An Exploratory Investigation Utilizing Repetitive Transcranial Magnetic Stimulation (rTMS) as a Tool to Decrease Pain and Improve Functioning in Veterans with Opioid Use Disorder

BACKGROUND AND SIGNIFICANCE

Opioid use disorder (OUD) is common among Veterans, with high morbidity and mortality. Despite the availability of opioid replacement therapies, many individuals continue to abuse opioids and relapse rates remain high (Fiellin et al., 2014). In 2015, it was reported that approximately 60% of Veterans returning from the Middle East and more than 50% of older Veterans in the VA health care system have chronic pain (Clancy, 2015). Veterans are nearly twice as likely to die from accidental opioid overdose than the general population (Bohnert et al., 2011). Further, post-traumatic stress disorder, a common comorbidity in the Veteran population, has been shown to negatively impact early engagement and retention of individuals in OUD treatment (Jaremko et al., 2015). *OUD is associated with elevated rates of posttraumatic stress disorder (PTSD), with lifetime PTSD prevalence up to 50% among individuals with OUD compared to 7% in the general population (Kessler et al., 2005). Importantly, people with OUD have a 42% increase in odds of PTSD, as well as more severe PTSD impairment and symptoms, compared to both non-users and individuals with other substance use disorders (Meier et al., 2014). 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 (Hartwell et al., 2012; Barth et al., 2013; McCauley et al., 2014). The significant comorbidity of OUD, PTSD, and chronic pain has been explained both through overlapping neurobiology and conceptual models. Specifically, for individuals with PTSD, stress enhances the rewarding properties of opioids and exacerbates the adverse effects of opioid withdrawal (Logrip et al., 2012). Erratic patterns of repeated withdrawal episodes in OUD exacerbate acute stress symptoms and increase vulnerability for development of PTSD. Further, stress dysregulation generated by PTSD impairs recovery from OUD by lowering the threshold for stress-induced relapse, and nociceptive alterations have also been reported (Scioli-Salter et al., 2015).* As is the case with other substance use disorders, opioid craving is commonly described by abstinent patients whether or not they are stabilized on buprenorphine (Northrup et al., 2015; Tsui et al., 2014). Subsequently, a treatment that reduces pain and craving, while also improving early engagement and retention in treatment, would improve recovery from opioid addiction, and could have particular salience for the Veteran population.

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 (Pascual-Leone et al., 1998). Single sessions of rTMS induce temporary changes, while 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 (Mayberg, 1997). rTMS applied over the DLPFC likely exerts its anti-depressant effect by acting to re-regulate these dysfunctional cortical-limbic circuits (Li et al., 2004). Single sessions of rTMS have little effect on depression; however, multiple sessions of rTMS have been demonstrated to be an effective (George et al., 2010; McDonald et al., 2011) and durable (Dunner et al., 2014; Levkovitz et al., 2015) 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 (George et al., 2014; Holtzheimer et al., 2010; Baeken et al., 2013). 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.

Accelerated rTMS: Lessening treatment burden toward enhancing adherence. In addition to establishing the dose-response curve for transdiagnostic psychosocial impairment as opposed to disorder-specific symptoms, we also propose to innovate by utilizing a high-dose accelerated protocol. A therapeutic course of rTMS for depression typically consists of approximately 30-40 minutes of high-frequency (i.e., 10 Hz) treatment on each weekday, for 4 to 6 weeks. This schedule can be burdensome and reduce adherence. More recently, a number of groups have examined the safety, feasibility, acceptability, and effectiveness of accelerated rTMS delivery (Holtzheimer et al., 2010; McGirr, et al., 2015; Tovar-Perdomo et al., 2017) during which sessions are repeated on the same day to reduce total days of treatment, typically spaced by at least 30 minutes. Safety has also been assessed with both structural and metabolic imaging as well as neurocognitive testing, which has shown no adverse effects on neural integrity and modest gains in cognition (Holtzheimer et al., 2010; McGirr, et al., 2015; Tovar-Perdomo et al., 2017). Furthermore, acceptability results have suggested that accelerated protocols could increase adherence and

decrease interruptions to daily obligations (Holtzheimer et al., 2010; McGirr, et al., 2015; Tovar-Perdomo et al., 2017).

