Protocol Title: Neuroplasticity Following Theta-Burst Stimulation in Cocaine Use Disorder
Abbreviated Title: TBS in Cocaine Use
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PRÉCIS:

Objectives: Illicit drug use affects tens of millions of Americans and costs nearly $200 billion annually in health care costs and lost productivity. Cocaine dependence accounts for 25% of reported lifetime drug dependence though few successfully abstain with treatment. For efforts toward positive long-term outcomes, it is imperative to identify risk factors of poor outcomes, specialized treatments, neural mechanisms that change with treatment, and predictive measures of treatment outcomes. Substance abusers are known to have dysregulation in cue reactivity, reward processing, executive control, and intrinsic network connectivity. Non-invasive brain stimulation (NIBS) has proven effective at reducing drug craving in nicotine, alcohol, and cocaine users. Here, intermittent theta-burst stimulation (iTBS), a type of NIBS, delivered to left dorsolateral prefrontal cortex (dlPFC) is implemented to modulate substance abuse related circuit dysregulations and assess the relationship of iTBS-induced changes in circuitry to ongoing cocaine use.

Study population: Recruitment from the Baltimore, Maryland area will take place for this protocol. For the Pilot, 20 cocaine dependent (CD) individuals will be recruited. (The Pilot was completed in July 2018). For the Expanded Feasibility Study, 45 healthy adults (HC) and 90 CD individuals will be recruited. All of the HC group will receive **both active- and sham-iTBS in a within-subject crossover design**. **Half (45) of the CD group will receive active-iTBS and half (45) will receive sham-iTBS**. The Expanded Feasibility Study groups will be matched on demographic measures (e.g., age, IQ, sex).

Design: The Pilot is designed to be a tolerability pilot where iTBS parameters are assessed in CD participants. The first half of the Pilot participants will be inpatient (for initial close observations) and the second half will be outpatient (closely reflecting the Expanded Feasibility Study). Throughout the Pilot, clinical measures will be collected and participants closely monitored. The general outline for the Expanded Feasibility Study is to characterize the treatment cohort (vs. HC) and assess effectiveness of iTBS over the left dlPFC in altering task and resting brain activity. The iTBS intervention consists of 30 sessions over a 2-3week (10 treatment days) period as an add-on to a treatment-as-usual, contingency management, which will begin as soon as the iTBS treatment is completed. Structural and functional magnetic resonance imaging, neural measures of cue reactivity, reward processing, executive control, and intrinsic network connectivity will be collected to identify differences between CD and HC participants at baseline. In CD participants, neural measures along with cocaine use will be tracked longitudinally to assess neuroplastic changes, along with safety monitoring. Contingency management will begin when iTBS sessions are done and will continue for 11 weeks. A 3-month follow-up period follows the end of CM. The Expanded Feasibility Study includes ~43 visits.

Outcome parameters: Two main comparisons are of interest. First, baseline differences in neural measures between CD and HC participants will be identified. CD participants are expected to show dysregulations in these functions, relative to HC participants. Second, neural plasticity related to these functions due to iTBS treatment and reduction in cocaine use will be measured. The active-iTBS intervention is expected to be effective in reducing cocaine use, relative to the sham-iTBS intervention. Normalization of circuit dysregulation is hypothesized to be associated with reduction of

cocaine use. Overall, the current protocol is designed to test whether iTBS to left dlPFC is efficacious in altering brain circuitry related to chronic cocaine use.

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I. BACKGROUND

A. The Problem

Addiction is a widespread, complex neurobiological disease[1]. Reportedly, 25 million Americans use illicit drugs costing $193 billion annually in areas such as health care and lost productivity[2]. Nearly 10% of Americans report lifetime drug dependence but only 25% have sought treatment[3]. Many who seek treatment do not successfully eliminate drug use behavior. As recidivism remains disturbingly high for those who enter treatment, there is substantial and immediate need to thoroughly identify risk factors for poor treatment outcomes, potential treatment targets, and more efficacious interventions. The longer an individual remains in treatment, the more outcomes improve[4] highlighting the primary need to establish successful, potentially specialized, treatments that retain individuals throughout treatment. Cocaine dependence is the most often reported illicit drug dependence with nearly 25% of Americans reporting a lifetime drug dependence also reporting cocaine dependence[3]. Cocaine use in Maryland overall is below the national average at 15.4% but use in Baltimore is slightly above the national average at 26.5%[5]. Therefore, studying cocaine users in Baltimore could affect change locally with the potential to generalize more broadly.

Presented here is a brief summary of cognitive and affective dysregulations previously identified in individuals with cocaine dependence, providing potential functional targets for therapeutic interventions. Ultimately, some of these targets may also serve as biomarkers for treatment efficacy. Overall, it is important to delineate the relationship between cocaine dependence and abnormalities in neural measures. Following this summary, a novel non-invasive brain stimulation (NIBS; intermittent theta-burst stimulation or iTBS) intervention is proposed. Several NIBS techniques have been implemented in an attempt to reduce craving for nicotine, alcohol, and cocaine, with repetitive transcranial magnetic stimulation (rTMS) as the most common NIBS applied. Implementation of iTBS can be less time consuming and found to be more tolerable by participants thus offering the potential for widespread application. This is an initial step toward developing a new, efficacious treatment for cocaine dependence.

A protocol is proposed with a Pilot designed to assess tolerability of iTBS parameters to employ in a subsequent Expanded Feasibility Study assessing neuroplasticity related to the intervention was completed. The iTBS experimental treatment will be an add-on to a contingency management (CM) treatment as usual (TAU) that has been implemented successfully to reduce cocaine use (albeit with minimal long-term efficacy following CM). Neural risk factors will be monitored during and after treatment to identify changes with treatment. Cocaine use will also be tracked to inform any neural changes and treatment efficacy. Malleable risk factors identified here will be prime targets for future studies and treatment development.

This proposal allows for a comprehensive neural picture of cocaine dependence. As discussed below, functional differences within tasks will be acquired with blood oxygenation level dependent (BOLD) fMRI and non-task related group differences will be identified with measures of structural, diffusion tensor imaging (DTI), functional connectivity (e.g., resting state measures), arterial spin labeling (ASL), magnetic resonance spectroscopy (MRS). Specific cognitive and affective constructs probed in this protocol are discussed in detail below. Changes in neural measures will be assessed in relation to reductions in cocaine use.

B. Dysregulation in Addiction

Several cognitive and affective differences have been identified between generally healthy individuals and individuals with substance dependence. Broadly, substance users have been identified to have dysregulation in attention, working memory, reward processing, executive control (e.g., response inhibition and error-processing) relative to healthy individuals[6-10]. Of specific interest here, are the neural deficiencies related to cognitive and affective processes identified in cocaine dependent individuals (CD). These systems engage brain regions that have been implicated to be dysregulated by the disease including dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), inferior frontal gyrus (IFG) orbitofrontal cortex (OFC), striatum, hippocampus, basolateral amygdala, and insula[7-9]. Dopaminergic dysfunction is thought to be at the

heart of many of these group differences[11] specifically dopamine (DA) released from the ventral tegmental area (VTA) into the nucleus accumbens (NAcc), prefrontal cortex (PFC), and amygdala. This DA system dysfunction has been linked to initiation and maintenance of addictive behaviors[12]. Drug use increases DA release in the mesocorticolimbic (MCL)-DA system[13-15], which is thought to be an important element in learning, goal-directed behavior, and reward processing[16, 17]. Allocation of attention with respect to goal-directed behavior has also been linked to DA release[18]. Chronic drug use is associated with hypodopaminergic states[19-21] suggesting treatments targeting the MCL-DA system may be essential for treating addiction (although it should be noted that dopamine agonist therapy is generally ineffective in cocaine dependence). Explicit modulation of the MCL-DA system by eliciting craving, reward processing, and executive control will inherently require the activity within dlPFC, ACC, IFG, OFC, striatum, hippocampus, basolateral amygdala, and insula; all areas implicated in addiction, differentiate CD from HC individuals, and are hypothesized to serve as targets for potential modulation.

Cognitive and affective dysregulation in CD individuals has been shown in cue reactivity, reward processing, executive control, and intrinsic network connectivity. Cue-induced hypoactivations have been related to addiction severity[22] suggesting a malleable network, at least with increased exposure to cocaine. Alternatively, these cue-induced hypoactivations could be preexisting and related to addiction severity. Identifying the sequential relationship between hypoactivations and addiction severity is difficult without longitudinal methods. Nonetheless, several hypo- and hyperactivations have been identified in samples of substance users. Hyperactivations from cue processing in sensory association cortex, motor cortex, and PCC elicited to cues have been associated with relapse to cocaine use[23] and ACC activation has predicted relapse to nicotine[24] and alcohol[25]. Neural activity related to reward processing within the caudate has differentiated CD from HC[26, 27] as well as CD and former CD participants[27]. These functional differences may derive from reduced striatal volume in CD relative to HC participants[28]. The amygdala has also been implicated in reward

processing in addition to perception of fearful and threatening stimuli[29]. Response inhibition executive control tasks elicit hypoactivation for CD relative to HC participants in medial prefrontal regions, supplemental motor area, insula, and ACC[30, 31]. Findings from error-processing executive control tasks are somewhat mixed with hypoactivation measured in the ACC[31-33], MFG/pre-SMA, left insula, left inferior frontal gyrus[31] and hyperactivation in the ACC, MFG, inferior parietal lobe, angular gyrus[34], and insula[35] in CD compared to HC participants. Event-related potentials (ERPs) measures of error-processing thought to originate in the ACC[36, 37] also differentiate CD from HC participants[38-40]. Both fMRI[41] and ERP[40, 42, 43] measures of error-processing have been used to predict drug treatment outcomes. Intrinsic network connectivity is often measured by analyzing resting-state seed-based network connectivity. Such analyses have proven useful in identifying network connectivity differences in CD[44-47] as well as other substances of abuse[48-54]. Overall, previously published tasks will be implemented to elicit cue reactivity[55-57], reward processing[58-62], response inhibition[63-65], error-processing[63-65], and intrinsic network connectivity.

C. Non-Invasive Brain Stimulation (NIBS)

NIBS is designed to transiently stimulate localized cortex[66-69] and their subcortical connections. NIBS is thought to change the baseline electrical steady-state of the targeted region by applying alternating magnetic pulses to the scalp to induce current in underlying neuronal tissue. With the wide range of research and clinical applications, rTMS has become a prominent excitatory stimulation method[68, 69]. Therapeutic effects of rTMS have induced long-term plastic changes with side-effects such as pain near the application site and muscle twitching which are experienced by about 36% and 20% of participants, respectively[70]. Serious adverse events, such as seizures, are rare[71] and considered unlikely during NIBS applications. During a traditional rTMS session, 3000 pulses at 10 Hz are applied over 37.5 minutes[70, 72]. The large number of pulses and length of protocol can prove difficult to complete for some participants. A viable alternative is iTBS[71, 73] where only 600 total pulses in 50 Hz bursts of 3 pulses

separated by 200 msec for 2 seconds are applied at a frequency of .1 Hz over about 3 minutes. The post-iTBS shift in electrical baseline has been shown to exceed the duration measured for rTMS[74-76] while requiring far fewer stimulations and less time to implement. Three TBS stimulation paradigms have been described[73] each administering 600 pulses: iTBS wherein 2 seconds of pulses (i.e., train) are administered every 10 s for a total of 200 s; intermediate TBS (imTBS) wherein a 5 s train is administered every 15 s for a total of 120 s; continuous TBS (cTBS) wherein a 40 s train is administered.

rTMS has most often been applied effectively for treatment-resistant depression[77, 78], but has also been explored in other disorders[79]. Stimulation over the left dlPFC is common and is now an FDA approved intervention for treatment-resistant depression[79] with substantial evidence for reducing depression symptoms[80]. Network connectivity between the dlPFC and ACC is normalized with this treatment[81] suggesting network malleability with NIBS stimulation. In fact, broad activity changes[81] and increases in DA release in the caudate nucleus[82, 83] have been found with left dlPFC stimulation. Therefore, stimulation of the left dlPFC is a potential intervention tool in disorders of the DA system, such as addiction[84, 85]. Considering DA is related to plasticity necessary for learning and memory[13], targeting deficiencies in the DA system in substance users with NIBS could be specifically useful. Applications of high frequency (thought to be excitatory) rTMS over left dlPFC have been successful in reducing craving for cocaine[86-88] and nicotine[89]. Only a single rTMS session was implemented although there is evidence that more sessions affect greater, longer-lasting reductions in cocaine craving[87, 88]. iTBS and cTBS over left and right dlPFC, respectively, were more effective at treating depression than rTMS[90, 91]. Applying iTBS, also thought to be excitatory, over left dlPFC has the potential to modulate the neural regions associated with dysregulations of addiction.

The cognitive and affective dysregulations of addiction are associated with neural activity in the ACC, insula, or striatum and could be modulated by left dlPFC NIBS[81]. Cocaine craving[86-88, 92] has been reduced with NIBS but implementing NIBS targeted at long-term reduction of substance use has yet to be explored. Adding iTBS to a TAU has

been effective in smoking cessation treatment[93] and could be added to TAUs targeting other substances of abuse. A new application of the iTBS intervention is proposed here and is modeled after the rTMS implementation designed to reduce symptoms of depression. For depression, positive effects occur after 26-28 NIBS sessions[94, 95]. To decrease time to positive effects, multiple rTMS sessions have been implemented in a single day. As many as 10 daily sessions[96], though more modest schedules of 2 sessions per day for 10 days[97] to 4 sessions per day for 5 days[98], have also been implemented. By implementing multiple treatment sessions in a single day, the scheduled duration of treatment is condensed. This condensed schedule could increase retention rates compared to longer treatment schedules and be easier to implement in clinical settings. A single study has implemented multiple NIBS sessions a day in a sample of cocaine users[92]. In that study, participants received two 120 second trains of cTBS with a 60 second break between trains over mPFC. A total of 3,600 cTBS pulses were administered over a 5-minute period. This protocol reported no adverse events and was effective in reducing cocaine craving while administering 600 more pulses than a traditional rTMS session (3,000 pulses) in much less time (5 minutes) than a traditional 30 minute rTMS session. The treatment reduced resting activity in the ventral striatum while also reducing subjective cocaine craving. Another group administered 3 iTBS sessions (1,800) pulses with only a 15-minute break between trains of 600 pulses[99, 100]. This group identified no benefit to administering subsequent iTBS sessions before after-effects had dissipated from a previous administration. To account for after-effects between iTBS administrations, a break of at least 30 minutes is necessary. Based on the above, we propose administering 3 iTBS sessions totaling 1,800 pulses per day in a cocaine dependent sample. However, tolerability of multiple daily iTBS sessions within CD participants will be first established in a Pilot before initiating the Expanded Feasibility Study.

D. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): Risk Minimization and Data Integrity

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) belongs to the coronavirus family, a major cause of upper respiratory infections world-wide that is also is known to have neurotropic properties [reviewed in (Li et al. 2020b; Ng Kee Kwong et al. 2020; Yashavantha Rao and Jayabaskaran 2020)]. SARS-CoV-2 is the cause of the current Coronavirus 2019 disease (COVID-19) which has infected over 19 million individuals and claimed the lives of about 750,000 worldwide as of August 10, 2020. https://coronavirus.jhu.edu/map.html

COVID-19 can produce neurologic manifestations ranging from loss of taste and smell to dizziness, headache, confusion, mild cognitive impairment, encephalitis, autoimmune Guillain Barre Syndrome and acute cerebrovascular disease [reviewed in (Ahmed et al. 2020; Leonardi et al. 2020; Li et al. 2020a; Montalvan et al. 2020; Niazkar et al. 2020)]. There are several possible mechanisms by which SARS-CoV-2 may impact the brain: (1) Direct invasion through the cribriform plate, (2) Retrograde transmission through cranial nerve axons in the periphery, (3) Hematogenous spread through infecting vascular endothelial cells, (4) Indirect impact through an exaggerated inflammatory response, and (5) Indirect impact through severe respiratory infection-induced hypoxia [reviewed in (Ahmed et al. 2020; Troyer et al. 2020; Zhou et al. 2020)].

While current published reports of brain involvement in COVID-19 patients come from severe hospitalized cases, it is highly likely that the virus also impacts the brain in mild or even asymptomatic cases. For instance, loss of smell in mild cases suggests that SARS-CoV-2 can affect the brain regardless of the presence of respiratory symptoms. Regional alterations in brain structure (voxel-based morphometry and diffusion tensor imaging) have already been documented in recovered COVID-19 patients (Lu et al 2020). Given this wide range of possible CNS effects, it is likely that COVID-19-associated changes may also alter BOLD signal which is dependent on both neuronal and vascular functioning. Further, substance users may be particularly vulnerable to CNS effects given evidence of structural, functional and neurochemical differences from non-substance users at least some of which may represent damage resulting from chronic exposure to substances of abuse. Vascular changes evident in

substance use disorders (ref Weis and Buttner 2017; doi: 10.1016/B978-0-12-802395-2.00014-6) may also predispose substance users to the vascular effects of COVID-19. Given the wide range of potential impact and differential impact of COVID-19 infection on both healthy control participants and those with a substance use disorder, understanding participants' COVID-19 status may be important for the integrity of our research data. Therefore, we will assess SARS-CoV-2 antibodies in order to assess for possible effects. We will use COVID diagnostic testing to exclude participants with active infection. We are NOT studying the SARS-CoV-2 virus in this protocol, nor are we evaluating the safety or efficacy of a COVID-19 diagnostic test or antibody test.

As long as the SARS-CoV-2 pandemic continues, it will be important to minimize person-to-person contact in order to reduce the risk of transmission. Thus, a number of procedural changes, detailed below, will be necessary as long as there is significant risk of disease spread.

II. TOLERABILITY PILOT [PILOT COMPLETE – Last Enrollee Was June 2018]

A. Study Objectives

The Pilot is designed to establish tolerability criteria for administering iTBS to cocaine users, initially as inpatient followed by an outpatient cohort. The cohort recruited for this Pilot will closely mimic the treatment population for the Expanded Feasibility Study. This two-step design allows for more complete monitoring of the initial participants receiving this novel iTBS intervention. rTMS has been administered as many as 10 times a day with as many as 30,000 pulses delivered. One group administered 3 iTBS sessions (1,800 pulses) with only a 15-minute break between trains of 600 pulses[99, 100]. In an abundance of caution and in the absence of previously published data in CD participants, we propose to limit iTBS to only 3 daily intervention sessions with at least a 60-minute interval between sessions. This method is designed to increase the cumulative dose of iTBS each day while staying well within tolerability thresholds. Considering a previous group has administered 3 iTBS sessions (1,800

pulses)[99, 100] in a 1 hour window, we expect 3 iTBS sessions (1,800 pulses)[92] administered within a 2 hour window will also be well tolerated.

B. Primary Goal

The primary goal of the Pilot is to establish tolerability of 3 daily iTBS sessions with an inter-administration interval of at least 60-minutes in CD participants.

C. Experimental Design

CD individuals will be recruited from the greater Baltimore community. Twenty participants will be recruited to ensure the target number of participants (n = 10) will complete the two-week pilot protocol. The first half (n = 5) of these participants will be enrolled as inpatients and the second half (n = 5) will be enrolled as outpatients. Participants will be consented to the protocol and complete several questionnaires prior to starting the iTBS treatments. The consent and questionnaire completion will require one or two visits prior to enrolling in the treatment protocol.

Initially, 5 (who complete) participants will stay in the on-campus inpatient facility approved by the NIDA Clinical Director's office while they participate in this iTBS protocol. In general, participants will arrive at the inpatient facility on Sunday afternoon. Participants will be escorted by study staff to and from the inpatient unit on treatment days, which may include automotive pick-up service (e.g., shuttle, taxi). Three sessions of iTBS will be administered each of the 10 weekdays over a 2-week period with a duration between iTBS administration of at least 60-minutes. Participants will be allowed to go home over the weekend between the first and second week of the pilot. Generally, they will be released Friday afternoon and return Sunday afternoon for the second week of the pilot. Alternatively, participants may be admitted on Monday afternoons, begin treatment on Tuesday for 5 consecutive days, and be discharged on Saturday. They will return Monday for the second week of treatment.

Other than stimulations over the motor cortex to identify resting motor threshold (RMT), all iTBS administrations will be over the dlPFC. Cognitive and affective

measures (see Study Procedures below) will be monitored throughout the 2-week period. Recruitment curves (i.e., ratio of GABA and glutamate) will be measured at orientation, on four separate days of iTBS administration, and each of the follow-up visits. Recruitment curves are collected with a sequence of single TMS pulses over about a 5-minute period. Generally, six single pulses are delivered over the motor hotspot at seven different intensities relative to that participant's identified RMT (90% of RMT, 95%, 100%, 105%, 110%, 115%, & 120%). Motor evoked potentials will be recorded during the recruitment curve sessions. The sequence of pulses will be randomized with a jittered inter-stimulation-interval between about 5 and 10s. In the absence of significant and unexpected adverse events, an additional 5 (who complete) participants will be recruited to adhere to a similar treatment schedule but as outpatients to better model the Expanded Feasibility Study design.

All participants will be observed for a minimum of 2 hours after iTBS completion before being discharged. Before administering iTBS each day, participants will be assessed for any lingering or delayed effects from iTBS with the TBS Monitoring Questionnaire (Appendix 1). Contact attempts will be made by phone approximately 1-3 days after completion of their treatment to assess any residual or delayed effects from the iTBS. Also, two post-treatment follow-up visits for participants who complete at least 7 of 10 days of iTBS treatment will be attempted to assess, RMT, recruitment curve, drug use, and any behavioral changes post-treatment (may repeat some or all characterization measures and assessments of drug use). The first attempted follow-up visit will be approximately 1 week post-treatment and the second will be after approximately 4-weeks post-treatment.

D. Inclusion and Exclusion Criteria

i. Description of the Study Population

We will enroll 20 CD individuals willing to participate in an open-label iTBS feasibility and tolerability study who and meet the inclusion and exclusion criteria outlined below. Twenty CD participants will be recruited to obtain the necessary number of (n = 10)

completers. Screening will be conducted under the NIDA screening protocol 06-DA-N415 to determine eligibility (Pilot Eligibility Checklist; Appendix 30).

ii. Recruitment

Individuals will be recruited primarily from material developed and distributed via NIDA's approved recruiting techniques such as advertisements circulated by newspapers, magazines, flyers, and online. Recruiting will also include radio ads and landing pages on the NIDA recruitment website, https://researchstudies.drugabuse.gov/. All approved recruiting methods described within this protocol may be applied. With these materials, participants may be recruited from the community using the NIDA IRP recruitment contractor.

Material will be developed and distributed via NIDA approved recruiting techniques such as advertisements circulated by newspapers, magazines, flyers, and online. All approved recruiting methods described within this protocol may be applied. With this material, participants may be recruited from the community using the NIDA IRP recruitment contractor. We may also use the services provided at the NIH Office of Patient Recruitment. We anticipate an average accrual rate of 1-2 participants per week.

