Identifying Electrophysiological Targets for Transcranial Magnetic Stimulation in Cocaine Use Disorder

NCT05631548

Version Date: 09/11/2023

This protocol describes both a pilot study and a main trial, which are registered as two separate records. Refer to pages 5-8 and 11,12 for the pilot study registered as ClinicalTrials.gov record NCT05631548.

Protocol Title:	Identifying Electrophysiological Targets for Transcranial Magnetic Stimulation in Cocaine Use Disorder
Principal Investigator:	Dr. Heather Webber
Co-Investigators:	Dr. Joy Schmitz, Dr. Scott Lane, Dr. Robert Suchting, Dr. Joao de Quevedo, Dr. Michael Weaver
Study Coordinator:	Jessica Vincent
Population:	Pilot Study: N = 5 participants with cocaine use disorder Main Trial: N = 75 participants
Number of Sites:	Single site
Study Duration:	Pilot Study: 1 year Main Trial: 5 years
Subject Duration:	Pilot Study: 3-4 days Main Trial: 5 days

Project Summary

Cocaine addiction is an often unremitting condition that leads to negative health outcomes[1]. Poor treatment responsivity may reflect measurable cocaine-induced brain changes, such as alterations in the dopamine reward system and hypoactivation of the prefrontal cortex[2]. Despite well-known effects of chronic cocaine use, treating deficits in dopamine functioning with pharmacological agents has been largely unsuccessful. There are currently no FDA-approved medications for the treatment of cocaine use disorder (CUD). Transcranial magnetic stimulation (TMS) is an approved treatment for several psychiatric disorders. Recent research shows promise for the use of TMS for CUD[3,4].

Despite considerable promise, there are addressable issues for optimizing treatment with TMS. The first issue has to do with stimulation sites. In accordance with the depression literature, the majority of rTMS studies have stimulated dlPFC to rectify the prefrontal hypoactivation commonly observed in addiction. Other prefrontal structures involving emotional and reward functioning are also potential sites for TMS[5], including dorsomedial PFC (dmPFC) and its connections to anterior cingulate cortex (ACC). dmPFC is a promising target for TMS, as cocaine users show reduced dmPFC and ACC activity in response to pleasant emotional images/monetary outcomes[6–8], and reduced functional connectivity of mesocorticolimbic circuits[9]. A second issue involves identifying relevant biomarkers for TMS effects. Two event-related potential (ERP) components that are sensitive to treatment change (RewP and LPP)[10,11] and capture reward/emotional processing could potentially serve as biomarkers for assessing the effects of iTBS relative to sham. Measuring both RewP and LPP will provide critical information on whether TMS alters overall reward functioning or a bias toward drug rewards compared to non-drug rewards. We propose to conduct the first study that assesses the effects of iTBS to the dmPFC on physiological measures of reward functioning. This pilot study is aimed at establishing feasibility for a larger clinical trial. Recruitment of participants for the larger main trial will begin upon receiving NIH grant funds (application currently under review) and will specifically compare iTBS to the dlPFC and dmPFC to sham (no stimulation).

Background Information

Cocaine use disorder (CUD) is a significant public health problem for which treatments are only moderately effective.

Chronic use of psychostimulants leads to changes in neural circuitry, including the dopamine reward system[2]. These changes in neural function are in part responsible for the hallmark features of stimulant addiction: increased

UTHealth Houston
IRB NUMBER: HSC-MS-21-0813
IRB APPROVAL DATE: 09/11/2023

sensitivity to drug cues due to sensitization[12], reduced executive functioning due to reduced prefrontal activity[13], and withdrawal-induced reduced sensitivity to natural rewards due to hypodopaminergic tone[14]. Despite these well-known effects of stimulant use, treating deficits in reward functioning have largely failed. There are no FDA-approved medications for the treatment of CUD. Alternative approaches that directly target neural circuits may hold promise for treating CUD-related deficits.

Transcranial Magnetic Stimulation (TMS) is a promising treatment for CUD.

TMS is an approved treatment for depression, obsessive compulsive disorder, and nicotine use[15,16]. Clinical research has also shown promising results for the use of rTMS (repetitive TMS) in the treatment of CUD[3]. It is well known that cocaine addiction is associated with changes in prefrontal (e.g., dorsolateral prefrontal cortex [dlPFC], orbitofrontal cortex, and anterior cingulate cortex[ACC])[5,17–19] functions including executive and emotional control, inhibition, decision-making, and processing of motivationally salient stimuli[13]. As a result, the majority of TMS studies aim to increase the activity of the prefrontal cortex by applying excitatory stimulation to the left dlPFC. Anatomically, stimulation of pyramidal neurons in dlPFC could also rectify changes in reward system networks observed with chronic use of drugs, as it projects to midbrain dopamine cells within the ventral tegmental area and substantia nigra. The hypothesized result would be an increase in dopamine within the nucleus accumbens[20].

Preliminary evidence in humans supports this hypothesis. Multiple sessions of active rTMS of 5-15 Hz to dlPFC appear to reduce self-reported craving, cocaine positive urines, and other unwanted symptoms[3,4,21–27]. In addition to traditional 10/15Hz rTMS, intermittent theta burst stimulation (iTBS) has also shown early success in lowering cocaine use and craving. Importantly, iTBS protocols take about 3 minutes to complete compared to the 15 minutes it takes for a 15Hz protocol and has similar clinical effectiveness for treatment of depression[28]. Steele et al. (2019) reported iTBS to left dlPFC reduced cocaine use and craving[29], while Sanna et al. (2019) reported no differences in 15 Hz stimulation compared to iTBS to the bilateral PFC on cocaine use[30]. Taken together, iTBS to either area could be useful in treating CUD.

TMS to dorsomedial PFC (dmPFC) is a potential therapeutic target for CUD. While dlPFC has been the conventional target for CUD based on the depression literature, recent studies have provided preliminary evidence that TMS to dmPFC could be beneficial in treating depressive symptoms[31–33]. Similar to depression, dmPFC is also implicated in reduced emotional and reward functioning in addiction. For example, functional connectivity in emotional and reward circuits are reduced in cocaine dependent individuals, including medial PFC with amygdala and dmPFC with hippocampus[9]. Similarly, fMRI response to pleasant images is reduced in the dmPFC in cocaine users compared to healthy controls[7]. More broadly, studies have shown that medial PFC and ACC are reduced in response to differences in monetary outcomes compared to controls[6,8,34,35]. Yet, no studies have directly compared dlPFC and dmPFC in a sham-controlled design for CUD.

Electroencephalogram (EEG) is a relevant and useful biomarker of TMS effects on brain function.

While some research has looked at the effects of TMS on neuroimaging measures[36–41], thus far, the majority of TMS studies have focused on subjective measures of craving as the main outcomes. However, evidence suggests that subjective measures may not capture the substantial heterogeneity in risk for relapse[3], especially in persons with substance use disorders, who may lack insight[42]. Despite longstanding debate in the literature, there is no accepted self-report measure of craving. Recognizing these limitations, researchers have turned to psychophysiological responses as an indirect measure of craving.

The current proposal will utilize event-related potentials (ERPs) as objective biomarkers to assess the effects of TMS on overall reward sensitivity and cue reactivity, two main constructs associated with CUD treatment outcomes[43,44]. ERPs directly measure brain activity with excellent temporal precision and reliability[45]. ERP paradigms are well-researched and widely used, with published guidelines for best practices[46]. In our work leading up to this proposal, we have successfully integrated EEG measurements into the clinical trials research setting and have demonstrated how ERP components can be used to classify cocaine users based on risk for relapse[47]. The Reward positivity (RewP) and the late positive potential (LPP) are ERP components associated with reward and emotional processing and are ideal candidate biomarkers of treatment response.

Reward sensitivity as a target in treating CUD with TMS. The RewP is an ERP component that occurs over the medial fronto-central electrodes ~250-350ms after reward feedback[48] and is more positive to wins compared to losses. The RewP is thought to reflect a reward prediction error signal from midbrain dopamine neurons to the ACC[48–55].

Research has linked dopamine with the generation of the RewP[56–60], and thus, is theorized to be an indicator of overall reward sensitivity or anhedonia[61,62]. In fact, anhedonia has been shown to account for a significant amount of variance in predicting RewP amplitude in individuals with CUD[63]. Recent evidence suggests that the time-domain RewP effects are better described by decomposition into theta (3-7Hz) and delta (<3 Hz) activity using time frequency analysis[64–66]. Theta and delta activity may represent different aspects of reward feedback processing[67–70], with theta indexing simple stimulus characteristics and delta capturing complex features such as expectancy and magnitude of reward[66,71]. *Importantly, only delta-related activity is associated with depressive symptoms[62], and thus, could be key in evaluating reward sensitivity in CUD*. The RewP is sensitive to TMS manipulation[72,73], is reliable[48,74], and is known to change with treatment[11,75], and thus, is well positioned to serve as a biomarker of change in reward sensitivity observed after TMS treatment. *While prior studies demonstrated TMS effects on the RewP when stimulating dlPFC[72,73], stimulation to dmPFC may be optimal given the connection between ACC and dmPFC[76,77].*

Cue reactivity as a target in treating CUD with TMS. The LPP is an ERP component occurring over the centro-parietal electrodes (starting ~400ms post stimulus) that is larger to unpleasant and pleasant compared to neutral images[78,79]. The LPP is thought to be marker of motivated attention toward emotionally salient cues and cue reactivity[80], as studies in drug users show that the LPP is enhanced in response to drug cues[10,81–84] and is associated with craving[84]. The LPP is thought to arise from a complex network of brain areas, including the visual cortex, amygdala, prefrontal cortex, and insula[85–87]. Further, visual representations of rewarding stimuli are mediated by the dopamine system[88] and thus, LPP could be altered by TMS manipulation via these networks. Importantly, the LPP changes with treatment and abstinence status[89] and is altered by TMS over the PFC. In one study, prior to treatment cocaine users displayed a larger LPP response to drug compared to pleasant images, and this pattern flipped after treatment[10]. Therefore, the LPP may serve as a biomarker of cue reactivity change observed after TMS treatment. Specifically, measuring both RewP and LPP will provide critical information on whether TMS alters overall reward functioning or a bias toward drug rewards compared to non-drug rewards. It is unknown if stimulation to the dlPFC or dmPFC would be more effective in manipulating the LPP amplitude. fMRI studies of cue reactivity implicate dlPFC and dmPFC in the processing of drug cues in addiction[90], so both stimulation sites should have an effect on LPP to drug/non-drug cues.

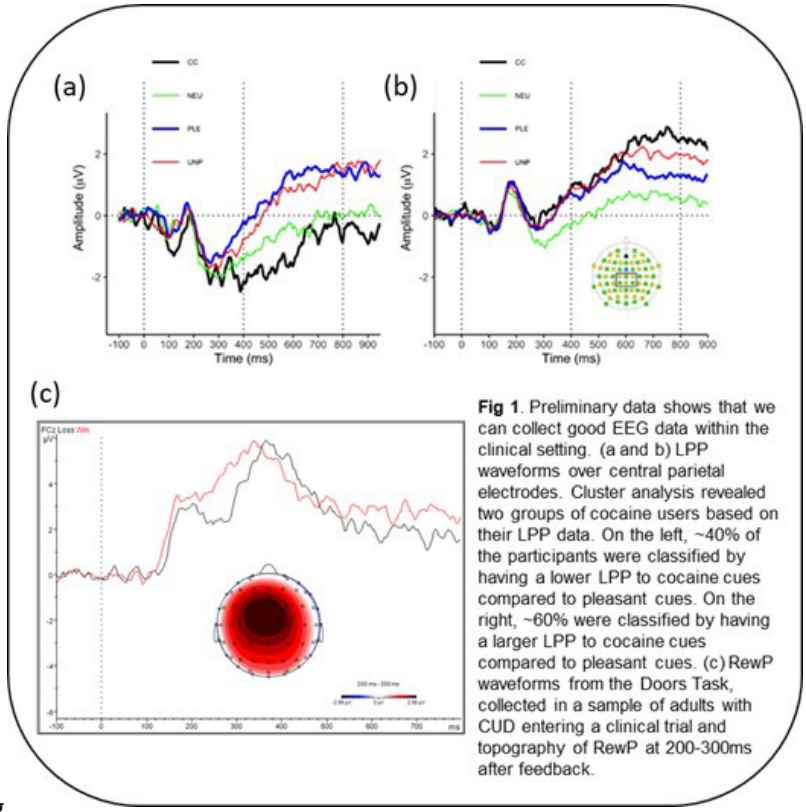


Fig 1. Preliminary data shows that we can collect good EEG data within the clinical setting. (a and b) LPP waveforms over central parietal electrodes. Cluster analysis revealed two groups of cocaine users based on their LPP data. On the left, ~40% of the participants were classified by having a lower LPP to cocaine cues compared to pleasant cues. On the right, ~60% were classified by having a larger LPP to cocaine cues compared to pleasant cues. (c) RewP waveforms from the Doors Task, collected in a sample of adults with CUD entering a clinical trial and topography of RewP at 200-300ms after feedback.

