the striatum (dorsal and ventral) as well as several other brain regions with known roles in salience (anterior insula & anterior cingulate), drug cue reactivity, and executive control. This will be achieved by extracting the average BOLD signal timecourse and the percent signal change during the cocaine cue versus neutral cue blocks from *a priori* anatomically defined regions of interest (ROIs), including the striatum (ventral striatum and dorsal striatum), insula, inferior frontal gyrus, and anterior cingulate cortex. Ventral striatal and dorsal striatal ROIs are derived from the FSL Oxford-GSK-Imanova striatal atlas, mapped via probabilistic diffusion tractography [34] in agreement with anatomical projection zones from the frontal cortex [35]. Percent signal change in these areas will be compared between groups receiving real versus sham cTBS (Aim 1). These data will be interpreted relative to changes in a positive (auditory cortex) and a negative (primary visual) control region. We will also perform a whole brain seed-based connectivity analysis with the area under the coil as our seed of interest.
Alternative outcomes: Known factors that contribute to variability in brain stimulation treatment response include gender and age (Ziemann & Sieber 2010). Variance in these factors may preclude the detection of a true positive. Consequently, these factors will be included as covariates in the analyses. The scalp-cortex distance will be calculated using Standardized automatic segmentation software developed by our laboratory (BrainRuler 1.0,MATLAB Central repository open source) [36] From an exploratory hypothesis-generating perspective, for Aims 1 & 2 we will also perform whole brain psychophysiological interaction analyses to evaluate if there are other neural areas that are modulated by TBS that we would have missed in our primary ROI-based strategy.

RIGOR AND REPRODUCIBILITY: Strategies to Ensure a Robust and Unbiased Approach: The proposed study will achieve robust and unbiased results via explicit inclusion/exclusion criteria; randomization of treatment condition order and examination of order effects; sham control; double blinding; sophisticated compliance monitoring at MUSC; use of validated MRI, laboratory, and interview/self-report measures; explicit hypotheses; power estimates; planned handling of attrition and missing data; and careful consideration of potential confounds. Methodology is reported in a detailed and fully transparent manner to support replication

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Sources of Material: A total of 144 individuals will be enrolled in the current project. The behavioral assessments, as well as biological data (laboratory and neuroimaging results) will be collected only after

obtaining informed consent, and for research purposes only. These records will be kept by Dr. Badran in password protected confidential electronic files with restricted access.

Confidentiality Procedures: As the PI, Dr. Badran will assure all procedures protecting study data designed to guard subject confidentiality conform to the MUSC Research Protection Program requirements. Additionally, the MUSC IRB must approve all procedures and safety precautions before the study can begin. All data (clinical evaluations, MRI data, TMS data) will be stored securely in locked offices or laboratories accessible only by study staff. Further, all information that could potentially identify a subject directly is removed from all study data. This includes electronic and paper assessments, MR images, and biological samples. This will be replaced with a unique four-digit code. The key to linking the code to subject identity will be kept separately from study data, in a locked electronic file. Only study staff involved in clinical recruitment and assessment will have access to individually identifiable private information. All other study staff will only have access to the coded identifier.

14.0 Withdrawal of Subjects

Female participants who become pregnant during the study will be withdrawn from the study. Additionally, the Investigator has the right to withdraw a participant at any time.

15.0 Risks to Subjects

The main study procedures include brain stimulation, a medication trial, clinical evaluation, MRI, and completion of questionnaires. Although these procedures do carry minimal risk, the primary risks of the study are a) adverse effects of study medications, b) emotional distress, c) incidental findings, and d) loss of confidentiality. The primary risks are described below:

1. Magnetic Resonance Imaging. Because the MRI machine acts like a large magnet, it could move metallic objects in the MRI room during the examination, which could harmful to the participant. To prevent such an event from happening; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If a participant has a piece of metal in their body, such as a fragment in their eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, they will not be allowed into the MRI room and cannot have a MRI.

Having a MRI may be uncomfortable, particularly regarding feelings of claustrophobia and the loud banging noise during the scan. Participants will be asked to wear earplugs to avoid possible hearing impairment.

2. Transcranial Magnetic Stimulation:

a. Investigational Device Exemption: Transcranial Magnetic Stimulation is an investigational device. The IRB at MUSC (in cooperation with the FDA) have determined repetitive TMS to be a non-significant risk intervention.

b. Potential Risks of TMS

1). *Potential risk of a seizure:* The major risk using repetitive TMS subjects is the possibility of inducing a seizure. We have now studied and given rTMS to more than several hundred subjects over past 15 years. None of these patients has developed a seizure. We will exclude patients with a prior history of seizures.

2). *Potential for scalp discomfort and headaches:* Some people report mild discomfort when the magnetic pulses are applied over the scalp. A small number of people (~5%) report headache following TMS. However, the headaches are temporary and manageable with common over-the-counter pain remedies.

