Official Title: H-coil TMS to reduce pain: A pilot study evaluating relative efficacy of the H1 vs H7 coil
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Study Title: H-coil TMS to reduce pain: A pilot study evaluating relative efficacy of the H1 vs H7 coil

Principal Investigator, Co-investigator(s): Colleen Hanlon, PhD

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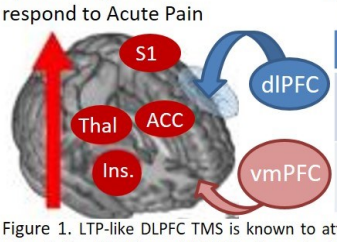
Background, Rationale and Context

Chronic pain is a serious public health problem with estimates as high as nearly half of the adult population experiencing some form of pain that lasts for more than 6 months (Andersson, Ejlertsson et al. 1993).

Evaluating rTMS as a new, non-pharmacological approach to treating pain. rTMS is a non-invasive brain stimulation method that is currently FDA-approved for the treatment of major depressive disorder. The typical figure of 8 coil design administers repeated trains of stimulation that can cause long-term potentiation (LTP) or depression (LTD) effects on targeted cortical areas as well as monosynaptic projections (Bohning, Shastri et al. 2003, Bestmann, Baudewig et al. 2004, Denslow, Lomarev et al. 2005, Siebner, Bergmann et al. 2009, Fox, Buckner et al. 2012). These cortical targets must be within 2 cm of the skull. The H1 and H7 coil designs are also capable of administering repeated trains of stimulation to effect cortical areas,at greater depths (4 to 5 cm below the coil) than the traditional figure of 8 coil (Roth, Amir et al. 2007). High frequency rTMS to a key area of executive control, the dorsolateral prefrontal cortex (dlPFC), is currently under investigation as a treatment for conditions such as pain (Lefaucheur, Antal et al. 2008, Galhardoni, Correia et al. 2015, Moisset, de Andrade et al. 2015) and addiction (Politi, Fauci et al. 2008, Barr, Farzan et al. 2011, Bellamoli, Manganotti et al. 2014, Gorelick, Zangen et al. 2014, Grall-Bronnec and Sauvaget 2014, Trojak, Meille et al. 2015, Terraneo, Leggio et al. 2016). The dlPFC plays a role in reducing self-reported pain (Lorenz, Minoshima et al. 2003, Freund, Klug et al. 2009, Wager, Atlas et al. 2011). Prior studies from our laboratory have demonstrated that 10 Hz rTMS applied to the left dlPFC decreases pain and the brain response to pain (Cho and Strafella 2009, Taylor, Borckardt et al. 2012, Taylor, Borckardt et al. 2013) in healthy controls, as well as clinical populations (Brighina, Piazza et al. 2004, Borckardt, Reeves et al. 2008, Brighina, De Tommaso et al. 2011, Umezaki, Badran et al. 2016). Furthermore, TMS-associated analgesia can be blocked by naloxone, an opiate antagonist, suggesting TMS-induced analgesia is endogenous-opiate mediated (Taylor, Borckardt et al. 2012, Taylor, Borckardt et al. 2013). Dr. Borckardt 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 (Borckardt, Weinstein et al. 2006). In contrast to the dlPFC, the mPFC plays a role in drug seeking behavior and is interconnected with several ROI's of the pain network (the dACC and the insula). Inhibitory rTMS over the mPFC may be an effective alternative target for reducing chronic pain.

A) Brain Regions that respond to Acute Pain



B) Proposed Strategies for Decreasing Pain Network Engagement in Opiate Users

Approach		Example	
↑	Executive Network	LTP-like	10-20Hz iTBS
↓	Limbic Network	LTD-like	1-5Hz cTBS

Figure 1. 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). This proposal will evaluate the relative effects of these two strategies on pain network activity, pain, and opiate craving.