Preliminary Data. The following preliminary studies indicate the feasibility of the trial and ability of the team to carry out the proposed research. Support for utilizing EEG to assess reward sensitivity and cue reactivity in CUD: We are currently completing a NIDA-funded F32 project (1F32DA048542) titled "*Using event-related potentials to predict treatment outcomes in cocaine use disorder*". This project is utilizing identical EEG tasks to elicit the RewP and LPP at a baseline assessment before participants receive treatment of CUD. *Fig 1* displays the LPP waveforms collected from this project on the Picture Viewing Task and the RewP waveforms from the Doors Task. *Fig 1* shows variability in the LPP amplitude, suggesting that individuals with higher LPP at baseline may be more likely to benefit from TMS treatment compared to those with smaller LPPs (i.e., they have more room to reduce LPP response). *Fig 1* also shows preliminary data collected from the Doors Task, showing a typical RewP response (more positive to wins, negative to losses). Together, these results highlight the feasibility of utilizing these ERP components to assess reward sensitivity and cue reactivity in CUD and the ability of the team to collect high quality and relevant EEG data in a clinical setting.

Summary of Significance

The current study will provide critical preliminary data for a larger clinical trial that will test the effects of iTBS to the dlPFC and iTBS to the dmPFC compared to sham on both cocaine use and physiological measures of reward functioning. The pilot study will focus on assessing the effects of dmPFC alone, as prior studies have already indicated that iTBS to the dlPFC can alter EEG[91,92]. We hypothesize that reward sensitivity and cue reactivity, as measured by RewP and LPP, respectively, will demonstrate utility as biomarkers of TMS effects. There is an urgent need to improve treatments for CUD in the wake of recent trends indicating rising cocaine use and overdose deaths[93]. Research indicates that a decreased RewP to wins and increased LPP to cocaine cues are potential targetable physiological patterns for TMS manipulation. This proposal is significant because it will 1) establish feasibility of a novel stimulation site utilizing a biomarker approach and 2) lay the ground work for a future larger clinical trial comparing the novel site to a traditional site and sham. For the main study, we will compare the effects of dmPFC to dlPFC and sham. We hypothesize that dmPFC compared to dlPFC or sham will lead to greater changes in EEG measures of reward functioning (i.e., RewP and LPP).

Aims and Hypotheses

Pilot Study

Specific Aim 1: To assess the effects of active iTBS to dmPFC on EEG measures of reward sensitivity and cue reactivity.
Hypothesis 1a. Primary hypothesis: iTBS will increase the amplitude of the RewP and switch the drug>pleasant LPP bias to pleasant>drug compared to sham iTBS.

Specific Aim 2: To assess the effects of active iTBS to dmPFC on cocaine craving in cocaine users.
Hypothesis 2a: Primary hypothesis: iTBS to dmPFC compared to sham iTBS will reduce cocaine craving (Minnesota Cocaine Craving Scale) in cocaine users.

Primary Outcome Measures

1. Reward sensitivity as assessed by the Reward Positivity – the RewP is an EEG component that will be measured immediately before and immediately following iTBS sessions on the test day.
2. Cue reactivity as assessed by the Late Positive Potential to drug vs. pleasant cues – the LPP is an EEG component that will be measured immediately before and immediately following iTBS sessions on the test days.

Secondary Outcome Measures

1. Craving – craving will be assessed immediately before and immediately following iTBS sessions on the test days.
2. Pain – pain will be assessed via a Visual Analogue Scale (1-10) immediately before and immediately following iTBS sessions on the test days.
3. Cognitive function – a brief assessment of cognitive function will be included immediately before and after the iTBS sessions on the test days.

Main Trial

AIM 1: Assess effects of iTBS to left dlPFC and dmPFC compared to sham on reward sensitivity.
Primary Hypothesis 1a: Active iTBS relative to sham will increase the amplitude of the RewP/delta power to rewards compared to non-rewards.
Exploratory Hypothesis 1b: iTBS to dmPFC will result in a greater increase in the RewP/delta power compared to dlPFC.

AIM 2: Assess effects of iTBS to left dlPFC and dmPFC compared to sham on motivated attention.
Primary Hypothesis 2a: Active iTBS relative to sham will switch the drug>pleasant LPP bias.
Exploratory Hypothesis 2b: iTBS to dmPFC will result in a greater increase in LPP to pleasant images.

EXPLORATORY AIM 3: Identify individual differences in iTBS response with baseline characteristics.
Exploratory Hypothesis 3a: We will explore CUD severity, impulsivity, and craving as predicters of iTBS effects.

Primary Outcome Measures

1. Reward sensitivity as assessed by the Reward Positivity – the RewP is an EEG component that will be measured immediately before and immediately following iTBS sessions on the test day.
2. Cue reactivity as assessed by the Late Positive Potential to drug vs. pleasant cues – the LPP is an EEG component that will be measured immediately before and immediately following iTBS sessions on the test days.

Secondary Outcome Measures

1. Craving – craving via the Minnesota Cocaine Craving scale will be assessed immediately before and immediately following iTBS sessions on the test days.
2. Pain – pain will be assessed via a Visual Analogue Scale (1-10) immediately before and immediately following iTBS sessions on the test days.
3. Cognitive function – a brief assessment of cognitive function will be included immediately before and after the iTBS sessions on the test days.
4. Behavioral reward learning – participants will complete the Pavlovian Go/No-Go task before and after iTBS sessions.
5. Anhedonia – the Snaith Hamilton Pleasure Scale (SHAPS) will be collected before and after iTBS sessions.

Study design

Pilot Study

Pilot Design. Five individuals will serve as pilot subjects to assess protocol feasibility prior to launching the main trial (currently under review at NIH). We will enroll five individuals with CUD. The pilot subjects will complete the screening intake through our currently approved protocol (HSC-MS-05-0322) and a two-day test session. Each participant will complete two test days: A) iTBS to dmPFC and B) sham iTBS. The order (dmPFC or sham) of test days will be counterbalanced and double-blind. Recruitment of additional 75 participants for the main trial will begin upon receiving NIH grant funds (application currently under review).

Overall Research Strategy. Pilot participants (N = 5) with a primary CUD diagnosis will complete screening and baseline assessments prior to undergoing a two-day within-subjects pre-post EEG design. Participants will complete an EEG session, undergo the iTBS session (either dmPFC or sham), and then repeat the EEG session. The iTBS intervention will consist of 2 3-minute sessions with a 15-20-minute interval in between sessions.

Participants, Recruitment, and Setting. The study will be conducted at the Center for Neurobehavioral Research on Addiction (CNRA), where Dr. Joy Schmitz has been running treatment and non-treatment studies for CUD for over 10 years. The TMS portion of the study will be conducted in the Treatment Resistant Mood Disorders Clinic, where Dr. de Quevedo uses TMS to treat depression and mood disorders. Recruitment will follow typical CNRA protocols, including calls from protocol number HSC-MS-05-0322, and additionally distribute unique study flyers locally. Eligible participants will be between the ages of 18 and 65. Potential participants will attend an in-person intake over several days to determine eligibility based on the Structured Clinical Interview for DSM-5 (SCID)[94], Colombia Suicide Severity Rating Scale (C-SSRS)[95], Assault & Homicidal Danger Assessment Tool[96], urine drug screening, breath alcohol testing, a urine pregnancy test, and a TMS safety screen. Eligibility criteria will be assessed through our CPHS approved "General Evaluation of Eligibility for Substance Abuse/Dependence Research" protocol (HSC-MS-05-0322) and will be conducted by licensed counselors and research assistants. Please see Table 1 for the Schedule of Assessments regarding the general evaluation protocol. Individuals meeting moderate or severe criteria for substances other than cocaine, cannabis, or nicotine will be excluded. Other exclusionary criteria are: unstable psychiatric disorder, medical conditions

UTHealth Houston
IRB NUMBER: HSC-MS-21-0813
IRB APPROVAL DATE: 09/11/2023

contraindicated to TMS (e.g., medical implants, history of seizure or seizure disorder, medications lowering the seizure threshold, neurological conditions, moderate-to-severe heart disease), pregnancy, hairstyles incompatible with the EEG net, and head injury with loss of consciousness. See Protection of Human Subjects for a more detailed description of eligibility criteria.

Table 1. Schedule of Assessments – Pilot Study

	General Evaluation to assess eligibility (1-2 days)	Study Visits (2 days)
Structured Clinical Interview for DSM-5	X	
Urine drug screen (UDS)/breathalyzer	X	X
Pregnancy test	X	X
Colombia Suicide Severity Rating Scale/Assault & Homicidal Danger Assessment Tool	X	
TMS Safety Screen	X	
Timeline Follow Back	X	X
Montreal Cognitive Assessment (MoCA)[4]		X
EEG Tasks[1]		X
iTBS[2]		X
Minnesota Cocaine Craving Scale		X
Snaith-Hamilton Pleasure Scale		X
Safety Measures[3]		X

Note. [1]EEG tasks are collected before and after 2 sessions of iTBS – 3 minutes of resting EEG data, the Picture Viewing Task, the Doors Task. [2]iTBS – two sessions of iTBS, separated by 15-20 minutes rest. Either sham iTBS or iTBS to dmPFC. [3]Safety Measures – hours of sleep, Cocaine Selective Severity Assessment (CSSA; withdrawal), and AE/SAE form will be collected prior to iTBS. AE/SAE form will be completed both before and after iTBS sessions. [4] MoCA performed prior to 1st iTBS session and after 2nd iTBS session.

Payment and Compensation. Participants will be paid $35 for the screening/intake visits, plus compensation for parking/bus passes. Participants will receive $150 for each EEG/TMS evaluation days.

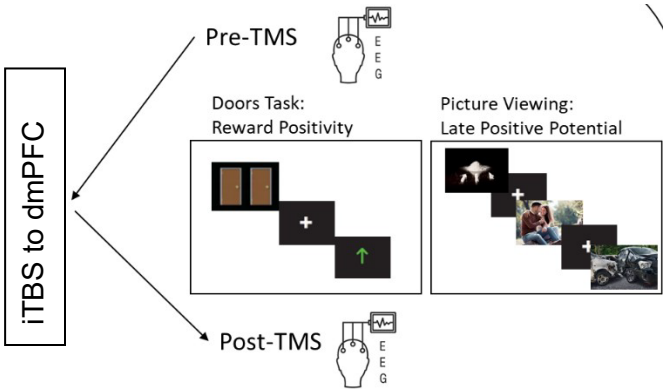
Baseline Screening. Participants will receive a psychiatric evaluation during the first week including a complete psychiatric diagnosis using the Structured Clinical Interview for DSM-5 (SCID-5) administered by trained licensed professional counselors under the supervision of a licensed clinical psychologist. Screening will include urine sample for urinalysis testing for drugs of abuse and pregnancy. In addition to the general evaluation, participants will complete the TMS Adult Safety Screen per Keel et al[97]. Upon completion of this intake evaluation, eligible participants will be invited to participate in the study.