Specific to a transdiagnostic sample of Veterans with affective/anxiety disorders, Co-investigator Mark George, M.D. (31) and colleagues demonstrated that delivering three high-dose sessions per day (i.e., 10 Hz; 6,000 pulses for 30 minutes; 18,000 pulses/day total) on each of consecutive three days was safe, feasible, and suggestive of rapid antidepressant effects. Also, these patients received in three days, nearly the equivalent dose of a conventional 4- to 6-week course.

In a recent further innovation, intermittent theta burst (iTBS) rTMS has been shown to be as efficacious as 10 Hz rTMS in remediating depression (Garrett-Mayer, 2006). Notably, a single session of excitatory iTBS rTMS entails 600 pulses in merely 3 minutes. More specifically, pulses are delivered in triplets at 50 Hz for 2 s (i.e., 5 Hz triplets) and repeated every 10 s for a total of 190 s (600 pulses). While the use of iTBS in accelerated protocols is only now emerging for the remediation of neuropsychiatric dysfunction, accumulating safety and efficacy results are promising, even among the most impaired and vulnerable patients (Lasonos et al., 2011). From a practical standpoint, theta burst sessions are typically spaced by 20-60 minutes apart with no requirements on the intervening time period. As such, veterans could potentially undergo multiple 3-minute sessions in a single day with more limited interference to daily demands than more conventional 10 Hz protocols.

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 (Kober et al., 2010), this imbalance may play a key role in the inability of those with substance use disorders to modulate drug craving and use (Kober et al., 2010; Hanlon et al., 2015; Sutherland et al., 2012; Volkow et al., 2010; Charboneau et al., 2013; Cousijn et al., 2013). 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: Bellamoli et al., 2014; Gorelick et al., 2014; Wing et al., 2013; Barr et al., 2011]. 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 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 (Li et al., 2013), providing further evidence of this relationship.

Two recent clinical trials demonstrated that multiple sessions of rTMS may have a more durable effect on craving and reduced drug use (Dinur-Klein et al., 2014; Terraneo et al., 2015) 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% (Dinur-Klein et al., 2014). 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% (Terraneo et al., 2015).

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 (Borckardt et al., 2007; Mylius et al., 2012), decrease the amount of self-administered morphine following open gastric bypass surgery (Borckardt et al., 2008), and decrease the affective and sensory components of pain following laparoscopic gastric-bypass surgery (Borckardt et al., 2014). 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% (Borckardt et al., 2013). 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% (Short et al., 2011), 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 (Taylor et al., 2013). Additionally, pre-treatment with naloxone (an opioid antagonist) blocks this effect, suggesting that rTMS exerts its action through the opioid system (Taylor et al., 2012).

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 opioid 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 feasibility and acceptability of a course of treatment in a treatment seeking, Veteran OUD population with chronic pain**. rTMS is becoming increasingly available at many other VAMC's; subsequently positive results in this line of research could be easily adopted across the country and potentially improve Veteran outcomes.

PRELIMINARY DATA

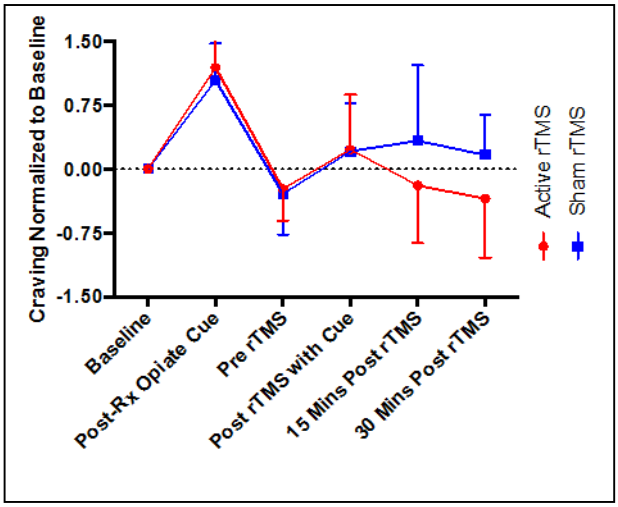
Expertise of Research Team: The current application involves a strong, multidisciplinary team of investigators with expertise in addictions (McRae-Clark, Sahlem, Hartwell, Hanlon, *and Brady*), pain (Borckardt), and brain stimulation (George, McRae-Clark, Sahlem, Hanlon, Borckardt) research *as well as statistics (Baker)*. The team is uniquely poised to complete the proposed project having the needed expertise, equipment, and access to the clinical population in question as well as a history of successful collaborations.