The scientific rationale for rTMS effects on pain. Executive control areas like the dlPFC help attenuate BOLD signal in the pain network (Seeley, Menon et al. 2007) of the brain (e.g. dorsal anterior cingulate cortex [dACC], the insula, and the thalamus (Apkarian, Bushnell et al. 2005, Farrell, Laird et al. 2005, Wager, Atlas et al. 2013, Cauda, Costa et al. 2014)) (Koski and Paus 2000, Paus, Castro-Alamancos et al.

2001, Cho and Strafella 2009). This finding suggests that connectivity between the dlPFC and the pain network will lower perceived pain (Lorenz, Minoshima et al. 2003, Freund, Klug et al. 2009, Wager, Atlas et al. 2011). While the mPFC is most often associated with craving or reward, it also shows activity during the regulation of pain (Petrovic, Kalso et al. 2002). Particularly, in patients with chronic, ongoing pain, there is evidence that normal regulatory mechanisms are disrupted, and pain processing is shifted towards these more emotionally oriented circuits, such as the mPFC (Baliki, Chialvo et al. 2006, Hashmi, Baliki et al. 2013). This alteration in brain function encourages the exploration of alternative treatment locations in this population.

Pilot data: Quantitative Sensory Testing of pain in NMPOU after a single session of rTMS (Strategy 1). Our group recently validated single-blind, sham-controlled LTP-like (10 Hz) rTMS as a tool to decrease pain and craving Patients (n=13) received a single session of real rTMS (10Hz left dlPFC) and sham rTMS (Imperatore et al. 2020). Real rTMS had a significant effect on pain thresholds but not sensory thresholds**.** In the proposed study we will be using a modified coil design 'H-coil') which stimulates a wider field than the typical Figure of 8 coil used in this previous experiment. The H-coil has also been FDA-approved for treatment of depression and is deemed to have the same safety profile as Figure 8 coils by the FDA. Here we will use two versions of the H-coil design (H1 and H7) to modulate the response to pain. Previous studies have demonstrated that the H1 coil, preferentially stimulates the left PFC (Roth, Amir et al. 2007). Whereas the H7 coil is able to stimulate the PFC diffusely, it most effectively targets the medial PFC (Tendler, Barnea Ygael et al. 2016).

INNOVATION. The proposed research is innovative in several ways. First, we are developing a conceptually innovative, alternative treatment strategy for pain, which involves non-pharmacologic modulation of the circuits responsible for the perception of pain, as well as craving. This would be a significant conceptual advance for the field of chronic pain management as well as addiction. While 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 the determination of the most effective regions of the brain to target with rTMS in individuals with chronic pain. **The knowledge gained from these Aims would be the basis for further examination in a larger Clinical Trial of TMS and would 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 individuals with chronic 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. Through these Aims we will know if the effects of rTMS on sensory threshold and pain threshold are greater when the executive control circuit is amplified (Strategy 1, Aim 1: dlPFC) or when the limbic reward circuit is dampened (Strategy 2, Aim 1: mPFC). Third, by using two novel coil designs, we can determine the relative efficacy of these two treatment strategies, as well as gain an initial insight into the absolute efficacy of rTMS as a method for managing chronic pain after a single TMS session.

Objectives

The long term goal of our multidisciplinary research team is to determine the optimal parameters, through which repetitive transcranial magnetic stimulation (rTMS among a population at risk for addiction and conversion to non-medical use of prescription opiate (NMPOU) and IV heroin use. Chronic pain is a serious public health problem with estimates as high as nearly half of the adult population experiencing some form of pain that lasts for more than 6 months (Andersson, Ejlertsson et al. 1993). While opiates are effective at treating acute pain, tolerance to the analgesic effects develops quickly, leading to high abuse liability and dependence potential. **Consequently, the development of a new, non-pharmacologic intervention to treat pain, such as repetitive transcranial magnetic stimulation (rTMS), which would provide**

analgesic benefit while also directly remodeling the neural circuitry responsible for cognitive control over opiate craving, would fill an increasingly urgent public health need.