TMS Session. The PI or a trained research assistant/nurse under the supervision of Dr. Joao de Quevedo, will perform the TMS at the Treatment-Resistant Mood Disorders Program at UTHealth, adjacent to the CNRA. TMS will be

UTHealth Houston
IRB NUMBER: HSC-MS-21-0813
IRB APPROVAL DATE: 09/11/2023

delivered with a MagVenture Mag Pro R30 with the Cool-B70 A/P coil with active liquid cooling and active/sham sides (Farum, Denmark). A member of the CNRA not involved in the study will be the only person aware of the randomization results and will program the system to ensure double blinding.). For dmPFC, we will measure approximately 25% of the nasion-inion distance, or Talairah coordinates X 0 Y+60 Z+60[32,98]. The first session will begin with the acquisition of the resting motor threshold (rMT; lowest stimulus intensity that elicits a visible twitch on 50% of the trials) on the contralateral hand. iTBS (triplet 50 Hz bursts, repeated at 5 Hz, 2 sec on and 8 sec off; 600 pulses per session) will be delivered at 80% of the rMT and will last ~3 minutes, consistent with current EEG-iTBS single day protocols[73,99]. The intensity can be lowered if the participant cannot tolerate the stimulation. Each participant will receive 2 sessions with a 15-20 minute interval between sessions[100]. Participants will complete the EEG protocol before the first iTBS session (baseline) and immediately following the two stimulation sessions. This will conclude participation for the pilot participants.

EEG Protocol. During the tasks described below, EEG electrode cap, amplified with BrainAmp MR and digitized using Brain Vision Recorder (Brain Products, Munich). Before collection, impedances will be maintained below 50 k(OHM). The sampling rate will be 500 Hz and data will be filtered with .1 Hz high-pass and 100 Hz low-pass filters. Resting data will be collected for 3 minutes (90-seconds eyes open and 90-seconds eyes closed). After collection, data reduction will be performed with a combination of programs including Brain Vision Analyzer 2, MATLAB (EEGLab; PCA Toolkit) and BESA. Both traditional windowed ERP (mean amplitude) and TFA approaches will be used to analyze the RewP. The LPP will be defined as the mean amplitude between 400-800ms post stimulus.



Reward Sensitivity: The Doors Task[59] will be used to elicit the RewP component, representing reward sensitivity[47,60]. The task is a guessing game, where participants guess which door contains a reward behind it. After selecting a door, the participants are notified if they found the prize by a green arrow pointing up or if they did not find the prize by a red arrow pointing down. Unknown to the participants, winning and losing outcomes are presented 50% of the time in a random order. The RewP is larger in response to rewards (wins) than non-rewards (losses). Self-reported anhedonia (Snaith Hamilton Pleasure Scale; SHAPS) will also be assessed as a secondary measure of reward sensitivity in addition to the RewP.

Cue Reactivity: The Picture Viewing Task will be used to elicit the LPP, reflecting the motivational salience of a stimulus. During this task, participants are asked to view a slideshow of images including pleasant, unpleasant, neutral, and cocaine-related images[61]. Pleasant and unpleasant images elicit a more positive LPP amplitude than neutral images[55]. In cocaine users, the LPP is also larger to cocaine images compared to neutral images, similar to pleasant and unpleasant images [10,101].

Other Measures.

Cocaine Use. Urine samples will be collected at the study visit and tested for the cocaine metabolite, benzoylecgonine (BE). Samples containing ≥ 300 ng/ml of BE will be considered positive. Additionally, the Timeline Follow Back[102] method will be used as a secondary self-reported measure of daily cocaine use in the month prior to participating in the study. These measures will be used to assess severity of cocaine use.

Cocaine Craving. Cocaine craving will be measured using the Minnesota Cocaine Craving Scale (MCCS)[103]. The MCCS is a widely used and reliable self-report measure of craving for cocaine, with 3 subscales (craving intensity, frequency, duration) and will be assessed before and after the EEG session.

Cognitive Function. The Montreal Cognitive Assessment (MoCA)[104] assesses multiple cognitive domains including attention, concentration, executive functions, memory, language, visuospatial skills, abstraction, calculation, and orientation. The MoCA will be administered twice on each study session day, prior to the first iTBS session and after the second iTBS session. Alternative equivalent forms will be used for the pre- and post-tests.

Safety outcomes. We will collect the following before the iTBS sessions: hours of sleep, UDS/TLFB, breathalyzer, the AE/SAE form, pain, and the Cocaine Selective Severity Assessment (CSSA – a measure of withdrawal). The AE/SAE form and pain will also be completed after the iTBS session. See Table 2 for the Study Visit Timeline.

Table 2. Study Visit Timeline – Pilot Study		
Assessment	Length of Time	Details
Assess safety:	5-10 min	UDS, TLFB, pregnancy, sleep, CSSA, C-SSRS, AE/SAE form
Cognitive Assessment	10 min	MoCA
Fit EEG cap:	30 min	Measure & place cap on head, gel electrodes
Complete EEG Session 1:	35 min	Resting EEG, Doors Task, Picture Viewing Task
Assess rMT:	10 min	Collect resting motor threshold
iTBS Session 1:	3 min	iTBS to dmPFC or sham iTBS
Rest:	15-20 min	Sit quietly
iTBS Session 2	3 min	iTBS to dmPFC or sham iTBS
Assess safety:	5-10 min	AE/SAE form
Cognitive Assessment	10 min	MoCA
Complete EEG Session 2:	35 min	Resting EEG, Doors Task, Picture Viewing Task

Main Trial

Design. The proposed study will use a within-subjects cross over design as shown in *Fig 2*. Non-treatment-seeking adults with a primary CUD diagnosis (N = 75) will complete screening and baseline assessments prior to completing three separate iTBS days (sham, dlPFC iTBS, or dmPFC iTBS), order counterbalanced across participants. On each day, EEG will be collected before and after 3 iTBS successive sessions (15-minutes between sessions). Days will be spaced at least 24-hours apart and will be completed within 2 weeks. We will aim to consent 115 participants to achieve 75 completed.

Setting and Participants. The study will be conducted at the Center for Neurobehavioral Research on Addiction (CNRA) in Houston, TX. Participants will be recruited through print, radio, and internet advertisements in the local media. Eligible participants will be non-treatment-seeking adults (ages 18-65) meeting DSM-5 criteria for current moderate-to-severe CUD. Potential participants will attend a multiday intake to determine eligibility based on a clinical interview (Structured Clinical Interview for DSM-5 (SCID)[94], Columbia-Suicide Severity Rating Scale (C-SSRS)[95], Assault and Homicidal Danger Assessment Tool[105]), urine drug screening, breath alcohol testing, urine pregnancy test, and TMS safety screen[97]. Individuals meeting moderate or severe criteria for substances other than cocaine, cannabis, or nicotine will be excluded. Other exclusionary criteria are: unstable psychiatric disorder, medical conditions or medications contraindicated to TMS (e.g., medical implants, history of seizure, see *Protection of Human Subjects* for a full list), pregnancy, impending incarceration, and inability to read or write. Day-of TMS session requirements will include: negative UDS for any substance other than cocaine and cannabis, 0% blood alcohol level, and > participants' typical number of hours of sleep (*Safety Outcomes*). Appointments will be rescheduled if these criteria are not met. Participants will receive compensation for travel and study visits to promote retention, including $35 for the screening, escalating payments ($40/hour for 1st session, $45/hour for 2nd and $50/hour for 3rd) for completion of the EEG/iTBS sessions, and $10 per visit for parking.

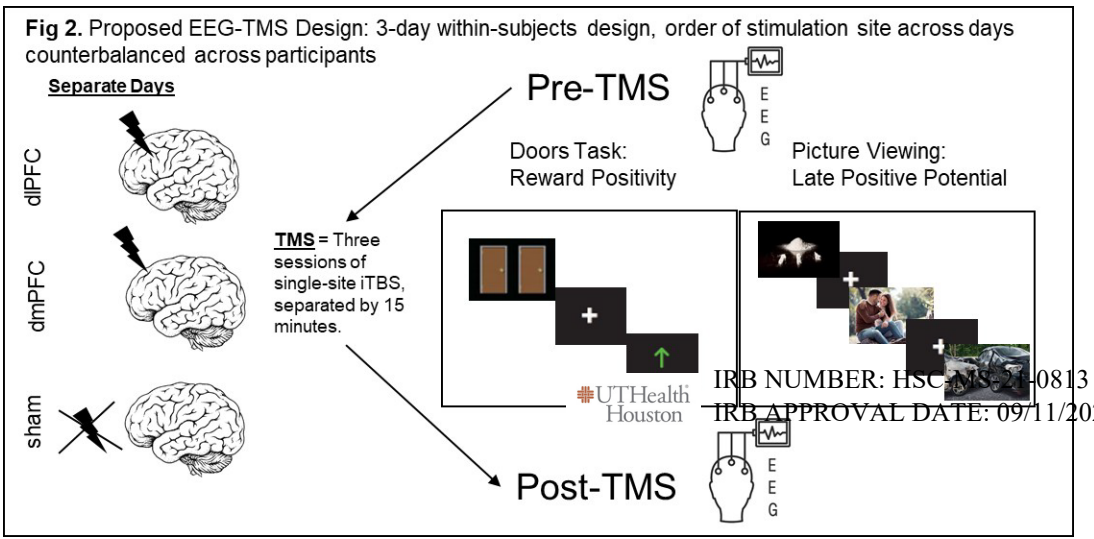


Fig 2. Proposed EEG-TMS Design: 3-day within-subjects design, order of stimulation site across days counterbalanced across participants

TMS protocol. The PI or a trained research assistant/nurse under the supervision of Dr. Joao de

Quevedo (*Biosketch*), will perform the TMS at the Treatment-Resistant Mood Disorders Program at UTHealth, adjacent to the CNRA. TMS will be delivered with a MagVenture Mag Pro R30 with the Cool-B70 A/P coil with active liquid cooling and active/sham sides (Farum, Denmark). A member of the CNRA not involved in the study will be the only person aware of the counterbalanced order and will program the system to ensure double blinding. For dlPFC, we will measure position F3, using probabilistic EEG placement. For dmPFC, we will measure approximately 25% of the nasion-inion distance, or Talairah coordinates X 0 Y+60 Z+60[32,98]. The first session will begin with the acquisition of the resting motor threshold (rMT; lowest stimulus intensity that elicits a visible twitch on 50% of the trials) on the contralateral hand. iTBS (triplet 50 Hz bursts, repeated at 5 Hz, 2 sec on and 8 sec off; 600 pulses per session) will be delivered at 110% of the rMT and will last ~3 minutes. The amplitude of the TMS can be lowered if the participant cannot tolerate the stimulation. The stimulation will start at a lower percentage and ramp up over time to acclimate participant to the feeling of stimulation. Each participant will receive 3 sessions per visit with a 15-20 minute interval between sessions to increase the likelihood of detecting acute effects[100]. Participants will complete the EEG protocol before the first iTBS session (baseline) and immediately following stimulation sessions (*Table 1)*.

Measures.

Baseline Measures. Urine samples will be collected at each study visit and tested for the cocaine metabolite, benzoylecgonine (BE) and other drugs of abuse. Samples containing ≥ 300 ng/ml of BE will be considered positive. Additionally, self-reported substance use will be assessed using the Timeline Follow Back[102] to assess cocaine use severity (number of days used in the past 30 days). Impulsivity will be measured with the Barratt Impulsiveness Scale (BIS-11)[106]. Cocaine craving (below) will also be measured at baseline.