Participant Testimonials:

We will develop videos clips or still ads using real participant testimonials with a photo and a quote from participants who are willing to have their photos and quotes used as ads. Participant testimonials are currently used at NIH (https://www.drugabuse.gov/related-topics/treatment/one-patients-story-nida-clinical-trials-bring-new-life-to-woman-struggling-opioid-addiction and https://www.nih.gov/health-information/nih-clinical-research-trials-you/personal-stories). We are interested in using high-impact quotes from similar interviews with our current and former participants (both treatment seeking and non-treatment) to improve the authenticity and relatability of our advertising campaigns.

We would ask participants if 1) they would like to tell us about their experience in this study and have us use their picture and quote used for advertising purposes. If they are interested, we may ask them questions such as those listed below, then develop the ads, submit to PILB and then to IRB. The ads would look very similar to current ads with a quote from the participant. These ads would be posted as currently approved ads do, in print, online, social media, and on the NIDA website. Past subjects may also be contacted via phone so that we may ask them if they are interested in doing a testimonial ad with NIDA. Participants will be notified that not all quotes will be used and that the final ad may not be published. They will also be asked to sign a media release form if they would like to have their photo and/or quote used in an ad.

"What would you say to someone who is thinking about being in this study?"

"How has being in this study affected your daily life?"

"When considering personal interactions throughout the duration of the trial, how would you describe your experience?"

iii. Inclusion Criteria

Participants must:

1. Be able to give valid informed consent.
2. Be 18 – 60 years of age.
    a. Justification: Many neural processes change with age, and these changes could introduce unwanted variability in both behavioral and MRI signals.
    b. Screening tool: Self-report. Government-issued forms of identification (e.g. driver's license, birth certificate).
3. Right-Handed.
    a. Justification: Differences in hemispheric dominance could confound iTBS administration and MRI measurements.
    b. Screening tool: Edinburgh Handedness Inventory.
4. Be in good health.

a. Justification: Many illnesses may alter neural functioning as well as fMRI signals.
b. Screening tools: Medical Assessment, Medical History and Physical Examination. Medical assessments include: Vital Signs, EKG, oral HIV test, height/weight measurements, urinalysis, and blood sample. Tests on the blood sample include CBC, complete metabolic profile, TSH, ESR, syphilis test, and HIV (if needed to confirm a positive salivary test for HIV). The following individual laboratory results will independently disqualify individuals: Cholesterol >250 mg/dl, Hemoglobin < 10 g/dl, WBC < 2400/µl, LFTs > 3 X upper normal limit, HCG positive, Casual serum glucose > 200 mg/dl, Urine protein > 1+, HIV positive. (Serum glucose over 140 mg/dl will be followed up with a fasting serum glucose assessment. Those with fasting glucose below 100 mg/dl may be considered for the protocol. Others will be rejected and referred for work-up.). Liver function will be evaluated with aspartate aminotransferase (AST) and alanine transaminase (ALT). A greater than 3 x upper normal limit for AST or ALT will disqualify individuals. MAI reserves the right to exclude at less extreme lab values if clinical judgment warrants exclusion.

5. Absence of a specific learning disability, ADHD or cognitive impairment.
    a. Justification: Participants must be able to perform a cognitively challenging task to a high standard.
    b. Screening tool: Adult ADHD Self-Report Scale with follow up clinical interview, Wechsler Abbreviated Scale of Intelligence (WASI), History of placement in special education classes for a learning problem.
6. Participants will meet DSM-5 criteria for current moderate to severe substance (i.e., cocaine) use disorder, without a period of continuous abstinence lasting a one-month period over the last year, other than in a controlled environment.
    a. Justification: cocaine use disorder, in regular users, is the focus of this protocol.

b. Screening tool: Potential diagnoses will be evaluated by a counselor using any one or more of the following: Drug Use Survey, SCID Screen Patient Questionnaire, *Mini International Neuropsychiatric Interview (M.I.N.I)*, Addiction Severity Index, and Brief Cocaine Cessation Motivation Assessment. The interviewer will supplement SCID with questions to assess for DSM-5 substance use disorders. The MAI may be consulted in this determination.

iv. Exclusion Criteria

1. History of any neurological disorder that would increase seizure risk from iTBS such as stroke, brain lesions, previous neurosurgery, any history of seizure or fainting episode of unknown cause, or head trauma resulting in loss of consciousness, lasting over 30 minutes or with sequela lasting longer than one month.
    a. Justification: Stroke, vascular lesions or head trauma can lower the seizure threshold and are therefore contra-indications for iTBS. Fainting episodes or syncope of unknown cause could indicate an undiagnosed condition associated with seizures.
    b. Screening tool: TMS safety Screen and Medical History.
2. Current DSM-5 moderate-severe substance use disorder on a substance other than cocaine, nicotine, marijuana, or opiates (provided they are currently stable on a buprenorphine containing medication for therapeutic maintenance) or meeting withdrawal criteria for alcohol or a sedative/hypnotic/anxiolytic, or tolerance criteria in an individual using 3 or more days/week, regardless of diagnosis. Individuals will be considered stable on a buprenorphine maintenance medication if they have been on a stable dose for at least 2-weeks prior to consenting to 17-DA-N002 and have provided at least 3 urine specimens negative for illicit opioids over the same 2-week period (10 business days) with at least one test collected within two business days of the start of the period, one collected within three business days of the end of the period and one collected at

least two days from either of the other two specimens. Urine results may be gathered at NIDA as part of screening or be provided by the buprenorphine maintenance prescriber. Communication between the buprenorphine maintenance provider and the MAI (or covering Staff Clinician) will be ongoing to establish continued illicit opioid abstinence between participant clearance and consent to 17-DA-N002. Individuals must be receiving their buprenorphine maintenance medication as take-home doses from an external (i.e., non-NIDA-IRP) provider.

   a. Justification: While use of multiple substances is the norm and some use will be allowed, the focus of the current protocol is on cocaine. However, participants with tolerance or withdrawal symptoms to alcohol or a sedative/hypnotic/anxiolytic will be at increased risk of a seizure from iTBS and will therefore be excluded. Individuals receiving buprenorphine maintenance and struggling with cocaine use are an ecologically valid population in the greater Baltimore area and do not increase risk of seizure.
   b. Screening tool: Drug Use Survey and SCID Screen Patient Questionnaire or M.I.N.I). The interviewer will supplement SCID with questions to assess for DSM-5 substance use disorders. Potential diagnoses will be further evaluated with a clinical interview with a counselor.

3. First-degree family history of any neurological disorder with a potentially hereditary basis, including migraines, epilepsy, or multiple sclerosis.
   a. Justification: Neurological disorders can lower the seizure threshold, and are therefore contra-indications for iTBS. First-degree family history of certain neurological disorders with a hereditary component increases the risk of the participant having an undiagnosed condition that is associated with lowered seizure threshold.
   b. Screening tool: TMS safety screening, Medical History.

4. Cardiac pacemakers, neural stimulators, implantable defibrillator, implanted medication pumps, intracardiac lines, or acute, unstable cardiac disease, with intracranial implants (e.g. aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or any other metal object in the body that precludes iTBS administration.
    a. Justification: Certain metal in the body is a contra-indication for iTBS administration, as this method involves exposure to a relatively strong static magnetic field that can move magnetic material not securely bound and rapidly alternating magnetic fields that can generate heat and current in metal contained in the body.
    b. Screening tool: Medical History, TMS safety screen.
5. Noise-induced hearing loss or tinnitus.
    a. Justification: individuals with noise-induced hearing problems may be particularly vulnerable to the acoustic noise generated by iTBS equipment.
    b. Screening tools: TMS safety screening.
6. Current use (any use in the past 4 weeks, daily use for more than a week within past 6 months) of any investigational drug or of any medications with psychotropic (e.g., benzodiazepines), anti or pro-convulsive action, or anti-coagulants. This will be determined at the discretion of the MAI.
    a. Justification: The use of certain medications or drugs can lower seizure threshold during use or withdrawal and is therefore contra-indicated for iTBS. Such medications may also alter neural functioning independent of the individual’s drug use or the effects of the iTBS and thus add more variability to our data.
    b. Screening tools: Medical history, Medical Assessments: Urine toxicology analysis for presence of a broad range of prescription and nonprescription drugs.
7. Lifetime history of schizophrenia, bipolar disorder, mania, or hypomania.

   a. Justification: The population of interest here is a healthy population with no psychiatric disorders other than substance use disorders. In participants with bipolar disorder, mania or hypomania, there is a small chance that iTBS can trigger (hypo)manic symptoms. As some degree of depressive symptoms is common in cocaine dependence and may result from the drug use, mild unipolar depression will not be exclusionary.
   b. Screening tools: SCID Screen Patient Questionnaire or M.I.N.I. Potential diagnoses will be further evaluated by a counselor.

8. History of myocardial infarction, angina, congestive heart failure, cardiomyopathy, stroke or transient ischemic attack, mitral valve prolapse, or any heart condition currently under medical care.
   a. Justifications: the risk of iTBS for individuals with a heart condition is unknown.
   b. Screening tool: physical assessment (EKG), medical history.
9. Pregnant or lactating women or women with reproductive potential who engage in heterosexual sex that may lead to pregnancy and not using a medically acceptable form of contraception (such as birth control pills, condoms, or a diaphragm with spermicide).
   a. Justification: it is unknown whether iTBS poses a risk to fetuses.
   b. Screening tool: Urine and/or serum pregnancy tests, and clinical interview.
10. Participation in any NIBS session (excluding the current protocol) less than two weeks ago. No NIBS exposure for treatment purposes in the last 6 months.
   a. Justification: in order to avoid possible carry-over effects from previous exposure to NIBS prior to participation in the proposed intervention, we will not enroll participants who have received any NIBS in the two weeks preceding enrollment or treatment with NIBS modality with the last 6 months preceding enrollment.
   b. Screening tool: TMS safety screen.

E. Clinical and Laboratory Methods

i. Study Procedures

Participants will be scheduled for multiple clinical assessment and data collection sessions to complete the protocol. These procedures will take place in the on-campus inpatient facility approved by the NIDA Clinical Director's office or at National Institute on Drug Abuse Intramural Research Program (NIDA-IRP) depending on availability of staff, facilities, and participants.

1. Screening

Candidate participants will be screened for participation based on the Inclusion and Exclusion criteria listed above. Informed consent will be obtained prior to the commencement of screening procedures. Initial phone screening will utilize the approved phone screen in protocol 06-DA-N415. During in-person screening, potential participants will be given some initial information regarding the study (see Appendix 3 & 4 "Fact Sheets"; Appendix 5 "TBS Information Sheet") to determine if they are interested in possible participation. The following assessments will be administered during screening:

Adult ADHD Self-Report Scale (ASRS v1.1[101]): This questionnaire is an 18-item checklist designed by the World Health Organization (WHO) and Workgroup on Adult ADHD to determine whether a participant is suffering from symptoms related to attention-deficit/hyperactivity disorder. Completion time: ~ 5 minutes.

Addiction Severity Index (ASI[102]): A semi-structured interview designed to provide information in 6 areas related to drug abuse and drug abuse treatment: medical, employment/support, alcohol and drug use, legal, family/social and psychiatric. Completion time: ~ 45-60 minutes.

Brief Cocaine Cessation Motivation Assessment (BCCMA)(Appendix 28): a semi-structured interview to assess the stage of change and motivation level for cocaine dependent participants. Completion time: 10-15 minutes.

Contact Information Form: This form requests multiple methods of contact for a participant, as well as the preferred contact method, preferred contact time, and emergency contact information. Completion time: < 5 minutes.

Drug Use Survey (DUS): An interviewer-administered questionnaire designed to collect information regarding lifetime history of substance use. Completion time: < 40 minutes.

Edinburgh Handedness Inventory[103]: This 12-item questionnaire assists in determining the dominant hand (or handedness) of a particular participant by inquiring which hand the participant uses for various tasks. Completion time: ~ 5 minutes.

Medical Assessments: Vital Signs, height/weight measurements, urinalysis, EKG, oral HIV test, blood draw for CBC, chemistries, thyroid and liver function, hepatitis screen, erythrocyte sedimentation rate, urine qualitative drug screen for cocaine, THC, benzo, morphine/opiates, MDMA, amphetamine /methamphetamine, methadone, buprenorphine, PCP, and oxycodone, urine toxicology which analyzes for presence of a broad range of prescription and nonprescription drugs, as well as urine and/or serum pregnancy testing for menstruating females. Breathalyzer for alcohol will be taken at this time as well. Completion time: 30-40 minutes.

Medical History and Physical Examination: This is a standard physical and detailed medical history and physical examination designed to capture the inclusion and exclusion criteria for NIDA-IRP protocols. It is administered by a Physician's Assistant or other credentialed medical staff. The estimated time to complete is variable. Completion time: 45 to 90 minutes.

Mini International Neuropsychiatric Interview (M.I.N.I)[104]*:* a brief structured interview for the major psychiatric disorders in DSM-5 and ICD-10. Follow up questions may ensue. Completion time: ~20 minutes. (Participants will complete either the MINI or the SCID).

Participant Safety – MRI Screening Form: A questionnaire that aids in determining appropriateness of MRI scan. Completion time: < 5 minutes.

SCID Screen Patient Questionnaire – Extended (SSPQ-X)[105] with follow up clinical interview: Computer-administered screening version of the Structured Clinical Interview for DSM-IV™ (SCID), used in assisting with diagnosis of DSM-IV Axis I disorders. Interviewer will supplement with questions to assess for DSM-5 substance use disorders. (Participants will complete either the MINI or the SCID).

TBS Information Sheet (Appendix 5): A general information sheet on TBS administration with common questions and answers is given to participants as an informational item only. Participants are given time to read the handout and to ask questions about it while in the clinic. Completion time: ~ 20 minutes.

TMS Safety Screen: A questionnaire that aids in determining appropriateness of administering TBS. Completion time: < 5 minutes.

Toronto Alexithymia Scale (TAS-20)[106]*:* A 20-item self-report questionnaire to assess emotional awareness. Completion time: ~ 10 minutes.

Wechsler Abbreviated Scale of Intelligence (WASI[107]*):* This is an abbreviated version of the Wechsler Adult Intelligence Scales – Third Edition that provides IQ measures of suitable reliability for matching subjects. Completion time: ~ 1 hour.

2. Nursing Assessment

After completing the consent interview and prior to study sessions, participants will undergo a nursing assessment, which, depending on the session type, may include measuring vital signs, a breathalyzer test for expired ethanol, an observed urine test for common abused drugs, a TMS safety questionnaire, and if females, a urine pregnancy test. Participants will also be asked when they last had NIBS and whether this was at NIDA or elsewhere. In addition, participants will be asked to report changes in medical history, recent over-the-counter, prescription, or other substance intake, time of last meal, hours slept the previous night, and, if female, last menstrual period and whether or not they are currently taking a contraceptive pill. Participants will be asked not to use alcohol or drugs for at least 24 hours prior to TMS sessions. Participants with a positive breathalyzer will be rescheduled. In the event of a positive drug test, an interview to

assess last drug use and a neuromotor assessment to test for acute intoxication will be performed. If participants test positive for drugs other than THC, or cocaine for the CD group, based on the MAI's judgment, they may be rescheduled, as will those who fail the neuromotor. However, if they test positive on a second occasion they may be excluded from the study. Inpatient participants will be searched upon intake (Appendix CC) and will have vital signs assessed in accordance with the standards of the inpatient unit. Upon intake, participants will complete a breathalyzer and urine drug screen. After all TMS sessions, participants will have their heart rate and blood pressure taken. Completion time: ~10-45 minutes.

3. Orientation and iTBS Sessions

After participants are consented and prior to treatment, they will complete baseline characterization measures and a training session where they will be oriented to iTBS and the recruitment curve. Individuals receiving buprenorphine maintenance will be required to sign a release of information allowing the MAI (or staff clinician) to monitor their medical status while enrolled in the study, both at NIDA and via clinical assessments performed by the buprenorphine maintenance provider and consultation with the outside provider.

Participants may be scheduled for an additional visit and the necessary additional time to complete these assessments prior to beginning the 10-day iTBS treatment session. Characterization measures include:

Attitudes Towards Risk Questionnaire (Appendix 7): A 34-item self-report with 5-point Likert scales that assess attitudes towards physical and psychological risk. Completion time: < 10 min.

Addiction Severity Index (ASI, Appendix 44): A semi-structured interview designed to provide information in 6 areas related to drug abuse and drug abuse treatment: medical, employment/support, alcohol and drug use, legal, family/social and psychiatric. Completion time: 45-60 minutes.

Brief Externalizing Inventory[108] *(Appendix 9)*: A 159-item self-report adapted from the full Externalizing inventory[109] used to assess a range of behavioral and personality characteristics that have been attributed to a broad psychological construct termed externalizing. These characteristics include: physical/relational destructive-aggression, boredom proneness, irresponsibility, problematic impulsivity, drug and alcohol use or problems, theft, fraud, rebelliousness, alienation, and blame externalizing. Completion time: ~ 15 min.

The Revised Social Anhedonia Scale (Appendix 42): A 40-item true-false self-report questionnaire intended to measure decreased pleasure derived from interpersonal sources. Completion time: ~10 minutes.

The Physical Anhedonia Scale (Appendix 43): A 61-item true-false self-report that taps a range of presumably pleasurable experiences involving eating, touching, feeling, sex, movement, smell, and sound. Completion time: ~15 minutes.

Cocaine Craving Questionnaire (CCQ[110]*; Appendix 11*): This measure includes 45 items that measure current craving for cocaine. Completion time: ~ 10 minutes.

Cocaine Craving Scale (CCS[111]*; Appendix 12*): Five questions on intensity and frequency of craving, both currently and in the preceding 24 hours that have been shown to possess short-term predictive validity of cocaine use. Completion time: < 5 minutes.

Cocaine use, Pattern, and Withdrawal Questionnaire (Appendix 13): This is an interview-guided questionnaire, designed by Dr. B. J. Salmeron, and has been successfully employed in previous studies. Completion time: ~ 10 minutes.

Montgomery-Asberg Depression Rating Scale (MADRS[112]; Appendix 14): A clinical assessment to identify symptoms of depression. This assessment is especially useful in identifying changes in depression symptoms over time. If a participant reports suicidal thoughts, the CDW Critical Item Alert System will be initiated following the NIDA SOP to address such responses. Completion time: < 10 minutes.

Modified Positive and Negative Affect Scale (Modified version of the PANAS; Appendix 15): Participants are asked to fill in a questionnaire about possible side-effects

since the last iTBS session (the TBS monitoring questionnaire), and a questionnaire about their affect (a modified version of the PANAS). The sole purpose for the modified version of the PANAS is to assess the answer to one single question ("Right now I feel … detached: rate from "not at all" to "extremely"). This is not in the original, validated PANAS-SF. Instead, the modified questionnaire is used as a device to ask this one single question, without calling unwanted attention to it by asking it as a single item. A self-report scale to assess state-level affect. Completion time: < 5 Minutes.

Profile of Mood States (POMS; *Appendix 16*): A questionnaire designed to measure present mood state by a list of adjectives on a 5-point Likert scale and measures six dimensions of affect, including tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. The measure has been shown to produce reliable and valid profiles of mood state[113, 114]. Completion time: ~ 5 minutes.

Scale for the Assessment of Positive Symptoms for Cocaine-Induced Psychosis (SAPS-CIP[115], Appendix 32): The SAPS-CIP is a modification of the Scale for Assessment of Positive Symptoms designed to focus on psychotic symptoms related to cocaine use. We will use the hallucinations and delusions sections which have been shown to be particularly useful in assessing cocaine-induced psychosis. If endorsed, the MAI (or staff clinician) will assess current psychosis and need for further evaluation and/or treatment. Completion time: < 30 minutes.

Cocaine-Induced Psychosis: Screener (CIP: Screener, Appendix 33): The CIP: Screener is designed for efficient assessment of cocaine-induced psychosis and will be used to assess changes, relative to baseline, throughout the protocol. Any worsening from baseline in cocaine-induced psychosis measured throughout the protocol will be evaluated by the MAI (or staff clinician). Completion time: < 5 minutes.

Sensation Seeking Scale V (SSS-V, [116]*; Appendix 17*): A 40-item self-report questionnaire that assesses individual differences in sensation seeking. The scale consists of four subscales (Boredom Susceptibility [BS], Thrill and adventure seeking

[TAS], Experience seeking [ES], and Disinhibition [Dis]) composed of 10-items each. Completion time: < 10 minutes.

Snaith-Hamilton Pleasure Scale (SHAPS, [117]*; Appendix 18*): A 14-item self-report scale designed to measure hedonic-tone/anhedonia. Completion time: ~ 5 minutes.

Temperament and Character Inventory[118] (Appendix 19): A widely used test that assesses dimensions of personality (e.g., harm avoidance, novelty seeking, reward dependence, and persistence) that are considered to be related to monoaminergic function. Completion time: ~ 25 minutes.

The Multidimensional Social Contact Circle[119] (Appendix 20): A self-report scale designed to measure social ties between the participants and their friend, family, co-workers, etc. Completion time: ~ 15 minutes.

Time-line follow back (TLFB; *Appendix 21*). The TLFB will be used to assess substance use behavior. This assessment will be either self-administered or administered by one of the investigators. Participants will read the instructions and/or will be guided by the therapist or investigator in filling out the calendar. A lifetime TLFB will be administered at the start of the protocol then on each visit to assess substance use between administrations. Completion time: 15 minutes to 2 hours.

Prior to the commencement of iTBS treatment sessions, participants will complete a training session where they will be oriented to iTBS and recruitment curve. Participant-specific approximation of the left dlPFC, identified using the BeamF3 heuristic[120], will be recorded as well as resting motor threshold (RMT). Orientation may take up to 1 hour and will precede the first iTBS treatment. RMT will be identified each iTBS treatment day and each day, after the first, will use measurements from the previous day as a guide.

The nurse assessment will take place every treatment day for both inpatient and outpatient participants. If inpatient participants are on any medications, the inpatient facility will provide them while they are on the unit, except for birth control pills which the participant should bring. Prior to iTBS, cognitive function will be assessed using a Trail Making Task (TMT; Appendix 22). Also, measures of mania (Young Mania Rating Scale

[YMRS]; Appendix 23), and suicidality (Columbia-Suicide Severity Rating Scale: Baseline [C-SSRS]; Appendix 24) will be collected prior to iTBS.

