Medical University of South Carolina
Protocol

PI Name: Gregory Sahlem
Co-I Names: Aimee L. McRae-Clark, Paul J Nietert, Mark S. George.

A Double-Blind, Randomized, Controlled Trial, Utilizing Accelerated Repetitive Transcranial Magnetic Stimulation (rTMS) as a Tool to Decrease Pain and Craving in Hospitalized Patients with Opiate Use Disorder

Once protocol is complete, save it as a Word document. Go back to the IRB application and upload the protocol.

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A. SPECIFIC AIMS

Prescription opiate use disorder (OUD) is common in the United States, with high morbidity and mortality. Despite the availability of opiate replacement therapies, many individuals continue to abuse opiates and relapse rates remain high (1). Uncontrolled pain (2-4) and opiate craving (5, 6) are both commonly reported by OUD individuals attempting abstinence, and likely contribute to relapse. As such, development of novel treatment strategies targeting pain and craving would have important clinical implications.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique which is currently FDA-approved as a treatment for major depressive disorder. TMS is actively being pursued as a treatment for chronic pain disorders as well as for substance use disorders. In chronic pain patients, there is promising data suggesting that treatment with excitatory rTMS to the dorsolateral pre-frontal cortex (DLPFC) can have an anti-pain effect. A single session of excitatory DLPFC rTMS can decrease the perception of laboratory induced pain (7, 8), decrease the amount of self-administered morphine following open gastric bypass surgery (9), and decrease the affective and sensory components of pain following laparoscopic gastric-bypass surgery (10). While the effects of a single session last for only approximately 1 hour, repeated sessions appear to have an additive and more durable effect, and following 15 sessions, the subjective experience of provoked pain has been shown to decrease by as much as 37% (11). In addition to the literature in laboratory induced pain, there is also preliminary data suggesting that rTMS may be an effective treatment for chronic pain disorders (12, 13). In substance use disordered populations, the use of rTMS has garnered significant attention as an innovative tool to decrease craving [see reviews: (14-17)]. Several single session rTMS studies have demonstrated that applying excitatory rTMS to the DLPFC can decrease cue-induced craving in nicotine, cocaine, and alcohol use disordered populations. As expected, single session studies have only found small temporary reductions in craving; however, these promising data have led to preliminary clinical trials using multiple sessions of rTMS in alcohol (18), nicotine (19) and cocaine (20) use disorders. The largest such clinical trial (n=130 smokers) demonstrated that 13 sessions of DLPFC rTMS resulted in six month tobacco abstinence rates of 33% (19).

To date there has been limited work examining the effect of rTMS on craving or pain in individuals with OUD. Drawing from the published literature suggesting that excitatory rTMS applied to the DLPFC can reduce both pain and craving, our group completed a preliminary sham-controlled crossover study in prescription OUD patients with chronic pain. Our data suggest that a single session of excitatory DLPFC rTMS *acutely* decreased opiate cue induced craving and thermal pain sensitivity in this group. The promising results from our single session trial parallel the single session results found in nicotine and cocaine use disordered populations

which subsequently translated into positive multiple session clinical trials. As such, it follows that a trial utilizing multiple sessions of rTMS in OUD patients may yield positive results.

The goal of this proposal is to investigate whether multiple sessions of rTMS applied to the DLPFC result in decreased craving (Aim 1) and pain (Aim 2) in treatment-seeking opiate users with or without chronic pain, who are currently hospitalized for opiate detoxification. Additionally, we will follow participants for four weeks to determine if treated participants have a higher rate of abstinence than un-treated participants (Exploratory Aim). These aims will be addressed through a double-blind, randomized, sham-controlled study. 40 participants (20/group) admitted to an inpatient community treatment facility for opiate detoxification will be given 18 sessions of either active or sham rTMS applied to the DLPFC, in an accelerated fashion over three days (6-sessions each day).

Aim 1: Determine if a course of excitatory rTMS applied to the DLPFC results in reduced cue-induced craving. We hypothesize that patients receiving active rTMS will have a greater reduction in cue induced craving (post-treatment vs. pre-treatment) as compared to those receiving sham rTMS. Cue craving will be assessed using a standardized measure (21) during a validated opiate cue paradigm (22).

Aim 2: Determine if a course of excitatory rTMS applied to the DLPFC results in decreased pain. We hypothesize that patients receiving active rTMS will have a greater reduction in pain (post-treatment vs. pre-treatment) as compared to those receiving sham rTMS. Pain will be assessed using clinically relevant subjective measures (23, 24). We will also assess pain using a validated quantitative sensory testing paradigm.

Exploratory Aim: Determine if participants receiving active rTMS have a higher rate of abstinence following treatment as compared to participants receiving sham rTMS. We hypothesize that participants receiving active rTMS will be more likely to be abstinent over the final two-weeks of the study period than those receiving sham rTMS. We will define abstinence as no self-reported opiate use over the final two weeks of the study, and a negative urine drug screen for opiates on the final post treatment assessment visit.

B. BACKGROUND AND SIGNIFICANCE

Prescription opiate use disorder (OUD) is a common problem in the United States with high morbidity and mortality. Approximately 1.9 million Americans suffer from prescription OUD (25), and 22,000 of those 1.9 million die each year due to accidental overdose (26). Economic costs are estimated at $55 billion per year (health care, criminal justice system, and workplace costs) (27). There have been advances in the treatment of OUD with the introduction of buprenorphine as a replacement therapy; however, relapse rates remain high (1). Recent data suggests that there is a high prevalence of untreated pain in OUD, and that in most cases pain was the initial reason for use (2-4). As is the case with other substance use disorders, opiate craving is commonly described by abstinent patients whether or not they are stabilized on buprenorphine (5, 6). *Subsequently a treatment that reduces pain and craving could improve the clinical course of opiate addiction.*

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that is able to alter cortical excitability and is FDA-approved to treat Major Depressive Disorder. Magnetic fields pass unimpeded through the scalp, skull and meninges, and can directly excite cortical areas. High frequency rTMS (greater than 5 pulses per second) increases cortical excitability (28). Single sessions of rTMS induce temporary changes; however, multiple sessions can induce more long-term changes.

