Study Title: Project Relief: Developing brain stimulation as a treatment for chronic pain

Principal Investigator, Co-investigator(s): Colleen Hanlon, PhD; Eric Donny, PhD; Heather Douglas, MD, Robert Hurley, MD/PhD

Sponsor or funding source: Internal

Background, Rationale and Context

Effective control of chronic pain is a top priority in the United States, as approximately 10% of adults have severe chronic pain – most of which is chronic lower back pain (CLBP)(National Institute of Health Statistics, 2006). CLBP is the leading cause of job-related disability and missed work. However, despite the advances in neuroscience over the past 20 years, we still largely treat CLBP pain with opiate narcotics, much as was done in the Civil War. In addition to their high abuse liability and dependence potential (1), only 30–40% of chronic pain patients declare they receive satisfactory (>50%) relief from their pain through pharmacological treatment (59). 96% of chronic pain patients using opiates reported insufficient control of pain, and on average opiate-using pain patients have experienced CLBP for more than a decade (59). A 2012 study demonstrated that patients with chronic pain resort to non-medical use of prescription opiates at high rates. This abundant use and misuse of opiates is a developing crisis, with 4.3 million users in 2014 (1), over 40% of prescription drug overdoses in the United States attributable to opioid analgesics (2), and total societal costs exceeding an estimated $55 billion (3). Of individuals who misuse opioids, 80 to 90% initiated after having a legitimate prescription (13, 14) and 81% endorse pain as their reason for non-medical prescription opioid use (NMPOU) (14). **Consequently there is a critical need for new, treatments that can treat pain and reduce reliance on opiates in individuals with chronic pain. The goal of this R21 proposal is to evaluate 2 novel non-invasive brain stimulation strategies to mitigate pain in CLBP patients that are currently taking chronic opiates or that are seeking an alternative to relieve pain.**

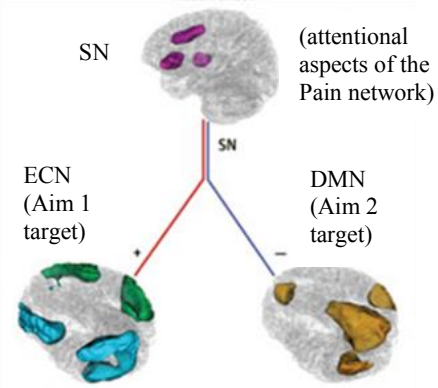

Figure 1. Dynamic Interaction of Core functional connectivity networks. Adapted from Lerman et al 2014 JAMA Psychiatry. The Salience Network (SN), Executive Control Network (ECN), and Default Mode Network (DMN) represent 3 Core neural networks in the brain which are dynamically coupled. During pain, the SN & DMN are positively correlated (red), whereas the SN & ECN are anticorrelated (negatively correlated, blue). The outcomes of these aims will allow us to investigate baseline networks dynamic in CLBP patients treated with or without opiates (which has never been done) and test the hypotheses that increasing activity in the ECN (LTP-like TMS; Aim 1), and decreasing activity in the DMN (LTD-like TMS) will dampen pain in CLBP patients. The acute effect of 16 days of TMS (interventional phase and maintenance phase) as well as 1&2 month durability will be assessed.

Evaluating rTMS as a new, non-pharmacological approach to treating pain in opiate using individuals. TMS is a non-invasive brain stimulation method that is currently FDA-approved for the treatment of major depressive disorder. Repeated trains of stimulation can cause long-term potentiating (LTP) or depressing (LTD) effects on cortical areas directly under the coil (approximately 2cm depth) as well as monosynaptic projections (15-19). Our group has previously demonstrated that LTP-like TMS to the dorsal prefrontal cortex (DPFC, a node in the Executive Control Network (ECN)) can decrease perceived pain as well as corresponding BOLD signal in the "Pain Network in healthy controls (7, 8, 30) and clinical populations (31-34). The Pain Network is an expansion of the Salience Network (SN; insula, dorsal anterior cingulate) which includes the thalamus and somatosensory cortex (4-6). The SN represents the attentional aspects of pain whereas the thalamus and somatosensory cortex represent somatic aspects of pain. The analgesic effects of DPFC TMS can be blocked by naloxone, an opiate antagonist, suggesting TMS-induced analgesia is opiate mediated (7, 8). Dr. Borckardt (Co-Investigator) was the first to demonstrate that when LTP-like DPFC rTMS was delivered in the postoperative recovery room, patients used less morphine in the hospital and required less

morphine long-term (9). **These data all suggest that LTP-like DPFC TMS is a promising candidate for treating pain (Strategy 1, Aim 1).** This study will be the first to merge these findings, aiming to investigate the effects of TMS in both chronic opiate users, and individuals that cannot find any alternative to help relieve their pain.

An alternative strategy is to apply LTP-like stimulation to the somatomotor cortex (LTP-like MC rTMS (Strategy 2, Aim 2). This strategy is based on our understanding of functional neural architecture, wherein the SN is modulated by 2 other core networks: the executive control network (ECN) and the default mode network (DMN) (Figure 1). As stated above, it is possible to attenuate activity in the SN through LTP-like TMS to the DPFC, a node in the ECN. It is also possible to attenuate the SN through LTP-like TMS to the somatomotor cortex (a node in the DMN) (Hanlon et al 2017). **The proposed study will be the first to employ a randomized, double-blind, sham-controlled design to parametrically evaluate the longitudinal effects of 12 days of rTMS, followed by 4 maintenance rTMS sessions, delivered to the DPFC (Aim 1) or the MC (Aim 2) on self-reported pain and the brain's response to pain. This will be done in a cohort of patients recruited from the community as well as Wake Forest University (WFU) clinics with chronic lower back pain that have not been able to find adequate pain relief, whether or not they are using prescription opiates for 3 or more months.**

The scientific rationale for rTMS effects on pain in CLBP patients. TMS is the only non-invasive tool available to directly activate a specific neural circuit in humans. Opiate dependent individuals have reduced functional connectivity (35) between regions of the Pain Network (e.g. dorsal anterior cingulate cortex [dACC], insula, and thalamus (4-6, 36)) and the ECN (e.g. DPFC (37)). Previous TMS studies have demonstrated that increasing activity in the ECN lowers perceived pain (27-29) and changes activity in nodes of the Salience Network (cingulate, insula) (30, 38, 39) which represent the attentional aspects of the pain network. One form of TMS is known as theta burst stimulation (TBS). **This biologically relevant pulse sequence, is translationally derived from preclinical studies in learning and memory, and has powerful effects on cortical excitability in humans (40), wherein the same LTP-like effects of 10 Hz TMS are achieved much faster with TBS.** As with traditional rTMS, TBS can induce LTP-like or LTD-like effects on by applying the pulses intermittently (iTBS, LTP-like) or continuously (cTBS, LTD-like) (40).

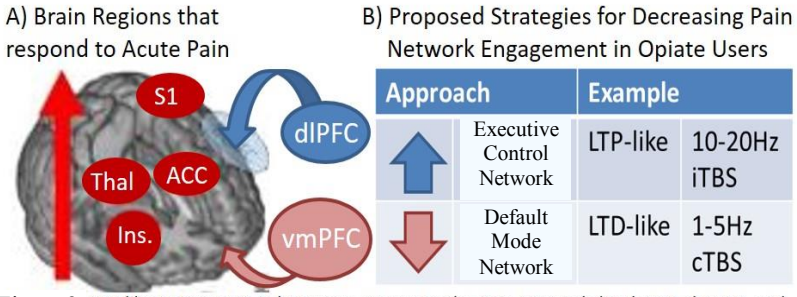

Figure 2. LTP-like DLPFC TMS is known to attenuate the Pain Network (Taylor et al 2013, and others). The LTD-like vmPFC TMS attenuates the ACC and Insula(Hanlon et al, under review) and is reciprocally related to the DLPFC (Dunlop et al 2016, and others).

While the promise of inducing a lasting neuroplastic change in the Pain Network of opiate dependent individuals is enticing, it is not clear that the 'plasticity potential' of these circuits is as high in chronic opiate users as in healthy controls. Our preliminary data evaluating TMS to the DPFC as a tool for dampening pain circuitry is promising (Aim 1, Strategy 1). However, given previously observed deficits in executive function in chronic pain patients on chronic opiates (44), data has revealed that it may be more efficacious to attenuate activity in the MC (Aim 2, Strategy 2). The rationale for this alternative hypothesis is that in patients with chronic, ongoing pain, normal regulatory mechanism are disrupted (34-36). This alteration in brain function encourages the exploration of alternative treatment locations in this population.

Early Feasibility Data: Quantitative Sensory Testing of pain in opiate using individuals after 10 sessions of rTMS (Strategy 1 and 2). Our group recently initiated a 10 day clinical trial of these 2 strategies as tools to decrease behavioral reports of pain. From June 2017 to October 2017 we were able to enroll and successfully acquire Quantitative Sensory Testing data from 10 individuals (5 of whom

received each strategy for 10 days). 8 of the 10 remained enrolled for the full treatment. The 2 that didn't finish were terminated due to a Hurricane in our area (Sept 2017). This initial feasibility trial is promising and individuals appear to be receiving pain relief (as demonstrated by their continued engagement). However, without a rigorous sham control group or longitudinal neuroimaging data, the results of this pilot study will be limited to Quantitative Sensory Testing. Through this R21 mechanism we hope to be able to build upon the early success of this trial by including a rigorous, randomized, sham-controlled design which includes neuroimaging data necessary to understand mechanisms of action of these innovative new treatment approaches.