Other than stimulations over the motor cortex to identify RMT, all iTBS administrations will be over the dlPFC. During iTBS, participants will view cocaine cues (i.e., pictures; Appendix 25) with the instruction to try to inhibit any craving elicited by the cues in an attempt to elicit activation in networks specifically related to controlling responses and cocaine use/substance abuse in general[121]. During some of these sessions we may monitor hand muscle movement. Before and after each day of iTBS, participants will complete the TBS monitoring questionnaire and a questionnaire about affect (the modified version of the PANAS; see Appendix 1 & 15). A debriefing period for discussion of questions and issues related to the day's activities and scheduling/reminder of subsequent visits will conclude the session. A similar schedule of events will occur for each day of the 10-day treatment. Urine samples will be collected daily during the pilot phase. The TLFB will be collected the first treatment day during the inpatient phase and daily during the outpatient phase. The SAPS-CIP will be collected by the MAI (or staff clinician) at baseline and the 4-week follow-up visits. Recruitment curves (i.e., the ratio of GABA and glutamate) will be measured during orientation, on four days of iTBS administration, and each of the follow-up visits. Several characterization measures will be collected multiple times throughout the protocol. The following measures may be collected daily: TBS monitoring questionnaire, modified version of the PANAS, CCQ, CCS, TLFB, & CIP: Screener. The TLFB will cover time between the previously collected TLFB and the day of each collection. The CIP: Screener will be collected at baseline and any visit where the TLFB is administered and the participant reports cocaine use. Post-doctoral or MD level investigators can be trained by the MAI to administer the CIP: Screener. Any worsening from baseline in cocaine-induced psychosis measured throughout the protocol will trigger a follow-up evaluation by the MAI (or staff clinician). All but the TLFB and CIP: Screener, will be collected at the beginning and end of each day that includes MRI or iTBS. The POMS and MADRS will be collected at baseline, prior to first iTBS session, post final iTBS

session, and the first follow-up. The cocaine craving questionnaires will be used to assess post-cue-reactivity craving with the possibility of counselor intervention in the event of clinically significant craving. A response of 6 or 7 on the CCQ Likert scale for questions 3, 4, 16, 33, or 34 or a response of 1 or 2 question 28 would constitute clinically significant craving. Similarly, a response of 9 or 10 on the CCS Likert scale for question 1 would constitute clinically significant craving. The MAI or other NRB clinical personnel will intervene to mitigate craving before discharge if the participant's self-report of craving level arouses concern (in the participant or staff) in the context of conversation. After completing the two-week course of iTBS treatment, the TMT, YMRS, and C-SSRS (since last visit version) will be administered a second time.

Columbia-Suicide Severity Rating Scale (C-SSRS; Appendix 24): An interview-based questionnaire designed to assess acute suicidality. Two versions will be implemented. A baseline measure (with lifetime and past month symptom assessments) will be collected prior to the iTBS intervention and the 'since last visit' version will be collected post iTBS intervention. A researcher trained in administering these scales (e.g., the MAI, LAI, or AI) and approved by the MAI do so, will administer them. The MAI will oversee the training of this scale. If a participant reports any positive answer related to current suicidal tendencies (questions 1-5 for past month at baseline and since last visit assessments), the NIDA-IRP Critical Item Alert System in place in CDW will be initiated to address such responses (http://irp.drugabuse.gov/PolicyIndex.php). Completion time: < 15 minutes.

TBS Monitoring Questionnaire (Appendix 1): An interview-based questionnaire designed to assess symptoms related to iTBS administration. Completion time: < 5 minutes.

Trail Making Task (TMT; Appendix 22): The TMT is a cognitive test where participants are instructed to connect dots in numerical sequence or to alternate between numerical and alphabetical sequences. This task is designed to quickly assess working memory, visual attention, and task switching. Completion time: < 10 minutes.

Young Mania Rating Scale (YMRS; Appendix 23)[122]. An interview-based questionnaire designed to assess symptoms of mania. Completion time: < 15 minutes.

4. Follow-Up

Contact attempts will be made by phone 1-3 days after the last iTBS session to assess any acute behavioral or health related changes from treatment (Appendix 1). Additional contact attempts may include such methods as text, e-mail, and US mail if phone contact is not successful and if prior approval from the subject is obtained. Also, an attempt to schedule two post-treatment follow-up visits for participants who complete at least 7 of 10 days of iTBS treatment will be made to assess, RMT, recruitment curve, drug use, and behavioral changes post-treatment. Participants will be asked to repeat several of the characterization measures and assessments of drug use at these visits. The first visit will be scheduled approximately 1 week post-treatment and the second will be scheduled for approximately 4 weeks post-treatment. The nursing assessment for these visits will be similar to nursing assessments on other study days.

ii. iTBS Administration

1. Apparatus and Tests

To administer the iTBS treatment, a MagVenture MagPro 100 with MagOption (MagVenture Inc, Alpharetta, GA) machine equipped with a figure-8 coil will be used. RMT of muscles that move the contralateral hand will be determined at the beginning of each treatment day.

2. Localization of Dorsolateral Prefrontal Cortex

The BeamF3 heuristic[120] will be implemented to localize left dlPFC for each individual. This heuristic has been shown to have a reasonable approximation of MRI-guided localization of the left dlPFC without the need for an MRI scan (Note: an MRI-guided localization of the left dlPFC will be used in the Expanded Feasibility Study).

3. Motor Threshold Determination

In determining motor threshold, first the scalp position closest to the motor representation (the “motor hot spot”) is sought. Then the RMT at this location is determined. The hotspot is located during the initial session and verified at subsequent sessions, whereas the RMT will be measured every treatment day. In accordance with the manufacturer’s instructions and accepted standards, hand motor cortex will be stimulated to obtain RMT[123, 124].

Participants will be seated in a recliner in a comfortable resting position and fitted with earplugs. The TMS figure-8 coil will be placed over the hand-associated primary motor cortex. The coil will be held tangentially on the head with the handle pointing backward and 45° laterally from the midline. Using repeated single pulse, suprathreshold stimuli, the coil will be moved to determine the optimal scalp position for producing visible contralateral hand twitches. Pulses over this motor cortex location will be administered to identify the resting motor threshold using PEST[125] software. Responses will be either visually detectible motor twitches or motor evoked potentials of the muscles that move the contralateral hand. Recruitment curves will be measured as a proxy for the ratio between gamma amino butyric acid (GABA) and glutamate[126-128]. The recruitment curve will be monitored at orientation and at three time points relative to iTBS administration: 1) prior to iTBS administration; 2) immediately following iTBS administration; 3) at least 60 minutes following iTBS administration. This will be done for each administration of days 1, 5, 6 and 10 (note: ‘at least 60 minutes following’ will also serve as ‘prior to’ for the second and third administrations).

This entire procedure (hotspot and threshold determination) can take 30-90 minutes. If no motor hotspot can be determined within 1 hour or if the motor threshold exceeds 83% of maximal stimulator output, the participant may be discontinued from the study at the discretion of the LAI and/or MAI. Because the initial RMT determination will be catalogued, subsequent determinations on treatment days are expected to take very little time.

4. Stimulation Procedure

A pre-selected protocol is programmed into the iTBS stimulator[73]. Three pulses will be given at 50 Hz repeated every 200 ms for a 2 second duration followed by 8 seconds of no stimulation. This sequence repeats for a total of 190 seconds and 600 pulses. Magnetic field intensity will be set at a medium intensity and gradually increased, depending on participant tolerability, to the goal of 100% of that participant's observed daily RMT

iii. Discharge Procedures

If a participant experiences somatic or psychological symptoms that interfere with his/her ability to participate then he/she will be discharged from the study. The most frequent symptom is pain over the area of stimulation which could interfere with participation in the study. DLPFC stimulation has rarely been associated with mania. The investigators will monitor participants for changes in mood and may discharge a participant at any time if they believe that it is in the best interest of the participant.

iv. Participant Monitoring

The iTBS monitoring questionnaire, the modified version of the PANAS (see Appendix 1 & 15), and staff observation and interactions with participants will be assessed daily. A NIDA-IRP physician or physician's assistant knowledgeable about iTBS will be immediately available in the building whenever iTBS is administered and will be available by telephone or pager 24 hours a day for consultation or in the event of a medical emergency. If immediate medical intervention is required, the participant will be referred to an appropriate medical facility. Information on all adverse events will be cumulated and reported to the NIDA IRB with each continuing review application. Unexpected or serious adverse events (defined in accordance with NIH and NIDA IRP policy) will be promptly reported to the NIDA Clinical Director and IRB in accordance with NIH and NIDA IRP policy.

Seizure monitoring procedures: Participants will be monitored throughout each iTBS session for signs of seizures such as involuntary muscle movements or loss of consciousness. In the event of a seizure, staff will have immediate access to life support equipment and anti-seizure drugs. In the event of a seizure, the procedure outlined below[129] will be followed:

1. Protect patient's head and limbs from injury.
2. Ensure an adequate airway.
3. Call 911 to have the patient transferred to Johns Hopkins emergency room.
4. Observe Patient for:
    a. Initial movements/ sensations.
    b. Progression of movements.
        i. Change in respiratory status
        ii. Skin color
        iii. Incontinence
        iv. Level of consciousness
        v. Ability to communicate
        vi. Level of orientation
        vii. Duration of seizure activity

            If after two minutes, the seizure has not resolved, administer: midazolam IM, 10 mg that is contained in a lock box in the TMS suite.
5. Provide supportive care after the seizure resolves.
6. Orient patient to time and place.

Session video recording: If a potential adverse event occurs during iTBS stimulation, video footage of the session can help determine the nature of the incident. Thus, video will be recorded during threshold determination and during iTBS, barring any technical difficulties with recording instrumentation. If the session progresses without incident, this footage will be deleted within a week. Otherwise, during sessions with abnormal events, the video will be retained in accordance with NIH Records Management policy

(https://oma.od.nih.gov/DMS/Documents/Records/NIH_Intramural_Research_Records_Schedule.pdf) for 7 years after the completion of the study or when no longer needed for scientific reference, whichever is longer. This footage may be used by the MAI and any experts the MAI wishes to consult to determine the nature of the event. Participants will not be given the option to opt out of the video recordings. If they do not wish to be recorded, the alternative is to not participate in the study.

v. Risks

The side effects associated with TMS treatment in large clinical trials have been published[130]. Published consensus safety guidelines for TMS have resulted in reduced frequency of adverse events[131]. The following clinical data associated with depression treatments are provided to emphasize the extensive medical experience with TMS and its safety.

Unlike electroconvulsive therapy (ECT), TMS does not involve general anesthetic or inducing a seizure. Numerous sham-controlled trials and several meta-analyses support its efficacy in treating depression[94, 132-134]. The largest TMS sham-controlled trial to date involving 301 pharmacotherapy refractory depressed participants reported positive results[70]. Sessions of rTMS were conducted for 4 to 6 weeks five times per week. Stimulation was set at 120% RMT with 10 pulses per second for a total of 3000 pulses per session. Active rTMS was well tolerated, with low dropout rate for adverse events (4.5%) that were generally mild and limited to transient scalp discomfort or pain. In the current proposed study, iTBS will be used, which is similar to rTMS but with higher participant compliance and a lower level of stimulation (100% of RMT compared to 120% of RMT for rTMS).

III. EXPANDED FEASIBILITY STUDY

This phase of the study began after IRB and FDA approval, and completion of the FDA review of Pilot data.

A. Study Objectives

The Expanded Feasibility Study of this protocol is designed to implement the iTBS administration parameters established from the Pilot with a large sample of treatment seeking CD participants. HC participants will be recruited as a comparison group and participate in two days of iTBS (1 active day and 1 sham day of iTBS). Regardless of group, each day of iTBS will include 3 iTBS sessions with at least a 60-minute interval between administrations.

Note that a 3-minute iTBS application is referred to as a SESSION and 3 iTBS sessions is referred to as a DAY of treatment. Therefore, each DAY of iTBS treatment includes 3 iTBS SESSIONS and 10 DAYS of iTBS treatment includes a total of 30 iTBS SESSIONS.

All participants will complete the same battery of characterization instruments. Participants who successfully complete the iTBS orientation phase (receiving either active or sham iTBS as randomly assigned) will be eligible to participate in iTBS treatment days. CD participants will be scheduled for 10 DAYS of iTBS treatment and receive either active or sham iTBS (assigned randomly prior to orientation). HC participants will be scheduled for 2 DAYS of iTBS and receive 1 DAY of active iTBS (3 active sessions with at least 60 minutes between sessions) and 1 DAY of sham iTBS (3 sham sessions with at least 60 minutes between sessions) with at least 1 week between days. The order of these days will be counterbalanced. Note that 3 sessions of iTBS is well under the minimum number needed to assess efficacy clinically for a treatment effect in depression[71] and has been previously safely carried out in healthy controls [99, 100, 135]. **These 3 published studies administer iTBS more aggressively than proposed here.in healthy controls without adverse events. One study administered 2 iTBS sessions back-to-back in healthy controls without adverse events[135]. Two studies administered 3 iTBS sessions with 15 minutes between sessions in healthy controls without adverse events[99, 100].**

B. Goals

The primary goal is to characterize neurobiological processing of and behavioral responding in cue reactivity, reward processing, executive control, and intrinsic network connectivity differences between HC and CD participants at baseline, during and following iTBS intervention. The Expanded Feasibility Study is powered to assess neuroplastic changes between completers in the CD group who receives active iTBS (N = 30), the CD group who receives sham iTBS (N = 30), and the HC group who receives a within-participant active/sham iTBS manipulation (N = 40). Specifically, we will test for potential neural plasticity over time in the CD cohort and relate any changes to treatment group ongoing substance use (i.e., reductions or maintenance of use). Each CD participant is expected to complete a total of 8 MRI scan sessions across 5 days over a 14-week period 1. Multiple MRI scan sessions will allow for direct comparisons of neural plasticity within participants over time.

C. Aims

1. To characterize neural differences between CD and HC participants at baseline.
2. To determine if iTBS alters networks related to cognitive/affective function by:
    a. Identifying networks and cognitive/affective functions that change with acute treatment in both HC and CD.
    b. Identifying networks and cognitive/affective functions that show sustained change (2 weeks after end of treatment) with chronic treatment in CD.
3. To determine if imaging measures can reliably predict which individuals will respond to treatment, either at baseline or after completion of treatment.
4. To determine the trajectory of neural plasticity related to chronic iTBS and cocaine abstinence.
5. To monitor safety of iTBS applied in cocaine dependent individuals.

D. Hypotheses

1. Functional imaging correlates of cue reactivity, reward processing, executive control, and intrinsic network connectivity will differentiate CD and HC participants at baseline.
2. Within the CD group, measures of cue reactivity, reward processing, executive control, and intrinsic network connectivity will be predictive of treatment success and reduction in drug use.
3. Acute iTBS will alter cue reactivity, reward processing, executive control, and intrinsic network connectivity in both CD and HC.
4. Within the CD group, chronic Active iTBS, relative to Sham, will modulate cue reactivity, reward processing, executive control, and intrinsic network connectivity, which will relate to changes in drug use after the 2-week treatment.
5. Within the CD group, chronic Active iTBS, relative to Sham, will modulate cue reactivity, reward processing, executive control, and intrinsic network connectivity such that neuronal processing in CD participants following iTBS will approximate that in HC (i.e. normalize processes).

E. Experimental Design

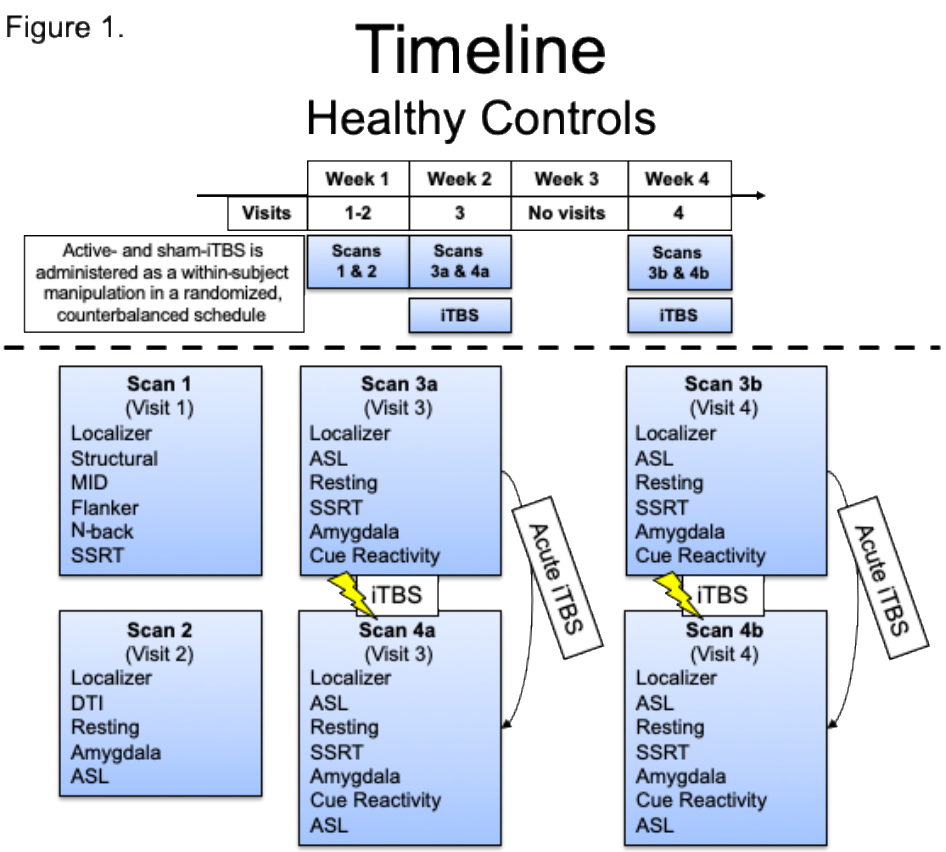
Two groups of participants will be recruited: 1) treatment seeking cocaine dependent individuals (CD; n = 90; 45 Active-iTBS and 45 Sham-iTBS); 2) matched community healthy controls (HC; n = 45; within-subject crossover iTBS manipulation). Fifty CD participants in each group will be recruited to obtain the necessary number of participants (n = 30) to complete treatment (see power analysis calculated to ensure necessary power for MRI measures). CD participants may stay in the on-campus inpatient facility approved by the NIDA Clinical Director's office while they participate in this iTBS protocol. The inpatient unit will be available to every CD participant to increase compliance with protocol scheduling. In general, participants will arrive at the inpatient facility the day before their iTBS session. CD participants will be escorted by study staff to and from the inpatient unit on treatment days, which may include automotive pick-up service (e.g., shuttle, taxi). **We will implement a within-subject crossover Active-**

and Sham-iTBS method with the HC participants to provide for the necessary sham control.

All participants will receive a post-iTBS nursing assessment and cognitive assessment prior to discharge. An approximate timeline is described below but may vary to account for participant, staff, and facility availability. **All participants, regardless of group, will be scheduled to complete baseline data collection (Characterization; Figures 1 & 2**: Visit 1). An initial scan (Scan 1) will be performed to acquire MRI localization to be used in the iTBS protocol as well as cognitive and affective characterization imaging tasks (week 1); Visit 2) clinical characterization instruments (per protocol 10-DA-N457) and MRI scan (Scan 2; week 1) [participants may be scheduled to complete these characterizations over more than one day, if needed to ensure completion prior to the first iTBS day];

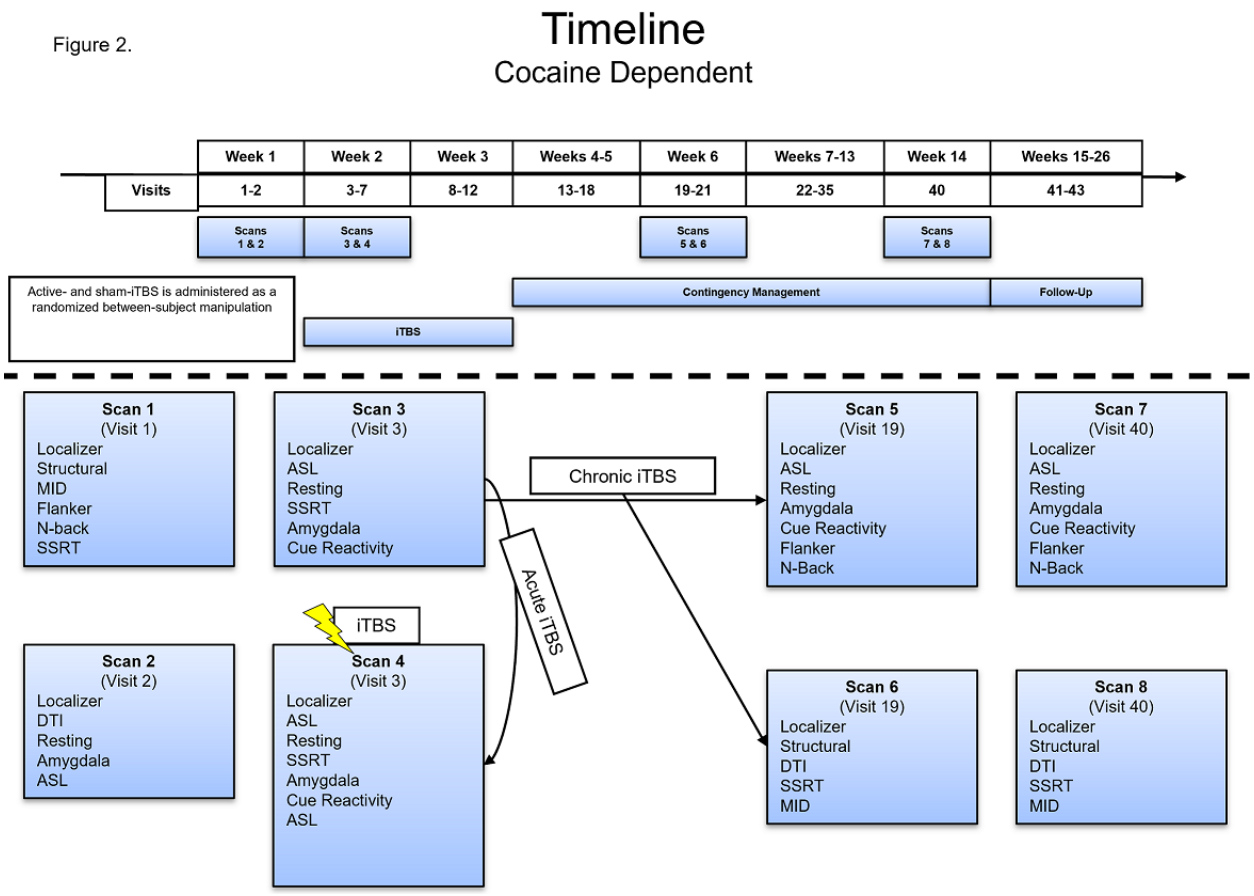
HC participants will be scheduled to participate in 2 days of iTBS (Figure 1): Visits 3-4) Each day, HC participants will receive either Active or Sham-iTBS in a randomized and counterbalanced schedule. Each day will include 2 MRI scan sessions (Scans 3a/4a & 3b/4b), 1 before and 1 after the iTBS intervention. These 2 visits will be identical except for the within-subject manipulation of Active- vs Sham-iTBS administration. At least 1 week will pass between HC visits 3 (Scans 3a & 4a) and 4 (Scans 3b & 4b).

Figure 1.



After visits 1 and 2 (described above), **CD participants will be scheduled to participate in the following visits (Figure 2)**: Visit 3: the first iTBS treatment day, which also includes two, pre/post-acute iTBS MRI scan sessions (Scans 3 & 4; week 2). Visits 4-12: iTBS treatments in CD (weeks 2-3); Visits 13-40: urine samples will be acquired from participants to assess cocaine use and is the start of CM (week 4); Visit 19: Two scan sessions (Scans 5 & 6; week 6) will be completed; Visit 40: two scan sessions (Scans 7 & 8; week 14) will be completed; Additional monthly follow-up visits (Visits 41-43; weeks 18, 22, & 26, respectively) with weekly phone contact in between (9 calls; weeks 15-26) will be attempted to assess post-treatment drug use patterns.

Figure 2.



The MRI scans (1 & 2) will assess differences between groups prior to the iTBS intervention. The MRI scans from scan 4 will be compared to scan 3 to assess neuronal modulations related to acute iTBS administration. Scans 5-8 will be compared to scans 1-3 to assess neural plasticity post-treatment modulated by chronic Active-iTBS (vs. Sham) administration. All scan sessions will be approximately 2 hours in duration.