The dorsolateral pre-frontal cortex (DLPFC) is a key node in the executive control network. Current and historical evidence suggests that in major depressive disorder there is an imbalance of so called cognitive control (exerted by the executive control network) over deeper limbic regions (29). rTMS applied over the DLPFC likely exerts its anti-depressant effect by acting to re-regulate these dysfunctional cortical-limbic circuits (30). Single sessions of rTMS have little effect on depression; however, multiple sessions of rTMS have been demonstrated to be an effective (31, 32) and durable (33, 34) antidepressant treatment. Further, although single daily-sessions given over a period of four to six weeks are often utilized, studies support the efficacy of accelerated treatment courses, where multiple sessions are given each day over a shorter period of time (35-37). The advantages of accelerated treatment paradigms include more rapid delivery of treatment (with more rapid improvement) and fewer needed visits, thus likely enhancing compliance and reducing attrition.

In substance use disorders there is mounting evidence that there is an imbalance of neural activity between the executive control network and the reward network. As the executive control network is thought to have a modulatory effect on the reward network (38), this imbalance may play a key role in the inability of those with substance use disorders to modulate drug craving and use (38-44). If in fact an imbalance of these two networks results in craving, then it would follow that either the application of excitatory rTMS to the executive control network or inhibitory rTMS to the reward network would result in decreased craving. More than 20 studies have confirmed this relationship [see reviews:(14-17)]. The majority of these studies applied single sessions of excitatory stimulation to the DLPFC, with the idea that this type of stimulation can result in enhanced executive control network modulation of the reward network and less reactivity to drug cues. Of note, another study demonstrated that inhibitory rTMS applied to the DLPFC resulted in increased craving (45), providing further evidence of this relationship.

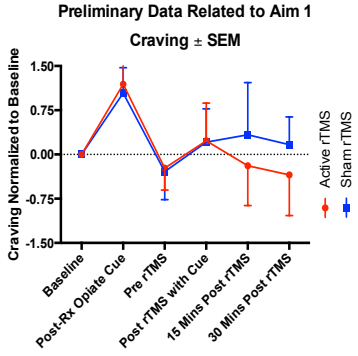
Of note, two recent clinical trials demonstrated that multiple sessions of rTMS may have a more durable effect on craving and reduce drug use (19, 20) than a single session treatment. The largest trial (n=130 smokers) demonstrated that 13 sessions of excitatory DLPFC stimulation resulted in six-month tobacco abstinence rates of 33% (19). The second clinical trial demonstrated that 8 sessions of DLPFC rTMS decreased cocaine cue-induced craving and resulted in one-month abstinence rates of 69% (20).

In chronic pain patients, there is also promising data suggesting that treatment with excitatory rTMS applied to the DLPFC can have an anti-pain effect. Even a single session of excitatory DLFPC rTMS can decrease the perception of laboratory induced pain (7, 8), decrease the amount of self-administered morphine following open gastric bypass surgery (9), and decrease the affective and sensory components of pain following laparoscopic gastric-bypass surgery (10). While the effects of a single session last for only approximately 1 hour, repeated sessions appear to have an additive and more durable effect, and following 15 sessions the subjective experience of provoked pain has been shown to decrease by as much as 37% (11). In addition to the literature in laboratory induced pain, there is also preliminary data in the treatment of chronic pain. In a study of fibromyalgia patients, 10 sessions of excitatory DLPFC rTMS reduced average daily pain by 30% (12), a comparable magnitude to the effect of duloxetine and pregabalin (FDA-approved medications for pain). In a similar fashion to the anti-depressant and anti-craving mechanisms of action, the analgesic effect of excitatory DLPFC rTMS also appears to be associated with executive control modulation of limbic sub-cortical pain structures (46). Additionally, pre-treatment with naloxone (an opioid antagonist) blocks this effect, suggesting that rTMS exerts its action through the opioid system (46, 47).

In sum, studies across substance use disorders (including OUD) suggest that dysfunction of the executive control network and reward network are associated with drug cue-reactivity. Excitatory rTMS applied to the DLPFC (a key node in the executive control network) reduces craving, and has translated to two recent positive clinical trials. It has also been demonstrated that excitatory rTMS applied to the DLPFC has an anti-pain effect that is mediated through the opiate system. We have successfully applied rTMS to an OUD population with promising early results. The next step in the development of this novel treatment for OUD is to determine the effects of a course of treatment in a treatment seeking OUD population with chronic pain.

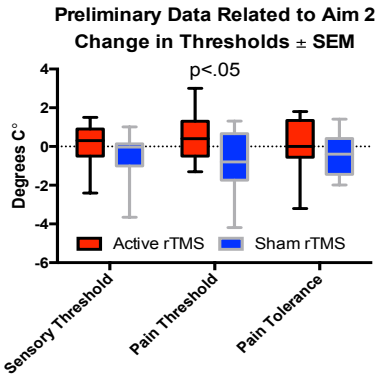
C. PRELIMINARY STUDIES

Of direct relevance to the proposed project, the investigative team has demonstrated 1) The ability to conduct a trial using an accelerated rTMS treatment paradigm in acutely ill inpatients and; 2) the ability to apply rTMS to an OUD population, while determining its effect on craving and pain.



1) Recently the investigative team completed a trial in acutely suicidal, depressed inpatients. In that trial we demonstrated the feasibility of delivering an accellerated course of rTMS (the equivalent of 18 sessions over three days), to acutely ill inpatients (35). 16 of 18 participants in the active group and 20 of 21 in the sham group completed the three day course. These findings demonstrate our team's ability to recruit acutely ill inpatients into an rTMS based trial and the feasability of this treatment paradigm.

