Study Title: Developing brain stimulation as a treatment for chronic pain in opiate dependent individuals

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NCTPROTOCOL TITLE:

Developing brain stimulation as a treatment for chronic pain in opiate dependent individuals

PRINCIPAL INVESTIGATOR:

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1.0 Objectives / Specific Aims

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 dorsolateral prefrontal cortex (DLPFC, 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 somatosensory cortex(4-6). The analgesic effects of DLPFC TMS can be blocked by naloxone – suggesting that the analgesic effects of LTP-like DLPFC TMS are opiate mediated. Additionally, DLPFC 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 DLPFC TMS is a promising candidate for treating pain (Strategy 1, Aim 1).**

An alternative strategy is to apply LTD-like stimulation to the medial prefrontal cortex (LTD-like mPFC 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 DLPFC, a node in the ECN. It is also possible to attenuate the SN through LTD-like TMS to the ventral medial prefrontal 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 DLPFC (Aim 1) or the MPFC (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 MUSC 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 DLPFC (iTBS), MPFC (cTBS), 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 DLPFC rTMS as a tool to dampen pain and the engagement of the Pain Network. Hypothesis 1: DLPFC 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 MPFC rTMS as a tool to dampen pain and the engagement of the Pain Network. Hypothesis 1: MPFC 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.

2.0 Background

BACKGROUND AND SIGNIFICANCE. 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.**

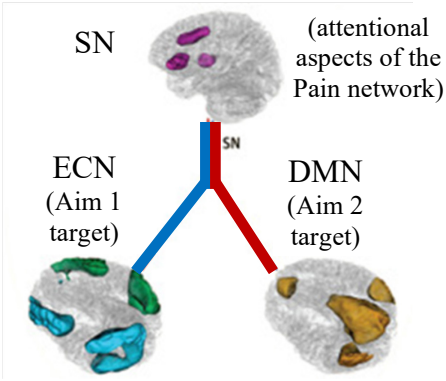

Figure 1. Dynamic Interaction of Core functional connectivity networks. Adapted from Lerman et al 2014 JAMA Psychiatry. The Salience Network (SN), Executive Control Network (ECN), and Default Mode Network (DMN) represent 3 Core neural networks in the brain which are dynamically coupled. During pain, 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 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 10 days of TMS 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 dorsolateral prefrontal cortex (DLPFC, 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 DLPFC 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 DLPFC 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 DLPFC 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 LTD-like stimulation to the medial prefrontal cortex (LTD-like mPFC 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 DLPFC, a node in the ECN. It is also possible to attenuate the SN through LTD-like TMS to the medial prefrontal 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 DLPFC (Aim 1) or the MPFC (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 MUSC 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.**

<u>The scientific rationale for rTMS effects on pain in CLBP patients using chronic opioids.</u> 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. DLPFC (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 10hz 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). 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 DLPFC 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), it may be more efficacious to attenuate activity in the MPFC (Aim 2, Strategy 2) which would likely target the affective components of pain. The rationale for this alternative hypothesis is that in patients with chronic, ongoing pain, normal regulatory mechanism are disrupted, and pain processing is shifted towards more emotionally oriented circuits, such as the MPFC (34-36). This alteration in brain function encourages the exploration of alternative treatment locations in this population.

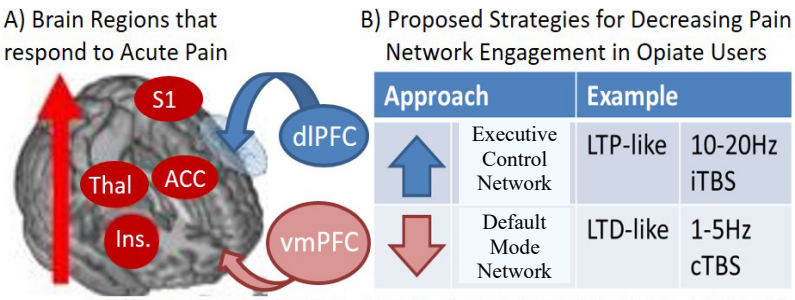

Figure LTP-like DLPFC TMS is known to attenuate the Pain Network (Taylor et al 2013, and others). The LTD-like vmPFC TMS attenuates the ACC and Insula(Hanlon et al, under review) and is reciprocally related to the DLPFC (Dunlop et al 2016, and others).