Aims 1 & 2 of this proposal will address the next critical steps in developing DPFC or MC TMS as a new, innovative treatment option for pain: 1) Do multiple sessions of rTMS have a sustainable impact on pain in CLBP patients? And 2) Are there consistent patterns of neural activity to pain that serve as a predictive biomarker for TMS efficacy in these individuals?

INNOVATION: The proposed research is innovative in several ways. First, we are developing a conceptually innovative, alternative treatment strategy for chronic pain, which involves non-pharmacologic modulation of the circuits responsible for the perception of pain. This would be a significant conceptual advance for the field of chronic pain management. While LTP-like DPFC rTMS has been promising as a tool for pain in non-opiate dependent individuals, the experiments outlined in this proposal represent a critical next step in their development for this CLBP population chronically using opiates. The knowledge gained from these Aims would be the basis for further examination in a larger Clinical Trial of TMS (R01) and would hasten the pipeline through which TMS could be developed as an evidence-based neuromodulation strategy for physicians and pain management providers to offer to patients with chronic lower back pain. Second, while most TMS investigations focus on the relative efficacy of stimulation at a single site (or a single functional network), by evaluating 2 strategies in this proposal we will be uniquely positioned to advance the field. Third, we are using a novel stimulation profile, theta burst stimulation (TBS) that was supported by our preliminary data, and is built on a foundation from learning and memory literature in preclinical research. This stimulation profile will significantly reduce the total time of active stimulation relative to 10 Hz rTMS, thus reducing patient burden. Fourth, we are including a mixed population of individuals with CLBP, which includes individuals currently taking prescription opiates, and individuals not currently taking prescription opiates, which may provide evidence about the mechanisms of action of rTMS and its ability to decrease pain.

Objectives

Effective control of chronic pain is a top priority in the United States, as approximately 10% of adults have severe chronic pain – most of which is chronic lower back pain (CLBP). However, despite the advances in neuroscience over the past 20 years, we still largely treat chronic pain with opiate narcotics, much as was done in the Civil War. In addition to their high abuse liability and dependence potential (1), only 30–40% of chronic pain patients declare they receive satisfactory (>50%) relief from their pain through pharmacological treatment (Attal et al., 2006). In these patients a common clinical practice is to escalate the dose of opiates as tolerance develops – which unfortunately has contributed to escalation in opiate overdose deaths (2), a resurgence of intravenous heroin use, and $55 billion in societal costs (3). **Consequently there is a critical need for new, treatments that can treat pain and reduce reliance on opiates in individuals with chronic pain.**

The goal of this R21 proposal is to evaluate 2 novel non-invasive brain stimulation strategies to mitigate pain and the brain's response to pain in CLBP patients that are currently taking chronic opiates, or that are seeking an alternative treatment for pain. Transcranial Magnetic Stimulation (TMS), can induce long term potentiation (LTP-like) and long term depression (LTD-like) effects on brain activity in a frequency dependent manner. Our group has previously

demonstrated that LTP-like TMS to the dorsal prefrontal cortex (DPFC, a node in the Executive Control Network (ECN)) can decrease perceived pain and corresponding BOLD signal in the "Pain Network' (7, 8, 10-12). The Pain Network is an expansion of the Salience Network (SN; insula, dorsal anterior cingulate) which includes the thalamus and somatomotor cortex(4-6). The analgesic effects of DPFC TMS can be blocked by naloxone – suggesting that the analgesic effects of LTP-like DPFC TMS are opiate mediated. Additionally, DPFC TMS delivered postoperatively leads to less patient administered morphine use (PCA-pump) in the hospital and less opiate use in the outpatient setting (9). **These data all suggest that LTP-like DPFC TMS is a promising candidate for treating pain (Strategy 1, Aim 1).**

An alternative strategy is to apply LT-like stimulation to the medial prefrontal cortex (LTP-like MC rTMS (Strategy 2, Aim 2). This strategy is based on our understanding of functional neural architecture, wherein the SN is modulated by 2 other core networks: the executive control network (ECN) and the default mode network (DMN). As stated above, it is possible to attenuate activity in the SN through LTP-like TMS to the DPFC, a node in the ECN. It is also possible to attenuate the SN through LTP-like TMS to the somatomotor cortex (a node in the DMN). **The proposed study will be the first to employ a randomized, double-blind, sham-controlled design to parametrically evaluate the longitudinal effects of 16 days of rTMS to the DPFC (Aim 1) or the MC (Aim 2) on self-reported pain and the brain's response to pain. This will be done in a cohort of patients recruited from the community as well as WFU clinics with chronic lower back pain that have not been able to find adequate pain relief, whether or not they are using prescription opiates for 3 or more months.** Participants will be randomized to receive rTMS to the DPFC (iTBS), MC, or sham (50% at each site), using a Latin square randomization. Resting state connectivity will be collected 3 times: before the 1st day of TMS, after the 12th day of TMS, and before the 16th day of TMS (the last day administered).

Aim 1. Evaluate DPFC rTMS as a tool to dampen pain and the engagement of the Pain Network. Hypothesis 1: DPFC TMS will attenuate the baseline brain response to pain (Pain Network activity) and increase activity in the ECN when the patient is given instructions to 'control' the pain.
Aim 2. Evaluate MC rTMS as a tool to dampen pain and the engagement of the Pain Network. Hypothesis 1: MC TMS will also attenuate the baseline brain response to pain (Pain Network activity) but will not effect the ECN or SN when the patient is given instructions to 'control' the pain.

(Exploratory Aim): We will evaluate if there are rate-dependent effects between baseline SN connectivity with the ECN and DMN and the efficacy of each TMS strategy on subjective pain. Data will be analyzed by using multivariate pattern analysis (MVPA) (2014). While the primary outcomes will be MRI V1 vs V2, we will also examine the relative 'durability' of the effects on pain by comparing the MRI data at the end of all TMS visits between and within groups with factor analysis.

The relative efficacy of these strategies will directly translate to development of a large clinical trial investigating rTMS as an innovative, new treatment option for pain in patients with CLBP.

Methods and Measures

Design

The proposed study will be the first to employ a randomized, double-blind, placebo-controlled design to parametrically evaluate the longitudinal effects of 16 days of rTMS to the DPFC (Aim 1) or the MC (Aim 2) on self-reported pain and the brain's response to pain. This will be done in

a cohort of patients recruited from WFU clinics and the outer community with chronic lower back pain. Participants will be randomized to receive TMS to the DPFC, MC, or sham (50% at each site), using a Latin square randomization. Resting state connectivity will be collected at each MRI scanning session. Quantitative Pain Testing will be collected 11 times. MRI data will be collected 3 times: before the 1st visit of TMS, before the 12th visit of TMS, and before the 16th visit of TMS.

Table 1. Study Design. Aim 1&2 will be conducted in parallel.

^primary goal: evaluate 2 TMS strategies as tools to decrease acute pain and brain reactivity to pain.

^secondary goal: durability

Screening	Group Assignment		
	Aim 1	dlPFC	Real
		dlPFC	Sham
	Aim 2	mPFC	Real
		mPFC	Sham

	Induction Phase				Maintenance Phase				Follow Up Phase							
	Week 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
TMS Sessions	XXX	XXX	XXX	XXX	X	X	X	X								
Clinical Assessments	XXX	XXX	XXX	XXX	X	X	X	X		X		X		X		X
Quantitative Urinalysis	X	X	X	X	X	X	X	X		X		X		X		X
Quantitative Pain Testing	X		X	X	X	X	X	X		X		X		X		X
Neuroimaging	X			X				X								

Setting

All study activities will take place at Wake Forest University of Health Sciences (WFUHS).

Dr. Hanlon's primary office and research laboratory is located in the Clinical Neuromodulation Laboratory in the Department of Cancer Biology. Dr. Hanlon's lab space will include a room dedicated for all research related activities including a space for screening participants and a space dedicated for TMS stimulation. It will contain a computer and desk for patient interviewing and a Magstim Bistim TMS system.

The MRI portion of the study will take place at the MRI center located on Medical Center Boulevard. This will utilize the Siemens 3T scanner in the MRI center.

Finally, recruitment efforts will come from the local community using flyers as well as traditional and social media outlets (radio, television, Facebook, Craigslist, local newspapers). Collaborative efforts will be maximized in order to recruit subjects from associated WFU pain clinics and pain programs.

Subjects selection criteria

Participants. We will enroll 48 men and women 18-75 years old with CLBP. These individuals may also have a history of current prescription opioid use (>3 months) for the treatment of pain. Participants will be recruited through WFU clinics as well as the outer community. Patients that have previously agreed to be contacted for research will be referred to the study or contacted via telephone. The risks of MRI and TMS to the unborn fetus are not well understood. Therefore, to be included, females must not be pregnant as determined by a urine pregnancy test and must be utilizing reliable birth control during the course of the study.

