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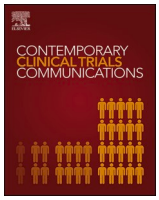

# Left ventromedial prefrontal cortex inhibitory rTMS as an anti-stress intervention in opioid use disorder: Trial design

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ABSTRACT

*Background:* In people with substance use disorders (SUDs), stress-exposure can impair executive function, and increase craving and likelihood of drug-use recurrence. Research shows that acute stressors increase drug-seeking behavior; however, mechanisms underlying this effect are incompletely understood. The Competing Neurobehavioral Decisions System theory posits that persons with SUDs may have hyperactive limbic reward circuitry and hypoactive executive control circuitry.

*Objective:* To investigate how inhibitory repetitive transcranial magnetic stimulation (rTMS) targeting the left ventromedial prefrontal cortex (vmPFC) may alter stress-induced executive dysfunction, emotion dysregulation, and drug-seeking in people with opioid use disorder.

*Methods:* We will examine effects of a psychological stressor combined with inhibitory (1Hz) left vmPFC rTMS in participants (N = 24) receiving opioid agonist treatment. Participants undergo guided imagery of autobiographical stressors paired with 10 sessions of active vmPFC rTMS vs. sham (within-subject randomized crossover). Stress-induced dysfunction will be indexed with cognitive (e.g., executive function), affective (e.g., emotional arousal), and behavioral (e.g., opioid-seeking) measures pre- and post-rTMS. To confirm changes are associated with altered neural activity in targeted regions, we will measure event-related potentials during key tasks using EEG. We hypothesize that stressors will increase executive dysfunction, emotion dysregulation, and drug-seeking, and that left vmPFC inhibitory rTMS will decrease limbic activation, which could translate to reduced craving and drug-seeking.

*Conclusion:* Our findings should offer insights into how neural networks modulate drug-seeking and associated dysfunctions in people with SUDs. The results of this and similar studies can advance theory and neuromodulation interventions for people with SUDs.

## 1. Introduction

### 1.1. Overview

Opioid use disorder (OUD) is a chronic, relapsing condition that is highly prevalent, disabling, and costly [1,2]. It is characterized by continued use of opioids despite negative consequences. Diagnoses of OUD have risen significantly over the past decade; in 2020, more than a half million people in the United States had a heroin use disorder and a further 2.3 million had a substance use disorder (SUD) involving prescription opioids [3].

Stress-exposure is problematic for people trying to recover from any SUD because it weakens inhibition of automatic behaviors (e.g., habitual substance use), impairs goal-directed behavior, and may increase drug craving and return to use [4–9]. In naturalistic observational studies, subjective stress severity positively correlates with craving severity [10,11]. Stress may alter activation of prefrontal cortices implicated in goal-directed behavior [12,13]. Furthermore, stressors impact motivational circuits that regulate self-control [14] especially limbic circuitry, thus promoting arousal and sensitivity to drug cues [11,15]. Understanding neural mechanisms by which stress-reactivity affects executive function is vital for developing interventions to improve treatment outcomes for people with SUD.

The Competing Neurobehavioral Decisions System (CNDS) model is

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a dual-systems model developed to account for apparent reduced self-control seen in people with SUDs [16,17]. The CNDS model suggests that people with SUDs have altered function and connectivity in frontocortical executive control regions such as the dorsolateral prefrontal cortex (dlPFC) and frontocortical limbic regions such as the medial PFC (mPFC) [18,19]. Specifically, dysfunction may occur in two fronto-striatal circuits: (1) increased limbic circuit activation resulting in hyper-sensitivity to drug cues; and (2) decreased executive control that diminishes ability to resist drug-craving. This CNDS model helps to explain why a person may continue drug use despite desiring or planning to stop [20]. These circuits are similarly impacted by acute stressors; however, the mechanisms by which this occurs are unclear.

Interventions that modulate dysfunctional neural pathways associated with SUDs offer a novel approach for improving SUD treatment efficacy. Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation (NIBS) technique that alters brain functioning by passing an alternating current through an electromagnetic coil placed on the scalp to generate a magnetic field, thereby inducing current in the neural region under the coil [21]. Repetitive TMS (rTMS) with multiple pulses over a short period of time is used for treatment because it induces longer-lasting effects compared to single or dual-pulse TMS [22]. rTMS is a promising tool for modulating emotion, cognition, and behavior. When treating psychiatric disorders, targeting one area of a neural network produces downstream effects in that network [23,24]. Findings from neuromodulation studies support a 'top-down' role in stress-reactivity [25,26]. For individuals with SUD, rTMS *in the absence of stress* appears to reduce drug craving and use [27–31]. Left dlPFC rTMS can improve executive function and may reduce stress-reactivity [32–34], and most studies using neuromodulation in SUDs have focused on this location. Alternatively, findings from neuroimaging and neuromodulation studies highlight the role of increased limbic activation under stress [35,36]. Multiple sessions of rTMS may be efficacious in reducing craving and substance use in people with SUDs seeking treatment [37,38], but the optimal target(s) and mechanisms of effects remain unknown. This lays the groundwork for developing rTMS targets and protocols for SUDs.