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 DLPFC or MPFC 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 DLPFC 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.

3.0 Intervention to be studied (if applicable)

See section 2.0 for more information about the interventions being investigated.

4.0 Study Endpoints (if applicable)

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.

5.0 Inclusion and Exclusion Criteria/ Study Population

Participants. We will enroll 48 men and women 18-75 years old with CLBP. These individuals can also have a history of current prescription opioid use (>3 months) for the treatment of pain. Participants will be recruited through MUSC 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. Able to read and understand questionnaires and informed consent.
4. 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)
5. Does not have metal objects in the head/neck.
6. 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.
7. 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.

Inclusion of Women and Minorities

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.

The population of Charleston, SC is 52.2% White, 41.1% African American, and1.6% Asian. 4.4% of the population is Hispanic/Latino. This is a relatively low percentage of Hispanic individuals based on national statistics. We will seek to enroll 5 Hispanic or Latino participants to be closer to the national average. Given the high concentration of African-Americans, all racial minorities will likely be black or African-American. We will strive however, to recruit a diverse population including American Indians, Asians, and Pacific Islanders if possible. As necessary, advertisements will be placed in newspapers and radio stations with primarily African-American or Hispanic readerships and listenership's (e.g., Charleston Post and Courier, The Charleston Free Press, WQMG FM).

6.0 Number of Subjects

48 participants will be enrolled in this research study.

7.0 Setting

General Facilities and Resources

The Medical University of South Carolina ranks in the upper third of federal research funds received by US medical schools and fosters cross-departmental collaborations as a means of integrating the basic and clinical sciences through its many research centers.

The Department of Psychiatry & Behavioral Sciences emphasizes excellence in clinical care, teaching, and research. MUSC Psychiatry is headquartered in its own building, the **Institute of Psychiatry** (IOP), where the majority of the department's faculty, residency training programs, research programs, and administrative offices are located. The department ranks among the top 15 psychiatry departments in the U.S., and the top 3 in the Southeast, in terms of funding from the National Institutes of Health. In FY2008 departmental faculty received 124 grant and contract awards, totaling $24.2 million in extramural research support. Ongoing research projects range from basic neuroscience and brain imaging, to clinical pharmacology and treatment studies. The department's Center for Drug and Alcohol Programs, which includes a major NIH-funded Alcohol Research Center, involves extensive collaboration with basic science and other clinical departments. The addictions program was ranked 9th in the nation by U.S. News & World Report (2009). The main research divisions in the Department are the Brain Stimulation Laboratory, Center for Drug and Alcohol Programs, Clinical Neuroscience Division, Family Services Research Center, Geropsychiatry Division, National Crime Victims Center, Public Psychiatry Division, and Weight Management Center.

The Brain Stimulation Laboratory (BSL) is located in a series of labs and offices (>3000 square feet) primarily located on the 5th floor of the Institute of Psychiatry (IOP). BSL studies use electromagnetic approaches as either research tools investigating neuroscience questions or as investigational or FDA approved treatments for brain diseases. Techniques actively being used by BSL researchers and their collaborators include: transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), transcranial direct current stimulation (tDCS), electroconvulsive therapy (ECT), deep brain stimulation (DBS) and epidural cortical stimulation (epCS). MUSC's BSL team has been a world leader in TMS research since 1995, performing basic research studies using TMS as well as using TMS in clinical trials for depression, pain and addiction.

Facilities and Resources Specific to the PI:

Dr. Borckardt's primary office and laboratory is in the Brain Stimulation Division of the Department of Psychiatry. She will utilize the resources of the Brain Stimulation Laboratory.

Dr. Borckardt manages the BSL suite located in the Center for Biomedical Imaging along with Dr. George. This suite contains a room (10ft x 10 ft.) dedicated for TMS stimulation. This room currently contains 2 computers, a desk for patient interviewing, and a Magstim Bistim TMS system.

