PROTOCOL TITLE:

Accelerated repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex for the reduction of craving in nicotine dependent individuals.

NCT03352609

1.0 Objectives / Specific Aims

The overall objective of this double blind, sham controlled study is to evaluate the feasibility, tolerability, and preliminary efficacy of using a single day accelerated course of repetitive transcranial magnetic stimulation (rTMS) to decrease smoking cue induced nicotine craving in smokers.

- **Aim 1: Determine if the delivery of a course of five rTMS sessions during a single day is feasible and well tolerated in participants with nicotine use disorder.** We will test the hypothesis that greater than 75% of participants who start the rTMS course will complete the 5 treatments, and greater than 75% of participants will tolerate a treatment dose of greater than 100% rMT.
- **Aim 2: Determine if nicotine dependent participants will experience a decrease in cue induced nicotine craving after 5 sessions of rTMS.** We hypothesize that participants receiving active rTMS will have a greater decrease in cue induced nicotine craving after a five session treatment course of active rTMS when compared to those participants receiving sham rTMS.

2.0 Background

Despite widespread knowledge of the dangers of tobacco smoke, smoking remains the leading cause of preventable death in the world, leading to approximately 6 million deaths a year [1]. In addition, tobacco smoking has a profound economic cost to society with direct medical costs of 170 billion dollars a year attributed to smoking [2]. In 2015, 68% of smokers reported a desire to quit and each year approximately 55% of smokers make a quit attempt, demonstrating that the majority of smokers wish to quit and are willing to attempt quitting [3]. There are several available interventions to increase the success rate of a quit attempt including counseling, quit-lines, nicotine replacement therapy, bupropion and varenicline. However, despite the desire to quit and several available smoking cessation aids available, only 7.4% of smokers were able to quit in 2015 [4] which demonstrates a need for novel smoking cessation interventions.

As nicotine is the primary psychoactive compound in tobacco smoke, nicotine craving is modified by smoking cessation interventions such as nicotine replacement therapy, bupropion and varenicline[5]. Similarly to other drugs of abuse, nicotine activates mesolimbic dopamine pathways in the brain[6]. Another area of interest in addictions is the function of the dorsolateral prefrontal cortex (DLPFC) which has been found to be important in processing craving for nicotine [7] and other substances such as alcohol[8]. This has led to interest in developing new addictions treatments through decreasing substance craving by non-invasive stimulation of relevant brain regions using repetitive transcranial magnetic stimulation (rTMS). rTMS involves the delivery of magnetic pulses through the scalp to alter cortical excitability. The application of rTMS to the DLPFC is an effective, safe, non-invasive treatment currently FDA approved for the treatment of Major Depressive Disorder [9, 10]. A recent review outlined 19 studies that have used rTMS to modify craving for nicotine, alcohol and cocaine [11]. A single session of stimulatory rTMS of the left DLPFC has demonstrated a decrease in cue induced nicotine craving [12] and a series of 10 sessions stimulating the DLPFC has been demonstrated to decrease smoking[13]. Additionally, a recent randomized controlled trial has further demonstrated clinical significance by using rTMS to induce smoking cessation in nicotine dependent individuals with 6-month abstinence rates of 33% for the active intervention compared to only 9% abstinence in the sham condition[14]. Further trials of rTMS for smoking cessation are ongoing or nearing completion.

One drawback of current rTMS treatment protocols is the several week course of daily treatment sessions. In the case of depression, a typical treatment protocol is daily treatments for 4-6 weeks providing 3,000 pulses a day[15]. In addictions, the course is less defined and a recent smoking cessation trial used daily treatments of 990 pulses for 2 weeks, plus three additional treatments during the third week[14]. There is evidence to suggest that the total number of rTMS pulses delivered may mediate the treatment response[16], raising the possibility of shortening treatment courses by delivering more pulses in a day. Several studies have demonstrated the safety and possible efficacy of delivering multiple treatment sessions in day for the treatment of depression. For example, improvement in both depression and anxiety has been demonstrated through the administration of 15 rTMS sessions for a total of 15,000 pulses over the course of two days [17]. Additionally, the safety of delivering 6,000 rTMS pulses three times daily for a total of 54,000 pulses in a 3-day course was well tolerated with a retention rate of 88%, and demonstrated a trend towards a more rapid decline in suicidality [18]. A recent feasibility study has begun to examine the impact of accelerated rTMS on alcohol relapse neuropathways [19]. Despite the promise of rTMS as a possible treatment for smoking cessation, and the promise of accelerated rTMS paradigms in reducing the duration, and patient burden of delivering rTMS, there have not yet been investigations using accelerated rTMS for smoking cessation. We subsequently propose to take the first step in developing an accelerated rTMS paradigm in smokers.