Preliminary Studies: Of direct relevance to the proposed project, the investigative team has demonstrated 1) significant experience with TMS research; 2) the ability to conduct a trial using an accelerated rTMS treatment paradigm and; 3) the ability to apply rTMS to an OUD population, while determining its effect on craving and pain. The team will be led by Dr. Aimee McRae-Clark, an established addictions researcher. Although the majority of her research to date has focused on treatment development for cannabis and cocaine use disorders, given the critical public health consequences of the opioid epidemic she has turned her focus to opioid addiction. As such, the SPiRE mechanism seems ideal as it supports senior investigators in their exploration of new research areas in which they have not been previously funded.

1) Members of the investigative team have conducted multiple trials of rTMS, including pivotal trials for FDA-approval of TMS for depression (George et al., 1997) and in substance using individuals (Hanlon et al, 2015; Hanlon et al., 2017; Sahlem et al., 2017).

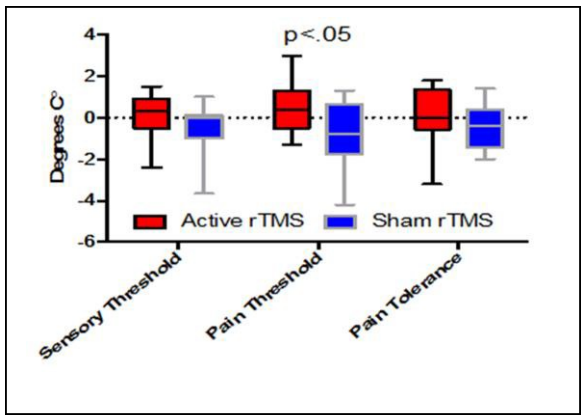
2) The investigative team completed a trial in acutely suicidal, depressed Veterans. In that trial we demonstrated the feasibility of delivering an accelerated course of rTMS (the equivalent of 18 sessions over three days), to acutely ill inpatients (George et al., 2014). Sixteen of 18 participants in 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 Veterans into an accelerated rTMS based trial and the feasibility of this treatment paradigm.

Figure 1. Change in craving ± SEM



3) The investigative team also completed a single-blind, sham controlled crossover study demonstrating that a single session of active 10Hz DLPFC TMS *acutely* decreases self-reported opioid craving and thermal pain sensitivity among opioid use disordered individuals both on and off buprenorphine (Breedlove et al., 2015). In addition to demonstrating that a single session of rTMS may have an effect on both craving (**Figure 1**) and pain (**Figure 2**) 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).

Figure 2. Change in pain thresholds ± SEM



Innovation: This pilot trial is innovative in several respects. 1: This trial will be the first randomized-controlled trial applying multiple sessions of rTMS to a cohort of OUD patients. This is important as it is well established that multiple sessions of rTMS have a larger and more durable effect than single sessions of rTMS. Furthermore, it is well known that in order to derive a meaningful clinical effect, the application of multiple sessions of rTMS are needed. 2: This will be the first trial testing an accelerated rTMS treatment paradigm using established rTMS doses in an addictions population. This is important as there is a clear dose response effect in rTMS, where larger doses of rTMS result in a larger clinical effect (George et al., 2010; McDonald et al., 2011). It is additionally important as OUD and other substance use disordered populations may be difficult to treat using the standard treatment paradigm of one session per day over several weeks. 3: This trial will be the first to use rTMS as an adjunct to standard of care opioid treatment. OUD patients, including Veterans, are difficult to engage in outpatient care. Subsequently, a treatment that encourages retention and integration early in the recovery process could have a significant impact on patient outcomes.