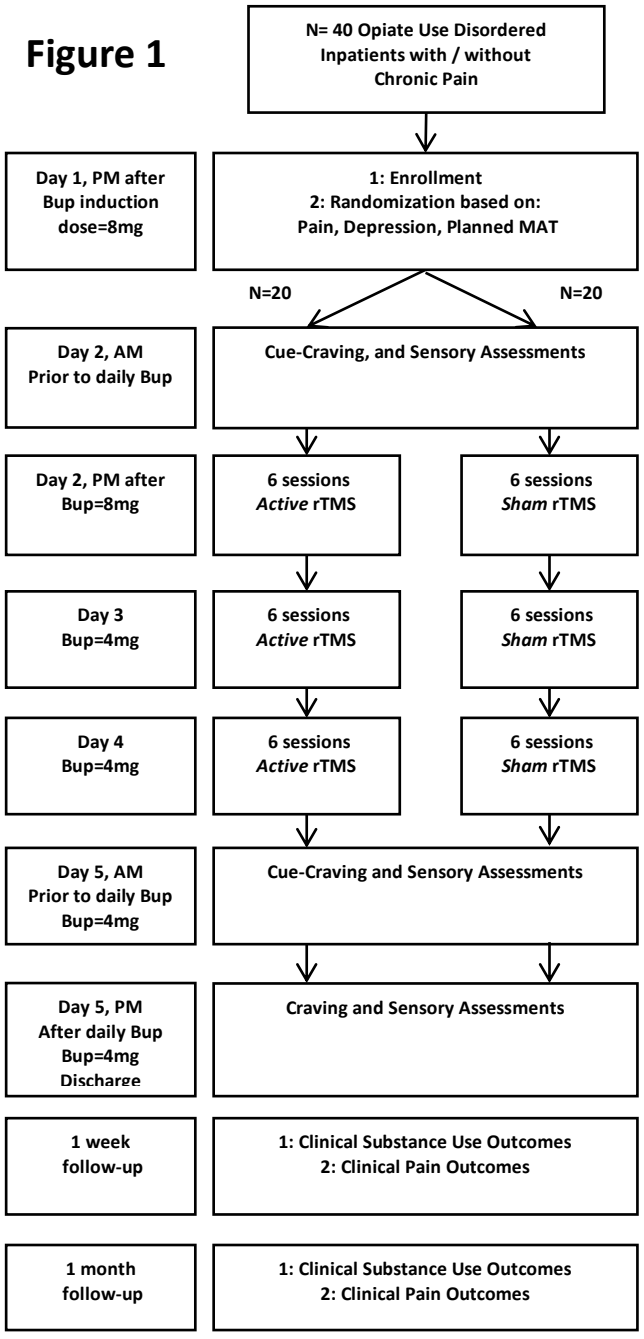
2) The investigative team recently completed a single-blind, sham controlled crossover study demonstrating that a single session of active 10Hz DLPFC TMS *acutely* decreases self-reported opiate craving and thermal pain sensitivity among opiate use disordered individuals (48). In addition to demonstrating that a single session of rTMS may have an effect on both pain and craving in this group, this small trial demonstrated that our group is able to feasibly deliver rTMS to this population, with a retention rate of 81% (13/16).



D. RESEARCH DESIGN AND METHODS (including data analysis)

C: Approach: General Overview (Figure 1): Our primary aims are to determine if 18 sessions of 10 Hz DLPFC rTMS decreases cue induced opiate craving (Aim 1) and decreases pain (Aim 2) in individuals with OUD with, or without chronic pain. Participants will be recruited from an inpatient unit for opiate detoxification. The majority of this study will take place over a 5-day period during which both primary aims will be accomplished. In an exploratory fashion we will also collect data at one, four, and 12 weeks following discharge to determine the interventions effect on substance use and pain. **Acute Phase:** We will screen, consent, enroll, and assess participants during an enrollment session which will occur following either a buprenorphine or methadone induction. The morning following induction, prior to their daily dose of buprenorphine or morphine, each participant will be randomized, and undergo both a opiate drug cue-craving paradigm, an inhibitory control/delay discounting paradigm, and a quantitative sensory testing paradigm (as outlined below). Participants will then receive a total of six sessions of rTMS on three consecutive days during the acute phase of the study (18 total treatments). On the day of discharge, prior to a final dose of buprenorphine or methadone, and several hours prior to actual discharge, the prescription opiate cue-craving, inhibitory control/delay discounting paradigm, and quantitative sensory testing paradigms will be repeated. Daily craving will be assessed during visual cue presentations, and daily pain will be assessed using validated questionnaires. **Continuation Phase:** Participants will either return in person, or receive a phone call at one and four weeks for follow-up for the collection of clinical substance use and pain outcomes. Additionally, the South Carolina Reporting and Identification Prescriptions Tracking System (SCRIPTS), will be accessed once, three months following the hospital discharge.

Figure 1



Bup=Buprenorphine; MAT=Medication Assisted Treatment; rTMS=Repetitive Transcranial Magnetic Stimulation

Quantitative Sensory Testing (QST): Repeated QST sessions will be conducted at the same time of day (during the morning, prior to receiving buprenorphine/methadone). Participants will not be permitted to take any prn analgesic medication for at least five hours prior to the QST sessions prior to assessment. **Testing paradigm:** Three types of pain will be assessed (mechanical pain; diffuse noxious inhibitory control; and thermal pain). First, each participants mechanical pain threshold will be estimated

using a digital pressure algometer. In this procedure (similar to (49)), the middle of the non-dominant supinator muscle will be located and marked (approximately 15% from elbow to wrist), and then pressure from the algometer will be increased at a rate of 10g/second until the participant perceives a shift in sensation from pressure to pain (the pain threshold). This procedure will be repeated three more times (for a total of four trials), with 30-seconds separating trials. Next diffuse noxious inhibitory control (DNIC) will be measured using the same protocol as above, but during mechanical pain assessments, participants will have their dominant hand submerged up to the wrist in a circulating ice water bath maintained at 4.5 degrees C (40 degrees Fahrenheit). After a 2-minute rest interval, thermal pain will be measured using the cold pressor test. During the cold pressor test, each participant will again submerge their dominant hand up to the wrist in a circulating ice water bath maintained at 4.5 degrees C (40 degrees Fahrenheit). On this trial however, they will leave their hand in until: first they perceive the sensation has shifted from cold to pain (pain threshold), and second when they perceive the inability to tolerate the pain (pain tolerance), at which point they will remove their hand. The maximum allowed duration for the cold pressor test will be 300 seconds (5-mins).