Contingency Management (CM): Drug use will be monitored following the iTBS treatment period with urine samples collected each week as outlined in table 1. Urine samples will be used for the TAU CM. Clinical trials research supports CM as an efficacious approach to cocaine use reduction[136-142]. With this evidence, CM was selected as the TAU. The qualitative urine analysis will be used to assess positive or negative urine samples for cocaine use. When a positive sample is recorded, that sample will be sent for quantitative 'additional use' analysis to the NIDA IRP's

Translational Analytical Core facility. If the positive sample immediately follows another positive sample, the quantitative results, are often available within 7-10 days, will be used to determine eligibility for CM payment. At the next participant visit, after the results are known, the participant will be notified of the test results and if that analysis suggests no additional use for the participant, CM payments will be paid accordingly. If the positive qualitative result follows a negative qualitative result, CM payment will be withheld and the amount rewarded the next negative (or no new-use) urine reset to $5, per Table 1. The quantitative result from the positive urine will be used as baseline for the next CM urine to determine if there has been new use. Follow-up of CD participants will continue without CM for up to 3 months post scans 7 and 8. Drug use will be monitored with a once-a-week phone contact and monthly in-person visits.

In the present study, participants have the possibility of earning $1075 during the CM program. Incentives for negative urine tests will escalate to $80 in the later portions of the program. A considerable amount of controlled clinical trials research supports CM as a promising and innovative approach to cocaine use reduction[136] even as a stand-alone intervention promoting abstinence[137-142]. However, most participants will not likely be abstinent throughout the CM period, which affects the amount of the total possible earned (e.g., an estimate of 45% of the total possible amount will be earned, reducing effective possible amount to ~$484. As is standard usage, we will implement an escalating schedule of incentive amounts with a reset penalty for detection of drug use (Table 1). A reset penalty is implemented if a cocaine positive urine sample is detected. Avoidance of the reset serves as a motivator for continued abstinence. Earned money will be distributed immediately after each negative urine test, generally by cash, check, or e-payment (e.g., PayPal) per NIDA IRP remuneration guidelines. Doing so provides immediate acknowledgement and reinforcement for the negative test. After money is earned, it belongs to the participant and is never taken back irrespective of subsequent drug use or other adverse behaviors. It is expected, based on previous experience with these types of interventions, that exposure to this incentive program will produce reduced overall amounts of cocaine use in the majority of participants with long periods

of sustained abstinence in some participants. Continuing CM through the last scan increases the possibility of obtaining scan data with similar amounts of drug use in both groups of participants. During the follow-up period after CM, we expect the groups to diverge in use patterns. Differences in the scan data will therefore, likely reflect differences between sham and real iTBS treatment uncontaminated in differences in drug use between the groups. We anticipate that the compensation for routine data collection visits plus the completion bonus at the end of the three-month follow-up will maintain participant engagement in this protocol.

Table 1. Contingency Management Schedule of Reinforcement

CM week	Study Week	Urine Sample	Award Amount ($) for Negative Urine Test	Running Total Amount ($)
	1	None	None	None
	2	None	None	None
	2	None	None	None
	2	None	None	None
	3	None	None	None
	3	None	None	None
	3	None	None	None
1	4	1	5	5
1	4	2	10	15
1	4	3	10	25
2	5	4	20	45
2	5	5	20	65
2	5	6	20	85
3	6	7	20	105
3	6	8	20	125
3	6	9	20	145
4	7	10	30	175

4	7	11	30	205
4	7	12	30	235
5	8	13	40	275
5	8	14	40	315
5	8	15	40	355
6	9	16	40	395
6	9	17	40	435
6	9	18	40	475
7	10	19	40	515
7	10	20	40	555
8	11	21	40	595
8	11	22	60	655
9	12	23	60	715
9	12	24	60	775
10	13	25	60	835
10	13	26	80	915
11	14	27	80	995
11	14	28	80	1,075.00

Introduction to Treatment: Before initiation of iTBS, a session will take place to assess and attempt to enhance individual motivation and preparation to reduce or eliminate cocaine use. During this session, participants may repeat some assessments, such as the BCCMA. This session is designed to inform the participant of the treatment trajectory, introduce the concept of CM, introduce techniques to manage cue-induced craving, and assess and enhance their motivation to quit using cocaine. This will be conducted by the MAI, study therapist, or designee.

F. Inclusion and Exclusion

i. Description of the Study Population

We will enroll 45 (within-subject crossover active- vs sham-iTBS manipulation) HC and 90 treatment seeking CD (45 active-iTBS and 45 sham-iTBS) individuals who meet the inclusion and exclusion criteria. Fifty CD participants in each group will be recruited

to obtain the necessary number of (n = 30) treatment completers (see power analysis; calculated to ensure necessary power for MRI measures). Screening will be conducted under the approved NIDA IRP general screening protocol to determine eligibility (Expanded Feasibility Study Eligibility Checklist; Appendix 31). Participants will also be required to enroll in the NIDA protocol 10-DA-N457 to gather characterization data not otherwise collected in this protocol but which will be used in the planned analyses. Generally, CD participants will be current cocaine users and HC participants will be non-users matched on measures including age, sex, ethnicity, race, etc.

ii. Inclusion Criteria

1. Be able to give valid informed consent.
2. Agree to also participate in study 10DAN457, where characterization information is gathered and shared with this protocol.
3. Be 22 – 60 years of age.
    a. Justification: Many neural processes change with age, and these changes could introduce unwanted variability in both behavioral and MRI signals.
    b. Screening tool: Self-report.
4. Right-handed.
    a. Justification: Differences in hemispheric dominance could confound iTBS administration and MRI measurements.
    b. Screening tool: Edinburgh Handedness Inventory.
5. Be in good health.
    a. Justification: Many illnesses may alter neural functioning as well as fMRI signals.
    b. Screening tools: Medical Assessment, Medical History and Physical Examination. Medical assessments include: Vital Signs, EKG, oral HIV test, height/weight measurements, urinalysis, and blood sample. Tests on the blood sample include CBC, complete metabolic profile, TSH,

ESR, syphilis test, and HIV (if needed to confirm a positive salivary test for HIV). The following individual laboratory results will independently disqualify individuals: Hemoglobin < 10 g/dl, WBC < 2400/µl, LFTs > 3 X upper normal limit, HCG positive, Casual serum glucose > 200 mg/dl, Urine protein > 1+, HIV positive. (less extreme serum glucose elevations will be evaluated for diabetes as clinically indicated.) Liver function will be evaluated with aspartate aminotransferase (AST) and alanine transaminase (ALT). A greater than 3 x upper normal limit for AST or ALT will disqualify individuals. MAI reserves the right to exclude at less extreme lab values if clinical judgment warrants exclusion.

6. Absence of a specific learning disability, ADHD or cognitive impairment
    a. Justification: Participants must be able to perform a cognitively challenging task to a high standard.
    b. Screening tool: SCID-research version, computerized Shipley-2 (cut-off of < 70 to be excluded), History of placement in special education classes for a learning problem.
7. CD Participants, and not HC participants, will meet DSM-5 criteria for current moderate to severe substance (i.e., cocaine) use disorder, without a period of continuous abstinence lasting a one-month period over the last year, other than in a controlled environment and currently seeking treatment. They will be using at least once a week in the month prior to enrollment.
    a. Justification: cocaine use disorder, in regular users, is the focus of this protocol.
    b. Screening tool: Potential diagnoses will be evaluated by a counselor using any one or more of the following: Drug Use Survey, SCID-research version and Brief Cocaine Cessation Motivation Assessment. The MAI may be consulted in this determination.
8. Treatment seeking CD participants

a. Justification: The population of interest is CD dependent individuals motivated to reduce or eliminate their cocaine use.
b. Screening tools: Brief Cocaine Cessation Motivation Assessment.

9. MRI compatible
    a. Justification: MRI is the primary data gathering tool
    b. Screening tools: current clinical procedures in use at the NIDA IRP

iii. Exclusion Criteria

1. History of any neurological disorder that would increase seizure risk from iTBS such as stroke, brain lesions, previous neurosurgery, any history of seizure or fainting episode of unknown cause, or head trauma resulting in loss of consciousness, lasting over 30 minutes or with sequela lasting longer than one month.
    a. Justification: Stroke, vascular lesions or head trauma can lower the seizure threshold and are therefore contra-indications for iTBS. Fainting episodes or syncope of unknown cause could indicate an undiagnosed condition associated with seizures.
    b. Screening tool: TMS safety Screen and Medical History.
2. Current DSM-5 moderate-severe substance use disorder on a substance other than cocaine, nicotine, marijuana, or opiates (provided they are currently stable on a medication assisted treatment) or meeting withdrawal criteria for a sedative/hypnotic/anxiolytic, or tolerance criteria in an individual using 3 or more days/week, regardless of diagnosis. Individuals will be considered stable on a maintenance medication if they have been on a stable dose for at least 2-weeks prior to consenting to 17-DA-N002 and have provided at least 3 urine specimens negative for illicit opioids over the same 2-week period (10 business days) with at least one test collected within two business days of the start of the period, one collected within three business days of the end of the period and one collected at least two days from either

of the other two specimens. Urine results may be gathered at NIDA as part of screening or be provided by the buprenorphine maintenance prescriber. Communication between the maintenance provider and the MAI (or covering Staff Clinician) will be ongoing to establish continued illicit opioid abstinence between participant clearance and consent to 17-DA-N002.

   a. Justification: While use of multiple substances is the norm and some use will be allowed, the focus of the current protocol is on cocaine. However, participants with tolerance or withdrawal symptoms to a sedative/hypnotic/ anxiolytic will be at increased risk of a seizure from iTBS and will therefore be excluded. Alcohol withdrawal will be assessed on ITBS days and rescheduled if in withdrawal. Individuals receiving maintenance treatment for OUD and struggling with cocaine use are an ecologically valid population in the greater Baltimore area and do not increase risk of seizure.
   b. Screening tool: Drug Use Survey and SCID-research version.

3. HC participants will not currently meet DSM-5 criteria for moderate to severe substance use disorder (excluding nicotine), and in the past, will not meet DSM-5 criteria for moderate to severe substance use disorder for cannabis or alcohol in the past 5 years or ever for other illicit substances. HC will not meet current withdrawal criteria for alcohol or sedative/hypnotics/anxiolytics, or tolerance criteria in an individual using 3 or more days/week. Urine toxicology positive for any illicit substance inconsistent with history given will also be exclusionary.
   a. Justification: The population of interest is a healthy control population with no substance use disorder. Current use of illicit substances or alcohol could impact on seizure threshold and is therefore contra-indicated for iTBS.
   b. Screening tools: SCID-research version. Potential diagnoses will be further evaluated by a counsellor, Drug Use Survey (DUS), Substance

Use Disorder Evaluation, Medical Assessments: urine qualitative drug screen is performed for cocaine, THC, benzo, morphine/opiates, MDMA, amphetamine /methamphetamine, methadone, buprenorphine, PCP, and oxycodone.

4. First-degree family history of any form of epilepsy with a potentially hereditary basis .
    a. Justification: First-degree family history of epilepsy with a hereditary component increases the risk of the participant having an undiagnosed condition that is associated with lowered seizure threshold.
    b. Screening tool: TMS safety screening, Medical History.
5. Cardiac pacemakers, neural stimulators, implantable defibrillator, implanted medication pumps, intracardiac lines, or acute, unstable cardiac disease, with intracranial implants (e.g. aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or any other metal object in the body that precludes iTBS administration.
    a. Justification: Certain metal in the body is a contra-indication for iTBS administration, as this method involves exposure to a relatively strong static magnetic field that can move magnetic material not securely bound and rapidly alternating magnetic fields that can generate heat and current in metal contained in the body.
    b. Screening tool: Medical History, TMS safety screen.
6. Noise-induced hearing loss or tinnitus.
    a. Justification: individuals with noise-induced hearing problems may be particularly vulnerable to the acoustic noise generated by iTBS equipment.
    b. Screening tools: TMS safety screening.
7. Current use (any use in the past 4 weeks, daily use for more than a week within past 6 months) of any investigational drug or of any medications with

psychotropic (e.g., benzodiazepines), anti or pro-convulsive action, or anti-coagulants. This will be determined at the discretion of the MAI.

a. Justification: The use of certain medications or drugs can lower seizure threshold during use or withdrawal and is therefore contra-indicated for iTBS. Such medications may also alter neural functioning independent of the individual's drug use or the effects of the iTBS and thus add more variability to our data.
b. Screening tools: Medical history, Medical Assessments: Urine toxicology analysis for presence of a broad range of prescription and nonprescription drugs.

8. Lifetime history of schizophrenia, bipolar disorder, mania, or hypomania.
    a. Justification: The population of interest here is a healthy population with no psychiatric disorders other than substance use disorders. In participants with bipolar disorder, mania or hypomania, there is a small chance that iTBS can trigger (hypo)manic symptoms. As some degree of depressive symptoms is common in cocaine dependence and may result from the drug use, mild unipolar depression will not be exclusionary.
    b. Screening tools: SCID-research version or M.I.N.I. .

9. Pregnant women or women with reproductive potential who engage in heterosexual sex that may lead to pregnancy and not using a medically acceptable form of contraception (such as birth control pills, condoms, or a diaphragm with spermicide).
    a. Justification: it is unknown whether iTBS poses a risk to fetuses.
    b. Screening tool: Urine and/or serum pregnancy tests, and clinical interview.
10. Participation in any NIBS session less than two weeks prior to admission. No NIBS exposure for treatment purposes in the last 6 months.

a. Justification: in order to avoid possible carry-over effects from previous exposure to NIBS prior to participation in the proposed intervention, we will not enroll participants who have received any NIBS in the two weeks preceding enrollment or treatment with NIBS modality with the last 6 months preceding enrollment.
b. Screening tool: TMS safety screening questionnaire.

11. Non-English speaking.
    a. Justification: To include non-English speakers, we would have to translate the consent and other study documents and hire and train bilingual staff, which would require resources that we do not have and could not justify given the small sample size for each experiment. Additionally, the data integrity of some of the cognitive tasks and standardized questionnaires used in this study would be compromised as they have only been validated in English. Most importantly, ongoing communication regarding safety procedures is necessary when participants are undergoing study procedures. The inability to effectively communicate safety procedures in a language other than English could compromise the safety of non-English speaking participants.
    b. Screening tool(s): self-report.

G. Clinical and Laboratory Methods

i. Study Procedures

Participants will be scheduled for multiple clinical assessment and data collection sessions to complete the protocol. Similar to the Pilot study, a 10 day iTBS treatment protocol will be implemented. Based on the Pilot, a schedule of 3 daily iTBS sessions with at least a 60-minute interval between administrations is outlined below.

Protocol completers are defined as CD participants who complete 10 iTBS days of treatment within 3 weeks and visit 19 (first post-treatment scan day). CD participants who complete at least 5 iTBS treatment days in 3 weeks are eligible to begin with CM and follow-up visits. All study visits, including those with MRI scans, will be offered to these individuals as if they had completed all 10 iTBS treatment days. An HC participant is considered a protocol completer after completing all scheduled visits (baseline characterization visits and 2 iTBS treatment days with MRI scans).

Overall, CD participants will complete about 43 visits and HC participants 5 visits, with 8 and 6 MRI scans collected for CD and HC participants, respectively. Most of the visits for CD participants will be to collect urine samples and implement CM. The order of procedures completed during each visit may vary slightly, depending on availability of staff and other resources (mock scanner, MRI, study rooms, etc.).

Each study visit day will start with a brief nursing assessment that includes a urine sample for drugs of abuse, a breathalyzer, and vital signs. A urine pregnancy test for females will occur weekly during the iTBS treatment and any visit that includes an MRI scan thereafter. If breathalyzer is positive for alcohol participants may be rescheduled. In the event of a positive drug test, an interview to assess last drug use and a neuromotor assessment to test for acute intoxication will be performed. If participants test positive for drugs other than marijuana, based on MAI judgment, they may be rescheduled. If urine is positive for other illicit drugs, and if there are no known TMS contraindications, the participants may be allowed to participate at the discretion of the MAI. Otherwise, participants will be rescheduled. The CD group is expected to be current users and will likely test positive for illicit drugs. These procedures are designed to identify if CD participants are currently impaired and if HC participants have recently used illicit or licit drugs. Participants who smoke will be allowed breaks to smoke to preclude acute nicotine withdrawal. If a participant runs out of cigarettes, we will provide them on an as-needed basis to avoid withdrawal, which requires us to reschedule the visit. All study visits will take place at National Institute on Drug Abuse Intramural Research Program (NIDA-IRP).

1. Screening

Candidate participants will be screened based on the Inclusion and Exclusion criteria listed above under the aegis of the approved NIDA IRP general screening protocol. During in-person screening, potential participants will be given some initial information regarding the study (see attached “Fact Sheets” and “TBS Information Sheet”) to determine if they are interested in possible participation. The following assessments will be administered during screening:

Brief Cocaine Cessation Motivation Assessment (BCCMA)(Appendix 28): a semi-structured interview to assess the stage of change and motivation level for cocaine dependent participants. Completion time: 10-15 minutes.

Contact Information Form: This form requests multiple methods of contact for a participant, as well as the preferred contact method, preferred contact time, and emergency contact information. Completion time: < 5 minutes.

Drug Use Survey (DUS): An interviewer-administered questionnaire designed to collect information regarding lifetime history of substance use. Completion time: < 40 minutes.

Edinburgh Handedness Inventory[103]: This 12-item questionnaire assists in determining the dominant hand (or handedness) of a particular participant by inquiring which hand the participant uses for various tasks. Completion time: ~ 5 minutes.

Medical Assessments: Vital Signs, height/weight measurements, urinalysis, EKG, oral HIV test, blood draw for CBC, chemistries, thyroid and liver function, erythrocyte sedimentation rate, urine qualitative drug screen for cocaine, THC, benzo, morphine/opiates, MDMA, amphetamine /methamphetamine, methadone, buprenorphine, PCP, and oxycodone, urine toxicology which analyzes for presence of a broad range of prescription and nonprescription drugs, as well as urine and/or serum pregnancy testing for menstruating females. Breathalyzer for alcohol will be taken at this time as well. Completion time: 30-40 minutes.

Medical History and Physical Examination: This is a standard physical and detailed medical history and physical examination designed to capture the inclusion and exclusion criteria for NIDA-IRP protocols. It is administered by a Physician's Assistant or other credentialed medical staff. The estimated time to complete is variable. Completion time: 45 to 90 minutes.

Mini International Neuropsychiatric Interview (M.I.N.I)[104]*:* a brief structured interview for the major psychiatric disorders in DSM-5 and ICD-10. Follow up questions may ensue. Completion time: ~20 minutes. (Participants will complete either the MINI or the SCID).

Participant Safety – MRI Screening Form: A questionnaire that aids in determining appropriateness of MRI scan. Completion time: < 5 minutes.

SCID-Research Version Structured Clinical Interview for DSM-5™ (SCID), used in assisting with diagnosis of DSM-5 Axis I disorders. (Participants will complete either the MINI or the SCID).

TBS Information Sheet: A general information sheet on TBS administration with common questions and answers is given to participants as an informational item only. Participants are given time to read the handout and to ask questions about it while in the clinic. Completion time: ~ 20 minutes.

TMS Safety Screen: A questionnaire that aids in determining appropriateness of administering TBS. Completion time: < 5 minutes.

Shipley-2, computerized version Completion time: ~ 45 minutes.

Brain Imaging Information Handout: A general information sheet on brain imaging research with common questions and answers is given to participants as an informational item only. Participants are given time to read the handout and to ask questions about it while in the clinic. Completion time: ~ 20 minutes.

Mock Scanner: Participants are taken to a mock MRI scanner during their screening visit. The scanner environment is explained to the participant and they are asked to lie in the scanner to make sure there are no problems with body fit or comfort. This gives

participants the opportunity to opt out of scanning experiments if they are not comfortable with the scanner environment. Completion time: < 10 minutes.

2. Nursing Assessments and Task Preparation

Nursing Assessment. After completing the consent interview and prior to study sessions, participants will undergo a nursing assessment, which may include measuring vital signs, a breathalyzer test for expired ethanol, an observed urine test for common abused drugs, a metal/MRI safety screening (scan sessions only), a TMS safety questionnaire (iTBS sessions only) and if female, a urine pregnancy test. Participants will also be asked when they last had NIBS and whether this was at NIDA or elsewhere. Participants with a positive breathalyzer will be rescheduled. In the event of a positive drug test, an interview to assess last drug use and a neuromotor assessment to test for acute intoxication will be performed. If participants test positive for drugs other than THC (current clinical practice by C. A. Hanlon and J. Downar is to not exclude THC positive participants [personal communication, July 19, 2018]), or cocaine for the CD group, based on the MAI's judgment, they may be rescheduled. However, if they test positive on a second occasion they may be excluded from the study. This will be made clear to the participant in the consent process. In addition, participants will be asked to report changes in medical history, recent over-the-counter, prescription, or other substance intake, time of last meal, hours slept the previous night, and, if female, last menstrual period and whether or not they are currently taking a contraceptive pill. After all TMS sessions, participants will have their heart rate and blood pressure taken. Participants will be asked to abstain from caffeine consumption for 12 hours prior to scan sessions, as well as alcohol and other drugs for 24 hours prior to TMS and scan sessions. Participants who use alcohol will be assessed for withdrawal smptoms with the CIWA-Ar and rescheculed if they show signs of withdrawal (>=8).

CD participants who opt to stay at the CRU will be searched upon intake (Appendix 29) and will have vital signs assessed in accordance with the standards of the inpatient

unit. Upon intake, participants will complete a breathalyzer and urine drug screen. Completion time: ~30 minutes.

Orientation. Prior to the commencement of iTBS treatment sessions, participants will complete a training session where they will be oriented to iTBS. Orientation may take up to 1 hour where the motor hotspot and resting motor threshold (RMT) will be recorded. RMT will be identified each iTBS treatment day. Each DAY, after the first, will use the motor hotspot from the previous day as a guide. Localization of left dorsolateral prefrontal cortex (dlPFC) stimulation site will be defined within-subject using MRI coordinates (see below). After motor hotspot, RMT and left dlPFC are identified, the participant will be oriented to iTBS (either active or sham as assigned). Participants who fail to tolerate iTBS at 100% of RMT during this orientation session will be discharged from the study, however their characterization assessments and scans will be retained to compare with CD.

Before commencing the visit 1 scanning sessions, participants will complete a training session where they will be oriented to the scanner environment and instructed on and practice the experimental tasks inside a mock scanner. Participants will complete baseline characterization measures at this time. Characterization measures may be completed on multiple visits if it is more convenient to the participant's schedule.

Mock Scanner. Individuals will receive training or refreshers, either verbally, on the bench, or in a mock scanner, during subsequent visits. Completion time: between 10 minutes and 1.5 hours.

Baseline and characterization questionnaires. A series of questionnaires related to cocaine use and dependence, withdrawal symptoms, psychological state, motivation to quit, and mood inventories as well as several characterization measures will be administered during the orientation visit or later sessions. Some characterization and state measures listed under this protocol may be completed under protocol 10-DA-N457, and vice versa. These data will be linked across protocols so that participants do not have to complete them more often than necessary.