RESEARCH DESIGN AND METHODS

Approach Overview (Figure 3): Participants will be recruited from the Ralph H. Johnson VAMC,local VA clinics, and Charleston Center. We will collect data at one week, four weeks, and three months following rTMS completion. **Acute Phase:** We will screen, consent, enroll, and assess participants during an enrollment session. Following enrollment, each participant will complete baseline measurements of opioid use, opioid craving, pain, and functioning (as outlined below). Following the enrollment session, each participant will be randomized and begin the acute treatment phase of the trial. *Participants will receive a total of six sessions of rTMS on three days during the acute phase of the study over a period of up to three weeks. A period of up to one-week in between treatment days will be allowed to maximize feasibility of intervention deliverability in this population while minimizing risk of a treatment gap that is too long to allow for a summation of effect.* On the third treatment day, pain assessments will be repeated. Craving and pain will be assessed using validated questionnaires. **Continuation Phase:** Participants will return at one week, four weeks, and three months for follow-up visits to preliminarily assess the intervention's impact on opioid use, pain, and functional outcomes.

Recruitment: Participants will be recruited from the Ralph H. Johnson VA Medical Center, other local VA clinics, ,Charleston Center, and through community and online advertising. Co-I Dr. Hartwell is Medical Director of the STAR program and will assist in participant referrals. CPRS chart review will also be utilized. Approximately four Veterans per month are initiated on buprenorphine medication assisted treatment (MAT), *the majority (77%) of which endorse chronic pain. As such, we do not anticipate any issue meeting recruitment goals for this pilot project; however, feasibility of recruitment will be assessed as an aim in this project.*

Integration of Study Procedures into Standard Care: Outpatient care for includes a combination of pharmacotherapy, psychotherapy, and social work interventions. Pharmacotherapy consists of medication assisted therapy, typically buprenorphine/naloxone. The study procedures will not interfere with this standard MAT treatment or other interventions. Patients being treated for OUD commonly have co-morbid symptoms of depression and anxiety (Gros et al., 2013); as such, antidepressant treatment will be allowed to enhance generalizability.

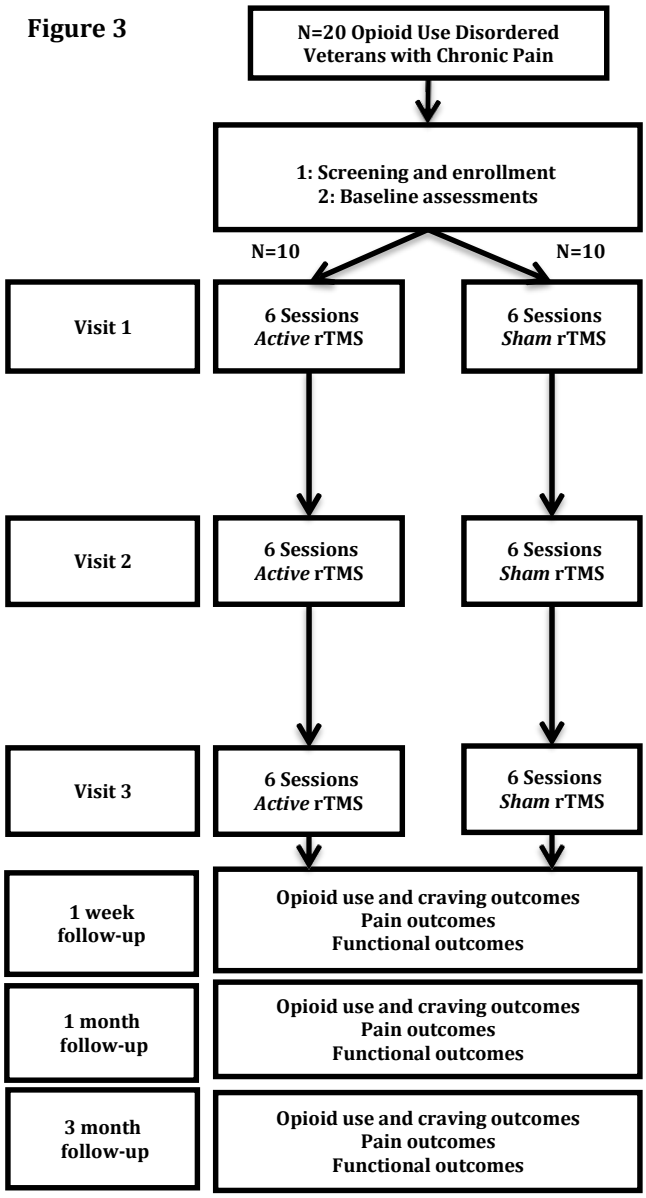
Inclusion Criteria: 1: Be able to provide informed consent and function at an intellectual level sufficient to allow accurate completion of assessments. 2: Meet moderate to severe DSM-5 criteria for OUD. Individuals may also meet criteria for other substance use disorders (with the exception of alcohol or benzodiazepines), but must identify opioids as their primary substance of abuse. 3: Report chronic pain for at least the past three months and have a Brief Pain Inventory Score ≥ 3. 4: Participants must be receiving Medication Assisted Treatment (MAT).