8.0 Recruitment Methods

Participants with chronic pain will be recruited via flyers placed throughout the MUSC campus, community, MUSC 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. Participants will also be recruited at community events using advertising materials. At these events, participants will have the opportunity to fill out a card stating that they are interested in being contacted about our research studies. These cards will contain their name, email, and phone number. They will be placed in a secure, opaque container in order to protect their identity, and will be destroyed after an initial contact has been made.

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 MUSC 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.

Subjects that are currently enrolled in the study will also be invited to participate in the recruitment of other subjects. If they choose to participate, they will be given coupons that can be distributed to other people (e.g., peers, acquaintances) who they think could be eligible and interested in the study. The individuals that are given these coupons can contact the study office themselves if interested in participating. If they decide to participate in the study, the currently enrolled subject will be given $10 for each coupon received from the enrollment of new participants. This recruitment tool is completely voluntary and if subjects elect not to participate, participation in this study will not be affected in any way. Participants will be screened and provide written informed consent to participate which will be obtained by study personnel. Participants will have an opportunity to ask questions and can discontinue participation at any time without penalty.

9.0 Consent Process

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 at the Center for Biomedical Imaging in the BSL 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.

10.0 Study Design / Methods

Multidisciplinary Team. We have assembled diverse talents to develop translational approaches to TMS treatment development for opiate dependence. Our team has extensive experience in: 1) TMS (Borckardt), 2) NIH trials in chronic lower back pain (Borckardt, Back), 3) pain management (Borckardt), 4) neuroimaging (Borckardt), and 5) statistical modeling (Borckardt, Lauer). In addition to providing critical effect size data for a planned R01, this grant will provide an opportunity for several MUSC trainees in the DART Resident research program (Jennifer Jones, MD), and a NIDA T32 (Tonisha Kearney Ramos, PhD) to get hands-on training with neuroimaging, TMS, and opiate dependent individuals. Dr. Brady will serve as a scientific advisor and meet regularly with the team to provide insight on outcomes and patient recruitment.

Overview. 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 DLPFC (Aim 1) or the MPFC (Aim 2) on self-reported pain and the brain's response to pain. This will be done in a cohort of patients recruited from MUSC clinics and the outer community with chronic lower back pain. Participants will be randomized to receive TMS to the DLPFC, MPFC, 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 12 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		X
Neuroimaging	X			X				X								

Participants. We will enroll 48 men and women 18-75 years old with CLBP that have a history of current prescription opioid use (>3 months) for the treatment of pain. Participants will be recruited through the community along with MUSC 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. **Sample size estimate:** 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 DLPFC, 16 real MPFC, 16 sham (50% at each site). Randomization will be handled by the MUSC data coordination center of the Biostatistical Unit (Abigail Lauer, biostatistician) and a Latin Square design with replacement will be used to ensure even enrollment across groups with replacement.

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.

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 sham rTMS treatment. Based on prior studies in our laboratory that have applied 10 days of TMS to various clinical populations,

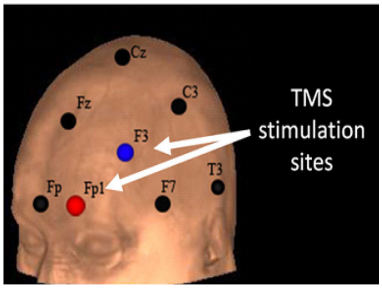

Figure 3. TMS stimulation sites, derived from EEG 10-20 landmarks.

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: After the MRI scans participants will be escorted into the Brain Stimulation room (30 feet away) 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) F3 (left DLPFC stimulation (Aim 1)), 2) FP1 (MPFC stimulation (Aim 2)). The angular position of the coil (pitch, yaw, roll) will be determined by the individual's cortical geography beneath FP1 and F3 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. 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). During each TMS session, we will take a non-identifiable photo of the participants' forehead (eyes covered with an index card) to ensure the coil is correctly placed each time they return to the lab. This will be cross-checked with the neuronavigation data.