2.0 Intervention to be studied

Study Intervention: Left dorsolateral pre-frontal cortex (LDLPFC) rTMS stimulation with parameters of each session delivering 3000 pulses of up to110% motor threshold 10hz stimulation, 5 seconds on 10 seconds off. The accelerated course will consist of 5 sessions delivered during a single day for a total of 15,000 pulses.

Control: Sham sessions will be delivered using an electronic sham system consisting of a coil that mimics the appearance and sound of TMS, combined with a transcutaneous electrical nerve stimulation (TENS) device which produces a small electric shock mimicking the feeling of real TMS. This type of sham has been demonstrated to be indistinguishable from active TMS, has been well tolerated in [9, 18], and successfully used in other clinical trials[20, 21]**.**

3.0 Study Endpoints:

Aim 1: **Determine if the delivery of a course of five rTMS sessions during a single day is feasible and well tolerated in participants with nicotine use disorder.** Primary endpoint will be the percent of participants starting the rTMS treatment who complete all 5 rTMS treatments in a single day.

Aim 2: Determine if nicotine dependent participants will experience a decrease in cue induced nicotine craving after 5 sessions of rTMS. Primary endpoint of difference in 0-100 averaged pre and post treatment smoking cue induced cigarette craving scores using an adopted QSU- B 10 questionnaire to measure smoking craving [12]. A secondary endpoint will be the trend of level of neutral cigarette craving evaluated between each rTMS treatment session. An exploratory endpoint will be comparison of participant self-reported level of smoking the week prior to treatment with smoking 1 and 2 weeks after treatment, assessed by phone call.

5.0 Inclusion and Exclusion Criteria/ Study Population

- Patients will be screened for eligibility by brief phone interview and in person interview at study visit.

Inclusion Criteria

- Outpatient Adults aged 18-70
- Cigarette Smokers smoking at least 1 pack (20 cigarettes a day) with current smoking status confirmed by exhaled CO reading of >10ppm day of visit.
- Ability to provide informed consent

Exclusion Criteria

- Current treatment with varenicline or bupropion
- Currently making a smoking quit attempt (not currently smoking).
- Current treatment with an antidepressant, anti-convulsant, anxiolytic, antipsychotic or mood stabilizer.
- Current episode of major depression determined by MINI interview.
- Current or past history of schizophrenia, schizoaffective disorder, anorexia nervosa, bulimia or bipolar disorder as determined by MINI.
- Current daily consumption of alcohol or current alcohol use disorder.
- Current substance use disorder except for nicotine or cannabis use disorder.
- Currently pregnant or lactating.
- Contraindications to rTMS including history of seizure, metal implanted above the neck, pacemaker or any brain lesion.
- Unstable medical conditions
- Suicidal ideation or history of suicide attempt within the last six months.
- Inability or unwillingness of subject or legal guardian/representative to give informed consent

6.0 Number of Subjects

We plan to recruit 30 participants, 15 sham rTMS and 15 active rTMS

7.0 Setting

The study evaluation and intervention will take place at two locations. The first location is the Charleston Ralph H Johnson VA Medical Center in the outpatient brain stimulation clinic. The second location will be MUSC's brain stimulation facility at 30 Bee Street, Charleston. The same model of rTMS machine and coil will be used at both locations.

8.0 Recruitment Methods

- Potential participants will be recruited from VA medical center clinics by distribution of fliers, and referral from providers. Additionally, study personnel may visit the VA smoking cessation group to provide information about the study to potential participants. We will also contact participants of other recent studies who provided consent to be contacted about future studies.
- Potential participants will be recruited by distribution of fliers, print advertisements, online craigslist advertisement and from MUSC internal medicine (UIM) clinic by distribution of fliers. Potential participants may be referred by clinicians. Additionally, we will contact participants of other recent studies who provided consent to be contacted about future studies.
- Compensation to study participants will be provided. Participants will receive $20 for the study screening portion of the visit and $120 if patient meets inclusion criteria and participates in the study.

9.0 Consent Process

Study personnel will obtain informed consent at the beginning of the study visit. The informed consent form includes a detailed description of the study procedures, along with statements regarding participants' rights to withdraw from the procedure at any time without consequences. The informed consent form will be explained to subjects in easy-to-understand language, and subjects will be instructed to read the form carefully prior to signing it. Consent will be documented by the signature of the participant on the informed consent agreement, accompanied by the signature of the individual obtaining the consent. We will obtain consent in a private office at each location.