Exclusion Criteria: 1: Pregnancy. 2: History of/or current psychotic disorder. 3: History of dementia or other cognitive impairment. 4: Active suicidal ideation, or a suicide attempt within the past 90 days. 5: Contraindications to receiving rTMS (including a history of seizures, or any implanted metal above the neck). 6: Unstable general medical conditions. 7: Current use of tramadol. 8: Active moderate or severe alcohol or benzodiazepine use disorder due to increased risk of seizure.

Screening and Eligibility Assessment: Individuals will be screened by the research study intake coordinator. An initial pre-screen focused on inclusion/exclusion psychiatric diagnoses, medical status, current medication regimen, and ability and willingness to commit to completion of study procedures will be used to initially determine potential study eligibility. Interested individuals will be given a full description of the study procedures and asked to read and sign an IRB-approved informed consent form before participating in a detailed, comprehensive screening and assessment phase. To ensure subjects are not experiencing any acute effects of alcohol, individuals whose breath or saliva alcohol concentration reading exceeds the instruments margin of error (0.002%) will not be allowed to participate until their BAC is not detectable.

Diagnostic/Descriptive Assessment: The *M.I.N.I. International Neuropsychiatric Interview 7.0 for DSM 5* will be used to assess psychiatric and substance use diagnoses, including assessment of opiate use. A medical history will be collected to ensure that the individual is eligible to participate, and the VA medical record may be reviewed to verify medications. In the event that an individual is found to be ineligible, he or she will be given an appropriate referral for further medical or other necessary care. If the individual is eligible, he or she will fill out questionnaires and provide a urine sample to verify self-report of substance use. If female, the urine will first be tested for pregnancy. If the pregnancy test is negative or the individual is male, the urine will be tested for drugs of abuse. A randomization/initial rTMS visit will be scheduled.

Figure 3



rTMS=Repetitive Transcranial Magnetic

Treatment Assignment: Eligible individuals will be randomized to receive active rTMS or sham treatment. Participants will be randomized using a stratified permuted random block design with block sizes of 2 and 4; *this will be utilized to maintain treatment assignment balance throughout the treatment enrollment period based on concomitant pain medication use (yes/no).*

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). We will use a standard resting motor threshold (rMT) determination to determine the TMS dose (Borckardt et al., 2006). Treatment will be delivered at 120% rMT. Each active rTMS treatment will consist of a total of 600 pulses of 50 Hz triplets for 2s, and repeated every 10s for a total of 190s of stimulation. Treatments will be delivered at the EEG coordinate for F3 (approximating the left DLPFC), and will be found using the Beam-F3 method (Beam et al., 2009). This is a treatment paradigm that has been used extensively in other trials (Borckardt et al., 2008; Short et al., 2011; George et al., 2014; Li et al., 2013). 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 real rTMS. This type of sham has been demonstrated to be indistinguishable from real rTMS, has been well tolerated (George et al., 2010; George et al., 2014) and successfully used in other clinical trials (Borckardt et al., 2008; Arana et al., 2008). During each session of rTMS we will present a series of opioid related images, including those utilized in previous studies (Garland et al., 2015; Garland & Howard, 2014). The application of drug cues during rTMS appears to enhance its efficacy (Dinur-Klein et al., 2014).Opiate craving and stress will be assessed before and after each TMS treatment.