Inclusion Criteria

1. Age 18-75 (to maximize participation)
2. Can currently be using prescription opiates
3. Has current chronic back pain (> 3 months)
4. Able to read and understand questionnaires and informed consent.

5. Is not at elevated risk of seizure (i.e., does not have a history of seizures, is not currently prescribed medications known to lower seizure threshold)
6. Does not have metal objects in the head/neck.
7. Does not have a history of traumatic brain injury, including a head injury that resulted in hospitalization, loss of consciousness for more than 10 minutes, or having ever been informed that they have an epidural, subdural, or subarachnoid hemorrhage.
8. Does not have a history of claustrophobia leading to significant clinical anxiety symptoms.

Exclusion Criteria

1. Any psychoactive illicit substance use (except marijuana and nicotine) within the last 30 days by self-report and urine drug screen.
2. Meets DSM-V criteria for current axis I disorders of obsessive-compulsive disorder, bipolar affective disorder, schizophrenia, dissociate disorders, eating disorders, and any other psychotic disorder or organic mental disorder.
3. Has current suicidal ideation or homicidal ideation.
4. Has the need for maintenance or acute treatment with any psychoactive medication including anti-seizure medications and medications for ADHD.
5. Females of childbearing potential who are pregnant (by urine HCG), nursing, or who are not using a reliable form of birth control.
6. Has current charges pending for a violent crime (not including DUI related offenses).
7. Does not have a stable living situation.
8. Suffers from chronic migraines.
9. Subject meets MRI and TMS exclusion criteria as measured by the MRI Safety Screen and TMS Adult Safety Screen, including (but not limited to) metal above the neck, history of traumatic brain injury, and history of seizures.
10. Participant does not have a stable phone number for contact through call and/or text.
11. Does not have a stable means of using WebEx (e.g. personal computer, Internet) for interaction with study personnel during COVID-19.

Sample Size

A power estimate for Aim 1 and 2 was prepared using an original fMRI dataset previously collected in our laboratory (8). In this experiment, 18 healthy controls performed the same fMRI pain paradigm as the present study before and after a single session of 10 Hz rTMS. Mean parameter estimates for the "heat pain vs. rest" condition were extracted from several *a priori* regions of interest. These data yielded an effect size which ranged from 0.70 (thalamus) to 1.08 (insula) ($n=15$ yields 80% power using a two-sided $p<0.05$). Allowing for a 10% dropout rate after the screening visit, and up to a 20% dropout rate at the end of the Treatment phase (Week 4), as well as a 10% data loss rate for MRI (Aim 2) due to individuals with excessive head motion in the MRI scanner, screening 58 individuals should lead to complete data from 48 individuals (16 real DPFC, 16 real MC, 16 sham (50% at each site). Randomization will be handled by a Latin Square design with replacement will be used to ensure even enrollment across groups with replacement. All individuals will be enrolled at WFUHS. Data analysis and quality assessment will be ongoing.

Due to several COVID related factors, including challenges with scheduling and hesitation that participants may have wearing a mask in the MRI scanner, some participants will not receive the MRI

portion of this experiment. This will not affect our total enrollment goals, nor compromise the scientific integrity of this study. Moreover, it will lower the risk associated with MRIs to these participants.

Interventions and Interactions

Participants. We will enroll 48 men and women 18-75 years old with CLBP that may or may not have a history of current prescription opioid use (>3 months) for the treatment of pain. Participants will be recruited through the community along with WFU clinics. Patients that have previously agreed to be contacted for research and have current chronic pain will be referred to the study. Our prior history with targeted enrollment (See Significance) indicates this is feasible within 20 months, leading to full completion by 22 months. **Exclusion criteria:** Typical MRI and TMS exclusionary criteria, including metal above the neck or implanted in the body, use of prescription medications that lower seizure threshold, a history of seizures or traumatic brain injury, pregnancy or trying to become pregnant, current substance use or dependence (other than opioids and nicotine), history of seizure disorder, and claustrophobia. Participants will provide written informed consent following explanation of the study.

General Methods

Screening Visit – Consent. Participants will receive a series of assessments designed to evaluate opioid dependence, psychiatric conditions, chronic pain and mood. These include the MINI International Neuropsychiatric Interview (46), Brief Pain Inventory (47), Timeline Followback (48), Becks Depression Inventory II (49), State-Trait Anxiety Inventory (50), the Pittsburgh Sleep Quality Index (PSQI), the Barratt Impulsiveness Scale (BIS), and Profile of Mood States (51). Data will be collected using REDCap™, and entered directly into the online portal to ensure security and prevent data loss.

During COVID-19, study personnel will interact with participant via the Wake Forest Baptist Health (WFBH) institutional WebEx videoconference software as necessary. Participants will remotely sign and date the informed consent document.

Intervention – MRI Visits 1-3. Following enrollment, participants will meet the study personnel for Assessment & MRI Scanning (details below). The procedures at MRI Visit 1 will be repeated at MRI Visit 2 (after 12 days of rTMS), and at MRI Visit 3 (after 16 days of rTMS).

rTMS Treatment sessions: After the Screening visit, patients will be randomized to receive 16 days of real or placebo rTMS treatment. Based on prior studies in our laboratory that have applied 10 days of TMS to various clinical populations, we expect 16 sessions of TMS treatments (3 days per week for 4 weeks, followed by 1 day a week for 4 weeks) will take 8 weeks, allotting time for a weekend (as is conventional in this field), holidays and/or one missed appointment. In the event that an individual drops out before completing the 16 TMS sessions, the number of sessions received will be a covariate in the analyses. Cortical Targeting: For the TMS visits, participants will be escorted into the Brain Stimulation Research Laboratory (Dr. Hanlon's research suite) where scalp localization will be performed for the TMS procedure. The Cartesian position of the coil (X,Y,Z) will be determined by standardized positions from the EEG 10-20 system: 1) (DPFC stimulation (Aim 1)), 2) (MC stimulation (Aim 2)). The angular position of the coil (pitch, yaw, roll) will be determined by the individual's cortical geography beneath using the individual's T1 scan for guidance. The locations and coil orientation will be indicated on a nylon cap which will be worn during the TMS sessions for dPFC placement only. We will then determine the participant's resting motor threshold (RMT, the minimal amount of stimulation required over the hand area of the primary motor cortex to induce contraction of the APB muscle of the hand 50% of the time) via the standardized PEST procedure (106, 107). The procedures for acquiring the

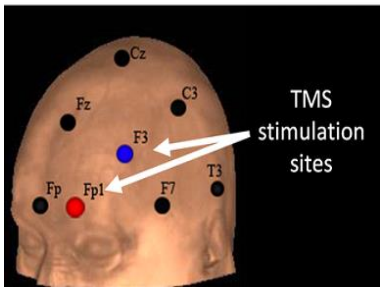

Figure 3. TMS stimulation sites, derived from EEG 10-20 landmarks.

motor threshold, performing cortical localization, standardized procedures, blinding, establishing standardized paradigms and training regimens for all staff, as well as safety and ring the experimental procedures are consistent with our prior publications (7,27, 54, 63, 69, 78, 111).

Strategy 1: iTBS to the left dPFC. For intermittent theta burst stimulation (iTBS) (Aim 1), participants will receive two sessions of iTBS stimulation per visit. Each session includes 20 trains of stimulation over the dPFC (middle frontal gyrus) (each train: 3 pulse bursts presented at 5Hz, 15 pulses/sec for 2 sec, 8 sec rest, 200 pulses/train; 110% RMT, MagPro; 600 pulses total) using a figure 8 coil (Coil Cool-B65 A/P).

Strategy 2: iTBS to the MC. This protocol is identical to that used for the DPFC explained above, with the exception of using 90% RMT rather than 110% RMT.

During each real and sham TBS session each day the amplifier output will be escalated ("ramping" in 5% increments over 30 seconds) to enhance tolerability. The time between the end of the TBS procedures and the beginning of the behavioral assessments will be compiled and used as covariates in subsequent analyses.

TMS ACTIVE SHAM system: The MagVenture MagPro system has an integrated, active sham which passes current through two surface electrodes placed on the scalp. The electrodes will be placed on the left frontalis muscle for all sessions. A patient ID card will randomize participants to receive either real or sham stimulation. This system maintains blinding by a gyroscope in the coil which indicates to the clinical staff whether the coil should be rotated up or down for this participant once the card is entered into the machine. One side of the coil is active, the other is sham. To assess the integrity of the blind (active sham) a questionnaire will be given to both the patients and to the research staff at day 1, 6, 10 to evaluate their opinion on whether they received real or sham, their level of confidence (Likert scale 1-10), and their rationale (text entry).