Prescription Opiate Cue Paradigm: Cue craving will be assessed using a standard craving questionnaire (21), before and after a validated cue paradigm (22). The drug cue paradigm consists of: a) an imagery induction script, b) in vivo cues (e.g., bottle of OxyContin pills, glass of water, pill crusher), and c) a video. This drug cue paradigm was successfully applied in our previous trial using rTMS in prescription opiate users.

rTMS Treatments: rTMS will be delivered via a MagPro double blinded rTMS Research System (MagVenture, Denmark) with a Cool-B65 Butterfly Coil (a combined active and sham coil). This system is FDA cleared for the treatment of depression, and only differs from the standard clinical system in its ability to be sham-controlled. We will use a standard resting motor threshold (rMT) determination to determine the TMS dose (50). Treatment will be delivered at 120% rMT. Each active rTMS treatment will consist of a total of 3000 pulses of 10Hz stimulation (5s-on,10s-off). Treatments will be delivered at the EEG coordinate for F3 (approximating the left DLPFC), and will be found using the Beam-F3 method (51). This is a treatment paradigm that has been used extensively in other trials (9, 12, 35, 52). Sham sessions will be delivered using an electronic sham system consisting of a coil that mimics the appearance and sound of TMS, combined with a TENS device which produces a small electric shock mimicking the feeling of active rTMS. This type of sham has been demonstrated to be indistinguishable from active rTMS, has been well tolerated (31, 35) and successfully used in other clinical trials (53, 54). During each session of rTMS we will present a series of prescription opiate related images, including those utilized in previous studies (55, 56). The application of drug cues during rTMS appears to enhance its efficacy (19). We chose an alternate cue paradigm during treatment (as opposed to the one used to assess cue induced craving) to avoid habituation to the drug cue. The P.I. will perform all resting motor threshold assessments, and closely supervise a specially trained research specialist, who will deliver rTMS treatments.

Recruitment, Participant Population, and Integration of Study Procedures to Standard Care:

Recruitment: Participants will be recruited from patients who have been admitted to the Charleston Center of South Carolina for detoxification. The Charleston Center is a community based drug and alcohol treatment facility that serves all of Charleston County. Over the past 12 months, approximately 400 patients were admitted for acute detoxification of opiates. The inpatient treatment team will refer interested participants, who will undergo a brief screen with research staff, and if meeting very general inclusion/exclusion criteria will meet with a qualified member of the research staff (most often the PI), for consent and enrollment.

Integration of Study Procedures Into Inpatient Care: During inpatient care, standard treatment includes a combination of pharmacotherapy, psychotherapy, and social work interventions. Pharmacotherapy consists of detoxification from opiates (using a standardized protocol), and the use of medications to treat co-occurring conditions. During detoxification patients are assessed twice daily using the Clinical Opiate Withdrawal Scale (COWS) (57), and then undergo either a standardized buprenorphine taper (8mg x 2 days, 4mg x 3 days), or a standardized methadone taper (30, 25, 20, 15, 10, 5). Induction using either medication occurs at approximately 10am on the first morning of admission. On each of the following four days, medication is given at approximately 10am, and patients are discharged on the final day of their taper following their final dose of

medication. Currently there are no regular group therapy sessions, and regular meetings with individual therapists, social workers, and prescribers are less than 60 minutes in duration each.

The study has been designed specifically to not interfere with any aspect of the normal unit operations. One of the qualified study members will meet with interested patients once they are stable on buprenorphine/methadone, and no longer in acute withdrawal, subsequently the study will not interfere with the initiation of buprenorphine/methadone. Patients who would like to participate in the study, will be consented, enrolled, and will complete baseline assessments prior to starting treatment. The opiate cue craving paradigm, inhibitory control/delayed discounting paradigm, and the quantitative sensory testing will be completed on the morning after being induced on buprenorphine/methadone (before any rTMS), and the morning of the last dose of buprenorphine/methadone on the discharge day (after all rTMS has been delivered). Subsequently assessments will occur at the same time of day, and prior to patients taking buprenorphine/methadone, without disrupting the normal dispensing of medications (which is approximately 10am). Six 15 minute treatments will be delivered each of the next three days with approximately 30 minutes in between each treatment. Given that all standard treatment meetings (see above) occur in windows of less than 60 minutes, and rTMS will be delivered on the same floor as detoxification, study treatment will not interfere with any of the standard of care interventions participants receive.

The study procedures will also not interfere with any of the standard of care pharmacotherapy commonly delivered during detoxification. There is no known added risk of rTMS during a buprenorphine/methadone taper (in our pilot trial several of our participants were stabilized on buprenorphine). The commonly used non-opiate medications including acetaminophen, hydroxyzine, and cyclobenzaprine, will be allowed during this study (but be held for at least 5 hours prior to each pain assessment). Patients being treated for OUD commonly have co-morbid symptoms of depression and anxiety (58). Subsequently, the initiation of antidepressant medications is common in the acute treatment setting, and will be allowed during this trial (and are commonly used safely with concurrent rTMS).

Inclusion Criteria:

1: Participants must be able to provide informed consent and function at an intellectual level sufficient to allow accurate completion of all assessment instruments.