Quantitative Sensory Testing (QST): Three types of pain will be assessed (mechanical pain; diffuse noxious inhibitory control; and thermal pain). First, each participant's mechanical pain threshold will be estimated using a digital pressure algometer. In this procedure (similar to (1)), 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). QST will be done on treatment Days 1 and 3 and at the one-week follow-up.,

Compensation and Retention: Participants will receive $40 for the screening visit, $40 for completion of each rTMS day, and $40 for each follow-up visit. Compensation will be given in the form electronic funds transfer.

Table 1. Assessment Instruments and Schedule

Instrument	Purpose/Domain	Screening	TMS Sessions 1-3	1 wk, 4 wk, follow- up
Informed Consent	Obtain informed consent	X		
Demographics	Characterize sample	X		
M.I.N.I. International Neuropsychiatric Interview	Assess DSM-5 psychiatric disorders	X		
Timeline Follow-Back: TLFB	Assess opioid and other substance use	X	X	X
Urine Drug Screen: UDS	Assess illicit drug use	X	X	X
Alcohol Breathalyzer	Assess alcohol use	X	X	X

Community Reintegration for Servicemembers	Assess community reintegration	X		X
Community Participation Index	Assess community functioning	X		X
ShortForm36 Health Survey: SF36	Assess quality of life	X		X
Patient Health Questionnaire nine (PHQ9)	Assess depression	X		X
Trait form of the State-Trait-Anxiety Inventory	Assess anxiety symptoms	X		X
Pittsburgh Sleep Quality Index: PSQI	Assess sleep functioning	X		X
Daily Pain Diaries (Numeric Rating Scales; NRS)	Assess pain level	X	X	X
Brief Pain Inventory: BPI	Assess pain severity and functional impairment	X	X	X
McGill Pain Inventory	Assess pain severity	X	X	X
Patient Health Questionnaire: PHQ-15	Assess health status	X		X
Treatment Services Review: TSR	Monitor services utilization	X		X
Best Guess Questionnaire	Assess rTMS blind integrity			
Adverse events	Assess tolerability of rTMS		X	

Data Management: Data will be managed using REDCap as specified in the DMAP.

Statistical Analysis: *Study feasibility will be primarily measured by a) the total number of rTMS sessions completed (out of 18 total sessions) b) the proportion of participants completing all of the rTMS session and c) the proportion of participants completing all of the rTMS sessions as well as the follow-up visits. Study tolerability will be measured as the total number of treatment emergent adverse events. Group differences (active rTMS vs. sham rTMS) in the feasibility and tolerability measures will be estimated using generalized linear models with appropriate distributions (Negative binomial for session and AE count and logit for study treatment completion).* In addition to study feasibility, efficacy measures (opioid use amounts, pain, and sleep quality) will be estimated for the entire cohort as well as estimates of between group differences. Changes in study efficacy outcomes from baseline to follow-up visits will be estimated and analyzed using appropriate statistical approaches. When parametric modeling assumptions can be made, changes over time and associated variability will be estimated between treatment groups 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). Although we will likely not be powered to detect between-group differences in binary outcomes (i.e. any 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. Efficacy 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, PTSD) are associated with a differential 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, and effect size of treatment to inform future trials will be estimated. ***Missing Data and Attrition:*** *Missing data in longitudinal studies can be a problematic feature but can be mitigated through study design considerations. We will make every effort to prevent attrition, e.g., telephone/text/e-mail reminders prior to visits, and reinforcing attendance at each visit. However, these methods do not ensure that all data will be collected, and appropriate analysis methods will be employed to accommodate missing data. Maximum likelihood estimation yields valid inferences assuming ignorable attrition (i.e., attrition is accounted for by covariates or the dependent variable measured prior to dropout). In addition, in keeping with the ITT, we will make every effort to continue assessments for the entire course of randomized treatment, even among those who stop participating in the study assigned intervention or fail to complete the full rTMS time course.*