Assessments: The primary dependent measures will be extracted from the Quantitative Sensory Testing for pain thresholds. Other assessments include: Brief Pain Inventory (BPI), the pain craving form, and subjective pain rating scales, delivered before and after TMS. Participants will also complete the Beck Depression Inventory (BDI-II), the Profile of Mood States (POMS), the Pittsburgh Sleep Quality Index (PSQI), the State-Trait Anxiety Inventory (STAI), and Barratt Impulsiveness Scale (BIS), which assesses anxiety and depression measures. Though these are not primary outcomes, the results will be used in post-hoc analyses of the data. All surveys will be filled out by the patient on tablet computers (Apple iPad/Microsoft Surface) and data entry will be done directly via Redcap Software.

MRI scanning: The MRI scanning session will last 30 minutes and will contain: 1) a high resolution anatomical image (T1-weighted MPRAGE (TR 1.9 sec, TE 2.26 ms, 2x GRAPPA, 1 mm isotropic)), 2) resting state functional connectivity (TA 7 minutes, voxel size: 2.5 x 2.5 x 2.5, TR = 2.6 s, TE = 25 ms, flip angle = 60°, FOV = 224 mm × 224 mm, matrix size = 64 × 64),**For each of the above strategies (Active rTMS or Active Sham) we will explore a series of SubAims designed to quantify the effects of rTMS on subjective pain, quantitative sensory testing, and brain reactivity to pain.**

SubAim 1- Evaluating Pain using Clinical Assessments and Quantitative Sensory Testing (QST): Using the Medoc ATS pressure algometer (Medoc Ltd Advanced Medical Systems, Ramat Yishai, Israel), 3 primary outputs will be compiled for each individual via the method of limits (54): sensory threshold, pain threshold, tolerance threshold. The algometer has a rubber tip that will be pressed into the right forearm for the procedure. Participants will indicate when they first detect the pressure change (sensory threshold), when it becomes painful (pain threshold), and when they can no longer tolerate the stimuli (tolerance threshold). When participants indicate tolerance, the operator will release the algometer. QST will be performed at the following timepoints: for the first TMS visit, the QST will be administered prior to the first TMS session and immediately following the second TMS session; for the remainder of the TMS visits and follow-up visits, QST will be performed prior to the first TMS session at each visit. The acute changes for TMS visit 1 will give one measure for acute pain changes pre/post TMS. **Pain**

Questionnaire. In order to evaluate current levels of pain, we will ask participants to rate their current level of pain and discomfort (scale, 0 through 10), each time the participant comes in (Table 1). On days where the individual receives rTMS, they will fill out this assessment between each TMS session. **Pain and Craving Questionnaire**: In addition to the Pain Questionnaire above, participants will also rate their urge to use a pain reliever (Scale 0 – 10) and the amount they would be willing to pay for a pain reliever (in US Dollars). This questionnaire will be used at the same time during each intervention visit as the Pain Questionnaire (Table 2).

SubAim 2: Evaluating Pain using Neuroimaging Data At baseline we expect that people with chronic pain will have elevated activations in the Pain Network. This will be analyzed through the resting state connectivity network. Following sham stimulation, we do not anticipate a significant reduction of this response. Based on prior studies by our group in non-opiate dependent individuals, following LTP-like stimulation of the DPFC, we expect a significant amplification of the DPFC (% BOLD signal change), and a reduction of the Pain Network (dACC, anterior insula) reflecting the increased influence of executive processes. MC TMS however will likely not have as large of an effect on ECN engagement during the instruction to Control the pain.

Outcome Measure(s)

A. **Quantitative Sensory Testing.** The QST pain assessment produces 3 output variables: sensory threshold, pain threshold, tolerance threshold (all expressed in kiloPascals). The hypothesis will be tested using a within-subject repeated measures design (time x treatment) wherein time is the repeated variable and Real or Placebo TMS is the grouping variable. Given that the purpose of this pilot study is to develop effect sizes for a subsequent R01, we will derive least-squares means effect sizes of this strategy on these thresholds. Secondary analyses will evaluate the relationship between QST levels and the neural response to pain, as well as the relationship between QST values and evoked cortical responses. Integrating these measures together will provide a more complete picture of how cortical activity is able to modulate the pain response.

B. **Questionnaires and Evaluations.** The Opiate Pain inventory produces 4 output variables of interest: level of discomfort, level of pain, urge to use opiates, amount willing to pay for an opiate. The hypotheses for the Aims will be tested using a within-subject repeated measures design (time x treatment) wherein time is the repeated variable and Real or Placebo TMS is the grouping variable. Given that the purpose of this pilot study is to develop effect sizes for a subsequent R01, we will derive least-squares means effect sizes of our research strategy on these 4 variables, to determine the unique contributions of this intervention.

C. **Neuroimaging Data (Aim 2):** Immediately following acquisition, functional structural data will be uploaded to a secure data server and converted to NIfTI format. All preprocessing and analyses will be performed using Statistical Parametric Mapping 12 (SPM12) in Matlab 2013 (Mathworks). Functional data will be corrected for magnetic field inhomogeneity and realigned (rigid-body, minimizing least squares differences) to the first image in the time series (Realign: Estimate and Unwarp). Non-linear deformations required for standard space normalization will be derived from each participant's anatomical image via a unified segmentation approach (Segment). After the mean realigned and unwarped functional image is coregistered to the skull stripped anatomical image (Coreg: Estimate) forward deformations (subject space to MNI standard space) will be applied (Normalise: Write). Finally, the data will be smoothed by an 8 mm full width half maximum Gaussian smoothing kernel (Smooth). Within-subject and between-group modeling. Data will be analyzed at the subject level using multivariate pattern analysis (Wager et al 2013 "An fMRI-Based Neurologic Signature of Physical Pain" new England Journal of Medicine). The six motion parameters (translations and rotations) will be included in the design matrices as covariates to account for non-task signal.

Resting State Connectivity will be measured to compare MRI scan 1 to scan 2 – immediately after the treatment. MRI scan 3 will also be compared to these scans to see if there is a sustainable reduction in pain activity between these networks. Additionally factor analysis will be used to investigate the durability of the effects of each strategy on functional connectivity in each of the 3 Core networks (SN, ECN, DMN) using factor analysis longitudinally**. Covariates:** As an exploratory analysis we will also quantify the impact of several covariates which have previously been documented to affect the brain response to pain and pain thresholds (sex, Becks Depression Inventory score, length of time using chronic opiates). Although all participants will have taken their daily dose of opiates, which has a stable pharmacokinetic profile, we will also consider time since last dose.

Expected (and alternative) Outcomes:

A. **Quantitative Pain Testing.** Based on our pilot data, we expect an interaction between treatment (Real DPFC of MC TMS vs. Sham) and time (Before vs. After rTMS) on the painfulness QST measure but no effect on sensory or tolerance levels. Alternative outcomes: It is possible that individuals will experience a small level of acute pain relief from their normal regimen of medication. We will be collecting information on opiate dose and timing at each visit to be used as potential covariates. Further, there is the possibility that pain tolerance will rise, possibly also reflecting improvements in executive function.

B. **Qualitative Pain Assessment.** We expect reductions in pain and discomfort when comparing active vs sham. However, based on prior data in opiate dependent individuals, we expect the effect size of DPFC rTMS in to improve measures of Control but not measures of mood, whereas MC will have a larger effect on mood.

C. **Neuroimaging.** At baseline we expect that there will be elevated activations in the Pain Network in individuals with chronic pain. Following sham stimulation, we do not anticipate a significant reduction of this response. Based on prior studies by our group in non-opiate dependent individuals, following LTP-like stimulation of the DPFC, we expect a significant amplification of the DPFC (% BOLD signal change), and a reduction of the Pain Network (dACC, anterior insula) reflecting the increased influence of executive processes.

   Alternative outcomes: Though pilot data suggest that a single treatment will acutely reduce self-reported pain, it is possible that the neural circuits in opiate dependent individuals do not have the same 'plasticity potential' as in controls. If we fail to replicate prior work showing DPFC activation, this could reflect executive deficits (58), suggesting that the MC TMS will be more efficacious.

Exploratory Analysis: We will evaluate if there are rate-dependent effects between baseline SN connectivity with the ECN and DMN and the efficacy of each TMS strategy on subjective pain. Data will be analyzed by using multivariate pattern analysis (MVPA) (2014). While the primary outcomes will be MRI V1 vs V2, we will also examine the relative 'durability' of the effects on pain by comparing the MRI data at the 1 month follow up between and within groups with factor analysis. **Integration of Brain based and Behavioral Based Outcomes with Gender and other Demographic Variables:** Finally, we will compare the relative efficacy of these two types of TMS using the behavioral and neuroimaging measures. Specifically, we will determine the effect sizes for DPFC and MC (relative to sham) stimulation on reducing the 1) the neural and 2) behavioral responses to pain, as well as 3) changes in clinical assessment metrics (see Approach). We will investigate the role of baseline cortical responsiveness on the pain response, as well as how changes in that evoked response are related to changes in both pain and craving measures. This will be specifically addressed as a factor of gender as

well, given that there are established differences in sensitivity to pain and prevalence of opiate dependence between men and women.

Analytical Plan

See Outcomes Measures for the main plan of analysis.