Participants will complete the following questionnaires; only the CD group will complete the assessments marked with an *:

Attitudes Towards Risk Questionnaire (Appendix 7): A 34-item self-report with 5-point Likert scales that assess attitudes towards physical and psychological risk. Completion time: < 10 min.

**Addiction Severity Index (ASI, Appendix 44)*: A semi-structured interview designed to provide information in 6 areas related to drug abuse and drug abuse treatment: medical, employment/support, alcohol and drug use, legal, family/social and psychiatric. Completion time: 45-60 minutes.

Brief Externalizing Inventory[108] *(Appendix 9)*: A 159-item self-report adapted from the full Externalizing inventory[109] used to assess a range of behavioral and personality characteristics that have been attributed to a broad psychological construct termed externalizing. These characteristics include: physical/relational destructive-aggression, boredom proneness, irresponsibility, problematic impulsivity, drug and alcohol use or problems, theft, fraud, rebelliousness, alienation, and blame externalizing. Completion time: ~ 15 min.

The Revised Social Anhedonia Scale (Appendix 42): A 40-item true-false self-report questionnaire intended to measure decreased pleasure derived from interpersonal sources. Completion time: ~10 minutes.

The Physical Anhedonia Scale (Appendix 43): A 61-item true-false self-report that taps a range of presumably pleasurable experiences involving eating, touching, feeling, sex, movement, smell, and sound. Completion time: ~15 minutes.

*Cocaine craving likert scales (Appendix 11): “How much are you craving right now?” and “On average, how much of a problem has craving been for you over the past week?”

**Cocaine use, Pattern, and Withdrawal Questionnaire (Appendix 12)*: This is an interview-guided questionnaire, designed by Dr. B. J. Salmeron, and has been successfully employed in previous studies. Completion time: ~ 10 minutes.

Montgomery-Asberg Depression Rating Scale (MADRS[112]; Appendix 13): A clinical assessment to identify symptoms of depression. This assessment is especially useful in identifying changes in depression symptoms over time. If a participant reports suicidal thoughts, the CDW Critical Item Alert System will be initiated following the NIDA SOP to address such responses. Completion time: < 10 minutes.

**Modified Positive and Negative Affect Scale (Modified version of the PANAS; Appendix 14):* Participants are asked to fill in a questionnaire about possible side-effects since the last iTBS session (the NIBS monitoring questionnaire), and a questionnaire about their affect (a modified version of the PANAS). The sole purpose for the modified version of the PANAS is to assess the answer to one single question ("Right now I feel … detached: rate from "not at all" to "extremely"). This is not in the original, validated PANAS-SF. Instead, the modified questionnaire is used as a device to ask this one single question, without calling unwanted attention to it by asking it as a single item. A self-report scale to assess state-level affect. Completion time: < 5 Minutes.

Profile of Mood States (POMS; *Appendix 15*): A questionnaire designed to measure present mood state by a list of adjectives on a 5-point Likert scale and measures six dimensions of affect, including tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. The measure has been shown to produce reliable and valid profiles of mood state[113, 114]. Completion time: ~ 5 minutes.

**Scale for the Assessment of Positive Symptoms for Cocaine-Induced Psychosis (SAPS-CIP[115], Appendix 32):* The SAPS-CIP is a modification of the Scale for Assessment of Positive Symptoms designed to focus on psychotic symptoms related to cocaine use. We will use the hallucinations and delusions sections which have been shown to be particularly useful in assessing cocaine-induced psychosis. If endorsed, the MAI (or staff clinician) will assess current psychosis and need for further evaluation and/or treatment. Completion time: < 30 minutes.

**Cocaine-Induced Psychosis: Screener (CIP: Screener, Appendix 33):* The CIP: Screener is designed for efficient assessment of cocaine-induced psychosis and will be

used to assess changes, relative to baseline, throughout the protocol. Any worsening from baseline in cocaine-induced psychosis measured throughout the protocol will be evaluated by the MAI (or staff clinician). Completion time: < 5 minutes.

Sensation Seeking Scale V (SSS-V, [116]*; Appendix 67*): A 40-item self-report questionnaire that assesses individual differences in sensation seeking. The scale consists of four subscales (Boredom Susceptibility [BS], Thrill and adventure seeking [TAS], Experience seeking [ES], and Disinhibition [Dis]) composed of 10-items each. Completion time: < 10 minutes.

Snaith-Hamilton Pleasure Scale (SHAPS, [117]*; Appendix 17*): A 14-item self-report scale designed to measure hedonic-tone/anhedonia. Completion time: ~ 5 minutes.

Temperament and Character Inventory[118] (Appendix 18): A widely used test that assesses dimensions of personality (e.g., harm avoidance, novelty seeking, reward dependence, and persistence) that are considered to be related to monoaminergic function. Completion time: ~ 25 minutes.

The Multidimensional Social Contact Circle[119] (Appendix 19): A self-report scale designed to measure social ties between the participants and their friend, family, co-workers, etc. Completion time: ~ 15 minutes.

Time-line follow back (TLFB; *Appendix 20*). The TLFB will be used to assess substance use behavior. This assessment will be either self-administered or administered by one of the investigators. Participants will read the instructions and/or will be guided by the therapist or investigator in filling out the calendar. A lifetime TLFB will be administered at the start of the protocol. An interim version with be administered at each visit to assess substance use between administrations. Completion time: 15 minutes to 2 hours.

**Risk Assessment Battery (RAB)* (Appendix 21): Self-administered questionnaire assessing HIV risk behaviors including drug use, needle use, sexual practices and HIV testing behavior. Completion time: < 10 minutes.

Debriefing. At the end of each visit, there will be a debriefing period for discussion of questions/issues related to the day's tasks, scheduling/reminder of subsequent visits. They will also schedule a time for their next session.

Urine Benzoylecgonine Test. Urine samples will be collected from all CD participants and will be used in the implementation of CM. These samples will be collected under observation of a same-sex observer to confirm its validity. The urine toxicology analysis will be used to assess a broad range of prescription and nonprescription drugs by metabolite quantitation using a dip card, which is a one-step urinalysis immunochromatography drug rapid test (5 minutes), to assess recent use of drugs of abuse. It is designed for qualitative screening of cocaine metabolite in human urine specimens and provides a preliminary analytical test result for on-site testing. Additionally, the urine sample, when positive for cocaine, will be sent for quantitative 'additional use' analysis in the NIDA-IRP Translational Analytical Core (TAC), for implementation of CM. Missing samples will be considered positive. Completion time: ~10 minutes.

3. MRI Scan Sessions

On all days with an MRI scan, participants are expected to complete several clinical assessments as well as experimental tasks (see Figures 1 and 2 for graphical summary). However, availability of staff, facilities and participant schedule may require some flexibility in timing and measures performed in the outline below. CD participants will be scheduled to complete all 8 scans described below and HC participants will be scheduled to complete up to scan 4. Because HC participants will have a within participant active vs sham manipulation (described below), they will complete scans 3 and 4 twice; once with active and once with sham iTBS (see Figures 1 and 2).

Pre-scan Assessment. Participants will complete a nursing assessment (as described above) upon arrival for each scan session. nursing assessments that occur on scan days will include an MRI safety screening.

Pre-scan task practice. Prior to each scan, participants will be reacquainted with the task instructions and will complete brief training runs. Completion time: ~30 minutes.

Self-report measures. At each scan session, participants will be administered several brief measures to assess current arousal (modified version of the PANAS), mood (POMS) and other withdrawal symptoms (CD participants only; Cocaine Craving Likert Scales, Cocaine use, Pattern, and Withdrawal Questionnaire). These measures will be administered on a computer in a private area. Completion time: ~30-40 minutes.

Drug Use. A urine sample will be collected from CD participants which will be used to implement CM.

Scan 1. Completed on visit 1: Localizer (~ 1 min); Structural scan (~ 5 mins); MID (~ 30 mins); Flanker (~25 mins); N-Back Task (~ 10 mins); SSRT (~ 15 mins); Approximately 2 hours.

Scan 2. Completed on visit 2: Localizer (~ 1 min); DTI (~ 10 mins); Resting (~ 10 mins); Amygdala task (~7 mins); ASL (~10 mins); Approximately 1.5 hours.

Scan 3. Completed on visit 3 (preceding the first iTBS treatment on the first treatment day): Localizer (~ 1 min); ASL (~ 10 mins); Resting (~ 10 mins); SSRT (~ 15 mins); Amygdala (~7 mins); Cue Reactivity (~ 15 mins): Approximately 1 hour.

Scan 4. Completed on visit 3 (following the last iTBS treatment on the first treatment day): Localizer (~ 1 min); ASL (~ 10 mins); Resting (~10 mins); SSRT (~ 15 mins); Amygdala (~7 mins); Cue Reactivity (~ 15 mins); ASL (~ 10 mins). ASL at the beginning and end of this scan session will measure trajectory of change of blood flow/neuronal activity over time after the TMS session. Approximately 1.5 hours.

Scans 5 & 7. Completed on visits 19 and 36: Localizer (~ 1 min); ASL (~ 10 mins); Resting (~10 mins); Amygdala (~7 mins); Cue Reactivity (~15 mins); Flanker (~25 mins); N-Back (~10 mins); Approximately 2 hours.

Scans 6 & 8. Completed on visits 19 and 36: Localizer (~ 1 min); Structural (~5 mins); DTI (~10 mins); SSRT (~15 mins); MID (~30 mins). Approximately 2 hours.

Debriefing. At the end of the scanning session there will be a debriefing period for discussion of questions and issues related to the day's tasks. They will also schedule a time for their next session.

4. iTBS Sessions

HC participants will be scheduled for 2 days of iTBS - 1 DAY of active iTBS and 1 DAY of sham iTBS, with at least a 60-minute interval between sessions and at least 1 week between DAY. The order of these days will be counterbalanced.

CD participants will be scheduled for 10 days of iTBS treatment and randomly assigned to receive either active or sham iTBS. Participants will initially be scheduled to complete all treatment DAYS in 2-weeks whenever possible, however, they will have up to 3 weeks to complete the 10 DAYS of treatment.

On iTBS days, participants will complete several questionnaires in addition to the iTBS treatments. During iTBS, participants will view cocaine cues (i.e., pictures; Appendix 25) in an attempt to control affective state across participants while also potentially eliciting activation in networks specifically related to cocaine use and substance abuse in general.

Pre-iTBS. Participants will complete a questionnaire about possible side-effects since the last iTBS session (the NIBS monitoring questionnaire) and a questionnaire about their affect (the modified version of the PANAS; see Appendix 1 & 15). Participants will also complete Trails A and B (Appendix 22) prior to and following iTBS administration each day. These assessments will also be collected at baseline prior to any TMS or iTBS administration to assess a true baseline measure for each participant. Also, measures of mania (Young Mania Rating Scale [YMRS]; Appendix 23), suicidality (Columbia-Suicide Severity Rating Scale: Baseline [C-SSRS]; Appendix 24) and depression (MADRS[112]; Appendix 14) will be collected prior to the first iTBS session in CD.

iTBS Session. Resting motor threshold will be determined daily, as described below. Recruitment curves will be measured during orientation (HC and CD), and in the CD group, before the first iTBS administration on iTBS day 1, after the last iTBS administration on iTBS day 10, and each of the follow-up visits with an MRI scan. Approximately 1 hour.

Post-iTBS. At the end of the visit, participants are asked to fill in a questionnaire about possible side-effects (the NIBS monitoring questionnaire), a questionnaire about their affect (the modified version of the PANAS; see Appendix 1 & 15), questionnaires assessing the blind will be administered (Appendix 46), and an assessment of pain will be administered (Appendix 46). The iTBS administrator will also fill out an assessment of the blind (Appendix 47). Questions about blinding and pain levels will be asked of the participant after the last iTBS session. Questions about blinding will be asked of the TMS operator after the last iTBS session. Participants will also complete Trails A and B (Appendix 22) after the final iTBS administration each day, prior to discharge. After the final iTBS session (i.e., on Day 10, prior to discharge), measures of mania (Young Mania Rating Scale [YMRS]; Appendix 23), suicidality (Columbia-Suicide Severity Rating Scale: Baseline [C-SSRS]; Appendix 24) and depression (MADRS[112]; Appendix 14) will be collected.Contact attempts will be made by phone 1-3 days after the last iTBS session to assess any acute behavioral or health related changes from treatment (Appendix 1).

5. Post-Treatment Follow-Up

Ongoing follow-up will be attempted for 24-weeks post-treatment and will include urine samples for implementation of CM, as outlined in Table 1, and assessments of substance use (participants may repeat some or all characterization measures and assessments of drug use). MRI scans will be performed about one month and three months after the start of iTBS treatments (on approximately visits 19 and 36) to assess neural plasticity related to abstinence, reduction, or continuation of drug use post-treatment. The ASI will be scheduled to be completed within 1-week of all follow-up

visits that include an MRI scan, along with the three mood measures (YMRS, MADRS and C-SSRS). ASI will also be completed at the final vist of the study. The first 12-weeks post-treatment follow-up appointments will be in-person. The next 12-weeks will consist of once-a-week phone contact attempts and once-a-month in-person visits to assess drug use post-treatment. Additional attempts will be performed only through means approved by the participant. These may include such alternative methods as text and e-mail if phone contact is not successful.

Questionnaires/Behavioral measures: Some or all assessments and/or tasks may be completed remotely via a secure platform approved by NIDA-IRP's ISSO, or via a secure web link set up by the NIDA-IRP BIS team. For this option, participants must have use of a private space with secure internet connection. Participants will be instructed how to complete the assessments/tasks via phone or encrypted video chat program approved by NIDA IRP's ISSO.

SARS-CoV-2 antibody testing: COVID-19 has been reported to be capable of producing long-lasting neurological effects that might include subtle cognitive deficits (Ritchie et al 2020). The prevalence of such deficits, if they exist, is unknown. Therefore, we will assess SARS-CoV-2 antibodies in order to assess for possible effects. How this data will be used will depend on the number of antibody-positive participants in the final cohort as well as future publications on the impact of antibody status on the data being gathered. We will not use antibody testing for diagnosis or treatment of participants, and participants will not be informed of the results, as they have no clear clinical significance and could be misinterpreted. We may collect about 1 mL of blood or up to 2mL of saliva for antibody testing. We may collect this sample at the first visit that includes an MRI scan and at other visits including an MRI scan if the participant has not been recently tested for COVID-19, and/or if subsequent scan(s) are more than a few weeks apart. If a participant has a documented history of positive COVID-19 diagnostic or antibody test, the MAI will determine whether antibody testing under this protocol is necessary.

ii. Experimental Measures

1. Imaging Measures

MRI Scanner Sessions. The total time that participants will be inside the scanner each session is approximately 2 hours (note: all times approximate and order of scans generally fixed but may be switched in the event of instrument problems or participant compliance).

The study may use the 3T MRI with custom pulse sequences and image reconstruction and analysis software (via CRADA with Siemens using sequences developed at various universities). All sequences are within FDA approved specific absorption radiation (SAR) limits. We believe this study is a non-significant risk (NSR) device study subject to the abbreviated IDE requirements of 21 CFR 812.2(b). The devices (custom pulse sequences and image reconstruction and analysis software), as used in this study, do not meet the definition of a significant risk (SR) device per 21 CFR 812.3(m) because:

1. It is not intended as an implant and presenting a potential for serious risk to the health, safety, or welfare of a subject because the MRI is not an implant.
2. It will not be used in supporting or sustaining human life and does not present a potential for serious risk to the health, safety, or welfare of a subject because MRI will not be used in supporting or sustaining human life.
3. It will not be for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presenting a potential for serious risk to the health, safety, or welfare of a subject because the MRI results will not be used to provide clinically relevant information for participants.
4. It does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject because the pulse sequences and image reconstruction and analysis software are used within the FDA approved SAR limits.

Per regulations, abbreviated IDEs (NSR device studies) do not require an application to the FDA as the IRB acts as FDA's surrogate for review, approval, and continuing review of these type of device studies.

2. MRI Measures

Arterial Spin Labeling (ASL) Scan. We will acquire ASL images to quantitatively assess potential changes in regional blood flow and thus neuronal activity resulting from iTBS. Completion time: ~ 10 minutes.

Diffusion Tensor Imaging (DTI) Scan. A DTI scan will be performed allowing for the assessment of white matter microstructure and tracks in both HC and CD. Completion time: ~ 10 minutes.

Structural Images. A set of high resolution structural MR images will be collected. The images will be acquired using a T1-weighed three-dimensional MPRAGE. Completion time: ~ 5 minutes.

3. fMRI Measures

Amygdala Reactivity Task: Participants will complete a simple perceptual task previously shown to produce robust bilateral amygdala activity[61, 143, 144], as well as top-down prefrontal regulation of amygdala reactivity[143, 144]. This is a blocked fMRI paradigm where participants are asked to either match faces or geometric shapes[145]. Completion time: ~ 7 minutes.

Cue reactivity: Participants passively view two kinds of stimuli, cocaine-related picture cues and neutral pictures (c.f., [55]), in a block design. The MAI or other NRB clinical personnel will intervene to mitigate craving before discharge in the event of clinically significant craving. A response of 6 or 7 on the CCQ Likert scale for questions 3, 4, 16, 33, or 34 or a response of 1 or 2 question 28 would constitute clinically significant craving. Similarly, a response of 9 or 10 on the CCS Likert scale for question 1 would constitute clinically significant craving. The MAI or other NRB clinical personnel will intervene to mitigate craving before discharge if the participant's self-report of

craving level arouses concern (in the participant or staff) in the context of conversation. Completion time: ~ 15 minutes.

Flanker: Participants will complete a modified Flanker task designed to yield sufficient error rates to study the signatures of error processing[146]. Participants respond to the central letter (e.g., H or S) of a congruent (HHHHH or SSSSS) or incongruent (HHSHH or SSHSS) stimulus array. To elicit comparable error rates, a participant specific, adjustable response time deadline will be calculated and implemented for each participant. Completion time: ~ 25 minutes.

Monetary Incentive Delay (MID) Task. The MID task was designed to identify brain circuitry involved with anticipation and receipt of monetary gains and losses[62, 147-149]. Participants respond within a time-window optimized to the participant's behavior during win, loss, or neutral trials with the aim to maximize overall winnings. A performance-based payment is payed equal to 10% of the theoretical total that they score on the task, with a maximum bonus payment of $53. Completion time: ~ 30 minutes.

N-Back. The n-back visual working memory task[150] will be administered to assess working-memory performance. During the n-back task, participants are presented with a series of single letters in a pseudorandom order and are required to decide whether the current stimulus matches that which appeared n items previously[150]. Completion time: ~ 10 minutes.

Resting Scan. An eyes open EPI scan to assess resting-state fluctuations will be conducted to provide information relating to trait and perhaps state connectivity between regions of interest. Completion time: ~ 10 minutes.

Stop Signal Reaction Time Task (SSRT). The task requires participants to execute a motor response (Go trials) on most trials and to withhold their response on some trials (Stop trials). On each trial, a target stimulus is displayed. On Go trials (e.g. ~75% of trials), participants respond as quickly as possible with a key press. For the Stop trials (~ 25% of trials), participants are instructed to stop their response when they receive a Stop signal (a visual cue) presented at a particular delay [stop-signal delay (SSD)]

subsequent to the target stimulus. The SSD value for the Stop trial is adaptively determined to ensure that participants inhibit their response successfully on 50% of trials[151]. Completion time: ~ 15 minutes.

4. Behavioral Measures

Two experimental tasks will be collected outside the scanner. The Stroop task will be administered as a baseline characterization instrument for both HC and CD and repeated in order to assess the effects of iTBS on prefrontal cortex function within one week of scans 5/6 and scans 7/8 in CD.. The Risk/Reward task will be collected once within the baseline characterization phase for both HC and CD and weekly after that throughout the protocol (when possible) for CD. A performance-based payment is payed equal to 10% of the theoretical total that they score on the task, with a maximum bonus payment of $6.60.Tasks administered on a iTBS day will be done prior to iTBS treatment.

Stroop/Drug Stroop: This is combined task that includes stimuli of both the Stroop task and the Drug Stroop task. During the Stroop task[56], participants are presented with color words (e.g., RED) in either congruent (e.g. red) or incongruent (e.g., blue) font colors. Participants are to report the font color for each stimulus. Due to the automaticity of reading the word, incongruent trials are more difficult than congruent trials leading to delayed responding and more errors than congruent trials. The Drug Stroop is similar to the Stroop task, participants are presented drug-related words or pictures (e.g., pipe, smack, and lighter) that have elicit behavioral and neural differences between users and non-users[57, 153, 154]. Completion time: ~ 15 minutes.

Risk/Reward Task[152]: In this task, participants make decisions about risks and rewards. Two parameters of interest are collected: Risk tolerance and ambiguity tolerance. These parameters measure known and unknown risks and have been linked to predicting relapse. This task will be collected once within the first 3 visits and weekly after that throughout the protocol (when possible). A performance-based payment is

payed equal to 10% of the theoretical total that they score on the task, with a maximum bonus payment of $6.60. Completion time: ~20 minutes.

iii. iTBS Administration

1. Apparatus and tests

To administer the iTBS treatment, a MagVenture MagPro 100 with MagOption (MagVenture Inc, Alpharetta, GA) stimulator equipped with a figure-8 coil will be used. Two separate coils will be utilized that are all similar in weight, appearance, and acoustic properties. One active coil will be unblinded and used to determine RMT and deliver pulses for the recruitment curves; the other will be blinded (one side active, one side sham). All personnel interacting with the participant will be blind to coil assignment. The Sham stimulation and preservation of the blind is described below.

2. Localization of Dorsolateral Prefrontal Cortex

iTBS stimulation will be targeted using specific coordinates (MNI coordinates: -50, 30, 36). The network connectivity with this coordinate has recently been shown to be most predictive of relapse to cocaine use (recently submitted internal lab data) and thus a promising target for iTBS stimulation. In this work, other dlPFC TMS target coordinates were tested and found to be not predictive of relapse to cocaine use.

3. Motor Threshold Determination

In determining motor threshold, first the scalp position closest to the motor representation (the “motor hot spot”) is sought. Then the RMT at this location is determined. The hotspot is located during the initial session and verified at subsequent sessions, whereas the RMT will be measured every treatment day. In accordance with the manufacturer’s instructions and accepted standards, hand motor cortex will be stimulated to obtain RMT[123, 124].

Participants will be seated in a recliner in a comfortable resting position and fitted with earplugs. The TMS figure-8 coil will be placed over the hand-associated primary motor cortex. The coil will be held tangentially on the head with the handle pointing backward and 45° laterally from the midline. Using repeated single pulse, suprathreshold stimuli, the coil will be moved to determine the optimal scalp position for producing visible contralateral hand twitches. Pulses over this motor cortex location will be administered to identify the resting motor threshold using PEST[125] software. Responses will be either visually detectible motor twitches or motor evoked potentials of the muscles that move the contralateral hand. Recruitment curves will be measured as a proxy for the ratio between gamma amino butyric acid (GABA) and glutamate[126-128]. The recruitment curve will be measured at orientation in both HC and CD, and before the first iTBS administration on iTBS day 1, after the last iTBS administration on iTBS day 10, and each of the follow-up visits with an MRI scan.in CD

This entire procedure (hotspot and threshold determination) can take 30-90 minutes. If no motor hotspot can be determined within 1 hour or if the motor threshold exceeds 83% of maximal stimulator output, the participant may be discontinued from the study at the discretion of the LAI and/or MAI. Because the initial motor hotspot determination will be catalogued, subsequent determinations on treatment days are expected to take very little time.