### 1.2. Summary and aims

Individuals with SUD may experience elevated limbic activity and diminished executive control via fronto-striatal circuit dysfunction, which may be augmented during stress-reactivity. We theorize left ventromedial PFC (vmPFC) inhibitory rTMS will decrease limbic activation, which could reduce anxiety, craving and substance use. Although CNDS theory indicates both dlPFC and vmPFC could be useful targets, we chose the vmPFC because it is associated with hyperactive limbic activity believed to drive stress-induced dysfunction. Most research thus far has focused on the dlPFC; there is a paucity of data on the effects of vmPFC rTMS.

**Aim 1** *examines effects of guided imagery stress on emotional arousal, executive function, and opioid motivation*. The primary behavioral outcomes are Wisconsin Card Sort Task (WCST) total errors, average Emotional Arousal Task (EAT) arousal rating to aversive vs. neutral images, and Drug Money Choice Task (DMCT) breakpoint. We hypothesize that relative to no-stress control condition, guided-imagery stressor will increase emotional arousal (i.e., increase in arousal rating for aversive [vs. neutral] images), decrease executive function (i.e., increase WCST total errors), and increase opioid-seeking behavior (i.e., increase in DMCT breakpoint). **Aims 2, 3 and 4** *examine effects of inhibiting vmPFC activity on stress-induced emotional arousal, stress-induced executive dysfunction, and opioid motivation, respectively*. The primary behavioral outcome for executive function is the WCST total error score, and the secondary neural outcome is average P300 amplitude during WCST error trials. The primary behavioral outcome for emotional arousal is average arousal rating to aversive vs. neutral images and the secondary neural outcome is average LPP amplitude to aversive vs. neutral images. The primary outcome for opioid motivation is the DMCT breakpoint. ERP measures for this outcome are exploratory, average P300 and LPP amplitudes will be measured following drug/money choices. We hypothesize that during stress, inhibitory relative to sham vmPFC rTMS will decrease the effects of stress on executive dysfunction, arousal to aversive images, and drug-choice motivation. Section 2.4 discusses these aims in detail.

## 2. Methods

### 2.1. Study design

A within-subjects randomized crossover, sham-controlled, double-blind design is being used to examine effects of 1Hz vmPFC rTMS in people with OUD receiving agonist medications for OUD (MOUD). The general protocol is identical for active and sham treatment and consists of ten, 30-min rTMS sessions delivered over 3 days. Throughout each session, subjective and physiological stress effects are assessed. Stress-induced dysfunction is indexed with carefully-selected cognitive (e.g., executive functioning), affective (e.g., emotional arousal), and behavioral (e.g., opioid-seeking) measures pre- and post-rTMS. To confirm changes are associated with altered neural activity in targeted regions, we measure event-related potentials (ERPs) during key tasks. The study received approval from the Wayne State University Institutional Review Board and is registered on ClinicalTrials.gov (NCT04920864); recruitment occurred between October 2021 and July 2024, enrollment is now complete, and data analysis is underway. Informed consent is obtained from all subjects prior to study enrollment. Participants are compensated for their time.

#### 2.1.1. Experimental procedures

Each participant completes two 3-day treatment protocol sessions (active rTMS and sham), each approximately 1-week apart. Participants complete an assessment battery on the day prior to starting the rTMS protocol (Assessment Visits 1 and 3) and immediately after the final two rTMS sessions (Assessment Visits 2 and 4). Fig. 1 shows the full study timeline. Assessment Visit 5 occurs ~1 week after Assessment Visit 4.

All Assessment Visits are structured identically. Supplementary Fig. 1 outlines the structure of the Assessment Visit Day and periodic measures. Participants are instructed to take their methadone/buprenorphine dose as usual that morning and smoke cigarettes as desired until the start of the session. At each Assessment Visit prior to testing, we evaluate past-week substance use with a standardized interview and confirmatory urine drug and breath alcohol tests. During rTMS treatment protocol visits, past 24-hr substance use is assessed via interview and confirmed using urine drug and breath alcohol tests.