Acute pain is associated with elevated MRI BOLD signal in targets of ascending nociceptive fibers including the insula, dorsal anterior cingulate (dACC), thalamus and somatosensory cortex (Apkarian, Bushnell et al. 2005, Wager, Atlas et al. 2013, Cauda, Costa et al. 2014) - the **'Pain Network'**. Perceived pain, and corresponding BOLD signal in the Pain Network, is attenuated by 10 Hz rTMS (a form of brain stimulation that results in long term potentiation (LTP) to the left dorsolateral prefrontal cortex (dlPFC, a node of the Executive Control Network) (Taylor, Borckardt et al. 2012, Taylor, Borckardt et al. 2013). Dr. Borckardt was the first person to demonstrate that when LTP-like dlPFC rTMS was delivered in the postoperative recovery room, patients used less morphine in the hospital and require less morphine long-term (Borckardt, Weinstein et al. 2006). These analgesic effects are now widely known, with over 33 clinical trials utilizing rTMS as a tool to decrease acute and chronic pain in various clinical populations (Galhardoni, Correia et al. 2015).

These data all suggest that LTP-like DLPFC rTMS is a very strong candidate alleviating chronic pain (dlPFC rTMS (Strategy 1, Aim 1)). An alternative approach, however, is to attenuate the Pain Network (mPFC rTMS, Strategy 2, Aim 1). In a cohort of 49 individuals with chronic pain, Dr. Hanlon (Primary Investigator) recently demonstrated that mPFC rTMS reduced baseline BOLD signal in multiple regions of interest (ROIs) **involved in craving which also overlap with the Pain Network** (e.g. dACC and Insula). **To parametrically evaluate these 2 promising treatment strategies, we have developed a studywherein a cohort of individuals will receive Quantitative Sensory Testing before and after rTMS with the H1 and H7-coil for dlPFC stimulation (Strategy 1), mPFC depression (Strategy 2), respectively.** We will also measure subjective pain ratings. We aim to:

Aim 1. Quantify the effects of LTP-like RTMS on Quantitative Sensory Testing Hypothesis: The mechanical pain tolerance of individuals in these two group will increase after one session of rTMS administered by the H1- and H7-coil design.

Aim 2. Evaluate the effects of rTMS on subjective experience of discomfort. Hypothesis: Subjective experience of discomfort will decrease in individuals after one session of LTP-like or LTD-like rTMS administered to the dlPFC and mPFC, respectively.
The relative efficacy of Strategy 1 vs 2 will directly translate to development of a large clinical trial of rTMS as an innovative, new treatment option for pain. .

Methods and Measures

Design

The proposed study will parametrically evaluate two promising treatment strategies of rTMS using the H1 and H7-coil. . Participants will receive TMS to the dlPFC and mPFC. This will be done in a cohort of individuals with chronic back pain recruited from the local community. Quantitative Sensory Testing (QST) and subjective pain ratings will be measured before and after the rTMS session.

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 TMS system.

Subjects selection criteria

Participants: We will enroll 60 men and women 18-75 years old. Participants will be recruited from the local community, 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. We will also advertise using traditional and social media outlets (radio, television, Facebook, Craigslist, local newspapers). Our prior history with targeted enrollment indicates this is feasible within 22 months, leading to full completion by 24 months. We will use referral coupons, provided to participants to expand our opportunities for enrollment (see Other Compensation, below). Exclusion criteria: typical TMS exclusionary criteria, including a history of traumatic brain injury, pregnancy or trying to become pregnant, and history of seizure disorder. Participants will provide written informed consent following a full explanation of the study and will have the opportunity to ask questions.

Inclusion Criteria

1. Age 18 - 75 (to maximize participation).
2. Able to read and understand questionnaires and informed consent.

Exclusion Criteria

1. Positive urine drug screen for cocaine, methamphetamine, or marijuana
2. Females who are pregnant (by urine HCG),
3. Suffers from chronic migraines. (>15 headache days/month for 3+ months)
4. Is at elevated risk of seizure (i.e., has a history of seizures, is currently prescribed medications known to lower seizure threshold).
5. Has a history of traumatic brain injury resulting in medical attention or having ever been informed that they have an epidural, subdural, or subarachnoid hemorrhage.