Sample Size Justification: A total of n=20 participants (n=10 per arm) will be enrolled. We anticipate that <20% of study participants will withdraw from the study or be lost to follow-up, meaning that ≥ n=16 participants are expected to complete the study. This sample size should allow us to assess feasibility and tolerability of the intervention, and ensure 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 project, we recognize that our final sample size will not result in a fully powered study design. 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 MERIT 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 disorders, will be assessed on a case-by-case basis and appropriate care will be arranged. In the case of suicidal ideation, standard STAR program operating procedures will be followed which entails contact of on-call STAR clinicians. 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.

Design Considerations: *Choice of treating participants likely undergoing buprenorphine treatment and using an accelerated (multiple sessions per day) treatment paradigm:* The standard rTMS treatment paradigm in depression is to treat outpatients using one session of rTMS each day, five times per week, for four to six weeks. We considered using this treatment paradigm; however, we chose to use an accelerated paradigm (multiple sessions per day), for the following reasons: 1: If treating outpatients with once daily sessions, there would likely be a great deal of variability in the number of attended sessions per week (OUD patients frequently miss appointments) and a large attrition rate (the opioid relapse rate is high amongst outpatients). 2: Patients are often seen frequently early in treatment (leaving an opportunity for an acute intervention that could easily be applied in other facilities). 3: Our preliminary evidence suggests that rTMS is tolerated while participants are on buprenorphine. *Choice of including participants with co-morbid depressive symptoms:* Because rTMS is known to have an anti-depressant effect we considered excluding patients with concurrent depressive symptoms to avoid the potential confound of improved depression driving anti-pain and anti-craving effects. We chose to include these patients as there is a high rate of comorbid depression in this population (Gros et al., 2013), and excluding these patients would reduce the generalizability of our findings. We will control for depression statistically by including depression as a covariate in analyses. *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.

Operational Plan and Research Timetable: Funding for two years is requested. The first three months will be used for submitting regulatory documents, staff training and preparing for study initiation. Eighteen months will be needed for patient recruitment and data collection. The final three months will be used for data analysis, dissemination, and MERIT grant submission. At a recruitment rate of approximately 1-2 participants per month, we should have no difficulty in completing the study in the proposed timeframe.

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. Twenty opioid use disordered patients will be recruited from a pool of patients receiving treatment at the Substance Treatment and Recovery (STAR) program at the Ralph H. Johnson VA Medical Center, Charleston area VA clinics, and Charleston Center. Inclusion/exclusion criteria that apply to all participants are listed below:

General Inclusion / Exclusion Criteria Inclusion 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 moderate to severe DSM-5 criteria for OUD. While individuals may also meet criteria for use disorders of other substances (with the exception of alcohol or benzodiazepines), they must identify opioids as their primary substance of abuse.

3: Participants must report chronic pain for at least the past three months and have a Brief Pain Inventory score≥ 3.

4: Participants must be receiving Medication Assisted Treatment (MAT).

Exclusion Criteria:

1: Participants who are pregnant.

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

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

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).

6: Those with unstable general medical conditions.

7: Those who are currently using tramadol.

8: Those with active moderate or severe alcohol or benzodiazepine use disorder 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. Data will be collected with paper and pencil and then entered into the VA REDCap database, which is a secure, password protected web-based data collection system. Coded data will be stored separately from the informed consent and HIPAA documents. Paper records will be stored in an office in the Ralph H. Johnson VAMC 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, pain, and addictions. 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 opioid users.

The common clinical dose of rTMS in depression is 36 treatments with 3000 pulses per treatment, for a total of 108,000 pulses. We will deliver a total of 18 treatments over 5 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 and addictions 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, there has only been one documented seizure. 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. 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.

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 screening process.

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.