Results will be analyzed initially using descriptive statistics. Comparison between groups will be done using chi square tests for proportions, and t-tests or ANOVA procedures for continuous variables. Regression analysis will be performed to identify independent outcome predictors. Other inferential statistical analysis will be conducted as appropriate.

Human Subjects Protection

Potential Risks

The risks fall into three categories: risks associated with psychological assessment, risks associated with repetitive TMS and risks associated with MRI scanning.

Risks of psychiatric interviewing (minimal risk):

1. Some participants may get emotionally distraught when disclosing sensitive personal stories. Some participants may feel anxiety about disclosing substance use histories and reporting some aspects of their demographics.

Risks associated with MRI scanning (minimal risk):

1. The major potential risks for MRI are all subsumed under the risks for TMS and primarily include risks to individuals who have metallic implants, pacemakers, or pregnant women. These individuals will be excluded from the study.
2. Participants may feel restless or uncomfortable when lying in the MRI scanner.

Risks associated with repetitive TMS (FDA-designated minimal risk):

Repetitive TMS has been considered "non-significant risk" by the FDA (2007) when applied at similar intensities, durations, and frequencies to those being used in this protocol. Additionally medial prefrontal and dorsolateral prefrontal continuous theta burst stimulation in a manner identical to this protocol has been designated minimal risk by the MUSC Institutional Review Board for healthy adults as well as individuals with nicotine deopendence.

1. Potential risk of a seizure: In designing this experiment, we have followed the latest safety guidelines for TMS. Despite these precautions, there is a chance of a seizure as a result of rTMS. Eight seizures have been noted in previous studies, with six of them occurring in healthy volunteers without any history of seizures, brain tumors or traumatic brain injuries. All of these seizures have occurred during rTMS with the participant in the treatment chair and a trained operator on hand. All seizures have stopped by themselves without any medication. No participants have had any problems after the seizures. WFUHS has a plan for dealing with fainting and seizures, and **every TMS researcher involved in providing TMS treatment for this protocol (Key Personnel) will have extensive TMS training from the PI on the study as well as a skills test associated with collecting an accurate motor threshold (which is one of the largest factors that promotes safety).** Additionally, if a participant has a seizure an emergency response team will be called. Most seizures, including those caused by rTMS, last less than 60 seconds and do not require any medication. Participants will be evaluated by a physician associated with the WFUHS Brain Stimulation Laboratory following recovery from the seizure. Any participant who has a seizure cannot continue with the study.

A note about theta burst stimulation: The relative risk of having a seizure is related to the strength of the TMS stimulation (% motor threshold) and the frequency (typically 1Hz-20Hz, or theta). There are

published safety tables for fixed frequency rTMS paradigms (eg 1hz, 5 Hz, 10 Hz, 20 Hz). For individuals receiving TMS doses within these ranges and without other risk factors, (medication, significant sleep deprivation, etc.), TMS has been deemed a non-significant risk by the FDA. For some brain stimulation protocols (like theta burst), there are no currently published safety tables, but there are at least 6 review articles that demonstrate that theta burst is likely minimal risk to non-significant risk. These studies largely show that the risks/safety of theta burst protocols are comparable (or perhaps less than) 10Hz or 20 Hz rTMS.

Other potential risks:

2. Potential for scalp discomfort and headaches: Some people report mild discomfort when the magnetic pulses are applied over the scalp. A small number of people (~5%) report headache following rTMS. However, the headaches are temporary and manageable with common over-the-counter pain remedies.
3. Potential hearing loss: The TMS coil generates a high-energy click that may cause hearing damage. Humans exposed to TMS have shown temporary increases in auditory threshold (especially at high frequencies) lasting at least 5 minutes and less than 4 hours.
4. Safety in case of pregnancy: This protocol will exclude pregnant women. The risks of using TMS with pregnant women are currently unknown. Please inform the research team if you are pregnant or think that you might have become pregnant during the study. A pregnancy test will be performed before the experiment begins.
5. Potential for reflex syncopal event: Syncope is defined as a momentary loss of awareness and postural tone. It typically has a rapid onset, short duration, and spontaneous recovery. Although syncopal episodes are very rare with TMS (less than 1%), they typically occur during the motor threshold procedure before the rTMS treatment has begun. Individuals that are sleep deprived and have low or unstable blood pressure are at greater risk.
6. Interaction with electrical or metal implants: Electrically, magnetically or mechanically activated implants (such as cardiac pacemakers), as well as clips on blood vessels in the brain may be affected by rTMS (as well as MRI) and cause pain or abnormal signal propagation. Therefore individuals that have these implants and devices or suspect that they may have pieces of metal in their eyes, head, or body (e.g. bullets, shrapnel, fragments from metallurgy) will be excluded from the study.

Adequacy of protection against risks

(a) Recruitment and Informed Consent Identification of Subjects, Recruitment of Subjects and Informed Consent Process. Advertisements will be placed in local print and digital media. Interested individuals will email, call, or text the research center and will then be contacted via telephone and scheduled for screening and Visit 1. Only individuals that have previously given permission to be contacted for future research purposes will be called. Informed consent will be reviewed with the potential participant by a member of the key personnel on this proposal. The consent will be signed by the participant as well as one of the Key Personnel on the proposal. A copy of the consent will be given to the subject and the original placed in the research record.

(b) Security of Participant Information

For individuals that are enrolled in the study (invited for a screening visit) there will be two documents that contain their first and last names: the informed consent that includes the written

HIPAA authorization and a receipt for their compensation kept for tax purposes. Each of these documents will be kept in a separate 3-ring binder.

Each individual enrolled in the study will be assigned a unique patient ID number (starting sequentially from '100'). A folder will be created for each of these participants and labeled with their Patient ID number. The folder will contain the results of all of the testing for each individual. The patients will only be identified by number, not by name, on these documents. All information stored digitally for the enrolled participants will be labeled with the Patient ID number. As above all of the participant folders, along with the binders will be stored in a locked cabinet in Dr. Hanlon's research laboratory.

Protection Against Risks

Risks of psychiatric assessments:

All psychiatric assessments will be conducted by study personnel who have received formal training in clinical interviewing and have worked with substance dependent patients in the past.

Risks associated with MRI and TMS (minimal risk):

1. Although the TMS protocol that we are using has never been associated with causing a seizure, individuals that have a history of seizures, stroke, or other neurological impairment that might lower their seizure threshold will be excluded from the study. All study personnel will have received a formal education course in seizure detection, care, and treatment and a physician will be available to immidiately assist in stabilizing the participants in the event of a seizure Any participant who has a seizure cannot continue with the study.
2. We will exclude individuals with claustrophobia such that they are not exposed to this risk. Additionally participants will be given a pressure sensitive squeeze ball that they can use to indicate at any time that they would like to leave the scanner.
3. To protect against hearing loss concerns, participants will wear high fidelity earplugs throughout the scanning session.
4. Participants will be informed of potential risk of scalp discomfort and headache before they consent and will be told that they should feel free to take non-steroidal antiinflammatory agents after the TMS session if they have a headache.We will also exclude individuals with chronic migraines such that they are not exposed to this risk.
5. We will exclude pregnant females such that they are not exposed to this risk.
6. All participants that enroll in this study will complete a written MRI saftey screen. We will also use a handheld metal detector to ensure the participant has no metal in or on is/her body before entering the MRI scanning room.

Protocol for participants expressing suicidal ideation: All study team members performing the Becks Depression Inventory will have received online training from the Suicide Prevention Resource Center (https://training.sprc.org). Completion documentation will be saved on the laboratory drive. In the event that a participant expresses a desire to kill themselves (selects answer #2 or #3 on question #9 of the Becks Depression Inventory), the trained study team member will ask them about the level of detail of their thoughts. If the participant has a suicide plan to kill himself/herself, the study staff will recommend he/she speaks with the suicide hotline and initiate contact with the suicide prevention hotline (Durham Center Crisis Line at 1-800-510-9132) while the individual is in their presence. If the participant refuses to talk to the hotline and leaves, the study staff will call 911. The study staff member will also contact the PI via phone, email, or text as soon as possible to inform them of the situation.

Participants may withdraw from the study at any time or may be withdrawn from the study if the PIs feel it is in the best interest of the participant. All key personnel will undergo appropriate IRB training for dealing with human participants and will be trained by the PI at their site in all aspects of the study

interventions. Personnel listed in this protocol (as well as any rotating medical students, graduate students, psychiatry residents or fellows that may be exposed to this investigation as part of their reseaerch training exposre) will be required to maintain their certification of HIPAA training and Protection of Human Participants in Research training on an annual basis. Any new personnel without experience in human clinical research will be encouraged to attend the WFU Core Clinical Research Training Course, which is offered live and online throughout the year. Through these measures we will ensure that all study staff will be trained and will maintain ongoing understanding of research ethics and the rights of the participant during the consenting process and throughout an individual's participation in the study.

In the event of a medical emergency, a research participant will be transported to the Emergency Department at WFUHS. If a psychiatric crisis occurs, the Department of Psychiatry at either hospital will be contacted to arrange for either an emergency outpatient appointment or an in house psychiatric consult.