Sample Size

A power estimate for Aim 1 was prepared using an original fMRI dataset previously collected in our laboratory (Taylor, Borckardt et al. 2013). 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 $p<0.05$). Based on an anticipated 0.80 visit-visit retention rate, and allowing for a 10% data loss rate, enrolling 60 individuals should provide 60 sufficient data sets to ensure a scientifically meaningful result.

Interventions and Interactions

General Methods

Participants who have given permission to be contacted about this research will be screened (phone, in person or video as requested by the participant) for major inclusion/exclusion criteria.

Screening Visit – Consent. The consent process will occur in a private screening room in our lab space. After a full description of the study and review of the consent document with the participant, they will be given the opportunity to ask questions, and then sign the document. Participants will then be evaluated for

pregnancy (female only) and current drug use (via Urine Drug Screen). In the event that a female is found to have a positive pregnancy screen, a drug screen will not be done. The assessments during the consent visit include: Brief Pain Inventory (BPI) (Cleeland and Ryan 1994), Becks Depression Inventory II (BDI) (Beck, Steer et al. 1996), State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch et al. 1970) and Profile of Mood States (POMS) (M., M. et al. 1992), Pittsburgh Sleep Quality Index (PSQI), Quality of Life Scale (QOLS) and Chronic Pain Grading Scale (CPGS). Data will be collected using REDCap™, and entered directly into the online portal to ensure security and prevent data loss.

Intervention –rTMS. Consistent with established practices in the field a resting motor threshold will be acquired with the coil placed over the left primary motor area (Brainsway H1 and H7 TMS System). Resting motor threshold (RMT) is defined as the minimal amount of stimulation required over the hand area of the left primary motor cortex to induce contraction of the APB muscle of the hand 50% of the time via the standardized PEST procedure (Mishory, Molnar et al. 2004, Borckardt, Nahas et al. 2006). **Strategy 1: H1-coil rTMS to the left dlPFC** (20 min, 1980 pulses delivered at 18Hz in 55 trains, 36 pulses/train, 2 sec on, 20 sec off, 120% RMT allowing for a ramping period to promote patient comfort). This coil has the maximal effect on the DLPFC. **Strategy 2: H7-coil rTMS to the mPFC** (18 min, 2000 pulses delivered at 20 Hz in 50 trains, 2 sec on, 20 sec off, 100% RMT allowing for a ramping period to promote patient comfort). Both the H1 and H7 coil parameters are current FDA-approved therapies for depression (H1 coil) and obsessive-compulsive disorder (H7 coil). Low frequency rTMS stimulation in the past has been shown to attenuate the insula mPFC and striatum in cocaine dependent individuals (Hanlon, Dowdle et al. 2015).

Deleted:

Coil Design	Frequency	Amplitude	Pulses	Chair Time	On/Off
H1	18Hz	120%	1980	20 min	2 sec/ 20 sec
H7	20Hz	100%	2000	18 min	2 sec/ 20 sec

Table 1: This table depicts all the pertinent information of the 2 possible TMS treatments involved in this study.

Screening and TMS Visit. There will be 1 screening and 2 TMS visits. If eligible, a participant may complete TMS visit 1 on the same day as the screening visit. The procedures will be identical for each TMS visit, except for the type of TMS delivered (H1 or H7 coil). Each participant will be assigned to both coils, with TMS type. A participant may be assigned to receive either:

1.) real TMS from the H1 coil at TMS visit 1, H7 coil at TMS visit 2
2.) real TMS from the H7 coil at TMS visit 1, H1 coil at TMS visit 2

Evaluating Pain with Quantitative and Qualitative Methods

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 (Shy, Frohman et al. 2003): 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 intolerance, the operator will release the algometer. QST will be performed at two timepoints for each visit – prior to the rTMS session and after.