Table 3. Schedule of Activities by Visit (Order of Study Visit Number counterbalanced and randomized across participants) Main Trial

		Sham	dmPFC[1]	dlPFC[2]
Study Visit	Intake/Baseline	1	2	3
Screening Measures				
Informed Consent	X			
SCID DSM-5	X			
Addiction Severity Index	X			
Drug History KMSK	X			
TMS Safety Screen	X			
Safety Measures				
Urine Pregnancy Test (UPT)	X	X	X	X
Urine Drug Screen (UDS)	X	X	X	X
Breathalyzer	X	X	X	X
Vitals	X	X	X	X
Concomitant Medications Tracking Log	X	X	X	X
Columbia Suicidal Severity Rating Scale (C-SSRS)	X	X	X	X
Danger Assessment Tool	X	X	X	X
Cocaine Selective Severity Assessment (CSSA)		X	X	X
Hours of Sleep		X	X	X
TMS Side Effects Questionnaire*		X	X	X
Pain Visual Analogue Scale (VAS)*		X	X	X
Montreal Cognitive Assessment (MoCA)*		X	X	X
TMS				
Intermittent theta burst stimulation 3x with 15-minute intervals in between		X	X	X
Study Manipulation Measures				
Blinding Question		X	X	X
Main Outcomes				
EEG (Doors Task & Picture Viewing		X	X	X

Task)*				
Behavioral Reward (Pavlovian Go/No-Go)*		X	X	X
Other Measures/Outcomes				
Minnesota Cocaine Craving Scale (MCCS)*	X	X	X	X
Snaith-Hamilton Anhedonia Scale (SHAPS)*	X	X	X	X
Cocaine Use Timeline Follow Back (TLFB)	X	X	X	X
Barratt Impulsiveness Scale (BIS-11)	X			
PROMIS Sleep Disturbance/Impairment		X	X	X
Profile of Mood States (POMS)		X	X	X
Delay Task*		X	X	X
Cocaine Purchasing Task	X			
[1]dorsolateral prefrontal cortex; [2]dorsomedial prefrontal cortex; * measured before and after TMS				

EEG Measures. During the tasks described below, EEG will be collected using a 64-channel actiCAP electrode cap, amplified with BrainAmp MR and digitized using Brain Vision Recorder (Brain Products, Munich). Impedances will be maintained below 50 k(OHM). The sampling rate will be 500 Hz and data will be filtered with .1 Hz high-pass and 100 Hz low-pass filters. Data reduction will be performed with Brain Vision Analyzer 2, MATLAB, and BESA. Both ERP (mean amplitude) and TFA approaches will be used to analyze the RewP. While the main hypotheses will look at delta power, we will also examine changes in other frequencies, including theta, in exploratory analyses. The LPP will be defined as the mean amplitude between 400-800ms post stimulus[47,81] and a difference score (cocaine minus pleasant) will be used to assess LPP bias.

Reward Sensitivity. The Doors Task[59] will be used to elicit the RewP. Participants guess which door contains a reward behind it. After selecting a door, the participants are notified if they won by a green arrow pointing up or if they lost by a red arrow pointing down. Unknown to the participants, winning and losing outcomes are presented 50% of the time in a random order. Self-reported anhedonia (Snaith Hamilton Pleasure Scale; SHAPS) will also be assessed at each visit as a secondary measure of reward sensitivity.

Cue Reactivity. The Picture Viewing Task will be used to elicit the LPP, reflecting the motivational salience of a stimulus. During this task, participants are asked to view a slideshow of images including pleasant, unpleasant, neutral, and cocaine-related images[61].

Cocaine Craving. Cocaine craving will be measured using the Minnesota Cocaine Craving Scale (MCCS)[103]. The MCCS is a widely used and reliable self-report measure of craving for cocaine. It will be assessed before and after each iTBS session.

Behavioral Reward Learning. Participants will complete a Pavlovian Go/No-Go task to assess Pavlovian influences on instrumental learning[107–110]. In the first "learning" phase, participants learn whether to press a button or withhold a response to receive a monetary reward or avoid a loss. In the second "transfer" phase, participants perform a forced choice task, where each of the predictive cues in the learning phase are paired with each other. Participants must select the "most rewarding" cue.

Delay Discounting and Cocaine Demand. Both delay discounting and cocaine demand are measures that provide information about cost-benefit trade-offs and are often associated with substance use outcomes. Previous studies have shown that TMS might alter these principles[111]. The delay task will specifically measure delay discounting and will consist of 5 questions about whether the participant would hypothetically like to receive less money now or more money later [112]. The cocaine purchasing task will be used to assess how much cocaine the participant would be willing to use given incremental cost of cocaine[113,114].

Safety/Other outcomes. We will collect the following day-of measures before iTBS sessions: Profile of Mood States (POMS)[115], hours of sleep, Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance (SD) and Sleep-Related Impairment (SRI) short forms[116,117], UDS/TLFB, breathalyzer, withdrawal (Cocaine Selective Severity Assessment; CSSA[118]), and the TMS AE/SAE form. The TMS AE/SAE form will also be completed after iTBS sessions. The Montreal Cognitive Assessment (MoCA)[104] will be used to assess for changes in cognition and will be administered before and after the 3 iTBS sessions.

Analysis Plan

Pilot Study

Data Analytic Strategy.
Statistical Modeling. Analyses will primarily rely on generalized linear modeling (GLM) with a random intercept for participant. This model may fit normally or non-normally distributed outcomes as needed (e.g., Binomial with logit link for dichotomous outcomes). Analyses will be performed in Mplus[110] and R[111] via packages lme4[112], mediation[113], rstan[114], and brms[115]. *Inferences and Assumptions*. Bayesian inference will be used to directly evaluate the probability of the alternative hypothesis (i.e., that an effect of TMS exists). As a default, weakly informative priors will be used for all analyses (e.g., regression coefficients: $b \sim N[\mu=0,\sigma^2=10]$; error/dispersion terms: $\sim Half\text{-}Normal[\mu=0,\sigma^2=10]$) in order to emphasize the influence of the present data on posterior probabilities (PP). Sensitivity analyses will test a range of prior distributions to ascertain the degree to which analyses are robust to prior specifications[119]. Evaluation of posterior distributions will permit statements regarding the probability that effects of varying magnitudes exist, given the data. Bayesian models will be evaluated via PP threshold guidelines in the literature[120,121] suggesting that PP = 75% to 90% indicates moderate evidence, PP = 91% to 96% indicates strong evidence, and PP = 97% or above indicates very strong to extreme evidence. Bayesian analyses calibrate probability in terms of the prior distribution and are less influenced by multiple comparisons due to observation of the Likelihood Principle[122]. However, additional analyses will employ regularization (e.g., "horseshoe" priors) with best practices suggested by the literature[123–125] to maximize the robustness of any identified effects. Bayesian convergence and modeling assumptions will be evaluated by effective sample size, scale reduction factors ("rhat"), and posterior predictive checking. Violated assumptions will be addressed via model re-specification, variable transformation, robust estimation, stratification, and/or coefficient scaling where appropriate.

Specific Analyses. *Aim 1*. iTBS to dmPFC compared to sham will increase the amplitude of the RewP and switch the drug>pleasant LPP bias to pleasant>drug. GLM will model RewP amplitude as a function of time (pre vs. post iTBS session) and location (dmPFC or sham). GLM will model LPP amplitude as a function of time (pre vs. post iTBS sessions), condition (i.e., image type [pleasant, unpleasant, cocaine, and neutral]), and location (dmPFC or sham). *Aim 2*. iTBS will reduce cocaine craving (Minnesota Cocaine Craving Scale). GLM will model craving as a function of time (pre vs. post

iTBS sessions) and location (dmPFC or sham). *Non-Primary Measures*. Secondary analyses will also model pain and MoCA scores as a function of time (pre vs. post iTBS sessions) and location (dmPFC or sham).

Sample Size and Power Analysis. The current pilot study is focused on evaluating the feasibility of the current approach with respect to recruitment, retention, assessment procedures, and implementation. Although preliminary statistical analyses will evaluate the magnitude of any changes observed over time, these are not expected to provide a meaningful estimate that would generalize beyond the small sample observed here. By providing evidence for feasibility, the present study will inform a subsequent study with formal hypothesis testing. This approach to pilot studies[119] is explicitly in line with current literature on trial design.

Main Trial

General Data Analytic Strategy

Statistical Modeling. Analyses will rely on **generalized linear modeling (GLM)** with **multilevel (GLMM)** components where necessary to evaluate predictor-outcome relationships. These models may fit normally or non-normally distributed outcomes as needed (e.g., Binomial with logit link for dichotomous outcomes). GLMM may also account for correlated observations via inclusion of random effects (e.g., a level 2 intercept). **Preliminary analyses** will use GLM to evaluate relationships between baseline sample characteristics, predictors, and outcomes prior to formal hypothesis testing. **Confounders** are defined as any sample characteristics that demonstrate relationships with both the predictor and outcome in a given model[120,121]. Subsequent models will be tested with and without adjustment for each potential confounder; if resulting inferences are different, we will report both models; otherwise, we retain the simpler model. **Moderation analyses** will evaluate the potential influence of essential covariates and other baseline sample characteristics (including sex) by examining their higher-order interactions with model predictors. Analyses will be performed in R[122] via packages lme4[123], rstan[124], and brms[125].

Probability and Inference. Following the statistical literature[126], analyses will use dual frequentist and Bayesian inference. Frequentist results yield the probability of the data (or data more extreme), given the null hypothesis, while Bayesian results directly yield the probability of an alternative hypothesis[127,128]. As a default, weakly informative priors will be used for all Bayesian analyses (e.g., regression coefficients: $b \sim N[\mu=0,\sigma^2=10]$; error/dispersion terms: $\sim Half\text{-}Normal[\mu=0,\sigma^2=10]$) in order to emphasize the influence of the present data on **posterior probabilities (PP)**. Sensitivity analyses will test a range of prior distributions to ascertain the degree to which analyses are robust to prior specifications[129]. Evaluation of posterior distributions will permit statements regarding the probability that effects of varying magnitudes exist, given the data. With respect to **multiple comparisons**, frequentist analyses will evaluate all *a priori* defined primary outcomes (listed by name in the Specific Analyses) at the $\alpha=0.05$ (two-tailed) significance level and will employ false discovery rate (FDR) to control for Type I error across any exploratory or *post hoc* analyses. Bayesian models will be evaluated via PP threshold guidelines in the literature[130,131] suggesting that PP = 75% to 90% indicates moderate evidence, PP = 91% to 96% indicates strong evidence, and PP $\geq$ 97% indicates very strong/extreme evidence. Bayesian analyses calibrate probability in terms of the prior distribution and are less influenced by multiple comparisons due to observation of the Likelihood Principle[132]. However, additional analyses will employ regularization (e.g., "horseshoe" priors)[133–135] to maximize the robustness of any identified effects.

Modeling Assumptions. Evaluation of assumptions for frequentist models will use graphical evidence (e.g., residual plots) and formal statistical tests. Bayesian convergence and modeling assumptions will be evaluated by effective sample size, scale reduction factors ("rhat"), and posterior predictive checking. Violated assumptions will be addressed via model re-specification, variable transformation, robust estimation, stratification, and/or coefficient scaling where appropriate. **Intention-to-treat (ITT)** primary analyses will included all randomized participants; follow-up analyses may evaluate modified ITT samples should specific participants merit exclusion (e.g., randomized but never initiated the trial). A per protocol analysis will complement the primary ITT analysis as due diligence. **Missing data** patterns will be evaluated using Little's Test of Missing Completely at Random (MCAR)[136] for continuous outcomes and the Park and Lee approach[137] for discrete outcomes. Models will handle missingness via maximum likelihood, explicit modeling of missingness[138], and/or imputation with sensitivity analyses to evaluate the robustness of findings. Each approach is

robust to ignorable missingness (i.e., missing completely at random and missing at random). Pattern-mixture modeling will be used to address identified non-ignorable missing data patterns[139].

Specific Analyses

All statistical models (described below) will account for correlated observations via the best-fitting structure of random effects (i.e., lowest information criteria) found when fitting level-2 intercepts and/or slopes) for repeated measures (where necessary) and statistically control for potential confounders as defined above. Outcome variables will be modeled as difference scores to account for the pre/post design (i.e., post-iTBS minus pre-iTBS).

Hypothesis 1a (Primary): Active iTBS relative to sham will increase the amplitude of the RewP/delta power to rewards compared to non-rewards. GLMM will model the change in amplitude of the RewP/delta power to rewards as a function of iTBS condition, with random effects to account for repeated measures.

Hypothesis 1b (Exploratory): iTBS to dmPFC will result in a greater increase in the RewP/delta power compared to dlPFC. Follow-up testing of the model described above for Hypothesis 1a will evaluate pairwise comparisons between iTBS conditions.

Hypothesis 2a (Primary): Active iTBS relative to sham will switch the drug>pleasant LPP bias. GLMM will model the change in LPP bias as a function of iTBS condition.

Hypothesis 2b (Exploratory): iTBS to dmPFC will result in a greater increase in LPP bias (i.e., greater LPP to pleasant images compared to cocaine images). Follow-up testing of the model for Hypothesis 2a will evaluate pairwise comparisons between iTBS conditions.

Hypothesis 3a (Exploratory): Analyses will explore baseline CUD severity, impulsivity, and craving as predicters of iTBS effects on EEG. GLMM will model EEG outcomes as a function of the interaction between iTBS condition and each named predictor (in separate models): baseline CUD severity, impulsivity, and craving, controlling for constituent main effects.