2: Participants must meet DSM-5 criteria for moderate or severe OUD. While individuals may also meet criteria for use disorders of other substances (with the exception of alcohol or benzodiazepines), they must identify prescription opiates as their primary substance of abuse.

3: Participants must be admitted to the inpatient unit for opiate detoxification.

4: Participants must consent to random assignment.

Exclusion Criteria:

1: Participants who are pregnant will be excluded.

2: Participants with a history of/or current psychotic disorder will be excluded.

3: Participants with a history of dementia or other cognitive impairment will be excluded.

4: Participants with active suicidal ideation, or a suicide attempt within the past 90 days will be excluded.

5: Participants with contraindications to receiving rTMS (including a history of seizures, or any implanted metal above the neck) will be excluded.

6: Those with unstable general medical conditions will be excluded.

7: Those who are currently using naltrexone, or tramadol, will be excluded.

8: Those with alcohol or benzodiazepine use disorders will be excluded due to increased risk of seizure.

Schedule of Visits and Assessments:

	Assessment Domain	Baseline	Post	1 and 4 week F/U	3-Month SCRIPTS Review
Screening and Enrollment Eligibility:					
Mini International Neuropsychiatric Interview for the DSM-5 (MINI)(59): Structured interview to determine Axis I psychiatric conditions based on DSM-5 criteria.	**Psychiatric History**	**X**			
Patient Health Questionnaire Nine (PHQ9)(60): Self-Report measure of depressive symptoms.	**Depressive Symptoms**	**X**		**X**	
Time Line Follow Back (TLFB)(61) and Clinical Opioid Withdrawal Scale (COWS)(57): The TLFB is a validated measure quantifying drug use; average daily morphine equivalents will be calculated. The COWS is a validated measure quantifying withdrawal severity.	**Opiate Use and Withdrawal**	**X**			
Subjective Opioid Withdrawal Scale (SOWS) (68): The SOWS is a validated self-administered measure of opioid withdrawal.	**Opiate Withdrawal**	**X**	**X**		
The Barratt Impulsiveness Scale (BIS11) (69): The BIS is a validated questionnaire designed to assess the personality/behavioral construct of impulsivity.	**Impulsivity**	**X**			
The Pittsburgh Sleep Quality Index (PSQI) (70): Validated instrument used to measure the quality and patterns of sleep in adults.	**Sleep**	**X**		**X**	
Work Productivity and Activity Impairment Questionnaire (71): The Work Productivity and Activity Impairment (WPAI) questionnaire is a well validated instrument to measure impairments in work and activities.	**Functional Impairment**	**X**		**X**	
The Rand 36 Item Short Form Health Survey (73): Validated self-report to assess quality of life.	**Quality of Life**	**X**		**X**	
Aim 1: Cue induced Craving: Primary outcome: Change score in peak to final craving during cue paradigm.					
Prescription Opiate Craving Scale (21): Three item opiate craving scale. The three-item scale will also be administered at 1 and 4 week follow-	**Provoked Opiate Craving**	**X**	**X**		

ups, but there will be no cue provocation.					
Aim 2: Pain Outcomes: Primary outcome: Change score in thermal pain threshold and pain tolerance.					
Mechanical, Thermal, and DNIC Pain Assessment: See description above.	**Quantitative Sensory Assessment**	**X**	**X**		
Brief Pain Inventory (23) and McGill Pain Questionnaire (24): Self report measures assessing severity, functional impairment, and affective components of pain. Administered daily during the acute phase of the study and at both follow-up visits.	**Subjective Pain**	**X**	**X**	**X**	
Exploratory Aims: Substance Use: Primary outcome: Abstinence over the final two weeks of the study, as defined by no self-reported use and a negative final urine drug screen. **Executive function/inhibitory control: Will be measured using two validated computer tasks.**					
Urine Drug Screen	**Objective Substance Use**	**X**		**X**	
Time Line Follow Back (61): See above.	**Subjective Substance Use**	**X**		**X**	
South Carolina Prescription Monitoring Program: Online database of all controlled substance prescriptions filled in the state of South Carolina.	**Filled Prescription Opiates**				**X**
The "GoGo/NoGo" task: Participants are instructed to press a button in response to common (gray colored circles: 75% of trials) and rare (yellow colored circles: 12.5% of trials) Go stimuli and inhibit responding to rare NoGo stimuli (blue colored circles: 12.5% of trials). The task provides errors of omission and reaction times during Go trials, controls for novelty detection during processing of rare Go trials (yellow circles) and errors of commission on NoGo trials (blue circles).	**Inhibitory Control**				
Delayed Discounting Task: Participants will decide between a series of theoretical monetary rewards (exe: smaller rewards now, or larger rewards later) in a brief computerized task.	**Delayed Discounting**	**X**	**X**		

DATA MANAGEMENT AND STATISTICAL ANALYSIS: Data will be managed using REDCap. **DATA MANAGEMENT AND STATISTICAL ANALYSIS:** Data will be managed using REDCap. **Randomization:** Participants will be randomized to active or sham rTMS. Urn randomization will be used to ensure balance on three pre-specified covariates: depression status (HRSD at baseline ≥16 indicating moderate or greater depression), self-reported pain over the past three months, and planned use of replacement therapy following discharge. **Statistical Analysis**: Changes in study outcomes will be estimated and analyzed using several approaches. When parametric modeling assumptions can be made, changes over time will be compared between treatment groups (active rTMS vs. sham rTMS) using general linear mixed models (GLMMs). The

