Office Title:
Repetitive Transcranial Magnetic Stimulation (rTMS) for Nicotine Addiction

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Study Title: Developing rTMS as a potential treatment for nicotine addiction

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SPECIFIC AIMS

Cigarette smoking is the leading cause of preventable death in the United States[1, 2]. Unfortunately smoking cessation is difficult, with the majority quit attempts resulting in relapse[3-5] and the average smoker attempts to quit five times before a successful quit attempt. While a number of pharmacotherapeutic agents and cognitive behavioral therapies alone or in combination with medication have demonstrated efficacy [5, 6], even with combined treatment, the most common outcome at one-year following a quit attempt is relapse [7]. Only 6% of the 35 million smokers who report wanting to quit each year are successful in doing so for more than a month [8, 9]. Clearly, there is room for improvement in smoking cessation treatment.

Human brain imaging studies have provided insight into the brain regions associated with cue-induced cigarette craving, a frequent cause of relapse[10-12]. Furthermore, improved ability to resist cue-induced craving is associated with a reduction in cue-induced activation of limbic and prefrontal brain regions [12-14]. Transcranial magnetic stimulation (TMS) provides a non-invasive means of modulating brain neural activity[15, 16]. Neuroimaging studies of repetitive TMS (rTMS) over dorsal lateral prefrontal cortex (DLPFC) demonstrated that rTMS normalized brain areas of anomalous activity due to depression[17, 18]. Given this previous research, rTMS may reduce cue craving to smoking and treat nicotine dependence through modulating cortical and subcortical areas associated with smoking cue-induced craving.

To date, several studies have reported that rTMS reduced cue craving in nicotine dependence [19-22]. However, these studies are limited by small sample sizes, variation in stimulation parameters, and in some cases the lack of sham-controlled design and objective measures of tobacco smoking. Furthermore, in all of these studies, stimulation location was targeted to a fixed brain region based on standard skull landmarks. rTMS studies in depression have showed that antidepressant effects are likely depend on coil positioning [23, 24]. Personalized coil placement based on a pre-treatment MRI has the potential to enhance outcomes. Additionally the duration or reduced craving following rTMS has yet to be examined. Taken together, while rTMS has demonstrated promise in facilitating smoking cessation, further double-blind investigation is required to determine optimal stimulation parameters and the duration of effect of rTMS in smokers. Furthermore, MRI guided TMS may help us to identify the optimal stimulation location to enhance the effectiveness of the treatment.

This R21 will build on exciting pilot work and advance our knowledge concerning the potential utility of rTMS in smoking cessation by conducting a controlled, double-blind method comparing the impact of ten daily treatments of active rTMS and sham rTMS, on cue-induced craving and cigarette consumption in nicotine-dependent cigarette smokers with extensive monitoring of side effects and smoking outcomes. We propose to directly stimulate the left DLPFC with Brainsight in smokers. In the two years of project, we plan to recruit 42 cigarette males and females of all ethnic and racial groups between the ages of 18 and 60 to participate in the study. Specific Primary Aims include:

Aim 1: To determine under rigorous experimental conditions, whether 10 MRI guided rTMS of left DLPFC treatment sessions over a 2 week period result in superior clinical outcomes compared to sham rTMS in smoking cessation.

Hypothesis 1: We hypothesize that 10 rTMS sessions (15 minutes 10 Hertz active rTMS at 100% resting motor threshold-rMT) over DLPFC will significantly reduce cue-elicited craving and cigarettes per day as compared to sham rTMS.

Aim 2: To evaluate the longevity of clinical benefit of 10 rTMS sessions on smoking measures including cigarettes per day and level of nicotine dependence with following-up 3 months after the last rTMS session.

Hypothesis 2: We will predict that the effects of rTMS will dissipate over 3 months following-up time in some smokers. We also will predict that the effects of rTMS will last more than 3 months in other smokers. The following-up data will provide the best fit of the relapse-time data relative to a variety of parametric alternatives.