Strategy 1: iTBS to the left dlPFC. For intermittent theta burst stimulation (Aim 1), participants will receive 20 trains of stimulation over the dlPFC (middle frontal gyrus) (F3) (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: cTBS to the vmPFC. For continuous theta burst stimulation (Aim 2), participants will receive 1 train of stimulation over the left frontal pole (FP1) (each train: 3 pulse bursts presented at 5Hz, 15 pulses/sec for 40 sec, 600 pulses/train, 110% RMT, MagPro; 600 pulses total) using a figure 8 coil (Coil Cool-B65 A/P). This protocol has been shown to attenuate the mPFC and striatum in cocaine dependent individuals in the past (61-63) and has been more effective than 1200 or 1800 pulses of cTBS in attenuating depression (The time between the end of the TBS procedures and the beginning of the behavioral assessments, as well as the scalp-to-cortex distance (which effects the actual TMS dose given to the cortex) will be compiled and used as covariates in subsequent analyses.

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. The integrity of the double-blind procedure will be assessed by asking the patients and study personnel rate their confidence regarding whether they thought they received real or sham (scale 1-10). ●**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 Quantitative Sensory Testing (QST). Using the Medoc ATS thermal stimulator (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 thermode will be attached to the right forearm, and when the procedure begins it will begin heating from room temperature (32°C) at 0.2°C per second. Participants will indicate when they first detect the temperature 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 initiate rapid (>8°C per second) cooling. For safety, the thermode will be unable to exceed 51° and will initiate rapid cooling at that point. QST will be performed at two timepoints for each visit – prior to the initial MRI session and after the second MRI session. **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 before and after each 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 DLPFC, we expect a significant amplification of the DLPFC (% BOLD signal change), and a reduction of the Pain Network (dACC, anterior insula) reflecting the increased influence of executive processes. MPFC TMS however will likely not have as large of an effect on ECN engagement during the instruction to Control the pain.

Data Analysis Plan.

A. Quantitative Sensory Testing. The QST pain assessment produces 3 output variables: sensory threshold, pain threshold, tolerance threshold (all expressed in degrees Celsius). The hypothesis will be tested using a within-subject repeated measures design (time x treatment) wherein time is the repeated variable and Real or Sham 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 Sham 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.
The hot and warm blocks of thermal stimulus, as well as rating events, will be separately modeled in a boxcar fashion. 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 DLPFC of MPFC 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 DLPFC rTMS in to improve measures of Control but not measures of mood, whereas MPFC will have a larger effect on mood.

C. Neuroimaging. At baseline we expect that there will beelevated 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 DLPFC, we expect a significant amplification of the DLPFC (% BOLD signal change), and a reduction of the Pain Network (dACC, anterior insula) reflecting the increased influence of executive processes. MPFC TMS however will likely not have as large of an effect on ECN engagement during the instruction to Control the pain.
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. The results of the baseline cortical modulation assessment of pain (instruction to "control" the pain) will help resolve this alternative outcome. If we fail to replicate prior work showing DLPFC activation, this could reflect executive deficits (58), suggesting that the MPFC 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 DLPFC and MPFC (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.

11.0 Specimen Collection and Banking (if applicable)

Sources of Research Material:

1. The material used for analysis in this protocol is of a verbal report, biologic specimen, and brain images. All reports will be collected directly from the patients during the course of their participation in this study. Verbal report data will be collected from direct subject interview, questionnaires, and computer tasks. Biologic samples include urine samples. Urine samples are provided by natural means. Urine samples will be tested for metabolites in the CDAP laboratory located on the first floor of the Institute of Psychiatry.
2. Upon their enrollment in the study, subjects will be assigned a study identification number that will subsequently be used to identify their data in lieu of other personal identifiers. Only the study PI(s) will have access to the database linking subjects' names to their identification numbers.
3. Data generated during the course of this study will be used for research purposes only. All data will be collected and transferred according to HIPAA guidelines.

12.0 Data Management

Data management, acquisition, and transmission:

The Principal Investigator (PI) will be the primary party responsible for 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 a semi-annual basis. This Entity's reporting will be supported by the South Carolina Translational Research Institute, MUSC's CTSA. Quality control will include regular data verification (Integrity of the Consent and HIPAA, scores on the Assessments, MRI scanning information), study progress and subject status, any adverse events, and any protocol deviations. Protocol adherence will be monitored by the MUSC Institutional Review Board, who will also be given access to the reports from the PI to the ME.