GLMMs will allow us to estimate group-specific changes over time and overall effect sizes, along with the variation in those measures, while controlling for relevant baseline covariates (e.g. baseline craving, morphine equivalents, withdrawal). In an attempt to determine whether rTMS impacts craving and pain by reducing depressive symptoms, we will also examine models that do and do not control for changes in depression scores. Although we will likely not be powered to detect between-group differences in binary outcomes (i.e. drug use), such effects will be explored using generalized mixed models, and for time-to-event data (e.g. days to first opioid use), survival analysis models will be constructed. When parametric modeling assumptions do not appear to be valid, alternative (e.g. non-parametric) approaches will be used to estimate treatment efficacy and its precision. Primary outcomes will also be analyzed for evidence of differential treatment effects in subgroups determined by gender, race, and ethnicity. Post-hoc exploratory analyses using GLMMs within the active rTMS group will address whether specific characteristics (e.g. demographics, baseline craving, morphine equivalents, withdrawal) are associated with a better treatment effect. The subgroup-specific treatment effects and corresponding confidence intervals will be constructed and will be interpreted in terms of their clinical, rather than statistical, significance. **Sample Size Justification:** A total of n=40 participants (n=20 per arm) will be recruited. We anticipate that <20% of study participants will withdraw from the study or be lost to follow-up, meaning that ≥ n=32 participants are expected to complete the study. This sample size ensures that group-specific changes will be able to be estimated in a precise fashion, with 95% confidence intervals extending ~0.5 standard deviation units. Similarly, the overall effect size confidence interval will likely extend only 0.3 standard deviation units. As an exploratory and developmental R21 project, we recognize that our final sample size may not result in a fully powered study design. Nevertheless, our sample size will provide >80% power to detect large effect sizes (equivalent to a Cohen's d of 1.0), assuming 2-sided hypothesis testing and an alpha level of 0.05. Our preliminary work and work of others suggests that differences of this magnitude may be present within our proposed sample. For example, for Aim 1, recent investigations have found large effect sizes, with (20) reporting a d=0.84, and (18) reporting a d=0.98. For Aim 2, our recent single session study reported a d=0.65. Model based means and variability estimates will be derived from unadjusted and adjusted analyses and will be vital for designing a larger, more definitive trial in the context of a subsequent R01 submission. **Relapse, Drop-Out and Clinical Deterioration:** Every effort will be made to re-engage participants who miss appointments. Clinical deterioration, such as exacerbation of psychiatric or substance use disorder, will be assessed on a case-by-case basis and appropriate referral will be made. Participants will be considered drop outs if they do not come back for follow-up visits after three attempts to contact. With the exception of participants who formally withdraw from the study, we will attempt to assess early terminators at the time of discontinuation and at the post-treatment time points. These participants will be considered in the intent-to-treat efficacy analyses. **Strategies to Ensure a Robust and Unbiased Approach:** The proposed study will achieve robust and unbiased results via several design features including: explicit inclusion/exclusion criteria; randomization of treatment condition; the use of a validated sham control; use of validated laboratory and interview/self-report measures and methods; explicit hypotheses and corresponding planned statistical analyses; power estimates; planned handling of retention/attrition and missing data; and careful consideration of potential confounds. All experimental details are reported in a detailed manner to support replication. **Consideration of gender as a biological variable:** Though this trial is not powered to detect gender differences, we will perform our analysis using gender as a potential covariate. Should there be a potential gender difference found, we will use that data to power a larger trial

E. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

Targeted/Planned Enrollment Table
Total Planned Enrollment 40

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
	Sex/Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	1	1	2
Not Hispanic or Latino	19	19	38
Ethnic Category: Total of All Subjects*	40		
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	4	4	8
White	14	14	28
Racial Categories: Total of All Subjects*	20	20	40

The most recent information reported by the South Carolina Department of Alcohol and Other Drug Abuse Services reports 49.6% of those admitted to an inpatient unit for opiate detoxification are women, and 50.4% are men. Additionally, 91% are Caucasian, 7.2% are African American, and 1.7% are of another race. We expect our recruited population to have a similar demographic make-up, with the exception of being more ethnically diverse (Charleston is more diverse than other SC counties).

We will attempt to recruit all potential participants from the community. We will not exclude anyone based on age, gender, ethnicity, or race.

Review of Adverse Events: Adverse events (AEs) will be assessed daily by study personnel. The type of AE, severity of AE, and the relationship to the application of rTMS will be recorded. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) rules.

Compensation and Retention: Participants will receive $160 for completion of the acute treatment phase of the study, and $120 for in-person completion of both the one and four-week follow-up visits. If participants elect to complete the follow-up visits by phone, they will be compensated $60 per phone call. The total possible compensation will be $400. Compensation will be given in the form of Greenphire MasterCard debit cards.

PROTECTION OF HUMAN SUBJECTS
1. RISKS TO THE SUBJECTS
a. Human Subjects Involvement and Characteristics

Admission into the study is open to men and women and to all racial and ethnic groups, age 18-65. Forty opiate use disordered patients will be recruited from a pool of patients admitted to an inpatient unit for detoxification. Inclusion/exclusion criteria that apply to all participants are listed below:

General Inclusion / Exclusion Criteria

Inclusion Criteria:

1: Participants must be able to provide informed consent and function at an intellectual level sufficient to allow accurate completion of all assessment instruments.

2: Participants must meet DSM-5 criteria for moderate or severe OUD. While individuals may also meet criteria for use disorders of other substances (with the exception of alcohol or benzodiazepines), they must identify prescription opiates as their primary substance of abuse.

3: Participants must be admitted to the inpatient unit for opiate detoxification.

4: Participants must consent to random assignment.

Exclusion Criteria:

1: Participants who are pregnant will be excluded.

2: Participants with a history of/or current psychotic disorder will be excluded.

3: Participants with a history of dementia or other cognitive impairment will be excluded.

4: Participants with active suicidal ideation, or a suicide attempt within the past 90 days will be excluded.

5: Participants with contraindications to receiving rTMS (including a history of seizures, or any implanted metal above the neck) will be excluded.

6: Those with unstable general medical conditions will be excluded.

7: Those who are currently using naltrexone, or tramadol, will be excluded.