Subject Recruitment Methods

Participants with chronic pain will be recruited via flyers placed throughout the WFU campus, community, WFU clinics, broadcast messages, Craigslist, and via phone calls to individuals that have participated in previous studies with our group and have given permission to be contacted if other studies become available.

Advertisements will be placed around campus in approved locations, especially at WFU clinics. Other ads will be submitted to local newspapers as well as internet advertising to reach the general population (e.g. Craigslist, broadcast messages at WFU). Recruitment will also occur at community events where recruitment materials (such as pens, backpacks, and mugs) will be handed out to individuals. Interested individuals will call or text the research center and will then be contacted via telephone, phone screened, and scheduled for screening if eligible. If an individual declines study participation or is not eligible via phone screen, their information will be shredded and destroyed. Informed consent will be reviewed with the potential participant by a member of the key personnel on this visit. The consent will be signed by the participant as well as one of the Key Personnel on the proposal. A copy of the consent will be given to the subject and the original placed in the research record. The consent and HIPAA process will be done in Dr. Hanlon's research laboratory and facility. The MRI scans will be done at the MRI center and the TMS sessions will be done in the TMS laboratory located in Dr. Hanlon's research lab.

Additionally, a chart review will be conducted for research purposes. Potentially eligible patients will be identified. The potentially eligible patients in the PIs practice will be informed about the study as the PI feels is appropriate. Then potential patients who have agreed to be contacted for future research by logging their WFU Research Permissions preferences in MyChart will be contacted by phone and invited to participate. All other patients will be contacted through their providers to be informed of the study if the provider feels it is appropriate.

In 2016, the ratio of male:female individuals using opiates for pain was approximately 1:1. We will recruit in accordance with this ratio. There will be no exclusion criteria with respect to ethnic background.

Informed Consent

Individuals that have previously consented to be contacted about future research studies will be contacted and phone screened to determine preliminary eligibility. They will be scheduled for their screening visit, which will take place in a private, quiet screening room in the Clinical Neuromodulation Laboratory space in Dr. Hanlon's research suite. Informed consent will be reviewed with the potential participant by a member of the key personnel on this proposal. The consent will be signed by the participant as well as one of the Key Personnel on the proposal. A copy of the consent will be given to the subject and the original placed in the research record. All records will be stored in locked departmental files. Section

301(d) of the Public Health Service Act of November 4, 1988 also protects a layer of protection for the privacy of health information for individuals that engage in federally funded medical research.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed three years after closure of the study, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator (PI) will be the primary party responsible for data management, oversight, and accountability in terms of participant safety and consent. A conflict of interest will be avoided by secondary evaluation of records by a Monitoring Entity (ME) (aka. data safety monitoring board- DSMB) on an annual basis. Quality control will include regular data verification (Integrity of the Consent and HIPAA, scores on assessments, MRI scanning information), study progress, subject status, adverse events, and protocol deviations. Protocol adherence will be monitored by the Wake Forest IRB, who will also be given access to the reports from the PI to the ME.

Provisions to Monitor the Data to Ensure the Safety of Subjects

DSM Board Plan: Meet annually with the PI to discuss the information listed in "Content of ME/DSM report". This content of this meeting will be formalized in a report which will be circulated by email and digitally approved by the PI and ME/DSMB. The approved report will be sent to the Wake Forest IRB.

Content of DSM Report: The following information will be included in the DSM report- number of individuals consented, number of individuals enrolled, number of active participants, gender and race distribution of subjects, discussion and listing of all amendments to the proposal, any publications and/or scientific presentations related to the proposal, update on any resolved or unresolved AE/SAEs, review of any new scientific literature related to the safety and efficacy of this protocol.

Plans for Interim Analysis of Efficacy Data: Data from this study will be analyzed when a 50% recruitment goal is obtained. Final analysis will occur when all participants have finished the final follow-up phase of the study.

Responsibility for Data and Safety Monitoring: The PI, protocol-approved research team, and ME/DSMB are all responsible for data and safety monitoring. The PI will be most involved in data and safety oversight. The PI will discuss data integrity and inquire about safety/patient tolerance in weekly meetings with the research team.

Data Entry Methods: Data will be collected using REDCap™, which is a secure web application for building and managing online surveys and databases. REDcap™ supports online or offline data capture for research studies and operations. Participants and protocol-approved study personnel will enter data directly into the online portal to ensure security and prevent data loss.

Data Analysis Plan: Data for this study (behavioral assessments, functional MRI measurements) will be acquired by protocol-approved members of the research team, including graduate students and research specialists. These individuals will also perform data management and analysis under the guidance of the PI. Manuscript composition will be led by the PI and Co-Is, with the assistance of the research team.

Quality Assurance Plan: Weekly meetings will be held between the PIs and research team to discuss any data-related problems as well as qualitative comments received during data collection. Initial data analyses will examine distributions of variable scores, and comparability of baseline characteristics across conditions, any necessary adjustments to analyses will be made. Confidentiality protections are outlined below.

Statistical review of the study will be conducted annually by a Wake Forest biostatistician (including enrollment, retention, assessment inventories). Data collected in previous studies by our research group have demonstrated that after extended use in the MRI scanner environment (likely more than 5000 pulses) the strength of the induced magnetic field from the Magstim biphasic coil begins to drop in a non-linear fashion. Consequently, the intensity of the induced magnetic field from the Magstim coil will be assessed by protocol-approved study personnel and logged weekly (alongside with protocol use, number of pulses, intensity of pulses). This cumulative record of coil performance will be monitored and, when the intensity of the induced field had degraded 10%, we will switch to a new, identical Magstim coil.

Definition and Reporting of AEs/SAEs to the IRB: An adverse event (AE) is defined as any untoward medical occurrence in a study subject who was administered rTMS but does not necessarily have a causal relationship with this treatment. 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: death, life-threatening, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect.

All unexpected AEs will be reported to the Wake Forest Institutional Review Board (IRB) and Committee on Human Research within 48-business hours. Serious AEs will also be reported within 24-business hours. Follow-up of all unexpected and serious AEs will also be reported to these agencies. AEs/SAEs are documented and reported as per IRB requirements. Research staff will identify AEs and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome, and the need for change or discontinuation in the study intervention. AEs are documented on AE Logs and AE Case Report Forms. Additional relevant AE information, if available, will be documented in a progress note and stored in the research record as appropriate to allow monitoring and further evaluation. 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. We will report adverse events to the Medical Wake Forest IRB online per the IRB's guidelines.

Collection and Reporting of AEs and SAEs: As mentioned above, all AEs/SAEs are documented and reported as per IRB requirements. Research staff will identify AEs, verify event with the participant, and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome, and the need for change or discontinuation in the study intervention. AEs are documented on AE Logs and AE Case Report Forms. Additional relevant AE information, if available, will be documented in a progress note and stored in the research record as appropriate to allow monitoring and further evaluation. 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. If applicable, copies of medical records and injury reports will be retrieved and safely stored in the

subjects file. De-identified copies of reports will be sent to the Wake Forest IRB and ME/DSBM. 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.

Reporting of Unanticipated Problems, Adverse Events or Deviations: Any unanticipated problems, serious, and/or unexpected AEs, deviations or protocol changes will be reported within 24-72 business hours, depending on severity, by the principal investigator or designated member of the research team to the Wake Forest IRB and ME/DSMB.

Management of SAEs or Other Study Risks: As described above, SAEs will be immediately reported, within 24 business hours, to the ME/DSBM and Wake Forest IRB. For each SAE recorded, the research staff will follow the SAE until resolution, stabilization, or until the participant is no longer in the study as stated in the protocol. If applicable, copies of medical records and injury reports will be retrieved and safely stored in the subjects file. De-identified copies of reports will be sent to the Wake Forest IRB and ME/DSBM.

Reporting of ME/DSMB Reports to IRB: Any ME/DSMB reports will be reported to the Wake Forest IRB.

Report of Changes or Amendments to the Protocol: Any changes to the proposal/protocol must be approved by the Wake Forest IRB.

Trial Stopping Rules: The protocol will immediately be paused following notification of a SAE. Per IRB policy, the IRB and ME/DSMB will be notified within 24 business hours following the SAE notification. Should the reported SAE be confirmed as directly related to the protocol, the trial will be terminated. The device manufacturer will be notified within 72 business hours. Of note, according to the literature associated with the MagVenture device, there have been no clinical trials stopped or SAEs reported.

Conflict of Interest: Neither the PI, nor members of the research team have any Conflicts of Interest directly related to this protocol. The rTMS device used for the proposed study is manufactured by MagVenture.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB.

References

1. Quality CfBHSa. Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health. HHS Publication No SMA 15-4927, NSDUH Series H-50. 2015.
2. Center for Disease Control and Prevention NCfHS, National Vital Statistics, System, Mortality File. Number and Age-Adjusted Rates of Drug-poisoning Deaths Involving Opioid Analgesics and Heroin: United States, 2000–2014. In: Prevention CfDCa, editor. Atlanta, GA2015.
3. Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. Pain medicine. 2011;12(4):657-67. doi: 10.1111/j.1526-4637.2011.01075.x. PubMed PMID: 21392250.
4. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain. 2005;9(4):463-84. doi: 10.1016/j.ejpain.2004.11.001. PubMed PMID: 15979027.

5. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. N Engl J Med. 2013;368(15):1388-97. doi: 10.1056/NEJMoa1204471. PubMed PMID: 23574118; PubMed Central PMCID: PMCPMC3691100.
6. Cauda F, Costa T, Diano M, Sacco K, Duca S, Geminiani G, Torta DM. Massive modulation of brain areas after mechanical pain stimulation: a time-resolved FMRI study. Cereb Cortex. 2014;24(11):2991-3005. doi: 10.1093/cercor/bht153. PubMed PMID: 23796948.
7. Taylor JJ, Borckardt JJ, George MS. Endogenous opioids mediate left dorsolateral prefrontal cortex rTMS-induced analgesia. Pain. 2012;153(6):1219-25. doi: 10.1016/j.pain.2012.02.030. PubMed PMID: 22444187; PubMed Central PMCID: PMCPMC3530383.
8. Taylor JJ, Borckardt JJ, Canterberry M, Li X, Hanlon CA, Brown TR, George MS. Naloxone-reversible modulation of pain circuitry by left prefrontal rTMS. Neuropsychopharmacology. 2013;38(7):1189-97. doi: 10.1038/npp.2013.13. PubMed PMID: 23314221; PubMed Central PMCID: PMCPMC3656361.
9. Borckardt JJ, Weinstein M, Reeves ST, Kozel FA, Nahas Z, Smith AR, Byrne TK, Morgan K, George MS. Postoperative Left Prefrontal Repetitive Transcranial Magnetic Stimulation Reduces Patient-controlled Analgesia Use. Anesthesiology. 2006;105(3):557-62. PubMed PMID: 16931989.
10. Galhardoni R, Correia GS, Araujo H, Yeng LT, Fernandes DT, Kaziyama HH, Marcolin MA, Bouhassira D, Teixeira MJ, de Andrade DC. Repetitive transcranial magnetic stimulation in chronic pain: a review of the literature. Arch Phys Med Rehabil. 2015;96(4 Suppl):S156-72. doi: 10.1016/j.apmr.2014.11.010. PubMed PMID: 25437106.
11. Lefaucheur JP, Antal A, Ahdab R, Ciampi de Andrade D, Fregni F, Khedr EM, Nitsche M, Paulus W. The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to relieve pain. Brain Stimul. 2008;1(4):337-44. doi: 10.1016/j.brs.2008.07.003. PubMed PMID: 20633392.
12. Moisset X, de Andrade DC, Bouhassira D. From pulses to pain relief: an update on the mechanisms of rTMS-induced analgesic effects. Eur J Pain. 2015. doi: 10.1002/ejp.811. PubMed PMID: 26471248.
13. Shei A, Rice JB, Kirson NY, Bodnar K, Birnbaum HG, Holly P, Ben-Joseph R. Sources of prescription opioids among diagnosed opioid abusers. Curr Med Res Opin. 2015;31(4):779-84. doi: 10.1185/03007995.2015.1016607. PubMed PMID: 25661018.
14. Barth KS, Maria MM, Lawson K, Shaftman S, Brady KT, Back SE. Pain and motives for use among non-treatment seeking individuals with prescription opioid dependence. Am J Addict. 2013;22(5):486-91. doi: 10.1111/j.1521-0391.2013.12038.x. PubMed PMID: 23952895; PubMed Central PMCID: PMCPMC3748383.
15. Siebner HR, Bergmann TO, Bestmann S, Massimini M, Johansen-Berg H, Mochizuki H, Bohning DE, Boorman ED, Groppa S, Miniussi C, Pascual-Leone A, Huber R, Taylor PC, Ilmoniemi RJ, De Gennaro L, Strafella AP, Kahkonen S, Kloppel S, Frisoni GB, George MS, Hallett M, Brandt SA, Rushworth MF, Ziemann U, Rothwell JC, Ward N, Cohen LG, Baudewig J, Paus T, Ugawa Y, Rossini PM. Consensus paper: combining transcranial stimulation with neuroimaging. Brain Stimul. 2009;2(2):58-80. doi: 10.1016/j.brs.2008.11.002. PubMed PMID: 20633405.
16. Denslow S, Lomarev M, George MS, Bohning DE. Cortical and subcortical brain effects of transcranial magnetic stimulation (TMS)-induced movement: an interleaved TMS/functional magnetic resonance imaging study. Biol Psychiatry. 2005;57(7):752-60. doi: 10.1016/j.biopsych.2004.12.017. PubMed PMID: 15820232.
17. Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry. 2012;72(7):595-603. doi: 10.1016/j.biopsych.2012.04.028. PubMed PMID: 22658708; PubMed Central PMCID: PMCPMC4120275.
18. Bohning DE, Shastri A, Lomarev MP, Lorberbaum JP, Nahas Z, George MS. BOLD-fMRI response vs. transcranial magnetic stimulation (TMS) pulse-train length: testing for linearity. J Magn Reson Imaging. 2003;17(3):279-90. doi: 10.1002/jmri.10271. PubMed PMID: 12594717.

19. Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. Eur J Neurosci. 2004;19(7):1950-62. doi: 10.1111/j.1460-9568.2004.03277.x. PubMed PMID: 15078569.
20. Barr MS, Farzan F, Wing VC, George TP, Fitzgerald PB, Daskalakis ZJ. Repetitive transcranial magnetic stimulation and drug addiction. Int Rev Psychiatry. 2011;23(5):454-66. doi: 10.3109/09540261.2011.618827. PubMed PMID: 22200135.
21. Bellamoli E, Manganotti P, Schwartz RP, Rimondo C, Gomma M, Serpelloni G. rTMS in the treatment of drug addiction: an update about human studies. Behav Neurol. 2014;2014:815215. doi: 10.1155/2014/815215. PubMed PMID: 24803733; PubMed Central PMCID: PMCPMC4006612.
22. Gorelick DA, Zangen A, George MS. Transcranial magnetic stimulation in the treatment of substance addiction. Ann N Y Acad Sci. 2014;1327:79-93. doi: 10.1111/nyas.12479. PubMed PMID: 25069523; PubMed Central PMCID: PMCPMC4206564.
23. Grall-Bronnec M, Sauvaget A. The use of repetitive transcranial magnetic stimulation for modulating craving and addictive behaviours: a critical literature review of efficacy, technical and methodological considerations. Neurosci Biobehav Rev. 2014;47:592-613. doi: 10.1016/j.neubiorev.2014.10.013. PubMed PMID: 25454360.
24. Politi E, Fauci E, Santoro A, Smeraldi E. Daily sessions of transcranial magnetic stimulation to the left prefrontal cortex gradually reduce cocaine craving. Am J Addict. 2008;17(4):345-6. doi: 10.1080/10550490802139283. PubMed PMID: 18612892.
25. Terraneo A, Leggio L, Saladini M, Ermani M, Bonci A, Gallimberti L. Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: A pilot study. Eur Neuropsychopharmacol. 2016;26(1):37-44. doi: 10.1016/j.euroneuro.2015.11.011. PubMed PMID: 26655188.
26. Trojak B, Meille V, Achab S, Lalanne L, Poquet H, Ponavoy E, Blaise E, Bonin B, Chauvet-Gelinier JC. Transcranial Magnetic Stimulation Combined With Nicotine Replacement Therapy for Smoking Cessation: A Randomized Controlled Trial. Brain Stimul. 2015;8(6):1168-74. doi: 10.1016/j.brs.2015.06.004. PubMed PMID: 26590478.
27. Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain. 2003;126(Pt 5):1079-91. doi: 10.1093/brain/awg102. PubMed PMID: 12690048.
28. Freund W, Klug R, Weber F, Stuber G, Schmitz B, Wunderlich AP. Perception and suppression of thermally induced pain: a fMRI study. Somatosens Mot Res. 2009;26(1):1-10. doi: 10.1080/08990220902738243. PubMed PMID: 19283551.
29. Wager TD, Atlas LY, Leotti LA, Rilling JK. Predicting individual differences in placebo analgesia: contributions of brain activity during anticipation and pain experience. J Neurosci. 2011;31(2):439-52. doi: 10.1523/JNEUROSCI.3420-10.2011. PubMed PMID: 21228154; PubMed Central PMCID: PMCPMC3735131.
30. Cho SS, Strafella AP. rTMS of the left dorsolateral prefrontal cortex modulates dopamine release in the ipsilateral anterior cingulate cortex and orbitofrontal cortex. PLoS One. 2009;4(8):e6725. doi: 10.1371/journal.pone.0006725. PubMed PMID: 19696930; PubMed Central PMCID: PMCPMC2725302.
31. Borckardt JJ, Reeves ST, Weinstein M, Smith AR, Shelley N, Kozel FA, Nahas Z, Byrne KT, Morgan K, George MS. Significant analgesic effects of one session of postoperative left prefrontal cortex repetitive transcranial magnetic stimulation: a replication study. Brain Stimul. 2008;1(2):122-7. doi: 10.1016/j.brs.2008.04.002. PubMed PMID: 19759838; PubMed Central PMCID: PMCPMC2744083.
32. Brighina F, Piazza A, Vitello G, Aloisio A, Palermo A, Daniele O, Fierro B. rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. J Neurol Sci. 2004;227(1):67-71. doi: 10.1016/j.jns.2004.08.008. PubMed PMID: 15546593.
33. Brighina F, De Tommaso M, Giglia F, Scalia S, Cosentino G, Puma A, Panetta M, Giglia G, Fierro B. Modulation of pain perception by transcranial magnetic stimulation of left prefrontal cortex. J Headache Pain. 2011;12(2):185-91. doi: 10.1007/s10194-011-0322-8. PubMed PMID: 21350791; PubMed Central PMCID: PMCPMC3072504.