Sample Size and Power Analysis

The current proposal is powered with respect to the primary hypothesis in the study (Hypothesis 1a). G*Power v. 3.1.9.4 provides calculations from the frequentist perspective via a within-factor repeated measures model, a simplified version of the GLMM described above. Assuming a correlation among repeated measures $r = 0.50$ and two-tailed $\alpha = 0.05$, the current feasible sample size N = 75 provides 80% power to detect an effect size as small as Cohen's $f = 0.149$ (comparable to a small-to-moderate Cohen's $d = 0.30$). These estimates also broadly apply to Hypothesis 2a. Bayesian analyses proposed above will then provide a complementary analysis of all models that yields probabilistic estimates for all model effects, even in the context of relatively smaller sample sizes[140] (i.e., the available data for subgroup analyses or higher-complexity models).

Protection of Human Subjects

Inclusion Criteria:

1. be between 18 and 65 years of age at the time of the first study visit (iTBS session day)
2. meet DSM-5 criteria for current cocaine use disorder of at least moderate severity (≥ 4 symptoms)
3. have at least 1 positive urine BE specimen (≥ 300 ng/mL) during intake
4. be able to understand the consent form and provide written informed consent
5. be able to provide the following verifiable information for a minimum of 2 contact persons: full legal name, email address, local mailing address, and as applicable, home, work, and cell phone numbers

Exclusion criteria:

1. current DSM-5 diagnosis for substance use disorder (of at least moderate severity) other than cocaine, marijuana, or nicotine
2. in the opinion of the principal investigator (PI), the presence of any medical, neurological, psychiatric, or physical condition, disease, or illness that, may: (a) compromise interfere, limit, effect or reduce the subject's ability to complete the study; or (b) adversely impact the safety of the subject or the integrity of the data

3. has current or recent (within 3 months of potential enrollment) suicidal ideation, suicidal behavior, homicidal ideation or a homicidal plan sufficient to raise subject safety concerns based on the following assessments according to the PI:
    a. SCID-5
    b. C-SSRS Screener – Answers YES to Questions 3, 4, 5, or 6
    c. Assault & Homicidal Danger Assessment Tool – Key to Danger > 1
4. medical implants contraindicating TMS (i.e., aneurysm clips or coils, stents, implanted stimulators, implanted vagus nerve or deep brain stimulators, implanted electrical devices such as pacemakers or medication pumps, electrodes for monitoring brain activity, cochlear implants for hearing, any magnetic implants, bullet fragments, any other metal device or object implanted in your body closer than 30 cm from the coil)
5. history of brain surgery
6. history of an intracranial lesion or any medical or neurological diagnosis/condition associated with increased intracranial pressure (i.e., Idiopathic Intracranial Hypertension/Pseudotumor Cerebri) OR any of the following symptoms within 30 days of enrollment: headaches > 15 days/month, loss of vision or decreased vision
7. moderate-to-severe heart disease
8. history of stroke
9. is taking any antidepressant or antipsychotic medication at a dose above the maximum recommended dose or at a dose deemed to be potentially unsafe according to the PI; has taken any of the following medications, which are known to increase the risk of seizures, within 1 week of study enrollment; or does not agree to abstain from taking the following medications during study participation:
    1. clozapine[141]
    2. chlorpromazine[141]
    3. bupropion
    4. clomipramine hydrochloride
    5. amoxapine
    6. maprotiline hydrochloride
    7. diphenhydramine
    8. stimulants other than cocaine including the following:
        a. Dextroamphetamine and amphetamine
        b. Dextroamphetamine
        c. Lisdexamfetamine dimesylate
        d. Methamphetamine
        e. Methylphenidate
    9. tramadol
    10. isoniazid
10. having conditions of probation or parole requiring reports of drug use to officers of the court
11. personal history of epilepsy or seizure disorder and/or family history including a first-degree relative
12. serious head injury with loss of consciousness
13. impending incarceration
14. pregnant or nursing for female patients
15. inability to read, write, or speak English
16. for adolescent aged participants (18-21 only): any risk factor for neurocardiogenic syncope (history of syncope/ presyncope related to noxious stimuli, anxiety, micturition, or posture)?
17. hair style that is incompatible with EEG nets

Potential Risks

TMS. There are several potential risks of TMS administration. The most serious risk is risk of seizure or prolonged seizure (convulsive status epilepticus [CSE]), although most seizures associated with TMS are self-limiting. Overall, the risk of seizures is very low with TMS (< 1%) and specifically iTBS (<.02%)[142]. The risk of seizures should be low for the participants that are eligible for this study, as conditions and medications that lower the seizure threshold will be

exclusionary. Hearing impairment can occur without protection; however, the risk of this is extremely low in this study, as proper hearing protection will be used. There is also a risk for manic switch or psychotic episode, especially in patients with bi-polar disorder. Individuals with bipolar disorder or schizophrenia/psychotic symptoms will not be included in the study. There are also risks associated with magnetic field effects on functioning of other medical devices, but individuals with any medical implant will be excluded from the study. While the risks associated with TMS in substance using populations is still being evaluated, there are now several studies showing safety of TMS for these populations[3,24,25,27,29,30,40,143]. There is also a risk that TMS can affect cognitive functioning, such as working memory and executive function. However, the current literature on iTBS specifically is suggestive of improvement of cognitive functioning with iTBS to the prefrontal cortex, rather than harm. A recent systematic review reported that 6/8 iTBS studies showed significant improvements in working memory and executive function[144]. There is also one study showing that iTBS to the prefrontal cortex improved both working memory and executive function in stimulant users[145]. Other more common but milder risks include discomfort at the stimulation site, headache and neck pain, tingling, spasms, or twitching of facial muscles, and lightheadedness during the actual administration of TMS. These side effects usually rapidly disappear after stimulation. Sometimes headaches can persist after the TMS session is over and can be treated with over-the-counter medications.

Diagnostic Procedures. Items on certain questionnaires and interviews might be perceived as psychologically discomforting to some participants. While participants may be uncomfortable reporting these issues, the risks of serious sequelae are extremely low. There are also risks concerning loss of confidentiality.

EEG Session. Participants in the EEG session may experience skin irritation from the placement of the sensors, which is usually minor and goes away after a few hours. The presentation of emotional images and drug images in the Picture Viewing Task (e.g., mutilations or violence) may cause an affective response, which typically subsides rapidly after image presentation. Participants are shown example images beforehand and agree to watch the slideshow. They can also ask for the slideshow to be stopped at any time. Participants may also feel tired or bored while participating in the EEG session.

Adequacy of Protection against Risks

TMS. Participants will be made aware of the risks of TMS administration. We will primarily protect against TMS risks by excluding individuals from the study who are at risk for seizure or manic/psychotic episodes. Additionally, safety measures will be taken at each visit by the PI, trained research assistant, or nurse, including the AE/SAE form. We will also measure hours of sleep and recent drug/alcohol use to assess day-of eligibility criteria. Our risk mitigation strategy regarding a seizure/CSE, includes the following: 1) staff/PI/physician education about the signs and symptoms focal seizure with or without awareness and generalized seizure, 2) in the rare event of a seizure, the staff will perform the following: a) stop TMS immediately, b) turn subject on their side to reduce chance of aspiration, c) protect the participant from falling or hitting their head or other injury, d) call 911, e) time the length of the seizure. In the event of a seizure, anti-seizure medication may be administered, at the discretion of the physician present. The CNRA outpatient clinic is situated on the south side of the Texas Medical Center, a 2.1 square mile medical district. There are several options for emergency rooms, all within 2 miles. The study physicians (Dr. de Quevedo and Michael Weaver) will be available via phone to address additional patient safety issues. Participants experiencing any severe side effects from the TMS administration will be referred to the study physician for examination and recommendations before continuation of the TMS administration. Participants experiencing the more common, milder side effects such as headache or neck pain, will be monitored and referred to the study physician if symptoms do not subside or improve with over-the-counter analgesic. In the unlikely event that the participant cannot tolerate the side effects (such as facial twitching), the intensity can be lowered to reduce these effects.

Diagnostic Procedures. The potential risk of participant discomfort associated with collection of sensitive information will be described in the informed consent process. Further, while participants may be uncomfortable reporting these issues, the risks of serious sequelae are extremely low. Confidentiality will be protected in several ways. All information collected solely for research purpose will be kept in locked, restricted access files. Participant records will be coded and filed by a number code. Participant identities will not be revealed in any publication of the data. Individual participant information will be transferred to outside sources only with the express written request of the participant. Participants will receive a copy of their signed consent form.

EEG Session. Before applying the EEG net, we will show participants how it feels to have the blunted needle (which is used to inject gel into the sensors) come in contact with the skin. We will ask participants frequently if applying the sensors is bothering them and will stop at the request of the participant. The consent form details what types of images will be shown on the screen and they will be told that we can stop the experiment at any time if they no longer want to view the images. The participants are instructed to notify the experimenter of an adverse emotional reactions and if a participant experiences an adverse emotional reaction to the images, the task will be stopped immediately. The participant will meet with a study therapist before leaving the CNRA to make sure it is safe for them to leave.

Potential Benefits of the Proposed Research to Participants

There are no potential benefits to the individuals participating in this pilot portion of the study. All assessment and treatment services provided in the main trial of this study will be at no cost to the participant. Based on prior studies, the treatment may help in lowering cocaine use. Participants will be informed of any new information discovered during the study that might impact their treatment for CUD or other problems.

Data and Safety Monitoring Plan

Data Monitoring

The data will be collected and stored as described in the research strategy and protection of human subjects, and will follow the typical protocols set in place by the Center for Neurobehavioral Research on Addiction (CNRA). The CNRA protocols include: 1) staff training, 2) weekly audit of data collection/entry by the CNRA Quality Assurance Manager, 3) medical screening with results reviewed by on-site physician, 4) use of standardized assessments, 5) collaboration with Dr. Suchting who oversees data analysis and management. All data entry forms will only be accessible to trained research staff and will require double entry. Dr. Webber will be responsible for ensuring the above-mentioned protocols are in place before and during the proposed study.

Safety Monitoring

The CNRA has a DSM Board set for all CNRA studies. The PI will be responsible for making the DSM Board aware of the new protocol upon study initiation and for yearly update meetings. The DSM Board members will consist of the following individuals: Jan Blalock, Ph.D., Dept. of Behavioral Science, MD Anderson Cancer Center; William E. Fann, M.D., Dept. of Psychiatry, Baylor College of Medicine; Claudia Pedroza, M.D., Dept. of Pediatrics, UTHealth; and Daryl Shorter, M.D., Dept. of Psychiatry, Baylor College of Medicine. These individuals have served previously on the DSMB at the CRNA and have the relevant expertise and experience in monitoring clinical trials. The members of the DSM Board will be responsible for: 1) reviewing the research protocol and plans for data and safety monitoring, 2) evaluating the study progress, including data quality, participant recruitment rates, retention rates, outcome and adverse experience data, and risk versus benefit profile, 3) making recommendations to terminate or make changes to the trial because of safety concerns, and 4) ensuring protect the confidentiality of the trial data and the results of monitoring.

All Adverse events (AE) will be collected and reported to the PI on a daily basis. AEs are collected before and after the iTBS sessions on the study visit day. As most side effects are minor and disappear rapidly after iTBS administration, participants will be told to contact the study coordinator if side effects persist after treatment at home with over-the-counter analgesics. The study physician will be informed of any relevant AEs following TMS and will determine course of treatment or discontinuation of the study, if necessary. AEs will be reported to the CPHS on an annual basis. Serious adverse events (SAE) will be reported immediately (verbally within 24 hours) to the CPHS, DSMB, and to NIDA (if funded). A written report will follow within three days and will include: date of the AE, description of the AE, severity rating (Grade 1 to 4), assessment of cause, whether the AE indicates an increased risk for current or future participants, and whether changes to the informed consent form are necessary.