Delayed Discounting Assessment. Participants will be asked to choose between two conditions in which varying amounts and delays to behavioral outcomes (e.g., $50 now or $100 later) are presented. We will use magnitudes of $100 and $1000 which are the most thoroughly documented among the literature (101). Across consecutive choices, the delay to the larger outcome will be titrated until reaching the

participant's indifference delay (i.e., the delay at which s/he equally values both options). This indifference delay indexes individual participants' rates of delay discounting. [61].

Remuneration. Participants will receive $70 for their participation in this study (Screening: $10, TMS and QST: $20/visit x 2 visits, Study completion bonus: $20). Individuals that withdraw will be compensated for the portions of the study they completed. Participants will be provided with coupons that they may give to other people that they believe may be interested in the study. Those referred individuals can then call if they are interested in the study. If the referred individual subsequently is eligible for the study and completes all study visits, then the original participant will receive $10 for each participant that is referred. This will be completely voluntary and whether a participant refers others or not will have not affect their status in the study.

Comfort Level Survey. Participants will also be asked to conduct a survey measuring their comfort level during TMS after both treatment seasons. These questions will ask about the pain participants experienced during treatment, their comfort during treatment, and if they would be willing to have a more, identical treatment sessions. Data will be collected using REDCap™, and entered directly into the online portal to ensure security and prevent data loss.

Outcome Measure(s)

Quantitative Sensory Testing (SubAim A). The QST pain assessment produces 3 output variables: sensory threshold, pain threshold, tolerance threshold (all expressed in kiloPascals). The hypotheses for all Strategies will be tested using a within-subject repeated measures design (time x treatment) wherein time is the repeated 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 Strategy 1or 2on these thresholds.

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, etc.).

Strategy 1, Aim 1. LTP-like left dlPFC TMS as a tool to modulate the brain response to pain.
Rationale & Approach: Prior data from our group has demonstrated that LTP-like stimulation to the left dlPFC with the Figure of 8 Coil decreases pain perception and brain response to pain in Pain Network regions of interest. While these data are very promising as we seek to establish a non-pharmacologic intervention for chronic pain management, the use of the H1-Coil to administer LTP-like stimulation to the dlPFC needs further testing. Additionally, current treatment regimens require several consecutive days of treatment making them inaccessible for most people. To address this Aim we will measure (a) QST before and after a single session of LTP-like rTMS to the dlPFC to elucidate the short term effects of this therapy.

Expected (and alternative) Outcomes:
A. Quantitative Pain Testing. Based on our pilot data, we expect an interaction between treatment (LTP-like rTMS to the dlPFC vs. LTP-like rTMS to the mPFC) and time (Before vs. After rTMS) on the painfulness QST measure but no effect on sensory or tolerance levels. Alternative outcomes: Adverse events are relatively uncommon in rTMS, but the most commonly reported side effect is headaches which occur in about 23% of individuals that receive rTMS (Machii, Cohen et al. 2006). While these adverse events are uncommon, if a patient does experience one of them, their pain threshold will likely be negatively affected. We will have a large enough sample to control for these outcomes.

Strategy 2, Aim 1. LTP-like mPFC TMS as a tool to modulate the brain response to pain.
Rationale & Approach: Prior data from our group has demonstrated that LTD-like stimulation with the Figure of 8 coil to the left mPFC (frontal pole) will decrease the baseline excitability of the pain network

of the brain (the dACC and insula (Preliminary data)) and lead to decrease in perceived pain. While these data suggest that mPFC rTMS is able to modulate areas of the Pain Network (*and decrease craving which may be particularly beneficial to opiate dependent individuals*), it is not known if this strategy of treatment is as effective with the H7-coil design that allows for greater penetration of the mPFC with LTP-like rTMS. To address this Aim, we will measure the (a) QST before and after a single session of LTP-like rTMS to the mPFC to elucidate the short-term effects of this therapy.