34. Umezaki Y, Badran BW, DeVries WH, Moss J, Gonzales T, George MS. The Efficacy of Daily Prefrontal Repetitive Transcranial Magnetic Stimulation (rTMS) for Burning Mouth Syndrome (BMS): A Randomized Controlled Single-blind Study. Brain Stimul. 2016;9(2):234-42. doi: 10.1016/j.brs.2015.10.005. PubMed PMID: 26597930.
35. Upadhyay J, Maleki N, Potter J, Elman I, Rudrauf D, Knudsen J, Wallin D, Pendse G, McDonald L, Griffin M, Anderson J, Nutile L, Renshaw P, Weiss R, Becerra L, Borsook D. Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. Brain. 2010;133(Pt 7):2098-114. doi: 10.1093/brain/awq138. PubMed PMID: 20558415; PubMed Central PMCID: PMCPMC2912691.
36. Farrell MJ, Laird AR, Egan GF. Brain activity associated with painfully hot stimuli applied to the upper limb: a meta-analysis. Hum Brain Mapp. 2005;25(1):129-39. doi: 10.1002/hbm.20125. PubMed PMID: 15846813.
37. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci. 2007;27(9):2349-56. doi: 10.1523/JNEUROSCI.5587-06.2007. PubMed PMID: 17329432; PubMed Central PMCID: PMCPMC2680293.
38. Paus T, Castro-Alamancos MA, Petrides M. Cortico-cortical connectivity of the human mid-dorsolateral frontal cortex and its modulation by repetitive transcranial magnetic stimulation. Eur J Neurosci. 2001;14(8):1405-11. PubMed PMID: 11703468.
39. Koski L, Paus T. Functional connectivity of the anterior cingulate cortex within the human frontal lobe: a brain-mapping meta-analysis. Experimental Brain Research. 2000;133(1):55-65. doi: 10.1007/s002210000400.
40. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron. 2005;45(2):201-6. doi: 10.1016/j.neuron.2004.12.033. PubMed PMID: 15664172.
41. Hanlon CA, Canterberry M, Taylor JJ, DeVries W, Li X, Brown TR, George MS. Probing the frontostriatal loops involved in executive and limbic processing via interleaved TMS and functional MRI at two prefrontal locations: a pilot study. PLoS One. 2013;8(7):e67917. doi: 10.1371/journal.pone.0067917. PubMed PMID: 23874466; PubMed Central PMCID: PMC3706588.
42. Feil J, Zangen A. Brain stimulation in the study and treatment of addiction. Neurosci Biobehav Rev. 2010;34(4):559-74. doi: 10.1016/j.neubiorev.2009.11.006. PubMed PMID: 19914283.
43. Wing VC, Barr MS, Wass CE, Lipsman N, Lozano AM, Daskalakis ZJ, George TP. Brain stimulation methods to treat tobacco addiction. Brain Stimul. 2013;6(3):221-30. doi: 10.1016/j.brs.2012.06.008. PubMed PMID: 22809824.
44. Breedlove JL, A; Back, SE; Borckardt, JJ; Taylor, JJ; Badran, BW; Sahlem, GL; Rostami, R; Brady, KT; George, MS; and Hanlon, CA., editor. 10 Hz rTMS May Reduce Pain and Craving in Prescription Opiate Dependent Individuals: a pilot study. Annual Meeting of the Society of Biological Psychiatry; May 14th-16th, 2015; Toronto, On.
45. Nestler EJ. Molecular basis of long-term plasticity underlying addiction. Nature reviews Neuroscience. 2001;2(2):119-28. doi: 10.1038/35053570. PubMed PMID: 11252991.
46. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of clinical psychiatry. 1998;59 Suppl 20:22-33;quiz 4-57. Epub 1999/01/09. PubMed PMID: 9881538.
47. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Annals of the Academy of Medicine, Singapore. 1994;23(2):129-38. Epub 1994/03/01. PubMed PMID: 8080219.
48. Sobell LC, Sobell MB. Timeline Follow-Back. In: Litten RZ, Allen JP, editors. Measuring Alcohol Consumption: Psychosocial and Biochemical Methods. Totowa, NJ: Humana Press; 1992. p. 41-72.
49. Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation; 1996.

50. Spielberger CD, Gorsuch RL, Lushene RH. State-trait Anxiety Inventory. Palo Alto: Consulting Psychologists Press; 1970.
51. M. MD, M. L, F. DL. Profile of Mood States (POMS)–Revised Manual. San Diego, CA: Education and Industrial Testing Service; 1992.
52. Mishory A, Molnar C, Koola J, Li X, Kozel FA, Myrick H, Stroud Z, Nahas Z, George MS. The maximum-likelihood strategy for determining transcranial magnetic stimulation motor threshold, using parameter estimation by sequential testing is faster than conventional methods with similar precision. The Journal of ECT. 2004;20(3):160-5.
53. Borckardt JJ, Nahas Z, Koola J, George MS. Estimating resting motor thresholds in transcranial magnetic stimulation research and practice: a computer simulation evaluation of best methods. J ECT. 2006;22(3):169-75. doi: 10.1097/01.yct.0000235923.52741.72. PubMed PMID: 16957531.
54. Shy ME, Frohman EM, So YT, Arezzo JC, Cornblath DR, Giuliani MJ, Kincaid JC, Ochoa JL, Parry GJ, Weimer LH. Quantitative sensory testing: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2003;60(6):898-904. doi: 10.1212/01.wnl.0000058546.16985.11.
55. Petersen KL, Rowbotham MC. A new human experimental pain model: the heat/capsaicin sensitization model. Neuroreport. 1999;10(7):1511-6. PubMed PMID: 10380972.
56. Martin L, Borckardt JJ, Reeves ST, Frohman H, Beam W, Nahas Z, Johnson K, Younger J, Madan A, Patterson D, George M. A pilot functional MRI study of the effects of prefrontal rTMS on pain perception. Pain medicine. 2013;14(7):999-1009. doi: 10.1111/pme.12129. PubMed PMID: 23647651.
57. Upadhyay J, Lemme J, Anderson J, Bleakman D, Large T, Evelhoch JL, Hargreaves R, Borsook D, Becerra L. Test-retest reliability of evoked heat stimulation BOLD fMRI. J Neurosci Methods. 2015;253:38-46. doi: 10.1016/j.jneumeth.2015.06.001. PubMed PMID: 26072245.
58. Gruber SA, Silveri MM, Yurgelun-Todd DA. Neuropsychological consequences of opiate use. Neuropsychol Rev. 2007;17(3):299-315. doi: 10.1007/s11065-007-9041-y. PubMed PMID: 17690984.

59. Attal N, Cruccu G, Haanpää M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P. EFNS guidelines on pharmacological treatment of neuropathic pain. European journal of neurology. 2006 Nov 1;13(11):1153-69. PMID: 17038030

60. Dunlop K, Hanlon CA, Downar J. Noninvasive brain stimulation treatments for addiction and major depression. Annals of the New York Academy of Sciences. 2017 Apr 1;1394(1):31-54.

61. Hanlon CA, Dowdle LT, Austelle CW, DeVries W, Mithoefer O, Badran BW, George MS. What goes up, can come down: Novel brain stimulation paradigms may attenuate craving and craving-related neural circuitry in substance dependent individuals. Brain research. 2015 Dec 2;1628:199-209.
62. Hanlon CA, Dowdle LT, Correia B, Mithoefer O, Kearney-Ramos T, Lench D, Griffin M, Anton RF, George MS. Left frontal pole theta burst stimulation decreases orbitofrontal and insula activity in cocaine users and alcohol users. Drug and Alcohol Dependence. 2017 May 30.
63. Hanlon CA, Kearney-Ramos T, Dowdle LT, Hamilton S, DeVries W, Mithoefer O, Austelle C, Lench DH, Correia B, Canterberry M, Smith JP. Developing Repetitive Transcranial Magnetic Stimulation (rTMS) as a Treatment Tool for Cocaine Use Disorder: a Series of Six Translational Studies. Current Behavioral Neuroscience Reports. 2017:1-2.
64. Chistyakov AV, Rubicsek O, Kaplan B, Zaaroor M, Klein E. Safety, tolerability and preliminary evidence for antidepressant efficacy of theta-burst transcranial magnetic stimulation in patients with major depression. International Journal of Neuropsychopharmacology. 2010 Apr 1;13(3):387-93.