4. Stimulation Procedure

A pre-selected protocol is programmed into the iTBS stimulator[73]. Three pulses will be given at 50 Hz repeated every 200 ms for a 2 second duration followed by 8 seconds of no stimulation. This sequence repeats for a total of 190 seconds and 600 pulses. Magnetic field intensity will be set at a medium intensity and gradually increased to the goal of 100% of that participant's measured daily RMT, accounting for cortical distance as measured with a structural MRI, depending on participant tolerability. Cortical distance has been shown to be greater over dlPFC than motor cortex[155]. Also, group differences have been identified between CD and HC participants[156]. Therefore, these

differences will be adjusted within participant to ensure similar cortical excitation is achieved over the dlPFC as motor areas.

5. Sham Stimulation

The double-blind will be preserved by allowing research staff not present during the iTBS session to be responsible for randomizing the active and sham coil. Therefore, research staff present during the iTBS session may be responsible for clinical ratings. The sham coil setting is designed to mimic the auditory artifact and scalp sensations evoked by the real coil without stimulating the brain. The blinded coil has two sides that can be placed on the participant's head; one side active and one side sham. These sides look identical to the researcher and the participant but TMS/iTBS pulses are delivered from only the active side. Which side is facing the participant is determined by the TMS machine or by self-application. The TMS operator will use the coil as set up by the research staff not present ensuring that both the operator and the participant will not know the orientation (active or sham) of the coil. However, in experienced participants, the difference between real and sham iTBS, as well as the difference between different intensities of iTBS is likely to be noticeable. The TMS operator is responsible for verifying the correct iTBS sequence is loaded into the TMS stimulator prior to administering an iTBS session. If a CD participant is randomized to the sham-iTBS group, all iTBS sessions will be sham. Each HC participant will be randomly assigned to either sham- or active-iTBS for visit 3 then crossed over to the other iTBS administration for visit 4. Measurement of motor evoked potentials will be identical between active- and sham-iTBS groups. In an attempt to avoid placebo effects, it is emphasized to the participant that the sensation is related to the stimulation of scalp nerves and muscles, and brain stimulation itself cannot be felt. While our sham stimulation does produce a sensation that is comparably uncomfortable in at least some participants and can produce muscle twitches, it is not qualitatively identical to the active iTBS. Therefore, while efforts are taken to preserve the double-blind, it is possible that the participant and/or the experimenter will become unblinded to the treatment condition. Because of

this, a questionnaire assessing the blind will be administered to the participant (Appendix 46) and the iTBS administrator (Appendix 47). Also, an assessment of pain will be administered to the participant (Appendix 46).

6. Discharge Procedures

If a participant experiences somatic or psychological symptoms that interfere with his/her ability to participate then he/she will be discharged from the study. The most frequent symptom is pain over the area of stimulation which could interfere with participation in the study. DLPFC stimulation has rarely been associated with mania. The investigators will monitor participants for changes in mood and may discharge a participant at any time if they believe that it is in the best interest of the participant. Participants who fail to tolerate iTBS at 100% of RMT during their toleration session will be discharged from the study. Those with RMT over 83% of MSO will be discharged as the recruitment curves require administering pulses up to 120% RMT, which is only possible if RMT is 83% or less.

7. Participant Monitoring

The NIBS monitoring questionnaire (Appendix 1), Trails A and B (Appendix 22), and staff observation and interactions with participants will be assessed daily. A NIDA-IRP physician or Physician's Assistant knowledgeable about iTBS will be immediately available in the building whenever iTBS is administered and will be available by telephone or pager 24 hours a day for consultation or in the event of a medical emergency. If immediate medical intervention is required, the participant will be referred to an appropriate medical facility. Information on all adverse events will be cumulated and reported to the NIH IRB with each continuing review application. Unexpected or serious adverse events (defined in accordance with NIH and NIDA IRP policy) will be promptly reported to the NIDA Clinical Director and IRB in accordance with NIH and NIDA IRP policy (see DSMP below).

Seizure monitoring procedures: Participants will be monitored throughout each iTBS session for signs of seizures such as involuntary muscle movements or loss of consciousness. In the event of a seizure, staff will have immediate access to life support equipment and anti-seizure drugs. In the event of a seizure, the procedure outlined below[129] will be followed:

1. Protect patient's head and limbs from injury.
2. Ensure an adequate airway.
3. Call 911 to have the patient transferred to Johns Hopkins emergency room, if the seizure requires medication intervention to resolve or is otherwise clinically indicated.
4. Observe Patient for:
    a. Initial movements/ sensations.
    b. Progression of movements.
        1. Change in respiratory status
        2. Skin color
        3. Incontinence
        4. Level of consciousness
        5. Ability to communicate
        6. Level of orientation
        7. Duration of seizure activity

            If after two minutes, the seizure has not resolved, administer: midazolam IM, 10 mg that is contained in a lock box in the TMS suite.
5. Provide supportive care after the seizure resolves.
6. Orient patient to time and place.

Session video recording: If a potential adverse event occurs during iTBS stimulation, video footage of the session can help determine the nature of the incident. Thus, video will be recorded during threshold determination and during iTBS, barring any technical difficulties with recording instrumentation. If the session progresses without incident, this

footage will be deleted within a week. Otherwise, during sessions with abnormal events, the video will be retained in accordance with NIH Records Management policy (https://oma.od.nih.gov/DMS/Documents/Records/NIH_Intramural_Research_Records_Schedule.pdf) for 7 years after the completion of the study or when no longer needed for scientific reference, whichever is longer. This footage may be used by the MAI and any experts the MAI wishes to consult to determine the nature of the event. Participants will not be given the option to opt out of the video recordings. If they do not wish to be recorded, the alternative is to not participate in the study.

iv. Risks

The side effects associated with TMS treatment in large clinical trials have been published[130]. Published consensus safety guidelines for TMS have resulted in reduced frequency of adverse events[131]. The following clinical data associated with depression treatments are provided to emphasize the extensive medical experience with TMS and its safety.

Numerous sham-controlled trials and several meta-analyses support its efficacy in treating depression[94, 132-134]. The largest TMS sham-controlled trial to date involving 301 pharmacotherapy refractory depressed participants reported positive results[70]. Sessions of rTMS were conducted for 4 to 6 weeks five times per week. Stimulation was set at 120% RMT with 10 pulses per second for a total of 3000 pulses per session. Active rTMS was well tolerated, with low dropout rate for adverse events (4.5%) that were generally mild and limited to transient scalp discomfort or pain. In the current proposed study, iTBS will be used, which is similar to rTMS but a lower level of stimulation (100% of RMT compared to 120% of RMT for rTMS).

There are no published reports of iTBS related seizures. Dr. Eric Wasserman, a TMS expert and pioneer at NINDS, summarized the occurrence of seizures in Table 2 from largely unpublished reports. As shown, his survey reported a single iTBS seizure in a stroke patient who was at high risk for seizure. Also, his survey has determined that there is a 0.002% chance of a seizure in healthy participants. Several published reports

are available in which healthy control participants receive multiple iTBS sessions within a day without serious adverse events[99, 100, 135].

Table 2: Seizures by mode of stimulation

		Total			No elevated risk	
Mode	Seizures	Sessions	Risk	Seizures	Sessions	Risk
Single/Paired-pulse	13	112897	.12	3	100696	.030
Low-frequency (≤1 Hz)	3	90631	.03	0	54373	-.
High-frequency (>1 Hz)	4	82588	.05	1	76181	.01
Intermittent Theta Burst	1	16952	.06	0	2729	
Continuous Theta Burst	0	8568	.	0	4994	
H-Coil high-frequency	3	6924	.43	1	3094	.32
Totals	**23**	**318560**	**.07**	**5**	**242067**	**.02**

Note: Number of sessions and seizures for different modes of NIBS. Seizure risk is per 1000 sessions. There is 1 unpublished seizure related to iTBS but that occurred in a stroke patient (i.e., at high risk for seizure). The overall risk for NIBS-related seizure in healthy participants is 0.002% which is well below (500x) the prevalence of epilepsy (1%).

v. Additional Considerations

1. Reproducibility of Task Paradigms

One potential concern related to the present design pertains to the stability of the imaging and behavioral outcomes across repeated assessments. Most of the task paradigms were chosen based on literature suggesting they are relatively resistant to practice effects. For example, in interference tasks such as the Flanker or Stroop, hundreds-to-thousands of trials (or several hours of training) are generally needed before practice effects in behavioral measures can be observed[157-159]. If we assume that behavioral measures remain stable across repeated assessments, particularly error rates, it is also reasonable to assume that neurophysiological correlates of error processing are likely to be unaffected as well. Furthermore, our group has two ongoing

or completed protocols where task reproducibility was not compromised in several of the tasks we will implement here (i.e., Flanker, Stroop, the decision making task, MID, or SSRT). In addition, it should also be noted that participants will receive extensive and repeated training on all tasks throughout the protocol. This training, taking place on multiple days, is expected to help mitigate the impact of in-scanner practice effects on the measures of interest. The presence of a group receiving CM and sham-ITBS will also help control for any practice effects. Nonetheless, potential confound of practice effects will be examined and if observed, may be a potential limitation of the study.

2. Relationship to Other Protocols

All participants in this protocol will first enter the approved NIDA-IRP general screening protocol. Data from the screening protocol will be used to determine eligibility. Every participant in the Expanded Feasibility Study will also be enrolled in protocol 10-DA-N457 to obtain characterization information. Data obtained under the screening protocol and 10-DA-N457 may be shared with this and potentially other protocols.

vi. Statistical Analysis

Behavioral performance measures (e.g., response time, error rate, and hit rate) on each of the cognitive tasks as well as questionnaire data from each of the experimental conditions will be compared both within and between experimental groups using mixed, repeated-measures ANOVA, and linear mixed models. When assessing the statistical results from the behavioral and questionnaire data, a standard α-level of 0.05 will be used. Alpha-levels for multiple comparison follow-up tests will be corrected using an appropriate method (e.g., Bonferroni, Tukey, Scheffe).

Without knowing the final breakdown of completers and non-completers, we cannot definitively outline the planned analyses, but several options are possible. For example, if a substantial number of participants fail to complete 10 iTBS treatment days, this group could be included as a separate group for comparison. Further analyses with this group would depend on the characteristics of the group vis a vis the 10 iTBS treatment

day completers. On the other hand, if most participants fail to complete 10 iTBS treatment days, all participants who complete five days of treatment would be considered in the final analysis and the number of iTBS treatment days would be included as a covariate. In the end, the protocol allows for data collection to be maximally flexible while allowing the measurement of iTBS efficacy in treating cocaine use disorder.

An outline of proposed imaging analysis steps is presented below. Current techniques are outlined with the understanding that while these data are collected, new analysis techniques may be developed. These new techniques may be better suited to answer our questions with the data collected. Therefore, the specific analyses carried out at the end of this protocol are subject to change to reflect the most advanced and appropriate analysis techniques available.

The imaging data will be pre-processed and analyzed with Analysis of Functional Neuro-Images (AFNI[160]). All functional images will be directly registered upon high resolution MPRAGE anatomical scans obtained during the same imaging session. Location and intensity of activations from individual and/or grouped data will be translated into 3D stereotaxic coordinates[161]. Functional images of activation-induced BOLD signal changes will be determined using cross correlation or multiple regression analyses[162, 163]. The specific statistical analyses to be performed on the fMRI 3-D datasets will be dictated by the nature of the factors involved and the specific scientific question addressed. For example, ANOVA models (*3dANOVA, 3dANOVA2, 3dANOVA3*) can be used to test for differences between participant groups or iTBS condition. Differences in structural and functional measures between CD and HC participants will be assessed using between group comparisons (e.g., independent samples t-tests). Differences within the CD group across sessions will be assessed using within group comparisons (e.g., dependent samples t-tests). Correlation and multiple regression approaches will be used to test for an association between clinical assessment measures and task-specific neural measures (e.g., correlation between cocaine craving scores and neural activation in the striatum).

Each of the cognitive task paradigms was chosen to tap into specific psychological constructs and neural substrates that have been shown to be associated with cocaine dependence. Across each paradigm there are multiple dependent variables (i.e., RT, error rates, and neural signal) that will be examined to assess for effects with CD participants and contrast with HC participants. The initial independent variable of interest is the group variable, used to assess for differences between CD and HC participants. A simple independent samples *t*-test can be used to detect differences. Paired samples *t*-tests will be used to determine differences between active and sham iTBS conditions, as well as between longitudinal MRI measures. Ultimately, more advanced factorial designs will be used to explore differences between groups and sessions. The selected paradigms have overlapping neural circuitries. Although the primary analyses are conceived of as separate studies, the secondary analyses will integrate the results from each of the paradigms. These secondary analyses will be used to gain a more complete understanding of the neural circuitries involved in goal directed behavior and decision making in control populations as well as factors leading to addiction, drug seeking behavior, continued abstinence, and possible relapse in drug-addicted populations.

For MRI analyses, the AlphaSim program (within AFNI) will be implemented to correct for multiple comparisons. AlphaSim is a Monte Carlo simulation technique that provides a method for multiple comparison correction while persevering statistical power. Using random image generation, Gaussian filtering (to simulate voxel correlations), thresholding, and tabulation of cluster size frequencies, the program generates an estimate of the overall significance level achieved for various combinations of probability and cluster size thresholds assuming spatially uncorrelated voxels. Overall, simulations using this program indicate that by accepting a minimum cluster size it is possible to obtain an order-of-magnitude improvement in probability threshold over the value of probability threshold required if cluster size thresholding is not used.

General fMRI power. Since fMRI is the main outcome measurement utilized in the present protocol, the key power analysis pertains to the fMRI data. However, prospective power analyses for fMRI data are complicated for several reasons. First, fMRI data are analyzed in a hierarchal manner such that both the *intra*-participant variance from the time-course data and the *inter*-participant variance across individuals could affect statistical power. A large number of time points tend to mitigate effects of intra-participant variance, but temporal autocorrelation and scanner limitations limit the number of independent measurements per unit time and thus the number of independent time points that are collected. In addition, effect sizes and both types of variance will vary spatially. Because of this, a given study may have sufficient power to detect differences in some brain regions, but lack sufficient power in other regions where the null hypothesis is false. Finally, fMRI analysis consists of a very large number of non-independent multiple comparisons, greater than 1.5 million at the group level, necessitating correction methods less severe than a Bonferroni correction, as discussed above. Thus, a proper power analysis on fMRI data requires simulating all of these effects. Desmond and Glover[164] have performed such a simulation. They show for a relatively modest signal change of 0.5% during a cognitive task and with an intra-participant standard deviation of 0.75% and an inter-participant standard deviation of 0.5%, that 11 participants are required for a power of 0.8 using $p < 0.05$. Using a false positive rate of $p < 0.002$, a level more consistent with a cluster size threshold to correct for multiple comparisons[165], and with the variances kept the same, approximately 21 participants are needed for an expected signal change of 0.5% and 11 participants for a signal change of 0.75%. For more than ~100 independent time points, power (and hence the intra-participant variance) is relatively independent of the number of time points[164]. All current analyses should fall within this range.

There are no published reports of the effects of chronic application of iTBS in cocaine users with functional connectivity measures on which to base a power analysis and the acute effects of iTBS on functional connectivity alterations are not relevant to our study as we seek to understand neural changes after *chronic* application of iTBS.

Nonetheless, there is a single published report in a sample of participants with major depression where functional connectivity was measured pre- and post-rTMS treatment [166]. In this report, the mean functional connectivity pre-TMS (0.38 z-scored connectivity) was greater than post-TMS (0.22 z-scored connectivity) with an average standard deviation of 0.17 z-scored connectivity. We calculated the effect size to be 0.91. This effect size is likely unrealistically high due to 'double-dipping' in their analyses[167], a small sample size, and publication bias toward significant effects, all of which affect the effect size calculation and generalizability.

To better assess a more realistic effect size based on these findings, we simulated an effect size (N =10,000) based on the published means and standard deviations. The effect size that falls 1 standard deviation below the mean was 0.64. This effect is remarkably close to a published report comparing functional connectivity between healthy controls and cocaine users[44] without a TMS intervention (calculated effect size of 0.67).

Together, when assessing functional connectivity differences post-iTBS treatment between active and sham groups, we conservatively select an effect size 0.65 to capture a reliable effect while reducing the likelihood of committing a Type II error and a power level (1-β) of 0.8 to achieve an appropriate balance between the ability to detect significant differences and the number of participants needed. Therefore, for power analysis calculations (i.e., Statistical Analysis Plan), we anticipate a mean functional connectivity measure post-iTBS for the sham group to be 0.210 z-scored connectivity and active group to be 0.405 z-scored connectivity with a standard deviation of 0.299 z-scored connectivity, which produces an effect size of 0.65 and an estimated sample size needed per group to be 30 with a one-tailed *t*-test assuming a *p*-value of .05. We anticipate approximately 60% retention rate by visit 19, based on previous NIDA protocols. Therefore, 100 CD participants will be recruited at baseline, 45 active and 45 sham iTBS, to acquire the necessary 30 participants in each group for analysis.

IV. COLLECTION AND STORAGE OF HUMAN SPECIMENS OR DATA

Paper copies of research records such as 'Run Sheets' (i.e., procedural checklists) will be kept in study-specific binders kept in a locked cabinet, in a limited access locked room. Binders remain in this room at all times, apart from when required for study sessions. At the completion of each session paper records will be returned to the locked cabinet by the investigator or research associate responsible for the experimental session. Electronic research records and/or data (e.g., physiological, imaging, behavioral) obtained during experimental sessions is stored on password protected, network drives, or other secure application (e.g., CDW, RedCap, Qualtrics) in line with NIH policies, which have limited access. Data stored on these drives is identified by study number, participant ARC and/or task. No personal identifiers are stored with the data. Data will be stored indefinitely. Urine samples acquired for measurements of pregnancy and drug usage will be destroyed once valid assays have been obtained.

A. Genomic Data Sharing (GDS)

This protocol does not meet criteria to require a GDS plan.

B. Human Data Sharing (HDS)

The proposed research will include data from approximately 170 participants being screened for substance use disorders in the Baltimore, Maryland area. The final dataset will include self-reported demographic, behavioral, and imaging data and laboratory data from urine specimens provided. Because of the longitudinal nature of this protocol, we will be collecting identifying information. Even though the final dataset will be stripped of identifiers prior to release for sharing, we believe that there remains the possibility of deductive disclosure of subjects with unusual characteristics. Thus, we will make the data and associated documentation available to users only under a specific data-sharing agreement that provides for: (1) a commitment to using the data only for research purposes and not to identify any individual participant, (2) a commitment to securing the data using appropriate computer technology, and (3) a commitment to destroying or

returning the data after analyses are completed. Sharing will be limited to NRB protocols (current, future, and those in the repository) and restricted access to personnel with access to CDW and NRB network. No data with leave NIH without first obtaining a transfer agreement and IRB approval or OHSRP exemption. No additional funds are needed for this plan.

C. Participant Safety Monitoring

The NIBS monitoring questionnaire (Appendix 1), Trails A and B (Appendix 22), and staff observation and interactions with participants will be assessed daily. A NIDA-IRP physician or Physician's Assistant knowledgeable about iTBS will be immediately available in the building whenever iTBS is administered and will be available by telephone or pager 24 hours a day for consultation or in the event of a medical emergency. If immediate medical intervention is required, the participant will be referred to an appropriate medical facility. Information on all adverse events will be cumulated and reported to the NIH IRB with each continuing review application. Unexpected or serious adverse events (defined in accordance with NIH and NIDA IRP policy) will be promptly reported to the NIDA Clinical Director and IRB in accordance with NIH and NIDA IRP policy.

Seizure monitoring procedures: Participants will be monitored throughout each iTBS session for signs of seizures such as involuntary muscle movements or loss of consciousness. In the event of a seizure, staff will have immediate access to life support equipment and anti-seizure drugs. In the event of a seizure, the procedure outlined below[129] will be followed:

1. Protect patient's head and limbs from injury.
2. Ensure an adequate airway.
3. Call 911 to have the patient transferred to Johns Hopkins emergency room, if the seizure requires medication intervention to resolve or is otherwise clinically indicated.
4. Observe Patient for:

a. Initial movements/ sensations.
b. Progression of movements.
c. Change in respiratory status
d. Skin color
e. Incontinence
f. Level of consciousness
g. Ability to communicate
h. Level of orientation
i. Duration of seizure activity

If after two minutes, the seizure has not resolved, administer: midazolam IM, 10 mg that is contained in a lock box in the TMS suite.

5. Provide supportive care after the seizure resolves.
6. Orient patient to time and place.

Session video recording: If a potential adverse event occurs during iTBS stimulation, video footage of the session can help determine the nature of the incident. Thus, video will be recorded during threshold determination and during iTBS, barring any technical difficulties with recording instrumentation. If the session progresses without incident, this footage will be deleted within a week. Otherwise, during sessions with abnormal events, the video will be retained in accordance with NIH Records Management policy (https://oma.od.nih.gov/DMS/Documents/Records/NIH_Intramural_Research_Records_Schedule.pdf) for 7 years after the completion of the study or when no longer needed for scientific reference, whichever is longer. This footage may be used by the MAI and any experts the MAI wishes to consult to determine the nature of the event. Participants will not be given the option to opt out of the video recordings. If they do not wish to be recorded, the alternative is to not participate in the study.

MRI: At screening and on each study day involving an MRI scan, participants will fill out an MRI safety form to ensure that there is no change in the participant's suitability for MRI scanning. They will also have a urine drug screen and pregnancy test (females).

If urine drug screen is positive for drugs other than cocaine and THC, they will be rescheduled; if pregnant, females will be notified, referred if necessary for care, and discontinued from participation in the study. At all times during MRI scanning study, a scan operator will be present in the control room and participants will be able to communicate via an intercom. Participants will also have a device they can squeeze to alert the operator in case of an urgent issue.

Acute clinical needs: 'Red flags' observed during clinical assessments will be used to identify acute clinical needs. The first-level evaluation is participant interaction with a nurse at intake. NIDA nurses are well trained to identify abnormal behavior that may need immediate clinical attention. When such behavior is identified, a flag will be generated and the MAI will be contacted. A second flag level is programmed into the CDW system to be triggered if a participant endorses a specific state. The LAI will routinely review CDW files for such flags while the participant is at NIDA-IRP. A failsafe mechanism is in place such that remuneration cannot be disbursed with an unaddressed red flag. Therefore, participants who endorse specific states during a visit will be identified and assessed by clinical staff prior to discharge for the day.