10.0 Study Design / Methods

The study will be a double blind, sham controlled design comparing cue induced nicotine craving before and after five sessions of active or sham rTMS. Participants will be recruited and will undergo a short phone screen to see if they qualify. The study will involve a single visit and participants will be asked to abstain from smoking or using nicotine replacement during the study visit. At the beginning of the visit study personnel will obtain informed consent from participants and confirm participants meet study inclusion criteria through administration of the MINI neuropsychiatric interview[22], review of current medications, medical history , urine pregnancy test if indicated and confirmation of smoking status by exhaled CO reading of >10ppm. The participants smoking history will be taken using the time line follow back and the Fagerstrom Test for Nicotine Dependence (FTND) will be administered to evaluate the severity of nicotine dependence[23]. Participants will be randomized to receive either sham rTMS or active rTMS. Participants cue induced nicotine craving will be evaluated before and the rTMS session. A week and 2 weeks after the participant's rTMS, they will be contacted by telephone and asked their current level of cigarette consumption.

rTMS treatments: rTMS will be delivered via a MagPro double blinded rTMS Research System (MagVenture, Denmark) with a Cool-B65 Butterfly Coil (a combined active and sham coil). We will use a standard resting motor threshold (rMT) determination to determine the TMS dose [24]. Treatment will be delivered at up to 110% resting motor threshold. Each active TMS session will consist of a total of 3000 pulses of 10Hz stimulation (5s-on,10s-off)[12]. Each treatment day will consist of 5 sessions of rTMS, each separated by approximately 30 minutes. A prior accelerated rTMS investigation has separated

sessions by only 15-20 minutes and was well tolerated [25]. Treatments will be delivered at the EEG coordinate for F3 (which approximates the left DLPFC), and will be found using the Beam-F3 method [26]. Sham sessions will be delivered using an electronic sham system consisting of a coil that mimics the appearance and sound of TMS, combined with a transcutaneous electrical nerve stimulation (TENS) device which produces a small electric stimulus mimicking the feeling of real TMS. This type of sham has been demonstrated to be indistinguishable from real TMS, has been well tolerated in [9, 18], and successfully used in other clinical trials[20, 21]. During the rTMS, participants will watch a video of smoking related images.

Cue Induced Craving Assessment:
Cue induced nicotine craving will be evaluated before and after rTMS with a previously validated cue induced craving paradigm[12]. The cue induced craving paradigm presents neutral control images and smoking cue images in blocks and we will evaluate craving between each block using a visual analog scale described below. Participants will be asked to bring their cigarettes to study visit and will be instructed to hold, but not smoke, a cigarette.

The blocks will include scenic images (such as mountains), neutral control images (such as a person holding a pen), and cigarette-smoking cue images (such as a person lighting a cigarette) presented in four blocks with craving evaluated between each block. Physical cues such as a pack of cigarettes may be used as well.

Craving will be evaluated using a modified QSU-B [27] questionnaire using a 0-100 computerized visual analog scale (or paper based scale if computer is not available) designed to assess craving. The 10 QSU-B questions include the following: 1) I have a desire for a cigarette right now; 2) Nothing would be better than smoking a cigarette right now; 3) If it were possible, I probably would smoke now; 4) I could control things better if I could smoke; 5) All I want right now is a cigarette; 6) I have an urge for a cigarette; 7) A cigarette would taste good now; 8) I would do almost anything for a cigarette now; 9) Smoking would make me less depressed; 10) I am going to smoke as soon as possible.

12.0 Data Management

Data will be managed using REDCAP and all data entry will take place directly into REDCAP in a deidentified manner, so that PHI will not be stored in REDCAP. A printed key linking REDCAP participant number with the participant name and contact information will be kept in a locked filing cabinet at the study location (VA participant information will be locked in cabinet at the VA). The only required paper items will be the consent and HIPAA documents. There will however be emergency paper backups of the database should the database be unavailable for any reason. If data is collected on paper, the information will be immediately transferred to the REDCAP database, and the paper record will be kept in a locked filing cabinet.

Statistical Analysis:
In preliminary analyses, we will examine the change in craving from pre-treatment to post-treatment in both groups (active rTMS vs. sham rTMS), and will use an independent two-group t-test to evaluate the difference in magnitude of change between the two groups. In final analyses, we will fit a generalized linear model to examine the impact of active vs. sham treatment on the magnitude of change from pre- to post-treatment craving. We will control for baseline craving since it is expected to be a strong predictor of post-treatment craving and may be imbalanced between study groups.

The main objective of this pilot study is to establish feasibility and tolerability of the accelerated rTMS treatment, and to begin to explore the possible treatment effect. Therefore, we do not focus on statistical power for this project. We aim to recruit 15 patients per group, which will provide a good foundation for estimating likely effect size and planning future studies.