### 2.2. Participant recruitment & selection

Participants are recruited from the Detroit metropolitan area via advertisements in local SUD treatment clinics and online message boards (e.g., Craigslist). Interested individuals complete a brief standardized phone or online screening to determine potential eligibility. Individuals who complete the preliminary screening and are not initially excluded are scheduled for in-person screening (~6 h).

At in-person screening, informed consent is obtained and current sobriety from alcohol is verified (expired breath alcohol concentration <0.02 %). Participants are also asked whether they are currently intoxicated on any other substance and if they answer "yes" or the person running the visit believes they are intoxicated then they will be asked to reschedule for a time when they are not intoxicated. Participants are then eligible to complete the remainder of the screening, including: self-report measures of substance use and medical history, Structured Clinical Interview for DSM-5 (SCID-5) conducted by a masters-level trained clinical psychology student, vital signs measurement (resting blood pressure, heart rate, blood oxygen saturation), and

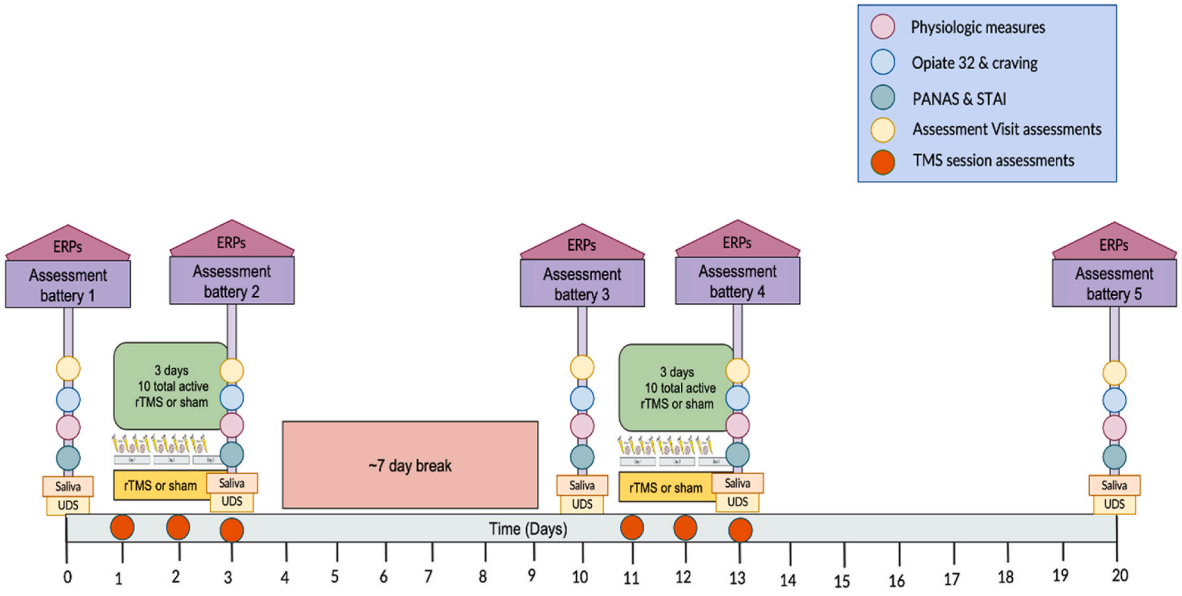


**Fig. 1.** Full study timeline.

TMS contraindications screening questionnaire (self-report). Eligibility requirements are shown in Table 1.

### 2.3. Study protocols

#### 2.3.1. Stress induction

Most studies exploring stress-reactivity use psychological and/or physical stressors [12,39,40] and caution is required when inducing stress in a treatment population. We use a guided-imagery stressor following research by Sinha et al. [6,41,42]. To ensure guided imagery is conducted correctly and induces the desired response, we conduct scene-development interviews during screening and a training session using a neutral guided-imagery scenario. We develop 3 individual stress scripts per participant; each can be used up to 2 times at random across the 5 assessment days. To ensure participants do not leave the visit feeling overly stressed, all participants complete a 10-min guided relaxation at the end of each assessment visit [6,41]. All stress and relaxation scripts are reviewed by a clinical psychologist (LHL) and rated using the Independent Scene Evaluation by at least 3 independent evaluators [9].