Data entry methods:

Data will be collected using REDCap™, and entered directly into the online portal to ensure security and prevent data loss.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects (if applicable)

Quality control will include regular data verification (Integrity of the Consent and HIPPA, scores on the Assessments), study progress and subject status, any adverse events, and any protocol deviations. Protocol adherence will be monitored by the MUSC Institutional Review Board, who will also be given access to the reports from the PI.

Responsible Conduct in Research Resources: At MUSC all faculty members and staff engaged in research must take an annual Responsible Conduct in research training module which includes the Collaborative Institutional Training Initiative on Protection of Human Subjects (https://www.citiprogram.org/) as well as modules customized to the facilities and expectations at MUSC. These resources, coupled with cross-departmental seminar series and NIH funded training opportunities in ethical conduct in research, provide an environment at the Medical University of South Carolina for Dr. Borckardt and the other study personnel on this proposal to obtain required annual training in human research ethics.

All key personnel will undergo appropriate IRB training for dealing with human participants and will be trained by the PI 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 research training exposre) will be required to maintain their certification of HIPPA 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 MUSC 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.

Data analysis plan:
Data for this study (behavioral assessments, functional MRI measurements) will be acquired by the members of the Dr. Borckardt's lab, including graduate students and research specialists. These individuals will also perform data under the guidance of the PI. Manuscript composition will be led by the PI, with the assistance of the research team.

Quality assurance plan:
The PI has weekly meetings with the research team to discuss qualitative comments received during data collection and any problems in data collection. Initial data analyses will examine distributions of variable scores, and comparability of baseline characteristics across conditions in case analyses need to be adjusted for these. Confidentiality protections are outlined below.

Statistical review of the study, will be conducted by a faculty member from the MUSC Provost-sponsored Biostatistical Collaborative Unit (see Facilities) (including enrollment, retention, assessment inventories) annually. 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 study personnel and logged weekly (alongside with use records from that week, 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. We do not anticipate this will occur within the 2-year period of this project.

Confidentiality and Privacy:

Section 301(d) of the Public Health Service Act, November 4, 1988 provides a layer of protection for health data reported by participants that have volunteered for federally funded research studies. Only members of the research team will have access to participant records. Records will be kept in a locked file cabinet in a locked office. Computer records are password protected and will identify participants by Patient ID number.

Definition and Reporting of AEs/SAEs to the IRB/FDA/NIDA:

An AE is defined as any untoward medical occurrence in a study subject administered rTMS that 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 Adverse Events (AEs) will be reported to the MUSC IRB and Committee on Human Research within 48-business hours. Serious AEs will 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 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 will 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. We will report adverse events to the Medical MUSC IRB online per the IRB's guidelines.

Incidental Findings Standard Operating Procedure:

Should an incidental finding occur, the posted CBI policy for incidental findings will be followed first and foremost (as posted on website on February 20, 2019) which states that CBI will:

1. Immediately notify the Principal Investigator (PI) of the study.
2. Request that the MRI technologist on duty transfer the study images to the clinical PACS system and notify the designated CBI radiologist.

Following review, the radiologist will contact the PI, discuss the clinical significance of the findings, and decide whether follow-up contact with the subject is necessary.

Should the radiologist contact the PI in writing and recommend follow-up contact, the PI will do the following:

1. Work with the research staff to identify the participant's name and get contact information
2. Contact one of the Study Personnel with a medical degree (MD or DO) regarding their availability to discuss the findings from the radiologist with the PI and with the participant.

    a. In the event that the PI and the study physician feel it is most appropriate for the physician to speak with the participant directly, the physician will be provided with the participant information as well as the radiologist report so they can speak with the subject and determine the appropriate course of action

b. In the event that the PI and the study physician feel comfortable having the PI speak to the participant directly, the PI will contact the participant as soon as possible.

3. A log will be kept for all attempts made to contact the subject along with detailed notes for these attempts

In the event that an obvious neurological abnormality is observed that would comprise the validity of the data for the study, the subject will be excluded upon PI discretion.