REFERENCES

1. Pomara C, Cassano T, D'Errico S, et al. Data available on the extent of cocaine use and dependence: biochemistry, pharmacologic effects and global burden of disease of cocaine abusers. *Curr Med Chem*. 2012;19(33):5647-5657. Accessed May 11, 2018. http://www.ncbi.nlm.nih.gov/pubmed/22856655
2. Volkow ND, Wang G-J, Fowler JS, Tomasi D, Telang F. Addiction: Beyond dopamine reward circuitry. *Proc Natl Acad Sci*. 2011;108(37):15037-15042. doi:10.1073/pnas.1010654108
3. Moretti J, Poh EZ, Rodger J. rTMS-Induced Changes in Glutamatergic and Dopaminergic Systems: Relevance to Cocaine and Methamphetamine Use Disorders. *Front Neurosci*. 2020;14. doi:10.3389/fnins.2020.00137
4. Ma T, Sun Y, Ku Y. Effects of Non-invasive Brain Stimulation on Stimulant Craving in Users of Cocaine, Amphetamine, or Methamphetamine: A Systematic Review and Meta-Analysis. *Front Neurosci*. 2019;13:1095. doi:10.3389/fnins.2019.01095
5. Goldstein RZ, Tomasi D, Rajaram S, et al. Role of the anterior cingulate and medial orbitofrontal cortex in processing drug cues in cocaine addiction. *Neuroscience*. 2007;144(4):1153-1159. doi:10.1016/j.neuroscience.2006.11.024
6. Goldstein RZ, Alia-Klein N, Tomasi D, et al. Anterior cingulate cortex hypoactivations to an emotionally salient task in cocaine addiction. *Proc Natl Acad Sci U S A*. 2009;106(23):9453-9458. doi:10.1073/pnas.0900491106
7. Asensio S, Romero MJ, Palau C, et al. Altered neural response of the appetitive emotional system in cocaine addiction: An fMRI Study. *Addict Biol*. 2010;15(4):504-516. doi:10.1111/j.1369-1600.2010.00230.x
8. Goldstein RZ, Alia-Klein N, Tomasi D, et al. Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? *Am J Psychiatry*. 2007;164(1):43-51. doi:10.1176/ajp.2007.164.1.43
9. Gu H, Salmeron BJ, Ross TJ, et al. Mesocorticolimbic circuits are impaired in chronic cocaine users as demonstrated by resting-state functional connectivity. *Neuroimage*. 2010;53(2):593-601. doi:10.1016/j.neuroimage.2010.06.066
10. Parvaz MA, Moeller SJ, Malaker P, Sinha R, Alia-Klein N, Goldstein RZ. Abstinence reverses EEG-indexed attention bias between drug-related and pleasant stimuli in cocaine-addicted individuals. *J Psychiatry Neurosci*. 2017;42(2):78-86. doi:10.1503/jpn.150358
11. Burkhouse KL, Gorka SM, Klumpp H, et al. Neural responsiveness to reward as an index of depressive symptom change following cognitive-behavioral therapy and SSRI treatment. *J Clin Psychiatry*. 2018;79(4). doi:10.4088/JCP.17m11836
12. Robinson MJF, Robinson TE, Berridge KC. Incentive Salience and the Transition to Addiction. In: Miller PM, ed. *Biological Research on Addiction*. Academic Press, San Diego, CA; 2013:391-399. doi:10.1016/B978-0-12-398335-0.00039-X
13. Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F. Imaging dopamine's role in drug abuse and addiction. *Neuropharmacology*. 2009;56(SUPPL. 1):3-8. doi:10.1016/j.neuropharm.2008.05.022
14. Ashok AH, Mizuno Y, Volkow ND, Howes OD. Association of stimulant use with dopaminergic alterations in users of cocaine, amphetamine, or methamphetamine a systematic review and meta-analysis. *JAMA Psychiatry*. 2017;74(5):511-519. doi:10.1001/jamapsychiatry.2017.0135
15. BrainsWay. BrainsWay receives FDA clearance for smoking addiction in adults. Published 2020. Accessed November 17, 2020.https://www.globenewswire.com/news-release/2020/08/24/2082476/0/en/BrainsWay-Receives-FDA-Clearance-for-Smoking-Addiction-in-Adults.html
16. FDA. FDA permits marketing of TMS for obsessive compulsive disorder. Published 2018. Accessed November 17, 2020. https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-transcranial-magnetic-stimulation-treatment-obsessive-compulsive-disorder
17. Moeller SJ, Konova AB, Parvaz MA, et al. Functional, structural, and emotional correlates of impaired insight in cocaine addiction. *JAMA Psychiatry*. 2014;71(1):61-70. doi:10.1001/jamapsychiatry.2013.2833
18. Kober H, Mende-Siedlecki P, Kross EF, et al. Prefrontal-striatal pathway underlies cognitive regulation of craving. *Proc Natl Acad Sci U S A*. 2010;107(33):14811-14816. doi:10.1073/pnas.1007779107

19. Ochsner KN, Silvers JA, Buhle JT. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Ann N Y Acad Sci*. 2012;1251:E1-E24. doi:10.1111/j.1749-6632.2012.06751.x
20. Diana M. The dopamine hypothesis of drug addiction and its potential therapeutic value. *Front Psychiatry*. 2011;2(NOV):64. doi:10.3389/fpsyt.2011.00064
21. Bolloni C, Panella R, Pedetti M, et al. Bilateral Transcranial Magnetic Stimulation of the Prefrontal Cortex Reduces Cocaine Intake: A Pilot Study. *Front psychiatry*. 2016;7(AUG):133. doi:10.3389/fpsyt.2016.00133
22. Cardullo S, Gomez Perez LJ, Marconi L, et al. Clinical Improvements in Comorbid Gambling/Cocaine Use Disorder (GD/CUD) Patients Undergoing Repetitive Transcranial Magnetic Stimulation (rTMS). *J Clin Med*. 2019;8(6):768. doi:10.3390/jcm8060768
23. Pettorruso M, Spagnolo PA, Leggio L, et al. Repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex may improve symptoms of anhedonia in individuals with cocaine use disorder: A pilot study. *Brain Stimul*. 2018;11(5):1195-1197. doi:10.1016/j.brs.2018.06.001
24. Martinez D, Urban N, Grassetti A, et al. Transcranial magnetic stimulation of medial prefrontal and cingulate cortices reduces cocaine self-administration: A pilot study. *Front Psychiatry*. 2018;9(MAR):80. doi:10.3389/fpsyt.2018.00080
25. Pettorruso M, Martinotti G, Santacroce R, et al. rTMS Reduces Psychopathological Burden and Cocaine Consumption in Treatment-Seeking Subjects With Cocaine Use Disorder: An Open Label, Feasibility Study. *Front psychiatry*. 2019;10:621. doi:10.3389/fpsyt.2019.00621
26. Gómez Pérez LJ, Cardullo S, Cellini N, et al. Sleep quality improves during treatment with repetitive transcranial magnetic stimulation (rTMS) in patients with cocaine use disorder: A retrospective observational study. *BMC Psychiatry*. 2020;20(1). doi:10.1186/s12888-020-02568-2
27. Terraneo A, Leggio L, Saladini M, Ermani M, Bonci A, Gallimberti L. Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: A pilot study. *Eur Neuropsychopharmacol*. 2016;26(1):37-44. doi:10.1016/j.euroneuro.2015.11.011
28. Blumberger DM, Vila-Rodriguez F, Thorpe KE, et al. *Effectiveness of Theta Burst versus High-Frequency Repetitive Transcranial Magnetic Stimulation in Patients with Depression (THREE-D): A Randomised Non-Inferiority Trial*. Vol 391.; 2018. Accessed March 24, 2021. www.thelancet.com
29. Steele VR, Maxwell AM, Ross TJ, Stein EA, Salmeron BJ. Accelerated intermittent theta-burst stimulation as a treatment for cocaine use disorder: A proof-of-concept study. *Front Neurosci*. 2019;13(OCT). doi:10.3389/fnins.2019.01147
30. Sanna A, Fattore L, Badas P, Corona G, Cocco V, Diana M. Intermittent Theta Burst Stimulation of the Prefrontal Cortex in Cocaine Use Disorder: A Pilot Study. *Front Neurosci*. 2019;13(JUL):765. doi:10.3389/fnins.2019.00765
31. Downar J, Sankar A, Giacobbe P, Woodside B, Colton P. Unanticipated Rapid Remission of Refractory Bulimia Nervosa, during High-Dose Repetitive Transcranial Magnetic Stimulation of the Dorsomedial Prefrontal Cortex: A Case Report. *Front Psychiatry*. 2012;3(APR):30. doi:10.3389/fpsyt.2012.00030
32. Downar J, Geraci J, Salomons T V., et al. Anhedonia and Reward-Circuit Connectivity Distinguish Nonresponders from Responders to Dorsomedial Prefrontal Repetitive Transcranial Magnetic Stimulation in Major Depression. *Biol Psychiatry*. 2014;76(3):176-185. doi:10.1016/j.biopsych.2013.10.026
33. Persson J, Struckmann W, Gingnell M, Fällmar D, Bodén R. Intermittent theta burst stimulation over the dorsomedial prefrontal cortex modulates resting-state connectivity in depressive patients: A sham-controlled study. *Behav Brain Res*. 2020;394:112834. doi:10.1016/j.bbr.2020.112834
34. Patel KT, Stevens MC, Meda SA, et al. Robust changes in reward circuitry during reward loss in current and former cocaine users during performance of a monetary incentive delay task. *Biol Psychiatry*. 2013;74(7):529-537. doi:10.1016/j.biopsych.2013.04.029
35. Meade CS, Lowen SB, MacLean RR, Key MD, Lukas SE. FMRI brain activation during a delay discounting task in HIV-positive adults with and without cocaine dependence. *Psychiatry Res - Neuroimaging*.2011;192(3):167-175. doi:10.1016/j.pscychresns.2010.12.011
36. Hanlon CA, DeVries W, Dowdle LT, et al. A comprehensive study of sensorimotor cortex excitability in chronic cocaine users: Integrating TMS and functional MRI data. *Drug Alcohol Depend*. 2015;157:28-35. doi:10.1016/j.drugalcdep.2015.07.1196