Endorsing suicidality on the MADRS is an example of a red flag. If a participant endorses this state while the MADRS is administered, a flag is generated, and usually addressed immediately by the clinician administering the MADRS. If a participant reports suicidal thoughts, the CDW Critical Item Alert System will be initiated following the NIDA SOP. Participants may also endorse acute states of depression or mania while participating in this study. Sleep patterns will be tracked to assess potential sleep deprivation. Significant sleep deprivation, or lack of sleep, may have a clinical impact on participants. If this occurs, the LAI will initiate the intervention protocol. This intervention may include referral and/or discharge from the study if clinically significant.

i. Primary Saftey Endpoints and Associated Stop Rules

Three outcomes will be monitored throughout the study as safety endpoints associated with a stop rule. As described below, we will track iTBS-induced seizures,

neurocognitive function, and clinically significant adverse events requiring outside evaluation. Chi-square tests will be calculated to test frequency differences between groups (active iTBS vs sham iTBS) for each of these endpoint measures. Each **stop rule** is described in detail below.

1. **Number of iTBS-induced seizures:** more than 1 iTBS-induced seizure resulting in hospitalization within any 10 consecutive participants who receive iTBS will result in a protocol hold until further evaluation by the PI, FDA, and DSMB. The Blind will be broken for any participant with an iTBS-induced seizure. We will also consult Dr. Alexander Rotenberg, M.D., Ph.D., Director, Neuromodulation Program within the Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston's Children's Hospital and Associate Professor of Neurology at Harvard Medical School. Dr. Rotenberg is a member of our DSMB and possesses the necessary clinical expertise to evaluate the proposed safety endpoints. No new iTBS sessions will be administered to any participant once this stop rule is enacted until evaluation of the events is concluded and it is deemed appropriate to proceed. However, participants who have completed their iTBS treatments may be scheduled for Contingency Management (CM), MRI scan, or follow-up visits.
2. **Cognitive performance on Trails B:** Neurocognitive function will be assessed with Trails A and B before and after each iTBS day. Although Trails A and B are usually administered in sequence, **only Trails B** will be evaluated in relation to this stop rule. A completion time for Trails B greater than 90 seconds[169] is considered abnormally long. Therefore, **if a participant requires more than 90 seconds to complete Trails B after iTBS, the following steps will be taken:**
    a. The participant will rest and be observed for 60 minutes after completion of post-iTBS Trails B.
    b. Trails A and B will be administered again after the 60 minute timeout period.

c. A score to complete Trails B a second time greater than 90 seconds will call for the MAI (or covering clinician) to evaluate the participant.
d. If the MAI (or covering clinician) deems outside evaluation or treatment is necessary, the participant will be discharged from the study and appropriate steps will be taken to seek an outside evaluation/intervention (e.g., an ER visit). The Blind will be broken for this participant at this time.

If more than 1 neurocognitive event identified with Trails B is seen within any 10 consecutive participants, the protocol will be put on hold until further evaluation by the PI, FDA, and DSMB. As above, Dr. Rotenberg will be consulted for his evaluation of the stop rule; CM, MRI scan, and follow up visits, may continue but iTBS will not be administered until the hold is resolved.

3. **Clinically significant adverse events (**i.e. **adverse events that require referral for further evaluation) likely related to iTBS.** For example, a mild headache after iTBS that resolves spontaneously or with over-the-counter medication will not be considered clinically significant. A severe headache that starts during or shortly after iTBS and fails to resolve with time and/or OTC intervention would prompt referral to an Emergency Department and will be considered clinically significant.
    a. If more than 1 clinically significant adverse event related to iTBS administration and having similar clinical features is seen within any 10 consecutive participants, the protocol will be put on hold until further evaluation by the PI, FDA, and DSMB. As above, Dr. Rotenberg will be consulted for his evaluation of the stop rule; CM, MRI scan, and follow up visits, may continue but iTBS will not be administered until the hold is resolved.

ii. Clinical Efficacy Cocaine Use Endpoint

1. **Clinically significant worsening of cocaine use behavior will be evaluated and monitored as follows:** Although neuroplastic changes in brain activity assessed with fMRI is our primary outcome variable of interest, we will measure cocaine use behavior (Appendices 13: Cocaine use, Pattern, and Withdrawal Questionnaire, & 21 Time-Line Follow back) at baseline and longitudinally throughout the protocol. Among the cocaine use behaviors assessed is maximum dollar amount spent during the longest lifetime binge. Chi-square tests will be calculated to test frequency differences between groups (active iTBS vs sham iTBS) for this endpoint measure. If a participant reports a binge amount in dollars that exceeds 3 X the greatest binge dollar amount, the following steps will be taken:
    a. The iTBS treatment for this participant will be paused
    b. The participant will be scheduled to return the next day for further evaluation, which will include reassessment of cocaine use behavior
        i. If the participant reports continued excessive cocaine binge behavior, the participant will be referred for alternative treatment. The Blind will be broken for this participant at this time.
        ii. If the participant reports a return to their normal cocaine use pattern, they will be scheduled for further evaluation in about 1 week.
    c. After about 1 week, cocaine use behavior will be re-assessed.
        i. If the participant reports further episodes of excessive cocaine binge behavior, the participant will be referred for alternative treatment. The Blind will be broken for this participant at this time.

ii. If the participant reports a return to their normal cocaine use pattern, they will be allowed to continue in the study. Their treatment schedule will be resumed at this point.

As soon as the increase is noted and at each follow-up visit, the MAI (or covering clinician) will assess precipitants to the change in cocaine use behavior to ascertain whether a significant life-event (e.g., death of a family member) could be related to a spike in cocaine use behavior (vs. the iTBS itself). Detailed evaluation of the situation is necessary to understand the clinical ramifications of continuing, or discontinuing, the iTBS administrations. If, at any point, the MAI (or covering clinician) concludes that iTBS was likely responsible for the change in cocaine use, the participant will not resume iTBS treatments.

If the participant has a second episode of excessive use in excess of 3 X their previous greatest binge dollar amount after resuming iTBS treatments, they will be discharged and referred for alternative treatment.

Participants who are to be discharged and referred for alternative treatment will be followed as clinically indicated for up to one month to track their clinical course and facilitate transfer to alternative treatment. The participant will be discharged at this point.

If more than 1 clinically significant worsening of cocaine use behavior is seen within any 10 consecutive participants, the protocol will be put on hold until further evaluation by the PI, FDA, and DSMB. As above, CM, MRI scan, and follow up visits may continue but iTBS will not be administered until the hold is resolved.

All research staff who administers iTBS to participants must meet the following training requirements:

1. Bachelor’s degree (or higher) in psychology or a biological or social science, with at least 6 months experience working in clinical research.

2. Certification in basic adult life support.
3. Working knowledge of the principles and practices of iTBS and the iTBS device being used in the study, including common side-effects and how to recognize them. Knowledge will be based on completing assigned readings given by the investigators and tutorial sessions with the investigators. Adequate level of knowledge will be assessed by passing (80% correct) a written examination constructed by the investigators.
4. Knowledge of the location of the emergency equipment and medication and how to engage the emergency response system. Only staff with the appropriate education, training, licensure, and certification will provide medical care or supervision to participants.
5. Practical demonstration of ability to perform 5 determinations of the RMT, under the supervision of a doctoral-level investigator or iTBS consultant before performing any iTBS procedures,
6. Performing the first 2 iTBS study sessions under the supervision of a doctoral-level investigator experienced in iTBS or the iTBS consultant identified above.

D. Consent Process

Informed consent will be obtained from each participant at entry into the study. The consent document will include details regarding all study procedures (e.g. iTBS and fMRI). The participant will be provided with the study consent form and instructed to review it prior to the consent session. An investigator authorized to obtain consent then meets with the participant in a private area to review the consent and confirms the participant understands the consent and answers any questions. Alternatively, the investigator may conduct the verbal review of the consent form via an encrypted video chat type program approved by NIDA's ISSO. The method of consent review will be determined at the discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject

will be maintained. When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Once the participant verbally demonstrates understanding to the investigator and agrees to the process, a consent quiz is administered. they are asked to sign and date the consent form. The investigator co-signs the consent form. The signatures may be hand written or obtained on an electronic consent form with a finger, stylus, mouse or the like. The signed consent and quiz will be a part of the participant's medical record and the participant will be given a copy of the consent form for his/her own records. Once the signed consent has been obtained, the investigator will note the participant's enrollment in the study in the CDW database. Only after this last step has been completed will study procedures begin.

Four consent documents, containing all required elements, are submitted with this protocol: Pilot: inpatient volunteers (Consent 1, 2: archived); 3) Expanded Feasibility Study: CD volunteers; 4) Expanded Feasibility Study: HC volunteers.

The informed consent document will be provided as a physical or electronic document to the participant as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomfort and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors as applicable, and to ask questions of any designated study investigator.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per the discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant, when in person) will be located in a private area (e.g., study room). When

consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed. Whether the consent process is in-person or remote, participants and investigators may view individual copies of the approved consent document or the same copy (e.g., the investigator may share their screen with the participant onsite or remotely).

Once the subject verbally demonstrates understanding to the investigator and agrees to the process, a consent quiz is administered. Participants will be required to correctly answer questions #5 and #7 of the quiz in order to be in the study (#5 states “I cannot be in this study if I have certain types of metal in your body (**T**/F)” and #7 states “I cannot withdraw from the study once I sign the consent form (T/**F**).” If the score on the consent quiz is less than 80% correct or the questions #5 and 7 are answered incorrectly, the investigator will review the incorrect answers with the participant and re-administer the consent quiz. Provided the participant scores at least 80% correct, the participant is invited to be consented. If the score on the quiz is less than 80% correct, the investigator will review the quiz results and clarify incorrect answers, then re-administer the consent quiz. Failure to obtain 80% correct with questions #5 and 7 also answered correctly on the second administration of the quiz excludes the participant from participating in the study. If the participant does score ≥ 80% on the consent quiz and questions #5 and 7 are also correct, they will be invited to sign the consent.

A signed informed consent document will be obtained prior to any research activities taking place. Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to the participant) or on the electronic document. Electronic signatures (i.e., the “signature” is digitally generated) will not be used. When a hand signature with a finger, stylus, mouse, or the like on an electronic document is used for the documentation of consent, this study will use one of the following electronic platforms to obtain the required signatures:

- Adobe Acrobat platform (which is not compliant with 21 CFR Part 11);
- Foxit (which is not compliant 21 CFR Part 11);

• DocuSign (which is not compliant 21 CFR Part 11);

The participant is provided a copy of the signed consent form for his/her own records. Enrollment is documented in the participant's electronic research record.

E. Rational for Participant selection

Participant selection will be based strictly on the inclusion and exclusion criteria. No preferences in participant recruitment will be made on the bases of gender, race, or ethnic background. Participants will be recruited from the local community. A sample comprised largely of Black or African American males is anticipated based on previous IRP studies recruiting cocaine dependent participants from the Baltimore area. However, all interested, eligible participants may be recruited and enrolled. The ethnic and racial summary reported below is based on the Treatment Episode Data Set[170] statistics of cocaine use in Maryland.

REQUESTED – PILOT STUDY POPULATION (Completed)						
	TOTAL ENROLLMENT REQUESTED			# COMPLETERS REQUIRED		
	FEMALE	MALE	**TOTAL**	FEMALE	MALE	**TOTAL**
CEILING	9	11	20	4	6	10

PILOT NIH TARGETED/PLANNED ENROLLMENT			
ETHNIC CATEGORY	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	0	0	0**
Not Hispanic or Latino	9	11	20
Ethnic Category: Total of All Participants*			20*
RACIAL CATEGORIES			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	5	7	12
White	4	4	8
Racial Categories: Total of All Participants*	9	11	20*

*The “Ethnic Category: Total of All Participants” must be equal to the “Racial Categories: total of All Participants.”

EXPANDED FEASIBILITY STUDY POPULATION						
	TOTAL ENROLLMENT REQUESTED			# COMPLETERS REQUIRED		
	FEMALE	MALE	**TOTAL**	FEMALE	MALE	**TOTAL**
CEILING	45	90	135	33	67	100

EXPANDED FEASIBILITY NIH TARGETED/PLANNED ENROLLMENT			
ETHNIC CATEGORY	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	1	2	3**
Not Hispanic or Latino	44	8	132
Ethnic Category: Total of All Participants*			135*
RACIAL CATEGORIES			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	27	54	81
White	18	36	54
Racial Categories: Total of All Participants*	45	90	135*

*The “Ethnic Category: Total of All Participants” must be equal to the “Racial Categories: total of All Participants.”

Justification for excluding individuals older than 60 years of age: Many cognitive processes change with age. In addition, the risk of difficult-to-detect medical abnormalities such as silent cerebral infarcts increases with age.

Justification for excluding Left-handed individuals: Some of the neural processes assessed in this protocol may be lateralized in the brain. In order to reduce potential variance, participants will be required to be right-handed.

Justification for exclusion of children: Children will not be included in the present study. This study focuses on cocaine dependence which generally necessitates participants have years of experience with cocaine and are over the age of 22. Therefore, children under the age of 22 will not be recruited.

Justification for exclusion of vulnerable population: There will be no inclusion of vulnerable populations in the current study. The study focuses on the effects of iTBS as an intervention to reduce cocaine use in CD participants using a diverse range of affective, cognitive, behavioral and neurobiological indices. To control for variance in these domains we need to exclude individuals suffering from mental illness, intellectual impairment or any other condition that may affect neurological functioning (e.g. HIV). Pregnant women are also explicitly excluded due to the unknown risks that iTBS and MRI poses to the unborn fetus.

Safeguards for vulnerable populations: Measures of intellectual functioning, mental health and HIV screening will be conducted under the approved NIDA IRP general screening protocol and used in the current protocol to identify and exclude individuals in vulnerable populations. Urine and/or blood serum pregnancy testing will also be employed in the current protocol to screen for pregnancy.

V. EVALUATION OF RISKS/DISCOMFORTS AND BENEFITS

A. Anticipated Benefit

CM is designed to help CD participants reduce their drug use throughout treatment. The iTBS administration is an experimental manipulation in this study and could yield generalizable knowledge about its potential therapeutic application as a treatment in drug abuse.

B. Risks and discomforts

i. Experimental Tasks

Participants may find the tasks that they are asked to perform during, before, and after scanning sessions boring, difficult, and/or frustrating.

Risk Minimization. In order to reduce discomforts associated with performing the experimental tasks, scanning sessions, and task sessions outside of the scanner are organized in such a way that participants will not perform tasks for extended periods of time and will be given a chance to rest between tasks. In addition, the tasks are designed to make performance neither too difficult nor too easy. Ideally, individual adjustments of task difficulty enable participants to remain actively engaged in the task.

ii. iTBS

iTBS is similar to rTMS which has has been considered “non-significant risk” by the FDA when applied at similar intensities, durations, and frequencies to those outlined in this protocol. Therefore, previous adverse events from rTMS are reviewed as potential risks for implementing iTBS.

1. Magnetic stimulation

iTBS uses magnetic pulses, and could therefore interfere with the function of pacemakers, implanted pumps or stimulators. Moreover, the use of magnetic pulses over the head could affect metallic objects inside the eye or skull. The effects of magnetic stimulation on fetal development are unknown.

Risk minimization: Participants will undergo TMS safety screening and will be excluded from participation if they have pacemakers, implanted pumps or stimulators, and metal objects inside the eye or skull. If they have a question about any metal objects being present in their body, they will be prompted to inform the physician. In addition, all magnetic objects (for example, watches, coins, jewelry, and credit cards) must be removed. Women of childbearing potential will have a weekly pregnancy test during iTBS treatment and each day of an MRI scan and pregnant women will be excluded.

2. Seizure

The greatest concern with iTBS treatment is the possibility of inducing a seizure. The Pilot was successfully completed without seizures. The tolerability parameters implemented in the study are well within recommended applications of iTBS, a form of TMS which has substantial published guidelines. The 1996 and 2008 International Consensus Safety Guidelines describe the maximum safe duration of an rTMS train based on intensity and frequency of the stimulation[131]. Since the issuance of these guidelines, the incidence of TMS-induced seizures worldwide is very low, estimated as "rare" [131]. There have been no reports of any participant developing epilepsy or repeated spontaneous seizures after rTMS. All rTMS-induced seizures to date have been transient and self-limiting, without long-term sequela[131, 132]. Concurrent medication has been implicated as a risk factor in some of the seizures reported with rTMS. Some have suggested that certain medications (e.g. tricyclic antidepressants and neuroleptics), should be contra-indicated in those receiving rTMS[131].

Risk Minimization: There is a small risk of seizures from iTBS; nonetheless, participants will be thoroughly monitored first in the Pilot (completed) then in the Expanded Feasibility Study to guard against potential negative effects of iTBS. Participants will undergo screening which will exclude those with a family history of epilepsy, participants who take medication that can affect the seizure threshold, and participants with recurring fainting spells. Psychotropic medications and use of illicit drugs (other than cocaine) associated with a reduction in the seizure threshold will also be exclusionary in this study. All staff administering iTBS will be trained in BLS. A physician or physician assistant will be available in the building while iTBS sessions are in progress and will be called in the event of any medical issue.

3. Vasovagal Syncope

A small number of vasovagal syncopes have been reported following rTMS stimulation. In a number of the reports on rTMS-induced seizures, it is unclear whether the event was a seizure or syncope[131].

Risk minimization: Participants undergo screening and are not admitted to the protocol if they have a history of fainting from an unknown cause. All staff administering iTBS will be trained in BLS. A physician or physician's assistant will be available in the building while iTBS sessions are in progress and will be called in the event of any medical issue. Throughout each study day containing a TMS/iTBS session, staff will regularly check with the participant for well-being and encourage them to report possible symptoms such as feeling faint.

4. Scalp Pain, Headache, and Other Minor Symptoms

Mild headache responding readily to non-opioid analgesics is the most common side-effect of iTBS reported in depression treatment trials. It may result from direct stimulation of superficial facial muscles or nerves and cause an uncomfortable facial twitch[132]. However, discomfort levels are quickly habituated to and painful sensations over the scalp decrease over sessions[70, 72]. In rTMS sham-controlled studies that reported rates of side-effects, about 28% of participants experienced headache and 39% experienced pain or discomfort during stimulation, compared with rates of 16% and 15%, respectively, after sham rTMS[132]. In a single case report, a 57-year-old women being treated for major depressive disorder reported a pulsating, localized dental twinge in the region of the upper left jaw associated with the rTMS treatment[173]. The pain disappeared during the inter-train interval but emerged again during the next train of stimuli. The pain was dependent on the stimulus intensity and remained despite repositioning of the coil. The cause of the pain is unclear, but may be due to stimulation of the trigeminal nerve by the rTMS magnetic field. An event will be reported as an adverse event when its severity either requires interruption of the normal flow of experimental procedures or requires a medication intervention.

Risk Minimization: Participants generally find iTBS more tolerable than rTMS which is widely used. In this expanded feasibility study, we are retaining the parameters that were used in the pilot study. This includes extensive monitoring and safeguards will be in place to assess any transient or long-term

uncomfortable side-effects of iTBS. Headaches and scalp pain usually go away promptly with nonprescription medication, such as acetaminophen. Coil heating will be avoided in the present study by using a cooled coil and by allowing the coil to cool off between treatment sessions. If a participant reports dental pain, iTBS will be stopped. Acetaminophen or other medications may be provided for treatment of pain, if necessary.

5. Acoustic Noise

Rapid excitation of the stimulation coil produces clicks that have resulted in transient increase in the auditory threshold of human participants. This should not occur if earplugs are used. Others have measured auditory thresholds with rTMS which we will use for our iTBS administration. Auditory thresholds were measured before and after 30 sessions of rTMS have been assessed given over 6 weeks in a depression treatment trial[174]. All participants wore earplugs during stimulation. No significant mean changes in hearing threshold were detected. Two participants showed small bilateral increases in threshold at mid to high frequencies, which returned to previous levels when retested 1 month later. FDA guidelines require testing of auditory threshold only if participants receive rTMS at a frequency higher than 1 Hz for four or more weeks. Auditory threshold will not be monitored in the current proposed study.

Risk Minimization: Participants will be fitted with earplugs to wear during the study to protect their hearing from the noise of the magnet. Participants with known hearing loss will be excluded. Investigators will ask each participant to report immediately any loosening or detachment of the earplugs during application of iTBS. If a participant reports or if an investigator observes that the earplugs have loosened or fallen out, investigators will immediately stop applying iTBS.

6. Other Complications

rTMS over dorsolateral prefrontal cortex has induced manic and hypomanic symptoms in a very small number of healthy and depressed participants. Three female participants reported hypomanic symptoms after single session of rTMS without a prior history of mood disorder[175]. Stimulation parameters were comparable to those used in depression treatment studies and studies of mood changes in healthy participants. Mild hypomania was reported in a patient with refractory recurrent unipolar depression[77]. This female patient had responded well to previous shorter courses of rTMS, but became hypomanic after nine treatment sessions in the third course. The hypomanic symptoms resolved when rTMS was reduced to treatment every second day. A 55-yr-old depressed male became hypomanic for the first time after 3 weeks of twice daily rTMS to the left dorsolateral prefrontal cortex and concomitant citalopram[176]. Over the following week, medication was stopped, but rTMS continued. His symptoms deteriorated into mania and rTMS was also stopped. The patient gradually became depressed again and five months later, a second course of 2 weeks of twice-daily rTMS also resulted in hypomania. Treatment intensity was decreased to once-a-day TMS treatment, and the patient returned to a normothymic state. rTMS may also have a therapeutic effect in mania, with high-frequency application to the right prefrontal cortex[177].

We are aware of six reports of mania induced by rTMS in patients with bipolar disorder[176, 178-181], in some cases while taking mood-stabilizing medications. In a trial of right prefrontal rTMS for post-traumatic stress disorder, two patients developed a manic episode after the third session[182]. One patient was randomized to 1 Hz rTMS and one to 10 Hz. Another participant in this trial developed a ‘mild rage attack, probably related to the stimulation’. Apart from manic symptoms, there is a single case report of high-frequency left prefrontal rTMS inducing transient persecutory delusions in a depressed, non-psychotic participant[183].

In all the above cases, the psychiatric side-effects induced by rTMS were transient, resolving with the cessation of rTMS or rapidly responding to pharmacological treatment.

Risk Minimization: Reports of manic symptoms occurred exclusively after unilateral or bilateral DLPFC stimulation but the risk for psychiatric complications appears to exist predominantly in participants with pre-existing psychiatric morbidity (all except one report), and in patients who are on antidepressants or antipsychotics. An important means of minimizing risk in the current proposed study is therefore to exclude this population. Participants will be informed of the small risk of transient mania or hypomania, informed of early symptoms to look out for, and instructed to contact the study physician if they believe they are experiencing any such symptoms.

iii. MRI scanning

1. Magnetic Field

When used on appropriately qualified individuals, MRI presents virtually no risk as long as technical scan parameters remain within FDA guidelines. There is no exposure to x-rays or radioactivity. The radio waves used have produced burns (most of these minor) in about one in a million exams. The field of the 3T scanner is higher than that of most clinical magnets and there is a remote chance of other risks associated with the stronger magnetic field that might include temporary dizziness with nausea and flickering light sensations. The magnet may move metal implants in the body, the motion of which could be painful and harmful. Metal implants may also cause burns from the radio frequency energy used. While inside the magnet, participants may experience an acute panic attack due to claustrophobia. Participants may also experience mild, remittable discomfort from lying in the scanner.