2. ADEQUACY OF PROTECTION AGAINSTS RISKS

a. Recruitment and Informed Consent

E-consent and the first diagnostic interview, will be an option if the participant is not able to come into the laboratory for consenting (Due to COVID-19, or any other in person limiting factor). The e-consent will be emailed through REDCap and approved research personnel will go through the e-consent with the participant over the phone or over video conferencing. The participant will receive a copy of the signed e-consent by email from the research personnel.

Participants will be recruited to the study from the STAR program. The study PI , Co-I, or other qualified, IRB-approved personnel 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 the Ralph H. Johnson VAMC 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 coded and stored in the VA REDCap system which is a secure, password protected, web-based data collection system. We will take careful precautions to maintain confidentiality for all subjects, using procedures we have used in other studies. Data will be compiled using codes in lieu of personal identifiers. Access to study data will be limited to research personnel. The application will provide: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields. Finally, it should be highlighted that **only coded data will be entered into the electronic database**. Thus, no protected health information (PHI) will be entered into the database. All paper records will be kept in a locked cabinet in Charleston VAMC research space (where Dr. McRae-Clark's VA office is located). A file of names, contact addresses, telephone numbers, and other research identification numbers will be stored separately on paper and on computer, for purposes of audit by VA R&D and MUSC IRB.

All investigators and project personnel will also complete a certified program of instruction in the protection of human subjects in research, such as the VA website tutorial, NIH website tutorial, or the University of Miami CITI course. These courses in the responsible conduct of research and the protection of human research participants will be completed in compliance with institutional, PHS, and NIH regulations.

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

MUSC IRB and VA R&D will review and approve the funded protocol, review patient consent forms, ensure protection of patient privacy and safety, and monitor the study on an on- going basis. Adverse events will be reported to MUSC IRB and VA R&D as they occur. Annual reports to MUSC IRB and VA R&D will indicate

enrollment rates, adverse events, new findings that may influence continuation of the study, and reports of the DSMB.

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. After the study data has been unblinded, we will offer open label treatment to those participants randomized to sham treatment. 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 OUD.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

This study may provide important information that can improve treatment for future patients with opioid 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

a. Summary of the Protocol.

This application proposes to investigate feasibility and acceptability of rTMS in opioid use disordered Veterans with chronic pain. Inclusion/exclusion criteria are outlined above.

b. Trial Management.

The study will be managed from Ralph H. Johnson VA Medical Center. 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 VA 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. Any significant actions taken by the local IRB and protocol changes will be relayed to VA RR&D.

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) and VA R&D 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. The MUSC IRB has a MOU to provide HHRP oversight for clinical research conducted at the Ralph H. Johnson VA Medical Center. Communication with the IRB is through email, memos, official IRB forms, and online reporting. A report will also be sent to the VA RR&D program officer assigned to the project.

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. The research staff will attach copies of source documents to the SAE report for review by the PI and for forwarding to the NIH program officer as appropriate within 2 weeks of the initial SAE report. In addition, the PI will provide a signed, dated SAE summary report, which will be sent to the VA RR&D Project Officer within two weeks of the initial SAE report.

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. McRae-Clark.

An interim analysis is not planned at this time.

i. DSM Plan Administration.

Dr. McRae-Clark will be responsible for monitoring the study, and will participate in weekly study meetings. A DSM report will be filed with the IRB and VA R&D on a yearly basis, unless greater than expected problemsoccur. 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. STATEMENT OF DISCLOSURE

No financial or contractual relationship exists between any organization involved in the proposed study that could constitute a real or apparent conflict of interest for either the PIs, Co-Is, or collaborators devoting $\geq$ 5% or more effort to the project.

7. ACKNOWLEDGEMENT OF VA POLICY TO INCLUDE WOMEN AND MINORITIES

The PI acknowledges receipt of VHA Handbook 1200.9 which delineates VA policy regarding the requirement for the inclusion of women and minorities in any DVA-sponsored research. The PI has carefully reviewed this policy and, hereby, provides assurance that if the proposed research outlined in the Letter of Intent is approved and funded, every effort will be made to include women and minorities in the study.