37. Hanlon CA, Dowdle LT, Correia B, et al. Left frontal pole theta burst stimulation decreases orbitofrontal and insula activity in cocaine users and alcohol users. *Drug Alcohol Depend*. 2017;178:310-317. doi:10.1016/j.drugalcdep.2017.03.039
38. Hanlon CA, Dowdle LT, Moss H, Canterberry M, George MS. Mobilization of Medial and Lateral Frontal-Striatal Circuits in Cocaine Users and Controls: An Interleaved TMS/BOLD Functional Connectivity Study. *Neuropsychopharmacology*. 2016;41(13):3032-3041. doi:10.1038/npp.2016.114
39. Kearney-Ramos TE, Dowdle LT, Mithoefer OJ, Devries W, George MS, Hanlon CA. State-Dependent Effects of Ventromedial Prefrontal Cortex Continuous Thetaburst Stimulation on Cocaine Cue Reactivity in Chronic Cocaine Users. *Front Psychiatry*. 2019;10(MAY):317. doi:10.3389/fpsyt.2019.00317
40. Kearney-Ramos TE, Dowdle LT, Lench DH, et al. Transdiagnostic Effects of Ventromedial Prefrontal Cortex Transcranial Magnetic Stimulation on Cue Reactivity. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2018;3(7):599-609. doi:10.1016/j.bpsc.2018.03.016
41. Hanlon CA, Kearney-Ramos T, Dowdle LT, et al. Developing Repetitive Transcranial Magnetic Stimulation (rTMS) as a Treatment Tool for Cocaine Use Disorder: a Series of Six Translational Studies. *Curr Behav Neurosci reports*. 2017;4(4):341-352. doi:10.1007/s40473-017-0135-4
42. Moeller SJ, Hajcak G, Parvaz MA, Dunning JP, Volkow ND, Goldstein RZ. Psychophysiological prediction of choice: Relevance to insight and drug addiction. *Brain*. 2012;135(11):3481-3494. doi:10.1093/brain/aws252
43. Courtney KE, Schacht JP, Hutchison K, Roche DJO, Ray LA. Neural substrates of cue reactivity: Association with treatment outcomes and relapse. *Addict Biol*. 2016;21(1):3-22. doi:10.1111/adb.12314
44. Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F, Baler R. Addiction: Decreased reward sensitivity and increased expectation sensitivity conspire to overwhelm the brain's control circuit. *BioEssays*. 2010;32(9):748-755. doi:10.1002/bies.201000042
45. Thigpen NN, Kappenman ES, Keil A. Assessing the internal consistency of the event-related potential: An example analysis. *Psychophysiology*. 2017;54(1):123-138. doi:10.1111/psyp.12629
46. Kappenman ES, Luck SJ. Best Practices for Event-Related Potential Research in Clinical Populations. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2016;1(2):110-115. doi:10.1016/j.bpsc.2015.11.007
47. Webber HE, de Dios C, Wardle MC, et al. Electrophysiological Responses to Emotional and Cocaine Cues Reveal Individual Neuroaffective Profiles in Cocaine Users. *Exp Clin Psychopharmacol*. 2021;30(5):514-524. doi:10.1037/pha0000450
48. Proudfit GH. The reward positivity: From basic research on reward to a biomarker for depression. *Psychophysiology*. 2015;52(4):449-459. doi:10.1111/psyp.12370
49. Holroyd CB, Coles MGH. The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychol Rev*. 2002;109(4):679-709. doi:10.1037/0033-295X.109.4.679
50. Nieuwenhuis S, Slagter HA, Von Alting Geusau NJ, Heslenfeld DJ, Holroyd CB. Knowing good from bad: Differential activation of human cortical areas by positive and negative outcomes. *Eur J Neurosci*. 2005;21(11):3161-3168. doi:10.1111/j.1460-9568.2005.04152.x
51. Martin LE, Potts GF, Burton PC, Montague PR. Electrophysiological and hemodynamic responses to reward prediction violation. *Neuroreport*. 2009;20(13):1140-1143. doi:10.1097/WNR.0b013e32832f0dca
52. Carlson JM, Foti D, Mujica-Parodi LR, Harmon-Jones E, Hajcak G. Ventral striatal and medial prefrontal BOLD activation is correlated with reward-related electrocortical activity: A combined ERP and fMRI study. *Neuroimage*. 2011;57(4):1608-1616. doi:10.1016/j.neuroimage.2011.05.037
53. Hauser TU, Iannaccone R, Stämpfli P, et al. The feedback-related negativity (FRN) revisited: New insights into the localization, meaning and network organization. *Neuroimage*. 2014;84:159-168. doi:10.1016/j.neuroimage.2013.08.028
54. Becker MPI, Nitsch AM, Miltner WHR, Straube T. A Single-Trial Estimation of the Feedback-Related Negativity and Its Relation to BOLD Responses in a Time-Estimation Task. *J Neurosci*. 2014;34(8):3005-3012. doi:10.1523/JNEUROSCI.3684-13.2014
55. Warren CM, Hyman JM, Seamans JK, Holroyd CB. Feedback-related negativity observed in rodent anterior cingulate cortex. *J Physiol*. 2015;109(1-3):87-94. doi:10.1016/j.jphysparis.2014.08.008
56. Schutte I, Deschamps PKH, van Harten PN, Kenemans JL. Dopaminergic and noradrenergic manipulation of anticipatory reward and probability event-related potentials. *Psychopharmacology (Berl)*.2020;237(7):2019-

2030. doi:10.1007/s00213-020-05515-x
57. Foti D, Hajcak G. Genetic variation in dopamine moderates neural response during reward anticipation and delivery: Evidence from event-related potentials. *Psychophysiology*. 2012;49(5):617-626. doi:10.1111/j.1469-8986.2011.01343.x
58. Glazer J, King A, Yoon C, Liberzon I, Kitayama S. DRD4 polymorphisms modulate reward positivity and P3a in a gambling task: Exploring a genetic basis for cultural learning. *Psychophysiology*. 2020;57(10). doi:10.1111/psyp.13623
59. Soder HE, Webber TA, Bornovalova MA, Park JY, Potts GF. A Test of Dopamine Hyper- and Hyposensitivity in Alcohol Use Tendencies. *Manuscr Submitt Publ*. Published online 2018.
60. Jocham G, Ullsperger M. Neuropharmacology of performance monitoring. *Neurosci Biobehav Rev*. 2009;33(1):48-60. doi:10.1016/j.neubiorev.2008.08.011
61. Foti D, Carlson JM, Sauder CL, Proudfit GH. Reward dysfunction in major depression: Multimodal neuroimaging evidence for refining the melancholic phenotype. *Neuroimage*. 2014;101:50-58. doi:10.1016/j.neuroimage.2014.06.058
62. Proudfit GH. The reward positivity: From basic research on reward to a biomarker for depression. *Psychophysiology*. 2015;52(4):449-459. doi:10.1111/psyp.12370
63. Parvaz MA, Gabbay V, Malaker P, Goldstein RZ. Objective and specific tracking of anhedonia via event-related potentials in individuals with cocaine use disorders. *Drug Alcohol Depend*. 2016;164:158-165. doi:10.1016/j.drugalcdep.2016.05.004
64. Başar E, Başar-Eroglu C, Karakaş S, Schürmann M. Gamma, alpha, delta, and theta oscillations govern cognitive processes. *Int J Psychophysiol*. 2001;39(2-3):241-248. doi:10.1016/S0167-8760(00)00145-8
65. Cavanagh JF, Zambrano-Vazquez L, Allen JJB. Theta lingua franca: A common mid-frontal substrate for action monitoring processes. *Psychophysiology*. 2012;49(2):220-238. doi:10.1111/j.1469-8986.2011.01293.x
66. Cohen MX, Elger CE, Ranganath C. Reward expectation modulates feedback-related negativity and EEG spectra. *Neuroimage*. 2007;35(2):968-978. doi:10.1016/j.neuroimage.2006.11.056
67. Foti D, Weinberg A, Bernat EM, Proudfit GH. Anterior cingulate activity to monetary loss and basal ganglia activity to monetary gain uniquely contribute to the feedback negativity. *Clin Neurophysiol*. 2015;126(7):1338-1347. doi:10.1016/j.clinph.2014.08.025
68. Bernat EM, Nelson LD, Steele VR, Gehring WJ, Patrick CJ. Externalizing Psychopathology and Gain-Loss Feedback in a Simulated Gambling Task: Dissociable Components of Brain Response Revealed by Time-Frequency Analysis. *J Abnorm Psychol*. 2011;120(2):352-364. doi:10.1037/a0022124
69. Bernat EM, Nelson LD, Holroyd CB, Gehring WJ, Patrick CJ. Separating cognitive processes with principal components analysis of EEG time-frequency distributions. In: Luk FT, ed. *Advanced Signal Processing Algorithms, Architectures, and Implementations XVIII*. Vol 7074. SPIE; 2008:70740S. doi:10.1117/12.801362
70. Bernat EM, Nelson LD, Baskin-Sommers AR. Time-frequency theta and delta measures index separable components of feedback processing in a gambling task. *Psychophysiology*. 2015;52(5):626-637. doi:10.1111/psyp.12390
71. Watts ATM, Bernat EM. Effects of reward context on feedback processing as indexed by time-frequency analysis. *Psychophysiology*. 2018;55(9):e13195. doi:10.1111/psyp.13195
72. Baker TE, Lesperance P, Tucholka A, et al. Reversing the Atypical Valuation of Drug and Nondrug Rewards in Smokers Using Multimodal Neuroimaging. *Biol Psychiatry*. 2017;82(11):819-827. doi:10.1016/j.biopsych.2017.01.015
73. Baker TE, Lin MH, Gueth M, Biernacki K, Parikh S. Beyond the Motor Cortex: Theta Burst Stimulation of the Anterior Midcingulate Cortex. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2020;5(11):1052-1060. doi:10.1016/j.bpsc.2020.06.009
74. Webber TA, Soder HE, Potts GF, Bornovalova MA. Preliminary evidence that digit length ratio (2D:4D) predicts neural response to delivery of motivational stimuli. *Biol Psychol*. 2018;132:91-95. doi:10.1016/j.biopsycho.2017.11.008
75. Webb CA, Auerbach RP, Bondy E, Stanton CH, Appleman L, Pizzagalli DA. Reward-Related Neural Predictors and Mechanisms of Symptom Change in Cognitive Behavioral Therapy for Depressed Adolescent Girls. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2021;6(1):39-49. doi:10.1016/j.bpsc.2020.07.010

76. Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn Sci*. 2011;15(2):85-93. doi:10.1016/j.tics.2010.11.004
77. Eickhoff SB, Laird AR, Fox PT, Bzdok D, Hensel L. Functional Segregation of the Human Dorsomedial Prefrontal Cortex. *Cereb Cortex*. 2016;26(1):304-321. doi:10.1093/cercor/bhu250
78. Lang PJ, Bradley MM. Emotion and the motivational brain. *Biol Psychol*. 2010;84(3):437-450. doi:10.1016/j.biopsycho.2009.10.007
79. Olofsson JK, Nordin S, Sequeira H, Polich J. Affective picture processing: An integrative review of ERP findings. *Biol Psychol*. 2008;77(3):247-265. doi:10.1016/j.biopsycho.2007.11.006
80. Schupp H, Cuthbert BN, Bradley MM, Cacioppo JT, Ito T, Lang PJ. Affective picture processing: The late positive potential is modulated by motivational relevance. *Psychophysiology*. 2000;37(2):257-261. doi:10.1111/1469-8986.3720257
81. Versace F, Lam CY, Engelmann JM, et al. Beyond cue reactivity: Blunted brain responses to pleasant stimuli predict long-term smoking abstinence. *Addict Biol*. 2012;17(6):991-1000. doi:10.1111/j.1369-1600.2011.00372.x
82. Engelmann JM, Versace F, Gewirtz JC, Cinciripini PM. Individual differences in brain responses to cigarette-related cues and pleasant stimuli in young smokers. *Drug Alcohol Depend*. 2016;163:229-235. doi:10.1016/j.drugalcdep.2016.04.025
83. Dunning JP, Parvaz MA, Hajcak G, et al. Motivated attention to cocaine and emotional cues in abstinent and current cocaine users - an ERP study. *Eur J Neurosci*. 2011;33(9):1716-1723. doi:10.1111/j.1460-9568.2011.07663.x
84. Franken IHA, Dietvorst RC, Hesselmans M, Franzek EJ, Van De Wetering BJM, Van Strien JW. Cocaine craving is associated with electrophysiological brain responses to cocaine-related stimuli. *Addict Biol*. 2008;13(3-4):386-392. doi:10.1111/j.1369-1600.2008.00100.x
85. Liu Y, Huang H, McGinnis-Deweese M, Keil A, Ding M. Neural substrate of the late positive potential in emotional processing. *J Neurosci*. 2012;32(42):14563-14572. doi:10.1523/JNEUROSCI.3109-12.2012
86. Sabatinelli D, Keil A, Frank DW, Lang PJ. Emotional perception: Correspondence of early and late event-related potentials with cortical and subcortical functional MRI. *Biol Psychol*. 2013;92(3):513-519. doi:10.1016/j.biopsycho.2012.04.005
87. Sabatinelli D, Lang PJ, Keil A, Bradley MM. Emotional perception: Correlation of functional MRI and event-related potentials. *Cereb Cortex*. 2007;17(5):1085-1091. doi:10.1093/cercor/bhl017
88. Hickey C, Peelen M V. Neural mechanisms of incentive salience in naturalistic human vision. *Neuron*. 2015;85(3):512-518. doi:10.1016/j.neuron.2014.12.049
89. Parvaz MA, Moeller SJ, Goldstein RZ. Incubation of cue-induced craving in adults addicted to cocaine measured by electroencephalography. *JAMA Psychiatry*. 2016;73(11):1127-1134. doi:10.1001/jamapsychiatry.2016.2181
90. Engelmann JM, Versace F, Robinson JD, et al. Neural substrates of smoking cue reactivity: A meta-analysis of fMRI studies. *Neuroimage*. 2012;60(1):252-262. doi:10.1016/j.neuroimage.2011.12.024
91. Baker TE, Lesperance P, Tucholka A, et al. Reversing the Atypical Valuation of Drug and Nondrug Rewards in Smokers Using Multimodal Neuroimaging. Published online 2017. doi:10.1016/j.biopsych.2017.01.015
92. Baker TE, Wood JMA, Holroyd CB. Atypical valuation of monetary and cigarette rewards in substance dependent smokers. Published online 2016. doi:10.1016/j.clinph.2015.11.002
93. Cano M, Oh S, Salas-Wright CP, Vaughn MG. Cocaine use and overdose mortality in the United States: Evidence from two national data sources, 2002–2018. *Drug Alcohol Depend*. 2020;214:108148. doi:10.1016/j.drugalcdep.2020.108148
94. First MB, Williams JBW, Karg RS, Spitzer RL. *Structured Clinical Interview for DSM-V Research Version*. American Psychiatric Association Publishing; 2015.
95. Posner K, Brown GK, Stanley B, et al. The Columbia-suicide severity rating scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266-1277. doi:10.1176/appi.ajp.2011.10111704
96. Hoff LA, Hallisey BJ, Brown L, Hoff MR. *People in Crisis: Clinical and Diversity Perspectives*. Taylor & Francis; 2011. Accessed January 23, 2022. https://books.google.com/books?hl=en&lr=&id=V12AUbxubNEC&oi=fnd&pg=PP1&dq=People+in+crisis:+Clinical+and+diversity+perspectives+&ots=9AtPhnCmmp&sig=FBPee-SOhBUvOEzRL2NVjKmNIF8#v=onepage&q=People