**Table 1**
Study inclusion and exclusion criteria.

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| (1) Meet lifetime DSM-5 criteria for OUD;<br>(2) In methadone or buprenorphine treatment for OUD;<br>(3) Age 21–70 yr;<br>(4) Right-handed;<br>(5) Males and non-pregnant/non-lactating females;<br>(6) Cognitively intact (total IQ score >80); | 1) Acutely under the influence of any substance, except methadone or buprenorphine;<br>2) Current, regular (>3 times/week) use of illicit drugs other than opioids;<br>3) Current alcohol and/or cannabis use >3 times per week, where each "time" was <3 alcoholic drinks or 1 marijuana "joint" equivalent;<br>4) Any past 24-hr use of drugs other than opioids or nicotine;<br>5) Medical conditions prohibiting the use of rTMS;<br>6) Lifetime psychotic, bipolar, or potentially antisocial personality disorder (the latter judged by clinician to pose risk to staff);<br>7) Untreated or uncontrolled past-year diagnosis of major depression, generalized anxiety disorder, obsessive compulsive disorder, or post-traumatic stress disorder;<br>8) Past-month SUD other than OUD or tobacco use disorder;<br>9) Acute/unstable illness making it unsafe for participation;<br>10) Any prohibited medications including medications that lower seizure threshold; certain psychiatric medications, or prescription pain medications; or 11) Chronic head or neck pain. |

#### 2.3.2. rTMS protocol

We use a Figure-of-8 (Fo8) coil to target the vmPFC. Low-frequency (1Hz) stimulation consists of 1800 pulses delivered continuously over 30-min. Each participant receives ten 30-min rTMS sessions over 3 days. Four sessions occur each day on days 1–2, and two sessions occur on day 3, with each session (within day) separated by ~30 min [28]. Fig. 2 illustrates an individual stimulation session visit. Research evidence suggests mental state during rTMS stimulation can impact response to rTMS [28]. Thus, standardizing participant mental state during sessions is important. Exposure to drug cues during rTMS for SUDs may increase rTMS effectiveness [43]; therefore, participants view a randomized series of drug-cue images and videos related to their preferred method of opioid administration (injection or non-injection). The list of drug images is available upon request.

Stimulation occurs at 110 % of resting motor threshold (RMT). To determine RMT, single-pulse TMS is used by placing the Fo8 coil on the scalp position of the *abductor pollicis brevis* muscle (thumb flexion). RMT is defined as the lowest TMS power setting that produces motor evoked potentials of ≥50 μV peak-to-peak amplitude on ≥50 % of trials. Alongside visual verification, EMG recording (1000Hz sampling) over the *abductor pollicis brevis* is used to monitor responses to TMS. Neuronavigation with a standardized MRI is used to locate the rTMS target site (left vmPFC) using the EEG 10-20 marker FP1 to represent this location; this method accounts for variability in skull size and was previously validated [44]. For the control (sham) condition, a placebo Fo8 coil (MagStim Rapid$^2$), which looks identical to the active coil, allows the same scalp placement, produces comparable auditory and tactile sensations as active stimulation without inducing an electromagnetic field, and enables double-blinded administration. Credibility of sham rTMS is routinely evaluated with a question to identify whether the participant believes they received active or sham rTMS during their visit: "*Do you think that you received the active or the sham rTMS protocol at today's*

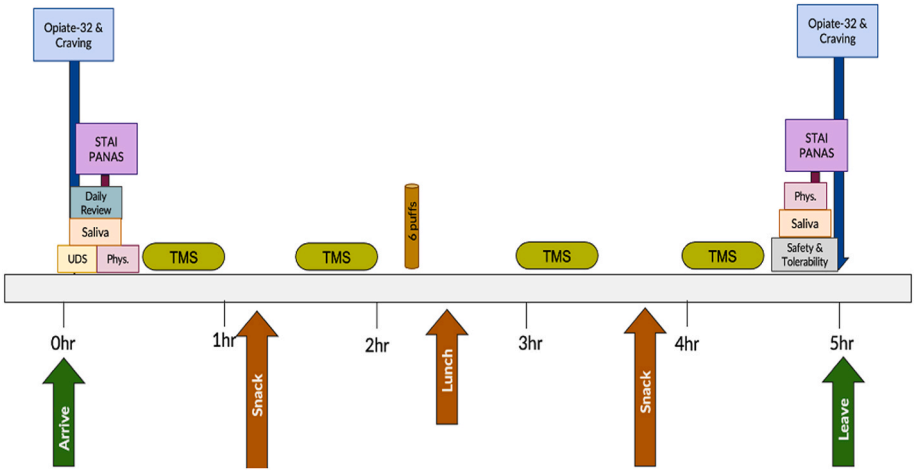


**Fig. 2.** Overview of study day timeline.

*visit?*".