Aim 3: To demonstrate whether the active rTMS and sham groups differ significantly in side effect profiles, and whether the frequency and severity of side effects decreases over the course of treatment.
Hypothesis 3: The frequency and severity of side effects will not differ between the active rTMS and sham groups, and decreases over the course of the treatment, suggesting adaptation or tolerance.

RESEARCH STRATEGY

1. Significance

Nicotine dependence remains a significant public health concern. In 2011, the World Health Organization (WHO) reported that tobacco use continues to be the leading global cause of preventable death, killing nearly 6 million people and causing hundreds of billions of dollars of economic damage worldwide each year [25]. In the United States, cigarette smoking is the leading preventable cause of mortality accounting for approximately 1 out of every 5 deaths [1]. On average, smokers die 13 to 14 years earlier than nonsmokers [26]. Cigarette smoking is the most common form of tobacco use and 45.3 million persons (19.3% of the population) are current cigarette smokers. Additionally the estimates for average annual smoking-attributable productivity losses are $96.8 billion and the total economic burden of smoking is approximately $193 billion per year [27].

The 2010 National Health Interview Survey revealed that approximately 70% of current smokers want to quit and 41% have tried to quit, however few of these attempts were successful with only 4.7% of current smokers able to stop smoking for at least three months [2]. Despite the availability of therapeutic options for smoking cessation, only 6% of the 35 million smokers who report wanting to quit each year are successful in doing so for more than a month [8, 9]. **Clearly, there is room for improvement in smoking cessation.**

One particularly salient feature of nicotine-dependent cigarette smoking is the ability of associated environmental cues to elicit craving and cigarette-seeking behaviors. The systematic study of craving has occurred primarily via cue reactivity paradigms [28, 29] in which nicotine-dependent individuals are exposed to cues previously associated with smoking (e.g., cigarette, lighter, ashtray) and subjective craving and physiological reactions are measured [30, 31]. Numerous laboratory-based studies, including studies conducted in our laboratories at Medical University of South Carolina (MUSC), have demonstrated that exposure to smoking-related cues elicits robust craving and measurable physiological reactivity among smokers [32]. These findings represent some of the most compelling evidence in support of a causal relationship between craving and cigarette smoking. Thus, the concept of craving has become an important focus of studies on smoking behavior, relapse and smoking cessation treatment. In conclusion, these findings imply that escalation of withdrawal symptoms, craving, and smoking urges during a quit attempt may contribute to smoking relapse. **The reduction of cue craving and smoking urges may facilitate the treatment of nicotine dependence and prevent relapse during a smoking quit attempt.**

Transcranial magnetic stimulation (TMS) is a noninvasive (and relatively painless) brain stimulation technology that can focally stimulate the brain of an awake individual [33, 34]. A localized pulsed magnetic field transmitted through a TMS coil is able to focally stimulate the cortex by depolarizing superficial neurons [35, 36] inducing electrical currents in the brain [16]. If TMS pulses are delivered repetitively and rhythmically, the process is called repetitive TMS (rTMS). rTMS for the treatment of depression was approved for one manufacturer by the U.S. Food and Drug Administration (FDA) in October, 2008 [37, 38] and for a different device in January 2013. Researchers are investigating rTMS potential treatment effects in other neuropsychiatric disorders (schizophrenia, pain, alcohol, cocaine, stroke) [39]. **Taken together, TMS techniques could be used to improve the efficacy of smoking cessation.**