8: Those with alcohol or benzodiazepine use disorders will be excluded due to increased risk of seizure.

b. Sources of Materials

Research material obtained from individual participants includes questionnaires and interviews with study personnel, and urine samples. All data will be directly input into REDCap which is a secure, password protected web-based data collection system. The only written research material will be the informed consent and HIPAA documents. These paper records will be stored in an office in the Roper Medical Office Building (RMOB) that is locked when not in use. Urine samples will never be marked with any identifying information. They will be discarded once read.

c. Potential Risks and Risk Mitigation Strategies:

Potential risks of rTMS: The use of high frequency rTMS has been FDA approved for the treatment of major depressive disorder since 2008. Our stimulation parameters (3000 pulses, 10Hz, 5-Seconds on 10-Seconds off) are nearly identical to the FDA approved protocol (3000 pulses, 10Hz, 4-Seconds On, 8-Seconds off), and have been used safely in many investigations including those in depression (35), pain (12), and addictions (48, 52). We chose to use the slightly longer train duration of 5-seconds rather than 4-seconds due to its safety and efficacy in many trials including our preliminary single session trial with opiate users.

The common clinical dose of rTMS in depression is 36 treatments with 3000 pulses per treatment, for a total of 108,000 pulses (33). We will deliver a total of 18 treatments over 3 days with 3,000 pulses per treatment, for a total of 54,000 pulses. We subsequently will be giving a substantially lower total dose to each participant than is commonly given to patients being treated for depression. Accelerated treatment paradigms (including those with 6 treatments delivered daily) have been safely delivered in both depression (35-37, 62), and addictions (63, 64) populations without any clear adverse effect.

Risk of Seizure: The most serious risk associated with the use of rTMS is seizure. Since the adoption and widespread use of standard safety guidelines in 1997(65), there has only been one documented seizure with the type of rTMS we will deliver. The risk of seizure has been estimated to be less than 0.1% which is lower

than the risk of seizure associated with pharmacologic antidepressants(66). The risk of seizure is related to the various stimulation parameters (intensity, frequency, train duration), location of application, pre-existing risk of seizure, and substance/medication factors. In the very rare event a seizure is caused, removing the coil is typically sufficient to stop the seizure, and there is no increased risk of subsequent seizure. In order to mitigate the risk of seizure we will carefully individualize the intensity of stimulus (by performing a resting motor threshold determination), treat using standard treatment protocols (used safely in other studies), and exclude potential participants at higher risk of seizure (those with a past history of seizures, those in withdrawal from alcohol or benzodiazepines etc).

Risk of Site discomfort and headache: Two relatively common risks associated with the use of rTMS include the risk of mild transient site discomfort during treatment (most patients), and the risk of headache (Approximately 5%) following treatment. Both of these potential side effects are typically mild. In terms of mitigating site discomfort, we will slowly ramp up stimulation intensity during the first three sessions. In our experience both clinically and experimentally this is a successful strategy. Additionally, due to the anti-pain effect of rTMS, participants rapidly adjust to stimulation. In the unusual circumstance that a headache is caused by rTMS, over the counter analgesics are sufficient to alleviate the headaches, and will be available to patients on the inpatient unit.

Pain task: The pain task may cause discomfort but will not cause injury. The task will be stopped when it becomes painful to the participant.

Potential hearing loss: The discharge of the rTMS coil generates a high-energy click that may cause cochlear damage. Humans exposed to rTMS have shown temporary increases in auditory threshold (especially at high frequencies) lasting at least 5 minutes and less than 4 hours. Foam earplugs can protect against these changes and will be worn during rTMS sessions.

Safety in the case of pregnancy: This protocol will exclude pregnant women. Pregnancy status will be confirmed as part of the standard admissions process.

Potential risks of cue Induced craving paradigm: Drug cues are known to increase craving, and subsequently the use of an opiate cue paradigm will likely increase craving for opiates. The craving induced will be transient (22), with craving approaching baseline within 90 minutes. Additionally, it is unlikely our delivered craving paradigm will induce craving that is more intense than the individual cues that participants will encounter once they leave the hospital. Given that all of our drug cues will be given while patients are admitted to the inpatient unit, it is highly unlikely that the increased opiate craving produced by the opiate cue paradigm will result in any substance use. Our final cue-craving paradigm will be delivered on the day of discharge, however it will be done several hours prior to discharge, and we will closely monitor the craving response patients exhibit. Study staff will stay with each participant until their craving has returned to baseline levels. In the unlikely event that the individual has prolonged cue-induced craving, the P.I. will provide an appropriate referral.

2. ADEQUACY OF PROTECTION AGAINSTS RISKS

a. Recruitment and Informed Consent

Patients will be referred to the study by the inpatient medical team. Medical records will not be reviewed to identify potential study participants. Qualified, IRB approved study staff will obtain informed consent. The informed consent form includes a detailed description of the study procedures, along with statements regarding participants' rights to withdraw from the procedure at any time without consequences. The informed consent form will be explained to participants in easy-to-understand language, and participants will be instructed to read the form carefully prior to signing it. Consent will be documented by the signature of the participant on the informed consent agreement, accompanied by the signature of the individual obtaining the consent.

b. Protections Against Risks

All study participants will be closely monitored for psychiatric and medical stability. If hospitalization is indicated during one of the follow-up visits, the patient will be hospitalized at MUSC or an appropriate referral will be made. All participants will be fully informed that they may withdraw from the experiment at any time without penalty.

To ensure confidentiality, all subject data will be directly input into REDCap which is a secure, password protected, web-based data collection system. All paper records (which will likely only be the consent and HIPAA document) will be kept in a locked cabinet in an office that will be locked at times when not in use. The research staff understands the importance of maintaining confidentiality, and this method of maintaining confidentiality has been effectively used by our research group in the past. All electronic databases are stored on HIPAA-compliant servers with restricted access. All co-investigators and study personnel have completed (or will complete upon hiring) training in Good Research Practices as mandated by the MUSC IRB.