Due to the existing data highlighting how individual differences impact rTMS response (in addition to stress response), we felt it was important for this study to be a within-subjects sham design. Given that rTMS protocols are designed to induce long-term changes, it is important to consider this in the timing of the study. The study design accounts for this in two ways. First, we will leave at least 1 full week between the first rTMS protocol session (active vs. sham) and the second rTMS protocol session (sham vs. active). This timeframe was chosen based on existing data suggesting that the majority of the rTMS effects from similar protocols had dissipated by 1 week later. Nonetheless, no studies have looked at the longevity of rTMS effects in this specific protocol, so the second way to account for this is through the cross-over design. Participants are randomly assigned to either active or sham first such that approximately half of the group receives active first and the other half receives sham first. By so doing, it will be possible to evaluate for the impact of protocol order when evaluated the data.

#### 2.3.3. ERP collection

During assessment visits, electroencephalography (EEG) signals are continuously recorded from 34 scalp electrode sites (10/20 system) using the ActiveTwo BioSemi system. Electrodes are placed on right and left mastoids, and electrooculogram recording captures eye-movement artifacts with 4 facial electrodes. The EEG trace is digitized with 64-bit resolution at 512Hz sample rate, and low-pass 5th-order sinc filter with half-power cutoff of 104Hz. Voltage from each active electrode is referenced online to a common-mode sense active electrode producing a monopolar (non-differential) channel. Event-related potentials (ERPs) are collected during each task listed in section 2.4 and are secondary outcomes intended to assess neural activity during each task's primary outcome.

### 2.4. Primary outcome measures

#### 2.4.1. Executive function

The Wisconsin Card Sorting Task (WSCT) measures the ability to shift categorization rules and affords insight into cognitive flexibility [45]. Participants are shown a set of 4 stimulus cards on each trial and asked to match their card to 1 of the 4 stimulus cards based on color, number, or shape, but are not told the categorization rule. After the participant attempts a match, feedback indicates whether they are correct but not why. This process continues until the matching rule changes. Participants are not aware the matching rule has changed until signaled their card choice was incorrect. They must keep trying to match the cards until they learn the new rule. The outcome for this task is perseverance errors, which occur when the participant follows an old rule despite feedback that the rule has changed. We use a modified task version with 3 blocks, each ~4 min, which takes 10–15 min to complete. Fig. 3 shows the structure of this task. During each block, participants must complete 7 choices correctly before the rule changes [46]. There is no time limit, but participants are asked to sort briskly and accurately. Each block contains 2 sequences of the color- > shape- > number sequence. After correct/incorrect feedback is given, there is a 1-sec interval until the next card is displayed. There is a 30-sec break between blocks.

#### 2.4.2. Emotional arousal

In the Emotional Arousal Task (EAT) participants are shown 15 aversive and 15 non-aversive International Affective Picture System (IAPS) pictures [47] counter-balanced with 5 blank images of a fixation cross. Each image is shown twice [48] (70 total image displays). After each image, participants rate the unpleasantness and arousal of each image using a 9-point visual analog scale [47]. The task (~15 min completion time) has 4 blocks of 15 images and 1 block of 10 images; there is a 30-sec break between blocks. This task is completed 5 separate times over the study duration, so we created 2 distinct image sets that were randomized into one of 5 distinct orders. Image set and image order were pre-assigned randomly. Selected images are listed in Supplemental Tables 1 and 2

#### 2.4.3. Drug motivation

The Drug/Money Choice Task (DMCT) is a 10-min procedure modified from a choice progressive ratio task developed in our lab [49,50] that asks participants to choose hypothetically between a fixed amount of their preferred opioid ($10 unit dose) or money ($2). There are 10 trials. On each trial, the words 'Drug' and 'Money' appear on the computer screen alongside the amount of "work" (mouse clicks) required for that trial. The work required increases on a progressive ratio schedule. The participant then makes a selection to indicate which choice they would like and then must complete the required amount of mouse clicks. If 'Drug' is chosen, the participant will earn a hypothetical $10 unit dose of the total drug for that trial. If 'Money' is chosen, the participant will earn a hypothetical $2 for that trial. Fig. 4 shows the general task structure. Drug breakpoint (when participants are no longer willing to work for drug) is the primary outcome.