To date, several human studies have begun to evaluate the effects of rTMS applied to the lateral or medial prefrontal cortex on cue-induced craving and cigarette consumption [19-22]. In one study, investigators[20] administered high frequency rTMS to the left DLPFC of treatment-seeking smokers. Subjects received 20 trains of either real or sham rTMS (20Hz, 90% motor threshold, 2.5 secs-on, 42.5 sec intertrain intervals for a total of 1000 pulses) over the left prefrontal cortex. While real rTMS was associated with significant reduction in terms of the number of cigarettes smoked in comparison with sham stimulation ($p < .01$), levels of craving did not differ significantly between the groups. In contrast, Amiaz and colleagues reported that rTMS (100% rMT, 10Hz, 20 train/day, total 1000 pulses) of the DLPFC reduced both cigarette craving and consumption [19]. In a preliminary parallel-groups sham-controlled trial of rTMS in combination with the nicotine patch in heavily nicotine-dependent smokers with schizophrenia [40], rTMS did not increase abstinence rates, but did significantly reduce tobacco cravings induced by short-term (30-60 minutes) abstinence, which was assessed before application of the nicotine patch. More recently, Rose and colleague used 10 versus 1-Hz TMS over the superior frontal gyrus (SFG) in 15 volunteer smokers and found that craving after smoking cue presentation was elevated in the 10-Hz SFG condition, whereas craving after neutral cue presentations was reduced [22]. These preliminary studies suggest that the location of the stimulation is critical and high frequency rTMS of the DLPFC, but not the medial area, might attenuate nicotine consumption and craving. Taken together, the significance of these effects are limited and further investigation is required to identify the appropriate stimulation parameters and targets needed to enhance the effectiveness of the treatment. **As such, future replication studies using a valid sham TMS and exploring the number of treatments and duration of effects are greatly needed to further investigate the therapeutic potential of rTMS in nicotine dependence. In particular, future studies using MRI to guide location will help to optimize the parameters for the use of rTMS in the treatment of nicotine addiction.**

In conclusion, nicotine dependence is the leading preventable cause of mortality in the world today. In spite of treatment advances, there is much room for improvement in the therapeutic approaches. Recent advances make it possible to utilize rTMS to modify behavior, cognitions and regional brain activity. Preliminary trials suggest potential therapeutic applications of rTMS in the area of nicotine dependence. **The purpose of this proposal is to preliminarily explore the efficacy of 10 daily MRI-guided DLPFC rTMS in decreasing cue-induced craving and cigarette consumption in nicotine-dependent cigarette smokers. Information gathered through this study will inform future studies in terms of optimal parameters for the use of rTMS in the treatment of nicotine-dependent smokers.**

2. Innovation

As mentioned above, several previous studies have demonstrated that rTMS applied to the lateral or medial prefrontal cortex can impact cue craving and/or consumption of cigarettes [19-22] . However, in all studies to date the form of sham TMS did not cause similar scalp or facial sensation compared to real TMS leading to questions about the validity of the comparisons. In the proposed study, we will use an active E-sham condition [41, 42] which produces scalp/facial sensations that are comparable to rTMS. In addition, studies to date have used a 5 cm rule for prefrontal location determination which is imprecise and as many as 30% of participants may have been treated over the supplementary motor area rather than the prefrontal cortex [43]. Finally, a meta-analysis [44] and a prospective clinical trial [45] suggest that use of a greater number of rTMS stimulations may be more effective in depression treatment. Previous rTMS studies in smoking used 1000 pulses, much less than the dosage of TMS pulses demonstrated to be efficacious in depression, and higher doses have not been explored. This R21 proposal is innovative in three respects: this is the first time that a double blind rTMS study will be compared to an active E-sham stimulation in smokers; in addition, we will use MRI to determine stimulation site over prefrontal cortex; finally, we will employ more stimulation pulses (3000 pulses) than previous studies, allowing us to quantitatively and qualitatively investigate both short and longer term effects of rTMS in smoking cessation.