3). *Potential hearing loss:* The discharge of the rTMS coil generates a high-energy click that may cause cochlear damage. Foam earplugs can protect against these changes and will be worn by the subjects and the researchers present during TMS sessions.

3. Incidental Findings: Magnetic Resonance Imaging: Some MRI scans can detect medical conditions, such as cancer, brain injury, and abnormal blood vessels; however, this functional MRI is carried out

purely for experimental purposes and we are not looking for brain disorders. Furthermore, the study researchers are not trained in diagnosing brain disorders; therefore, the researchers are not qualified to offer any medical opinions concerning the scan (good or bad). It is possible that the study researchers will notice something in a participant's scan that appears unusual and/or abnormal, if this occurs, the researchers will inform the participant of the finding and provide them with a copy of their scan, which they may take to a medical expert for further review and diagnosis. Being told about such a finding may cause anxiety as well as suggest the need for additional tests and financial costs. Any costs associated with clinical follow-up(s) are the participant's and/or the participant's insurance carrier's responsibility. Participants who do not wish to be informed of such findings will be advised to not participate in this study.

4. Breach of confidentiality: There is the potential risk of breach of confidentiality of clinical and laboratory information. Dr. Badran has experience as an investigator dealing with such sensitive information and has experience assuring that data is adequately protected. Safeguards to protect confidentiality include locked records and firewalls around password-protected electronic data, and all study data being coded, with the key linking the code with a participant's identity being kept on secure network storage as a password protected document. Similar safeguards are followed for storage and processing of MRI data. MRI data is stored on secure network storage maintained by MUSC, where the PI has dual appointment. The MRI scans are identified only by subject code, study code, and date of acquisition. Participants' initials will also be present on some questionnaires; however, the questionnaires containing the initials will be stored in a locked file cabinet.

5. Interview and psychiatric emergencies: Subjects may experience discomfort during the clinical interview and evaluations when discussing symptoms, life events, and social support. The Research Coordinator and Specialists will be experienced and skilled in interviewing subjects. Should the subject wish to stop or take a break, they will allow it. In addition, should the subject express any physical or psychological symptoms that are concerning or possibly represent an emergency, the study physician (Dr. Gray) or other approved study clinician will be contacted immediately to assess the subject and to determine the appropriate course of action. Possible situations where this would occur include but are not limited to thoughts of suicide, homicidal or violent thoughts, psychosis, or a change in the subject's physical status if they start feeling bad or complaining of new physical symptoms (such as chest pain, acute nausea, etc.). Importantly, the Research Coordinator/Specialist is not the only individual screening for such potential emergencies. These domains will be independently assessed by Dr. Gray/PA-C during the health and physical exam and any subsequent future clinical interview. Options for addressing such emergencies may include contacting the individual's mental health caregiver, referring for urgent evaluation and treatment, or emergent hospitalization.

ADEQUACY OF PROTECTION AGAINST RISKS

a. *Recruitment and Informed Consent.* Participants will be recruited from the general community through media advertising (print and online sources). The IRB approved Informed Consent (IC) will be obtained prior to the initial assessment. The consent will be explained orally and in the written form, and will be documented by the signature of the participant on the IC. Consent will be obtained in a private interview room so that the participant may ask any questions to the research staff.

b. *Protection against Risk.* Research staff will closely supervise participants throughout their enrollment in the study. Specific to the BAC assessment, if a participant's BAC is greater than 0.0 at any visit, the research staff will either a) ask the participant to remain in the laboratory until their BAC returns to

0.0, if they are driving, or b) work with the participant to ensure that they have alternative transportation home, including providing a taxi, if needed.

c. *Loss of confidentiality:* Paper-based information will be kept in on-site locked file cabinet(s) designated for study materials. Data collection instruments or forms containing participant names will be stored in separate secure locations from those instruments or forms containing subject identification (SID) numbers, and both will be stored separately from the master list linking the SID and names. Paper-based information will be accessible only to study personnel who need access to the information for study purposes. All electronic records will be stored on a password protected secure server with access limited only to study personnel who need access to the information for study purposes. All password protected hard-drive backups on will be stored in the PI's offices in a secure location. The results of drug and BAC testing will be stored in the same manner as other data (i.e. in separate location from any information containing participant PHI). The results will not be reported to any authority (e.g. employer or law enforcement) nor will they be available to them upon request.

16.0 Potential Benefits to Subjects or Others

Participants will not directly benefit from this study.

17.0 Sharing of Results with Subjects

The final results of the study will not be known until the conclusion of the trial, as the data analysts are blind to the treatment arms. The results will be made available to study participants following peer-review and publication of the manuscripts. Participants will not be notified of the results of the study.

18.0 Drugs or Devices (if applicable)

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