### 2.5. Secondary outcome measures

Secondary outcomes include ERPs collected during the primary outcome for each task in section 2.4 (WCST perseverance score, average EAT arousal rating to aversive vs. neutral images, and DMCT breakpoint), subjective measures of mood (PANAS, STAI) and craving, and

| Trial | Rule | Applied Rule | Sequence Correct | Feedback | Error Type |
|---|---|---|---|---|---|
| 1 | C | S | - | Wrong! | NP |
| 2 | C | C | 1 | Correct! | - |
| 3 | C | N | - | Wrong! | FMS |
| 4 | C | C | 1 | Correct! | - |
| 5 | C | C | 2 | Correct! | - |
| 6 | C | C | 3 | Correct! | - |
| 7 | C | C | 4 | Correct! | - |
| 8 | C | C | 5 | Correct! | - |
| 9 | C | C | 6 | Correct! | - |
| 10 | C | C | 7 | Correct! | - |
| 11 | S | C | - | Wrong! | NP |
| 12 | S | C | - | Wrong! | P |
| 13 | S | N | - | Wrong! | NP |
| 14 | S | S | 1 | Correct! | - |
| 15 | S | S | 2 | Correct! | - |

**Fig. 3.** Wisconsin Card Sort Task (WCST) Trials and Potential Responses
Example shows the 3 main task errors: Non-perseverative (NP), perseverative (P), and failure to maintain set (FMS).

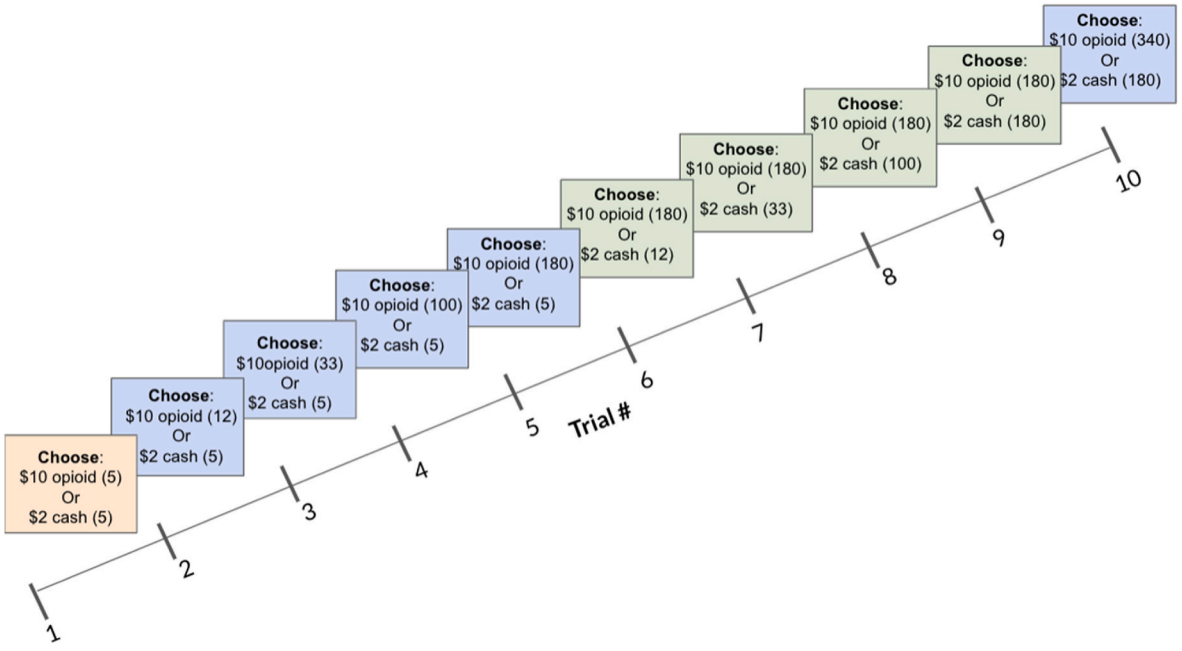


**Fig. 4.** General structure of the drug money choice task (DMCT).

stress biomarkers (BP, HR, and salivary alpha-amylase and cortisol).

*2.5.1. Periodic measures*

Periodic measures (e.g., secondary outcomes) are collected during Assessment Visits. Fig. 1 shows the full timeline of visits. In addition to periodic measures, primary outcomes (see Section 2.4) are examined at each Assessment Visit under stress conditions; these primary outcomes are also collected at screening, without stress, to provide a non-stress control.

Opioid craving and withdrawal symptoms. Craving is assessed using 3 questions, each measured on a 0–100 Visual Analog Scale (VAS): How strong is your current urge to use? How strong is your current desire to use? How much do you want to use? The Opiate-32 measures 16 withdrawal and 16 agonist symptoms, each rated by the participant on a scale from 0 to 4 [51].