in crisis%3A Clinical and diversity perspectives&f=false
97. Keel JC, Smith MJ, Wassermann EM. A safety screening questionnaire for transcranial magnetic stimulation. *Clin Neurophysiol*. 2001;112(4):720. doi:10.1016/S1388-2457(00)00518-6
98. Mir-Moghtadaei A, Giacobbe P, Daskalakis ZJ, Blumberger DM, Downar J. Validation of a 25% Nasion–Inion Heuristic for Locating the Dorsomedial Prefrontal Cortex for Repetitive Transcranial Magnetic Stimulation. *Brain Stimul*. 2016;9(5):793-795. doi:10.1016/j.brs.2016.05.010
99. Ryan J, Pouliot JJ, Hajcak G, Nee DE. Manipulating Reward Sensitivity Using Reward Circuit–Targeted Transcranial Magnetic Stimulation. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2022;7(8):833-840. doi:10.1016/j.bpsc.2022.02.011
100. Fitzgerald PB, Hoy KE, Elliot D, Susan McQueen RN, Wambeek LE, Daskalakis ZJ. Accelerated repetitive transcranial magnetic stimulation in the treatment of depression. *Neuropsychopharmacology*. 2018;43(7):1565-1572. doi:10.1038/s41386-018-0009-9
101. Dunning JP, Parvaz MA, Hajcak G, et al. Motivated attention to cocaine and emotional cues in abstinent and current cocaine users - an ERP study. *Eur J Neurosci*. 2011;33(9):1716-1723. doi:10.1111/j.1460-9568.2011.07663.x
102. Sobell LC, Sobell MB. Timeline Follow-Back. In: *Measuring Alcohol Consumption*. Humana Press; 1992:41-72. doi:10.1007/978-1-4612-0357-5_3
103. Halikas JA, Kuhn KL, Crosby R, Carlson G, Crea F. The measurement of craving in cocaine patients using the minnesota cocaine craving scale. *Compr Psychiatry*. 1991;32(1):22-27. doi:10.1016/0010-440X(91)90066-L
104. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *J Am Geriatr Soc*. 2005;53(4):695-699. doi:10.1111/J.1532-5415.2005.53221.X
105. Campbell JC, Webster DW, Glass N. The danger assessment: Validation of a lethality risk assessment instrument for intimate partner femicide. *J Interpers Violence*. 2009;24(4):653-674. doi:10.1177/0886260508317180
106. Patton JH, Stanford MS, Barratt ES. Factor structure of the barratt impulsiveness scale. *J Clin Psychol*. 1995;51(6):768-774. doi:10.1002/1097-4679(199511)51:6<768::AID-JCLP2270510607>3.0.CO;2-1
107. Frank MJ, Seeberger LC, O'Reilly RC. By carrot or by stick: Cognitive reinforcement learning in Parkinsonism. *Science (80-)*. 2004;306(5703):1940-1943. doi:10.1126/SCIENCE.1102941/SUPPL_FILE/FRANK.SOM.PDF
108. Guitart-Masip M, Huys QJM, Fuentemilla L, Dayan P, Duzel E, Dolan RJ. Go and no-go learning in reward and punishment: Interactions between affect and effect. *Neuroimage*. 2012;62(1):154-166. doi:10.1016/J.NEUROIMAGE.2012.04.024
109. Guitart-Masip M, Fuentemilla L, Bach DR, et al. Behavioral/Systems/Cognitive Action Dominates Valence in Anticipatory Representations in the Human Striatum and Dopaminergic Midbrain. Published online 2011. doi:10.1523/JNEUROSCI.6376-10.2011
110. Cavanagh JF, Eisenberg I, Guitart-Masip M, Huys Q, Frank MJ. Frontal theta overrides Pavlovian learning biases. *J Neurosci*. 2013;33(19):8541-8548. doi:10.1523/JNEUROSCI.5754-12.2013
111. Moro AS, Saccenti D, Ferro M, Scaini S, Malgaroli A, Lamanna J. Neural Correlates of Delay Discounting in the Light of Brain Imaging and Non-Invasive Brain Stimulation: What We Know and What Is Missed. *Brain Sci*. 2023;13(3):403. doi:10.3390/brainsci13030403
112. Koffarnus MN, Bickel WK. A 5-trial adjusting delay discounting task: Accurate discount rates in less than one minute. *Exp Clin Psychopharmacol*. 2014;22(3):222-228. doi:10.1037/a0035973
113. Yoon JH, de Dios C, Suchting R, et al. Initial development of a brief assessment of cocaine demand. *Behav Pharmacol*. 2021;32(4):351-355. doi:10.1097/fbp.0000000000000617
114. Yoon JH, Suchting R, de Dios C, et al. Decreased cocaine demand following contingency management treatment. *Drug Alcohol Depend*. 2021;226:108883. doi:10.1016/J.DRUGALCDEP.2021.108883
115. Shacham S. A Shortened Version of the Profile of Mood States. *J Pers Assess*. 1983;47(3):305-306. doi:10.1207/S15327752JPA4703_14
116. Buysse DJ, Yu L, Moul DE, et al. 781 Patient-Reported Outcome Measures-Buysse et al PATIENT-REPORTED OUTCOMES OF SLEEP DISTURBANCE Development and Validation of Patient-Reported Outcome Measures for Sleep Disturbance and Sleep-Related Impairments. *Sleep*. 2010;33(6). Accessed February 28, 2022. www.journalsleep.
117. Yu L, Buysse DJ, Germain A, et al. Development of Short Forms from the PROMIS Sleep Disturbance and Sleep-

Related Impairment Item Banks. *Behav Sleep Med*. 2011;10(1):6. doi:10.1080/15402002.2012.636266
118. Kampman KM, Volpicelli JR, Mcginnis DE, et al. Reliability and validity of the cocaine selective severity assessment. *Addict Behav*. 1998;23(4):449-461. doi:10.1016/S0306-4603(98)00011-2
119. Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. *J Psychiatr Res*. 2011;45(5):626-629. doi:10.1016/j.jpsychires.2010.10.008
120. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet*. 2000;355(9209):1064-1069. doi:10.1016/S0140-6736(00)02039-0
121. Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. *Stat Med Stat Med*. 2002;21:2917-2930. doi:10.1002/sim.1296
122. 3.5.1. RDCT. A Language and Environment for Statistical Computing. *R Found Stat Comput*. 2018;2:https://www.R-project.org.
123. Bates D, Machler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. Published online 2014. http://dx.doi.org/10.18637/jss.v067.i01
124. Stan Development Team. RStan: The R interface to Stan. R package version 2.18.2. Published online 2018.
125. Bürkner PC. brms: An R package for Bayesian multilevel models using Stan. *J Stat Softw*. 2017;80:1-28. doi:10.18637/jss.v080.i01
126. Wijeysundera DN, Austin PC, Hux JE, Beattie WS, Laupacis A. Bayesian statistical inference enhances the interpretation of contemporary randomized controlled trials. *J Clin Epidemiol*. 2009;62(1):13-21.e5. doi:10.1016/j.jclinepi.2008.07.006
127. McElreath R. *Statistical Rethinking: A Bayesian Course with Examples in R and Stan*. CRC Press, LLC; 2018. doi:10.1201/9781315372495
128. Gelman A, Carlin JB, Stern HS, Dunson D., Vehtari A, Rubin DB. *Bayesian Data Analysis (3rd Ed.)*. 3rd ed. CRC Press, LLC; 2013.
129. Spiegelhalter DJ. Incorporating Bayesian Ideas into Health-Care Evaluation. *Stat Sci*. 2004;19(1):156-174. doi:10.1214/088342304000000080
130. Jeffreys H. *Theory of Probability*. 3rd ed. Oxford University Press; 2006. doi:10.2307/3619118
131. Lee MD, Wagenmakers EJ. *Bayesian Cognitive Modeling: A Practical Course*. Cambridge University Press; 2013. doi:10.1017/CBO9781139087759
132. Berry DA. A guide to drug discovery: Bayesian clinical trials. *Nat Rev Drug Discov*.2006;5(1):27-36. doi:10.1038/nrd1927
133. Vehtari A, Gelman A, Gabry J. Practical Bayesian model evaluation using leave-one-out cross-validation and WAIC. *Stat Comput*. 2016;27(5):1413-1432. Accessed July 31, 2018. https://github.com/stan-dev/loo.
134. Carvalho CM, Polson NG, Scott JG. The horseshoe estimator for sparse signals. *Biometrika*. 2010;97(2):465-480. doi:10.1093/biomet/asq017
135. Piironen J, Vehtari A. *Sparsity Information and Regularization in the Horseshoe and Other Shrinkage Priors*.
136. Little RJA. A test of missing completely at random for multivariate data with missing values. *J Am Stat Assoc*. 1988;83(404):1198-1202. doi:10.1080/01621459.1988.10478722
137. Park T, Lee S-Y. A test of missing completely at random for longitudinal data with missing observations. *Stat Med*. 1997;16(16):1859-1871. doi:10.1002/(SICI)1097-0258(19970830)16:16<1859::AID-SIM593>3.0.CO;2-3
138. Best N, Thomas A. Generalized Linear Models: A Bayesian Perspective. In: *Generalized Linear Models: A Bayesian Perspective*. Marcel Dekker, Inc; 2000. Accessed April 26, 2021. https://books.google.com/books?hl=en&lr=&id=Y5AARf7oTNkC&oi=fnd&pg=PA387&dq=Bayeisan+Graphical+Models+and+Software+for+GLMs&ots=80WecFpr8y&sig=4Vde4uYsviJ3J30WUtZ6_m2_5sA#v=onepage&q=Bayeisan Graphical Models and Software for GLMs&f=false
139. Fitzmaurice GM. Generalized linear mixture models for handling nonignorable dropouts in longitudinal studies. *Biostatistics*. 2000;1(2):141-156. doi:10.1093/biostatistics/1.2.141
140. Lilford RJ, Thornton JG, Braunholtz D. Clinical trials and rare diseases: a way out of a conundrum. *BMJ*. 1995;311(7020):1621-1625. doi:10.1136/bmj.311.7020.1621
141. Górska N, Słupski J, Cubała WJ. Antipsychotic drugs in epilepsy. *Neurol Neurochir Pol*. 2019;53(6):408-412. doi:10.5603/PJNNS.A2019.0052

142. Stultz DJ, Osburn S, Burns T, Pawlowska-Wajswol S, Walton R. Transcranial Magnetic Stimulation (TMS) Safety with Respect to Seizures: A Literature Review. *Neuropsychiatr Dis Treat*. 2020;16:2989. doi:10.2147/NDT.S276635
143. Madeo G, Terraneo A, Cardullo S, et al. Long-Term Outcome of Repetitive Transcranial Magnetic Stimulation in a Large Cohort of Patients With Cocaine-Use Disorder: An Observational Study. *Front Psychiatry*. 2020;11:158. doi:10.3389/fpsyt.2020.00158
144. Lowe CJ, Manocchio F, Safati AB, Hall PA. The effects of theta burst stimulation (TBS) targeting the prefrontal cortex on executive functioning: A systematic review and meta-analysis. *Neuropsychologia*. 2018;111:344-359. doi:10.1016/j.neuropsychologia.2018.02.004
145. Wang L-J, Mu L-L, Ren Z-X, et al. Predictive Role of Executive Function in the Efficacy of Intermittent Theta Burst Transcranial Magnetic Stimulation Modalities for Treating Methamphetamine Use Disorder—A Randomized Clinical Trial. *Front Psychiatry*. 2021;12:774192. doi:10.3389/FPSYT.2021.774192