Risk Minimization. To ensure adherence to FDA guidelines for MRI, a trained MRI operator who has been instructed in these guidelines performs all machine manipulations. Other preventative measures include assuring that all equipment to be used during imaging sessions is MR compatible, that participants are familiar with the MRI environment (using the mock scanner), and that participants are aware of how to signal the MR operator if they need to do so during the

session. Furthermore, participants are screened prior to each MRI session for any MR contraindications, including metal implants, pregnancy, fear of small, enclosed spaces, and inability to lie still for prolonged periods of time.

2. Acoustic Noise

The sound generated by an MR system usually consists of a series of repetitive pulses. Acoustic noise is a result of the mechanical vibration produced by the gradient coils when the large currents are applied to them to create time varying imaging gradient fields. Some participants may experience temporary, reversible shifts in hearing threshold after MRI.

Risk Minimization: MRI compatible headphones and earplugs will be used for hearing protection. The use of these two devices in combination reduces the noise level to levels much lower than those required by the Occupational Safety and Health Administration (OSHA) regulations (Occupational Noise Exposure – 1910.95, www.osha.gov) regulations for lifetime exposure, and provides effective hearing protection for the participants. Nevertheless, some participants may experience temporary, reversible shifts in hearing threshold after MRI.

iv. Mock Scanner

Potential side effects associated with the mock scanner include mild backache from having to lie still for a prolonged period of time, temporary difficulty hearing soft sounds after the exam, and being uncomfortable being in a small enclosed space.

Risk Minimization. Pre-study screening for history of back problems or claustrophobia will minimize the likelihood of side effect from mock scanning. In addition, participants will be given adequate hearing protection to minimize hearing difficulties resulting from Classification of risk (for the study as a whole).

v. Research Involving NIH Employees as Participants

Potential risks should be considered for NIH staff when participating in an NIH protocol because NIH staff may be a vulnerable class of participants. NIH staff will not be allowed to participate in this protocol.

VI. PROTECTION OF PARTICIPANTS' PRIVACY AND CONFIDENTIALITY

Great care is taken to protect participants' privacy and strict participant confidentiality will be maintained throughout. Participants will be consented in a private setting. Participants will be assigned a code number without personally-identifying information following their first contact in the protocol. This number will be used throughout the experiment and will be on specimen samples, behavioral, physiological archival, fMRI/MRI, and iTBS data. The identity of participants will not be revealed at scientific meetings, in publications or other vehicles of public communication. The PI and co-investigators will use an ID code (e.g., ARC#), which is generated in a secure database on a closed network (Human Research Information System [HuRIS], aka CDW). Access to records in CDW is protected by a system of password-protected accounts and monitored by the Clinical Director (CD). Data downloaded for analysis will be identified only by participant number. A Certificate of Confidentiality is in place for the NIDA IRP and covers this protocol.

A. Medical Records

All medical history information is stored in the CDW database, which is password protected and has limited access. Any paper records are kept in a locked cabinet and access to these files is limited to study personnel, including study investigators, nursing staff and clinicians.

B. Research Records/Data

Paper copies of research records such as 'Run Sheets' (procedural checklists) used by investigators will be kept in study-specific binders. These binders are kept in a locked cabinet, in a locked room, which has limited access. Binders remain in this room at all times, apart from when required for study sessions. At the completion of each session paper records will be returned to the locked cabinet by the investigator or research associate responsible for the experimental session. Electronic research records and/or data (physiological, imaging, behavioral) obtained during experimental sessions is stored on password protected, network drives, or other secure application (e.g., CDW, RedCap, Qualtrics) in line with NIH policies, which have limited access. Data stored on these drives is identified by study number, participant ARC# and/or task. No personal identifiers are stored with the data outside of the participant's clinical research record (CDW).

C. Stored Samples

No biological samples will be stored for future use.

VII. STUDY AGENTS/INTERVENTIONS

This protocol uses iTBS as an add-on treatment intervention. We will use the MagVenture MagPro 100 with MagOption (MagVenture Inc, Alpharetta, GA) machine equipped with a figure-8 coil. This protocol is intended to determine efficacy of iTBS in reducing cocaine use and is participant to CRF Title 21, part 812. An IDE is necessary for this protocol and will be applied for after reviews from SRC and IRB.

The MRI is used as a data collection tool and all sequences and scans conducted are within FDA approved parameters and the scans are not conducted to assess safety or efficacy of the scans themselves.

VIII. PLAN FOR REPORTING UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

NIH OHSRP Policies 801 and 802 (effective July 1, 2019; supersedes SOP 16) will be followed for reportable events and non-compliance.

Please note that the PI is the sponsor for the IDE in this protocol until the sponsorship changes over to the NIDA-IRP's Clinical Director, effective October 1, 2019. The Sponsor will report to the FDA as required.

IX. DATA SAFETY MONITORING PLAN

A. Selection of a Data and Safety Monitoring Mechanism

1. Daily Study Monitoring: Data and safety for this protocol will be monitored by the Principal Investigator and MAI.
2. The FDA has approved an IDE for a "staged study" and reviewed a supplement to the IDE application that contained pilot data (See letter from the FDA). IRB approval of the Expanded Feasibility Study is contingent on the approval from the FDA after review of the pilot data (i.e., up to 20 enrollees to yield 10 participants who complete the two-week iTBS intervention). **[Approved by the FDA December 12, 2018].**
3. Overall Study Monitoring: Data and safety will be monitored by the NIDA-IRP Data and Safety Monitoring Board (DSMB).

B. Frequency of the Monitoring

The DSMB will review after:

1. Five participants complete the Pilot inpatient protocol.
2. Five participants complete the Pilot outpatient protocol. Barring any unforeseen adverse events in the Pilot, recruitment for the Expanded Feasibility Study will commence while the DSMB reviews data collected during the Pilot.
3. Every year, after the first participant receives iTBS treatment in the Expanded Feasibility Study, unless there has not been any iTBS administration in the one year reporting period. However, if that is the case, the DSMB will be notified of the lack of progress with explanation. The DSMB review will be requested one year following the next iTBS administration.
4. If either the primary or secondary stop rules are triggered (described below).

C. Stop or Change Rules

i. Primary Safety Endpoints and Associated Stop Rules

Three outcomes will be monitored throughout the study as safety endpoints associated with a stop rule. As described below, we will track iTBS-induced seizures, neurocognitive function, and clinically significant adverse events requiring outside evaluation. Chi-square tests will be calculated to test frequency differences between groups (active iTBS vs sham iTBS) for each of these endpoint measures. Each **stop rule** is described in detail below.

1. **Number of iTBS-induced seizures:** more than 1 iTBS-induced seizure resulting in hospitalization within any 10 consecutive participants who receive iTBS will result in a protocol hold until further evaluation by the PI, FDA, and DSMB. The Blind will be broken for any participant with an iTBS-induced seizure. We will also consult Dr. Alexander Rotenberg, M.D., Ph.D., Director, Neuromodulation Program within the Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston's Children's Hospital and Associate Professor of Neurology at Harvard Medical School. Dr. Rotenberg is a member of our DSMB and possesses the necessary clinical expertise to evaluate the proposed safety endpoints. No new iTBS sessions will be administered to any participant once this stop rule is enacted until evaluation of the events is concluded and it is deemed appropriate to proceed. However, participants who have completed their iTBS treatments may be scheduled for Contingency Management (CM), MRI scan, or follow-up visits.
2. **Cognitive performance on Trails B:** Neurocognitive function will be assessed with Trails A and B before and after each iTBS day. Although Trails A and B are usually administered in sequence, **only Trails B** will be evaluated in relation to this stop rule. A completion time for Trails B greater than 90 seconds[169] is considered abnormally long. Therefore, **if a participant**

requires more than 90 seconds to complete Trails B after iTBS, the following steps will be taken:

1. The participant will rest and be observed for 60 minutes after completion of post-iTBS Trails B.
2. Trails A and B will be administered again after the 60 minute timeout period.
3. A score to complete Trails B a second time greater than 90 seconds will call for the MAI (or covering clinician) to evaluate the participant.
4. If the MAI (or covering clinician) deems outside evaluation or treatment is necessary, the participant will be discharged from the study and appropriate steps will be taken to seek an outside evaluation/intervention (e.g., an ER visit). The Blind will be broken for this participant at this time.

   If more than 1 neurocognitive event identified with Trails B is seen within any 10 consecutive participants, the protocol will be put on hold until further evaluation by the PI, FDA, and DSMB. As above, Dr. Rotenberg will be consulted for his evaluation of the stop rule; CM, MRI scan, and follow up visits, may continue but iTBS will not be administered until the hold is resolved.

   3. **Clinically significant adverse events (**i.e. **adverse events that require referral for further evaluation) likely related to iTBS.** For example, a mild headache after iTBS that resolves spontaneously or with over-the-counter medication will not be considered clinically significant. A severe headache that starts during or shortly after iTBS and fails to resolve with time and/or OTC intervention would prompt referral to an Emergency Department and will be considered clinically significant.
      a. If more than 1 clinically significant adverse event related to iTBS administration and having similar clinical features is seen within any 10 consecutive participants, the protocol will be put on hold until further evaluation by the PI, FDA, and DSMB. As above, Dr. Rotenberg will be consulted for his evaluation of the stop rule; CM, MRI scan, and follow

up visits, may continue but iTBS will not be administered until the hold is resolved.

ii. Clinical Efficacy Cocaine Use Endpoint

1. **Clinically significant worsening of cocaine use behavior will be evaluated and monitored as follows:** Although neuroplastic changes in brain activity assessed with fMRI is our primary outcome variable of interest, we will measure cocaine use behavior (Appendices 13: Cocaine use, Pattern, and Withdrawal Questionnaire, & 21 Time-Line Follow back) at baseline and longitudinally throughout the protocol. Among the cocaine use behaviors assessed is maximum dollar amount spent during the longest lifetime binge. Chi-square tests will be calculated to test frequency differences between groups (active iTBS vs sham iTBS) for this endpoint measure. If a participant reports a binge amount in dollars that exceeds 3 X the greatest binge dollar amount, the following steps will be taken:
    a. The iTBS treatment for this participant will be paused
    b. The participant will be scheduled to return the next day for further evaluation, which will include reassessment of cocaine use behavior
        i. If the participant reports continued excessive cocaine binge behavior, the participant will be referred for alternative treatment. The Blind will be broken for this participant at this time.
        ii. If the participant reports a return to their normal cocaine use pattern, they will be scheduled for further evaluation in about 1 week.
    c. After about 1 week, cocaine use behavior will be re-assessed.
        i. If the participant reports further episodes of excessive cocaine binge behavior, the participant will be referred for alternative treatment. The Blind will be broken for this participant at this time.

ii. If the participant reports a return to their normal cocaine use pattern, they will be allowed to continue in the study. Their treatment schedule will be resumed at this point.

As soon as the increase is noted and at each follow-up visit, the MAI (or covering clinician) will assess precipitants to the change in cocaine use behavior to ascertain whether a significant life-event (e.g., death of a family member) could be related to a spike in cocaine use behavior (vs. the iTBS itself). Detailed evaluation of the situation is necessary to understand the clinical ramifications of continuing, or discontinuing, the iTBS administrations. If, at any point, the MAI (or covering clinician) concludes that iTBS was likely responsible for the change in cocaine use, the participant will not resume iTBS treatments.

If the participant has a second episode of excessive use in excess of 3 X their previous greatest binge dollar amount after resuming iTBS treatments, they will be discharged and referred for alternative treatment.

Participants who are to be discharged and referred for alternative treatment will be followed as clinically indicated for up to one month to track their clinical course and facilitate transfer to alternative treatment. The participant will be discharged at this point.

If more than 1 clinically significant worsening of cocaine use behavior is seen within any 10 consecutive participants, the protocol will be put on hold until further evaluation by the PI, FDA, and DSMB. As above, CM, MRI scan, and follow up visits may continue but iTBS will not be administered until the hold is resolved.

D. Advanced Plans for Any Interim Analyses and/or Futility Analyses

There are no current plans for interim analyses and/or futility analyses.

E. Information to be Monitored

1. Progress of the study, including assessment of participant recruitment and accrual and adverse events will be reviewed to determine whether there is any change to the risk/benefit ratio of the study. This information will be reported to the IRB at the time of continuing review.
2. Participants will be monitored for adverse events by study staff. Significant as well as mild adverse effects of iTBS stimulation will be monitored through questionnaires (see Appendix 1 & 15; NIBS monitoring questionnaire) before and after each iTBS session. At the start of each session, an events checklist will be asked for (i.e. how often do you experience these symptoms per week, per month?). Moreover, participants will be contacted, as described in the follow-up procedures, and will again be asked the questions from the NIBS monitoring questionnaire. The MAI will confirm that AE's have been appropriately reported and determine whether the risk to benefit ratio has changed.
3. The DSMB will periodically review the study to ensure appropriate safety monitoring measures are followed and to detect unforeseen patterns of adverse events that may indicate the study is riskier than originally assessed.
4. There are no external factors (e.g., developments in the literature, results of related studies, etc.) that may have an impact on the safety of participants or on the ethics of the research study.

F. Communication

1. The DSMB will receive access to information on any adverse events that have occurred as well vital signs from study visits and the results of follow-up assessments to assess post-participation changes in participants' drug use, particularly with regard to cocaine use.
2. The PI will report all adverse events according to established NIH IRB guidelines. The study does not involve any invasive procedures.
3. The PI and/or the CD will report DSMB findings and recommendations to the IRB. A written report will be provided by the DSMB to the CD and PI confirming

their review of the data and summarizing any recommendations. Furthermore, the DSMB will be required to report on any significant trends in the data that are indicative of negative or adverse events to the PI and the office of the CD.

G. Criteria for Study Withdrawal

A participant will be withdrawn from the study if he or she:

1. so requests, or withdraws consent.
2. is an HC participant whom requires study visits to be rescheduled more than twice for positive urine triage.
3. develops an exclusionary medical condition or medical problem, for which, in the MAI's judgment, it is in the participant's best interest to be withdrawn from the study.
4. becomes or is found to be pregnant.
5. Participants withdrawn from the study for any medical concerns will be referred for appropriate medical follow-up.

X. DATA/RECORDS MANAGEMENT

Medical and questionnaire data will be gathered in the CDW, a secure database on a closed network. Access to records in the CDW is protected by a system of password-protected accounts and monitored by the Clinical Director (CD).

Data (physiological, behavioral) obtained during experimental sessions is stored on password protected, network drives, which have limited access. Data stored on these drives are identified by study number, participant code number, and/or task. Some files may also include age, race and gender. No personal identifiers are stored with the data. Imaging data is stored on a password-protected LINUX computer with limited access. Data on this server is identified by participant number only with no other identifying information. These data are backed up nightly to a second secure server.

XI. COMPENSATION

All participants:

Participants will be compensated for their participation following the NIDA-IRP remuneration guidelines. Participants will be compensated for those parts of the study completed. Remuneration rates are summarized in table 3. In addition to the hourly rate ($20/hr for the first hour and $10/hr for subsequent hours each visit), participants will receive the following remuneration: Participants will be given their choice to have transportation provided or to have travel expenses (e.g., shuttle, taxi) reimbursed for each visit; Participants will be paid $50 per MRI scan (Controls – 6 scans - $300/ CD participants 8scans - $400). Participants are also paid for task performance, which has a maximum amount of $53 (max of $53 for the MID task) possible at each of three separate scan days. Task performance for the Risk/Reward task will also be paid with a maximum amount of $6.60 weekly (up to 3 for HC and 26 for CD participants) throughout the protocol. $10 will be given for each observed urine sample; $10 for the venipuncture for the COVID-19 antibody test. A stand-by incentive may be used to ensure a study slot is filled. That is, if a participant cancels at the last minute or is a no-show, a second participant may be called to fill that slot. The second participant will be called that day regardless and a $25 stand-by incentive will be payed if the participant answers their phone and are available for the study. The amounts summarized in table 3 may vary depending upon participant compliance and supplementary procedures that may be deemed necessary, such as repeat testing.

Cocaine-dependent Participants:

Contingency management cash payouts will be given for clean urine samples on the schedule outlined in table 1 Following NIH remuneration guidelines related to providing treatment, no hourly compensation will be offered for visits scheduled for only CM. On those days, participants will be compensated for urine samples and CM payments earned. Because the longitudinal measures are crucial to the aims of this protocol, additional completion incentives will be offered to participants.

Pilot (completed): A $50 incentive will be offered to participants during the pilot at the completion of each week of the iTBS administration.

Main Phase: A completion incentive will be given to CD participants during the Expanded Feasibility Study after completing completing the study (visit 43) ($200).

Alternatively, these participants may receive the total amount due in gift certificates, or payments can be made directly towards rent, mortgage, food, utilities, medical care, travel, insurance, clothing, etc. Inpatient participants may request payments prior to discharge. Payment types, as listed above, may be dispensed to a third party (e.g., spouse) via a staff member. This procedure is designed as a precaution to ensure no illicit substances will be introduced from an outside individual during the inpatient stay. To dispense payments prior to discharge, the participant must agree to this procedure. Outpatient participants may postpone payments or request smaller payments to reduce the potential trigger to use cocaine from cash-in-hand post-iTBS treatment. These participants may postpone or receive some or all their remuneration in the approved methods listed above. Participants will have up to 1-year after completing the study to receive full remuneration.

Healthy Controls:
HC participants will be offered a $25 completion incentive after completing all study procedures.
Travel: *Based on current NIDA IRP Remuneration guidelines, travel will either be: 1) provided for directly, 2) reimbursed or 3) they may receive a $15 flat rate per roundtrip to NIDA. Meals or snacks will be provided during study visits. Travel is arranged via a contract in place for the IRP Clinical Program. If participants come to NIDA as part of another study, they will receive travel compensation through only one protocol.*

Method of Payment: The NIDA IRP has a contractor in place for remuneration and payments will be made in accordance with NIDA IRP Remuneration guidelines and may include cash, check, gift card or electronic payment (e.g., PayPal). Remuneration will generally be in cash payments. However, NIDA IRP has limited cash disbursement so

participants may choose multiple payment methods if owed more than the daily limit. Participants may also choose to put payments towards rent, mortgage, food, utilities, and/or medical care. If participation runs into the evening or occurs on weekends, the amount due to the participant will be estimated on the low end, and the participant may return to NIDA another business day to pick up their balance, may receive balance due either at their next session, or receive their balance via a check in the mail or electronic payment (e.g., PayPal) (whichever they prefer). Compensation may also be given in the form of gift cards to local area stores. Participants who complete an MRI scan will also be offered a T-shirt with an ironed-on picture of their brain as part of their compensation.

Table 3a. Remuneration rates: Pilot – Inpatient (Complete)

	Rate	**Time/frequency**
Hourly rate (first hour)	$20/hour	1 hour per visit
Hourly rate (subsequent hours)	$10/hour	1-7 hours per visit
Compensation in addition to hourly rate:		
Urine Test	$10/test	Up to 14
Compliance Incentive	$50	Twice
Inpatient Compensation	$40/night	Up to 10 days
Total (max) per visit	$180	
Total (min) per visit	$70	
Total (max) overall	$1,640	

Table 3b. Remuneration rates: Pilot – Outpatient (Complete)

	Rate	**Time/frequency**
Hourly rate (first hour)	$20/hour	1 hour per visit
Hourly rate (subsequent hours)	$10/hour	1-7 hours per visit
Compensation in addition to hourly rate:		
Urine Test	$10/test	Up to 14

Compliance Incentive	$50	Twice
Total (max) per visit	$140	
Total (min) per visit	$70	
Total (max) overall	$1,230	

Table 3c. Remuneration rates: Expanded Feasibility Study – CD

	Rate	Time/frequency	Max
Hourly rate (first hour)	$20/hour	1 hour per visit	Varies
Hourly rate (subsequent hours)	$10/hour	1-11 hours per visit	varies
Compensation in addition to hourly rate:			
MRI scan	$50/scan	Up to 8 scans	$400
Task Performance (MID)	$53	Up to 3 scan sessions	$159
Task Performance (Risk/Reward)	$6.60	Up to 26 sessions	$171.60
Urine Test	$10/test	Up to 43	$430
Contingency Management	Variable	Up to 28 visits	$1075
Venipuncture for COVID-19 antibody test	$10	Up to 4	$40
Follow-up Phone contacts	$5	Up to 9 contacts	$40
Completion Incentive	$200	Visit 43	$200
Total (max) per visit	$299.6	(12 hour visit, 2 scans, urine test, task performance but not completion incentive)	N/A
Total (min) per visit	$10		N/A
Total (max) overall	$3975.60	(includes $1075 CM at 100% abstinence)	

The max overall payment is based on the following:

The total of the non-hourly rate earnings (See Table 3c above: $2,715.60) plus the estimated hourly pay based on 2 Baseline vists x 10hrs ($220), 9 iTBS visits without scan x 6hrs ($630), one iTBS/scan day x 12hrs ($130); 10 longitudinal data visits (weeks 3-5 and 7-13) x 1 hour each ($200) and 2 longitudinal follow-up scan visits x 10hrs ($220) and 3 post-CM follow-up visits at 1hour ($60). The CM *only* visits don't get hourly compensation.

Table 3d. Remuneration rates: Expanded Feasibility Study – HC

	Rate	Time/frequency	Max
Hourly rate (first hour)	$20/hour	1 hour per visit	varies
Hourly rate (subsequent hours)	$10/hour	1-11 hours per visit	varies
Compensation in addition to hourly rate:			
Urine Test	$10/test	Per visit (~4 visits)	$40
MRI Scan	$50/scan	Up to 6 scans	$300
Task Performance (MID)	$53	One 2 scan sessions	$53
Task Performance (Risk/Reward)	$6.60	Up to 3 sessions	$19.80
Compliance Incentive	$25	At final visit	$25
Venipuncture for COVID-19 antibody test	$10	Up to 2	$20
Total (max) per visit	$160		N/A
Total (min) per visit	$40		N/A
Total (max) overall	$937.80	(depending on total number of visits)	N/A

The max overall payment is based on the following (assuming 4 visits):

The total of the non-hourly rate earnings (See Table 3d above: $457.80) plus the estimated hourly pay based on 2 Baseline vists x 10hrs ($220), two iTBS/scan day x 12hrs ($260) is $937.80

XII. QUALITY ASSURANCE

A. Quality Assurance Monitor

The PI, LAI, and MAI will be monitoring data collection and the study on an ongoing basis. Quality assurance will be monitored by the NIDA Quality-Assurance Team on a schedule to be determined by the Clinical Director.

B. Quality Assurance Plan

We will use the quality-assurance plan that is in place under the aegis of the NIDA-IRP Clinical Director.

XIII. ALTERNATIVES TO PARTICIPATION OR ALTERNATIVE THERAPIES

Individuals who are not eligible to participate in this protocol or who no longer want to participate in this protocol may be able to receive substance abuse treatment outside of the study, under the care of their own physician. They will be given referrals, when appropriate, for substance abuse treatment programs in the community.

XIV. CONFLICT OF INTEREST

There are no conflicts of interests to report.

XV. DISTRIBUTION OF NIH GUIDELINES

NIH guidelines on conflict of interest have been distributed to all investigators. There are no conflicts of interest to report.

XVI. ROLE OF A COMMERCIAL COMPANY OR SPONSOR

This study is investigator-initiated and Institute-sponsored.

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XVII. **TECHNOLOGY TRANSFER**

There are no tech transfer agreements or confidential disclosure agreements necessary for this protocol.

XVIII. **REFERENCES**

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