Stress levels (subjective). Positive and Negative Affect Schedule (PANAS) is a validated assessment of positive and negative affect [52]. Anxiety levels are measured using the state subscale of the State Trait Anxiety Inventory (STAI) [53].

Physiological signs. Systolic/diastolic blood pressure (BP) and heart

rate (HR) are monitored using an automated sphygmomanometer 4 times throughout the Assessment Visit and immediately before and after each of the 10-session rTMS visits (see Fig. 2 and Supplementary Fig. 1 for specific timepoints) as stress biomarkers.

Saliva biomarkers. Saliva is collected via oral swab (SalivaBio Oral Swab; Salimetrics, State College, PA) 3 times throughout the Assessment Visit and immediately before and after the 10-session rTMS visits. To reduce measurement variability, we control timing of smoking, caffeine, and food/drink intake before collection. To collect samples, the subject holds a cotton salivette at a fixed position in their mouth, without chewing, for 5 min. Saliva samples are analyzed for α-amylase and cortisol levels. Saliva α-amylase is an indirect marker of β-adrenergic stimulation [54]. Saliva cortisol is a correlate of plasma cortisol levels and HPA axis activity [55].

#### 2.5.2. ERP measures

During the WCST, ERPs are measured each trial when feedback is given regarding response accuracy; the EEG trace is segmented beginning 200 ms before response feedback and continuing for 2000 ms [56]. The 200 ms window from −200 to 0 ms prior to feedback/stimulus onset is the baseline. Our focus is on perseverative errors, attributed to impaired set-shifting, which requires activation in the dlPFC and vPFC [57]. WCST performance is associated with a large parietal P3b wave during late trials after correct decision-making; amplitude of this parietal P3b decreases during set-shifting (early trials), and progressively increases while the rule remains in effect [58,59]. The P300 is divided into earlier (P3a) and later (P3b) portions. P3a is primarily associated with involuntary, bottom-up processing of a novel stimulus and is seen in the frontal cortex [56,60]. In contrast, P3b is primarily associated with voluntary top-down processing and temporal-parietal activity associated with attention and memory processing [56,60].

During the EAT, ERPs are collected once the image is displayed; the EEG trace is segmented each trial beginning 200 ms before image onset and continuing for 3000 ms. Emotional arousal is associated with activation in the vmPFC [61,62]. Amplitude of the late positive potential (LPP) is a sustained positive ERP component that tracks stimulus salience and intensity. The LPP is thought to reflect facilitated attention to emotional stimuli and indicates downstream processes related to amygdalar activity. LPP amplitude is associated with the level of mPFC activation in response to arousing stimuli [63]. Acute stressors selectively increase LPPs for unpleasant pictures compared with neutral stimuli in most populations [64].

During the DMCT, ERPs are time-locked to when the subject chooses to work for drug or money; the EEG trace is segmented each trial beginning 1000 ms pre-choice and continuing 2000 ms post-choice. Attentional bias towards drug-related stimuli is associated with dlPFC activation and drug-motivational salience is associated with mPFC activation [65,66]. P3b is the ERP component thought to be sensitive to risk magnitude and valence and, as such, it may be activated during tasks of reward-related decision-making [67]. LPP is believed to be sensitive to stimulus salience [68,69].

### 2.6. Statistical analysis

#### 2.6.1. Power analyses

We used effect sizes from extant studies to calculate sample size, based on the repeated

measures ANOVA (rmANOVA) module in G*Power 3.1 [70]. No studies have used this exact design (stress X rTMS) in participants with OUD, so to estimate sample size for the varying aims we reviewed data from studies of rTMS in persons with other SUDs and rTMS modulation of stress reactivity in different populations.

Specific studies used for effect size calculations can be found in Supplemental Methods 1. Based on previous studies, we adopted a moderate expected effect size of Cohen's $d = 1.0$, which, combined with a power of $1\text{-}\beta = 0.80$, $\alpha = 0.05$, and an assumed correlation between the repeated measures of 0.5, revealed a required total sample size of at least 12 to afford sufficient statistical power to reliably detect a main effect of rTMS [71]. Due to the findings from existing literature that effect sizes of psychological stressors are smaller than for pharmacological stressors (see Supplemental Methods 1) and to account for a 30 % drop out rate, we aim to enroll 24 participants in the study.