Participants will be taught about potential side effects of rTMS, and will be closely followed by both inpatient psychiatrists, and members of the research team. Pregnancy tests will be performed as part of normal admission procedures. Adverse events will be monitored throughout the study as described in the research strategy section.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECT AND OTHERS

As rTMS is an FDA approved treatment for depression, and preliminary evidence suggests that it also has anti-pain, and anti-craving effects. Research participants receiving active treatment may have improvement in craving, pain, and symptoms of depression. In addition to the potential direct benefits of participation in this study, participants will help investigators understand the utility of rTMS as a potential treatment for pain and craving.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

This study may provide important information that can improve treatment for future patients with opiate and other substance use disorders. The moderate risks of the investigation are considered reasonable in relation to the expected knowledge to be gained.

5. DATA AND SAFETY MONITORING PLAN

This section is based on the recommendations in NIDA's "Guidelines for Developing a Data and Safety Monitoring Plan" (www.drugabuse.gov/funding/dsmbsop.html). A detailed DSMP will be developed and approved by NIH program staff prior to study initiation.

a. Summary of the Protocol.

This application proposes to investigate the effects of rTMS on craving and pain on opiate use disordered patients with chronic pain. The primary outcomes of interest are craving (Aim 1) and pain (Aim 2). Inclusion/exclusion criteria are outlined above. Power calculations and sample sizes are in the Data Analysis Plan section.

b. Trial Management.

The study will be managed from the Addictions Sciences Division within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina. The target population is described above in the inclusion/exclusion criteria.

c. Data Management and Analysis.

Data will be entered by research assistants directly into a computer using standard database software using REDCap. The data analysis plan is outlined in the Data Analysis Plan section.

d. Quality Assurance.

Quarterly data audits will be conducted. Confidentiality protections are outlined above.

e. Regulatory Issues.

Potential conflicts of interest will be reported using the NIH rules for disclosure. Adverse Events (AEs)/Serious Adverse Events (SAEs) occurring during the course of the project will be collected, documented, and reported in accordance with protocol and IRB reporting requirements. All research staff involved with adverse event reporting will receive general and protocol specific AE/SAE training including identification, assessment and evaluation, and documentation and reporting. A research specialist will identify any potential adverse events during the course of the study from participant self-report and administration of the visit

assessments and procedures. The research assistant will provide information to a study physician, who will be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness.

f. Definition of AE and SAE.

An Adverse Event (AE) is defined as any untoward medical occurrence in a study subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment (ICH GCP). Any unwanted change, physically, psychologically or behaviorally, that occurs in a study participant during the course of the trial is an adverse event. A Serious Adverse Event (SAE) is defined as an adverse event that has one of the following outcomes:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect OR
- Requires intervention to prevent one of the above outcomes.

g. Documentation and Reporting.

AEs/SAEs are documented and reported as per protocol and IRB requirements. Research staff will identify adverse events and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome and the need for change or discontinuation in the study intervention. Adverse events are generally documented on AE Logs and AE Case Report Forms (CRFs). Additional relevant AE information if available should be documented in a progress note in the research record as appropriate to allow monitoring and evaluating of the AE. If the AE meets the definition for serious, appropriate SAE protocol specific reporting forms are completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization or until the participant is no longer in the study as stated in the protocol. When a reportable SAE is identified, the research staff will notify the MUSC Institutional Review Board (IRB) within 24 hours and complete the AE report form in conjunction with the PI. The MUSC IRB meets monthly and is located at 165 Cannon Street, Rm. 501, Charleston, SC 29425. Communication with the IRB is through email, memos, official IRB forms, and online reporting.

If complete information is not available when the initial 24-hour SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc.

We will report adverse events to the Medical University of South Carolina (MUSC) Institutional Review Board (IRB) online as soon as possible, but no later than 10 working days after the investigator first learns of the event. The MUSC IRB AE reporting requirements are as follows: All deaths that occur during the study or 30 days post termination from the study are required to be reported as adverse events even if they are expected or unrelated. Other adverse events are reportable to the MUSC IRB if the AE is unexpected AND related or possibly related AND serious or more prevalent than expected. All three criteria must be met for an AE to be reported to the MUSC IRB. The IRB definition of unexpected is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of related is that there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention. Reportable AEs are reviewed by the IRB Chair and reported to the IRB Board at the next meeting.

h. Trial Safety.

The potential risks and benefits and methods to minimize these risks are outlined above. The research staff will report any unexpected AEs or any scores of “severe” on the side-effect symptom rating form or any FDA-defined serious AEs to the PI within 24 hrs so that the PI can decide on the appropriate action. All unexpected AEs will be monitored while they are active to determine if treatment is needed. Study procedures will follow the FDA’s Good Clinical Practice Guidelines (www.fda.gov/oc/gcp). Any outside requests for information or any breaches in confidentiality will be reported to Dr.Sahlem.

An interim analysis is not planned at this time.

i. DSM Plan Administration.

Dr.Sahlem will be responsible for monitoring the study, and will participate in weekly study meetings. A DSM report will be filed with the IRB on a yearly basis, unless greater than expected problems occur. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of AEs, significant/unexpected AEs and serious AEs. We will report outcomes at the end of the trial.

j. DSM Board.

A Data Safety and Monitoring Board will be formed to monitor both the rate and severity of adverse events. This panel will include 3 clinicians with expertise in substance use disorders and a statistician.

k. Risk Benefit Ratio.

The assessments and questionnaires are non-invasive and have inherently minimal risks. Potential risks of concern are loss of confidentiality and adverse events to rTMS. As discussed above, our research team will attempt to minimize these risks. Knowledge gained by the proposed study would help fill an important void in development of a potential treatment for opiate use disorder.

6. CLINICALTRIALS.GOV REQUIREMENTS

In accordance with Public Law 110-85, this project will be registered at the ClinicalTrials.gov Protocol Registration System Information Website prior to study initiation.

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