Expected (and alternative) Outcomes:

A. Quantitative Pain Testing. Based on prior studies by our group, in non-opiate dependent individuals, with mPFC stimulation (Hanlon, Dowdle et al. 2015) Hanlon et al 2017 Drug and Alcohol Dependence, Kearney-Ramos et al 2018 Biological Psychiatry: CNNI)], we expect Real LTP-like stimulation to reduce activations in areas of the brain associated with pain processing (Fig 1). We will evaluate the null hypothesis that there is no significant effect on pain thresholds in patients before and after receiving frequency mPFC rTMS. Alternative outcome: Given the influence of TMS on the dACC and anterior insula, (Preliminary Data), it is likely that this novel target will in fact be able to effectively modulate pain. However, adverse events like headaches while not common, do happen and will likely negatively affect pain threshold and tolerance threshold.

Integration of single-session LTP-like rTMS on the dlPFC and LTP-like rTMS on the mPFC determining relative efficacy: We will compare the relative efficacy of Strategy 1 versus Strategy 2 using the QST and questionnaire measures. Specifically, we will determine the effect sizes for DLPFC vs mPFC (before and after rTMS) stimulation on reducing the 1) behavioral responses to pain, as well as 2) changes in questionnaire metrics (level of discomfort, level of pain levels, and affect).

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 interviewing, risks associated with quantitative pain testingand risks associated with repetitive TMS.

Risks of interviewing (minimal risk):

1. Some participants may feel anxiety about reporting some aspects of their demographics.

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 TMS: 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.

Other potential risks:

2. Potential for scalp discomfort and headaches: Some people report mild discomfort when the magnetic pulses are applied over the scalp. Some people (~35%) 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. Foam ear plugs can protect against these changes and will be provided to you during TMS sessions.
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 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.
7. Potential risks of quantitative sensory testing (QST): Quantitative sensory testing will be delivered with the Medoc Pathway system which is specifically designed for safe pain assessments. It

has built-in safety mechanisms (e.g., real-time visual and auditory feedback, threshold selection, and an easy to reach shut-off button). Participants may experience redness or irritation of the skin in the area stimulated, and vitamin E cream will be provided after the trial to reduce this potential. If redness occurs, it tends to go away on its own within about 60 minutes. The application of vitamin E cream may speed this up (i.e., redness goes away within about 20 minutes). Participants may also experience bruising in the area stimulated; bruising typically resolves itself within a few days.

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 call or text the research center and will then be contacted via telephone and scheduled for screening and Visit 1. Individuals that have previously given permission to be contacted for future research purposes will also 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 one document that contains their first and last names: the informed consent containing the HIPAA authorization. This document will be kept in a separate 3-ring binder.

Each individual enrolled in the study will be assigned a unique patient ID number.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 assessments:

All psychiatric assessments will be conducted by study personnel who have received trainingas a clinical research coordinator

Risks associated with 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 formal education, training on TMS andin seizure detection andcare. A physician will be available to assist in stabilizing the participants in the event of a seizure Any participant who has a seizure cannot continue with the study.
2. To protect against hearing loss concerns, participants will wear high fidelity earplugs throughout the TMS session.
3. 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.
4. We will exclude pregnant females such that they are not exposed to this risk.
5. All participants that enroll in this study will complete a TMS saftey screen.

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 research training exposure) 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.

Subject Recruitment Methods

Participants will be recruited via flyers placed throughout the health system, community, 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 in approved locations. Other ads will be submitted to local newspapers as well as internet advertising to reach the general population (e.g. Craigslist, BeInvolved). 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 TMS sessions will also 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 will be informed about the studyPotential 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. 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 with chronic painwas 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. 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 will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

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. Quality control will include regular data verification (Integrity of the Consent and HIPAA, scores on assessments), study progress, subject status, adverse events, and protocol deviations. Protocol adherence will be monitored by the Wake Forest IRB.

Provisions to Monitor the Data to Ensure the Safety of Subjects

Plans for Interim Analysis of Efficacy Data: Final analysis will occur when all TMS visits have been completed.

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) 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).

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 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. Dr. Hanlon has previously served as a consultant for the company that produces some of the equipment in this study (Brainsway).

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.

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