Reporting of IRB actions and ME/DSMB reports to NIDA
Any adverse events will be immediately reported to both the MUSC IRB and NIDA should this study (R21 proposal) be awarded. All ME/DSMB reports will be submitted to NIH/NIDA annually.

Report of changes or amendments to the protocol.
Any changes to the proposal/protocol must be approved by NIDA. Any amendments to the IRB protocol associated with the proposed work will be reported to NIDA should this proposal be awarded funding.

Trial stopping rules:
The protocol will immediately be paused following notification of a Serious Adverse Event (SAE). Per MUSC IRB policy, the Institutional Review Board and DSMB will be notified within 24 business hours following the SAE notification. SAEs will be reported to NIDA within 72 hours. 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 hours. Of note, there have been no clinical trials that have ever been stopped, nor SAE reported in the literature associated with the MagVenture device.

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 propose study are manufactured by MagVenture.

14.0 Withdrawal of Subjects (if applicable)

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.

Participants may withdraw from the study at any time or may be withdrawn from the study if the PI feels it is in the best interest of the participant. In the event of a medical emergency, a research participant will be transported to the Emergency Department at Medical University of South Carolina, which is within two blocks of the CAIR and the Brain Stimulation Laboratory in the Institute of Psychiatry. If a psychiatric crisis occurs, the Department of Psychiatry will be contacted to arrange for either an emergency outpatient appointment or an in house psychiatric consult.

15.0 Risks to Subjects

Potential risks/benefits for participants
The risks fall into three categories: risks associates 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):

Potential Risks of TMS

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 motor cortex 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 opaite dependence.

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. MUSC 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 to attend the MUSC Brain Stimulation Intensive training program wherein they will receive a Certificate of Completion after a written test of TMS didactics and safety measures** 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 MUSC Brain Stimulation Laboratory following recovery from the seizure. Any participant who has a seizure cannot continue with the study.

Other potential risks:

1. 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.
2. 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.
3. 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.

4. 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.
5. 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.

16.0 Potential Benefits to Subjects or Others

Potential benefits of proposed research

1. Although there is no direct monetary or medical benefit to the participants, they will be monetarily compensated for the time and effort required to participate in the study. From a biological perspective, they may benefit from the positive effects of real rTMS if they are randomized to those groups (iTBS and cTBS). From a psychological perspective all patients will likely benefit from the additional time they will spend in contact with the study team when they will be surrounded by educational materials and an environment that is generally supportive and encouraging despite their struggle with substance use disorders – a resource these individuals often do not have in their home environments.
2. The risks to subjects are reasonable in relation to the anticipated benefits they will gain. Risks to subjects can be satisfactorily minimized to keep the risk to benefit ratio acceptably low.

Importance of the knowledge to be gained

The proposed research is innovative in several ways. First, we are developing an alternative treatment strategy for pain, which involves non-pharmacologic modulation of circuits responsible for the perception of pain and craving. This is a significant conceptual advance for the field of addiction and chronic pain management. While LTP-like dlPFC TMS has been promising as a tool for pain in non-opiate dependent individuals, this proposal represents a critical next step in its development for an opiate dependent population. The knowledge gained from these aims would be the basis for further examination in a larger Clinical Trial of TMS (R01 submission planned October 2018) and hasten the pipeline through which TMS could be developed as a *neural circuit, evidence based* treatment option for physicians and providers of pain management to opiate dependent individuals. 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. Through these Aims we will determine if the effects of TMS on pain and craving are greater when the executive control circuit is amplified (Strategy 1, PMC) or when the DLPFC circuit is dampened (Strategy 2, Aim 2). Third, we are using a novel stimulation profile, theta burst stimulation (supported by our preliminary data). This stimulation profile will reduce the total time of active stimulation relative to standard10 Hz rTMS, thus reducing patient burden.

18.0 Drugs or Devices (if applicable)

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 dependence.

To safely administer TMS, every TMS researcher involved in providing TMS treatment for this protocol (Key Personnel) will have to attend the MUSC Brain Stimulation Intensive training program wherein they will receive a Certificate of Completion after a written test of TMS didactics and safety measures as well as a skills test associated with collecting an accurate motor threshold (which is one of the largest factors that promotes safety).

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.