15.0 Risks to Subjects

Potential risks of rTMS: The use of high frequency rTMS has been FDA approved for the treatment of major depressive disorder since 2008. Our stimulation parameters of 3000 pulses of 10Hz stimulation (5s-on,10s-off) are very similar to the FDA approved protocol (3000 pulses, 10Hz, 4-Seconds on, 8-Seconds off), and has been used safely in a prior rTMS study targeting nicotine craving [12]. The common clinical dose of rTMS in depression is 36 treatments with 3000 pulses per treatment, for a total of 108,000 pulses[28]. Prior accelerated rTMS studies in depression have safely delivered 6,000 pulse treatments three times a day, delivering 18,000 daily pulses for a total of 54,000 pulses over three days [18]. We will deliver 5 sessions of 3,000 pulses for a total of 15,000 pulses in a day meaning we will be giving fewer pulses than a typical course of rTMS and fewer daily pulses than a prior accelerated rTMS study safely provided. Accelerated treatment paradigms have been safely delivered in both depression[17, 18, 25, 29], and addictions [19, 30] populations without any clear adverse effect.

Risk of Seizure: The most serious risk associated with the use of rTMS is seizure. Since the adoption and widespread use of standard safety guidelines in 1997 [31], there has only been one documented seizure using a figure of eight coil like we will be using. The risk of seizure has been estimated to be less than 0.1% which is lower than the risk of seizure associated with pharmacologic antidepressants[32]. The risk of seizure is related to the various stimulation parameters (intensity, frequency, train duration), location of application, pre-existing risk of seizure, and substance/medication factors. In the very rare event a seizure is caused, removing the coil is typically sufficient to stop the seizure, and there is no increased risk of subsequent seizures. In order to mitigate the risk of seizure we will carefully individualize the intensity of stimulus (by performing a resting motor threshold determination), treat using standard treatment protocols and exclude potential participants at higher risk of seizure (those with a past history of seizures, those with known CNS lesions, those in withdrawal from alcohol or benzodiazepines, etc).

Risk of site discomfort and headache: Two relatively common risks associated with the use of rTMS include the risk of mild transient site discomfort during treatment (most patients), and the risk of post treatment headache (Approximately 5%). Both of these potential side effects are typically mild. In terms of mitigating site discomfort, we will slowly ramp up stimulation intensity during the first sessions. In our experience both clinically and experimentally, ramping initial sessions results in improved tolerability of treatment. Additionally, due to the anti-pain effect of rTMS participants rapidly adjust to stimulation. In the unusual circumstance that a headache is caused by rTMS, over the counter analgesics are typically sufficient to alleviate the headaches, and we will forewarn participants of the possibility of headache and the effectiveness of over the counter analgesics.

Potential for hearing loss: The discharge of the TMS coil generates a high-energy click that may cause cochlear 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 earplugs can protect against these changes and will be worn during TMS sessions.

Safety in the case of pregnancy: This protocol will exclude pregnant women. Pregnancy status will be confirmed during the baseline visit with a urine pregnancy test.

Safety in case of thoughts of harming self: If a patient endorses thoughts of suicide during the visit, the patient will be evaluated by a psychiatrist and appropriate referrals made for emergency treatment if needed or outpatient follow up. If evaluation is performed by a resident psychiatrist, the evaluation will be discussed with an attending psychiatrist.

Potential Risks of Cue Induced craving: Visualization of drug cues are known to transiently increase craving for substances including nicotine. These visual cues will be presented in the presence of study staff under close monitoring so participants will not be able to immediately smoke. Participants will be given referral information to providers to assist in smoking cessation should they wish to quit and additionally VA participants will be informed about the smoking cessation group at the VA.

Potential Loss of Confidentiality: There is risk that a participant may lose confidentiality due to collection and storage of protected health information. To minimize this risk, patient data stored in REDCAP will be deidentified using a participant ID number. The key linking this participant ID number to their name and contact information will be stored in a locked filing cabinet at each study location. VA PHI will be locked up at the VA and not leave its premises, nor be accessed by non-VA study personnel. The is also the potential that study personnel may have a legal obligation to break confidentially in the rare case of learning information such as the patient is an imminent risk to themselves/others or learning of potential child/elder abuse.

16.0 Potential Benefits to Subjects or Others

Evidence suggests that rTMS has anti-nicotine craving effects, and may help decrease the number of cigarettes smoked by smokers. Research participants receiving active treatment may experience a decrease in craving for cigarettes. Participants will be provided with resources and appropriate referrals should they wish to have assistance in quitting smoking. Additionally, this study will provide beneficial information to society which may help further the future development of rTMS as a safe and effective treatment for nicotine dependent individuals attempting to quit smoking.

18.0 Drugs or Devices

TMS devices will be stored in locked offices, and treatments will be delivered by qualified staff who are specially trained in the delivery of rTMS.

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