#### 2.6.2. Analysis strategy

All data are cleaned prior to analysis and variables checked for normality. The mixed study design has 2 repeated-measures factors for primary outcomes: rTMS/Sham Protocol x Pre/Post Session. **Aim 1** *examines effects of guided imagery stress on executive function, emotional arousal, and opioid motivation*. Primary outcomes are WCST perseverance score (cognitive flexibility), average EAT arousal rating to aversive vs. neutral images, and DMCT breakpoint. Paired *t*-tests will identify stress-related effects on these outcomes. **Aim 2** *examines effects of inhibiting vmPFC activity on stress-induced executive dysfunction*. Primary outcome is the WCST perseverance score; secondary outcome is average P300 amplitude during error trials. Two-way repeated-measures analysis of variance (rmANOVA) with session (pre vs. post protocol) and protocol (active vs. sham) as group variables will identify rTMS effects. **Aim 3** *examines effects of inhibiting vmPFC activity on stress-induced emotional arousal*. Primary outcome is average arousal rating to aversive vs. neutral images; the secondary outcome is average LPP amplitude to aversive vs. neutral images. Two-way rmANOVA with session and protocol as group variables will identify rTMS effects. **Aim 4** *examines effects of inhibiting vmPFC activity on stress-induced opioid motivation*. Primary outcome is the DMCT breakpoint; exploratory outcomes are average P300 and LPP amplitudes following drug/money choices. Two-way rmANOVA with session and protocol as group variables will identify rTMS effects.

## 3. Discussion

Research into mechanisms of NIBS has recently expanded [72,73], but gaps remain regarding precise mechanisms and impacts of various methodologies. Thus, we have a growing literature exploring ways that NIBS can affect SUDs and stressor response without the ability to appropriately compare and contrast between studies. A theoretical, mechanistic-driven approach to neural targets may be the most effective method for intervention development. In developing this approach, it is important to recognize that neural impairments associated with SUDs and negative effects of stressors can occur via multiple related but distinct neural pathways. Thus, there could be multiple NIBS targets, but these might have varied efficacy depending on the outcome of interest. In this study, we focus on executive function and emotional effects of rTMS and stressors alongside their impact on drug motivation.

Neurobiological theories of addiction suggest possible dysfunction in two fronto-striatal circuits: (1) elevated activity in the limbic circuit resulting in hyper-sensitivity to drug cues; and (2) decreased executive control that diminishes ability to resist drug-craving. These same circuits are also impacted by acute stressors. This lays the theoretical groundwork for developing rTMS targets and protocols for SUDs. We theorize that rTMS vmPFC inhibition will decrease limbic activation, which in turn could reduce anxiety and reduce craving and substance use. Although the theoretical framework indicates both dlPFC and vmPFC could serve as potential targets, we chose the vmPFC because it is associated with the hyperactive limbic activity that is theorized to be associated with stress-induced dysfunction. Further, most research to date has focused on the dlPFC so there are minimal data on effects of NIBS of the mPFC.

This project combines our knowledge of the effects of acute stressors with the CNDS model to build on the theory that stressors exacerbate existing dysfunctions of executive function and emotional arousal in people with SUDs. With this conceptual understanding, we aim to use NIBS to counteract effects of acute stressors in people undergoing

treatment for OUD. While focusing attention on theoretically-driven neural targets, we consider the role of biomarkers that reflect changes in these circuits and can be used to identify efficacious NIBS therapy. Just as biomarkers of stress-reactivity are integral for validating experimental stressors, biomarkers of NIBS responses are vital for confirming appropriate targeting and stimulation. At present, it is difficult to identify clear clinical targets for NIBS-related stress reduction; however, initial studies alongside a theoretical understanding of the mechanisms of these effects highlight key pathways for more rigorous exploration. There is significant room for further study within this field; by implementing more standardized methodology and increasing awareness of individual differences, reliable targets for NIBS intervention in SUDs and stress will be identified.

The results of this and similar studies promise key insights into future interventions for people with SUDs. Dysfunction in the two major CNDS pathways is related to common measurable factors associated with drug-use recurrence and treatment response. Measures of executive function, stress, and cue-reactivity can predict treatment response in individuals with SUDs [74,75]. Responses to these factors can provide insights into optimal interventional approaches. Understanding how these measures are reflected as aberrant neural activity provides insight into clinical targets and NIBS could become a preferred approach for these purposes.

## CRediT authorship contribution statement

**Tabitha E. Moses:** Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Danielle Lenz:** Writing – review & editing, Methodology, Investigation. **Leslie H. Lundahl:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Nicholas A. Mischel:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Christine Rabinak:** Writing – review & editing, Supervision, Methodology, Investigation. **Mark K. Greenwald:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

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## Declaration of competing interest

The authors declare that there are no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2024.101414.

## Data availability

No data was used for the research described in the article.

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