RESEARCH PLAN

Rationale. Several lines of evidence suggest that repetitive TMS (rTMS) over the left DLPFC can affect processes involved in nicotine addiction. First, stimulation of the DLPFC can induce release of dopamine in the

caudate nucleus [46]. Therefore, repeated stimulation may induce neuroadaptations in the dopaminergic system. Moreover, while administration of drugs induces an acute increase in dopamine levels, during withdrawal dopaminergic activity is reduced. Decreased dopaminergic activity has been associated with increased levels of craving and relapse [47]. Therefore, it is possible that even transient increases in dopamine released by TMS may help reduce levels of craving [48]. Second, the effects of brain stimulation can extend beyond the directly targeted area, including cross-hemispheric cortical and subcortical activity in remote neural networks connected to the stimulated regions [49, 50]. Therefore, given the ability of TMS to modulate cortical excitability, it is possible that TMS can alter neuroadaptations and synaptic plasticity in the brain reward system. Third, it is well known that the PFC is strongly implicated in drug-seeking behaviors. The DLPFC plays an executive role in controlled response inhibition through its connectivity. Therefore, it is possible that repeated DLPFC stimulation could lead to improved inhibitory control and thereby reduced levels of drug-seeking. These theoretical underpinnings have led researchers, including our group at MUSC, to conduct pilot studies to explore the impact of rTMS of the left DLPFC in reducing craving for cigarettes [19, 20, 22].
Several studies have shown that stimulation of the motor cortex can produce inhibitory or excitatory intermediate effects (lasting several minutes) following stimulation [51, 52]. Investigations of the intermediate effects of TMS have been used to develop a better understanding of brain functioning with respect to movement, vision, memory, attention, speech, neuroendocrine hormones and mood [53-60]. Longer-term effects of TMS (days to weeks) are not well understood at a neurobiological level, but there is some evidence to support longer-term effects on mood, seizure activity and pain [61-64]. As discussed above, rTMS for the treatment of depression was approved by the FDA in 2008. Thus, we hypothesize that 10 sessions daily active rTMS will induce a longer lasting decrease in cue-induced craving and a reduction in cigarette consumption.

In a recent pilot project conducted by our research team, rTMS at 100% resting motor threshold (rMT), 10 Hz, 5 seconds on, 10 seconds off, total 3000 pulses over DLPFC was tested in 14 non-treatment seeking nicotine-dependent smokers [42]. Compared to sham TMS, one session of high frequency DLPFC rTMS significantly reduced smoking cue-induced craving (Figure 1). In addition, the correlational analyses showed that the effect of rTMS on cue craving was positively correlated with Fagerstrom Test for Nicotine Dependence (FTND) score (Figure 2). This study was the first to show a clinically significant reduction in craving after prefrontal rTMS. However, we were not able to measure the duration of effect or whether repeated sessions might have added therapeutic effect. The current proposal extends this study, advancing it in a step-wise manner to a potential treatment. Further, we will use MRI to determine stimulation site instead of the imprecise 5 cm rule. Additionally, we will employ 10 session rTMS over two weeks period. We hypothesize that rTMS with the MRI TMS navigation will reduce cue-induced craving and cigarettes per day more than will sham TMS.

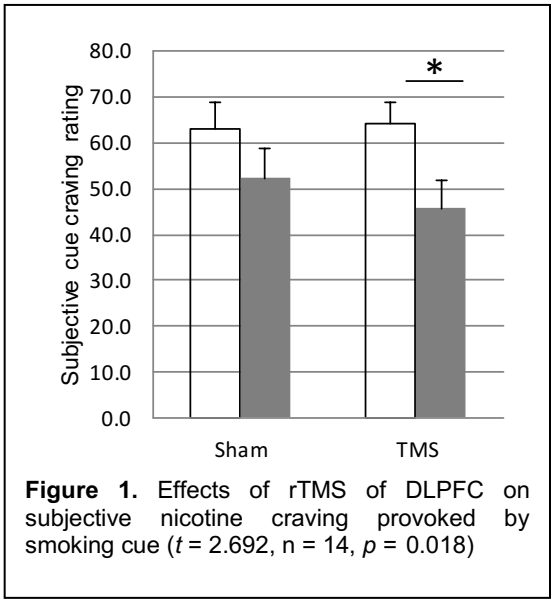
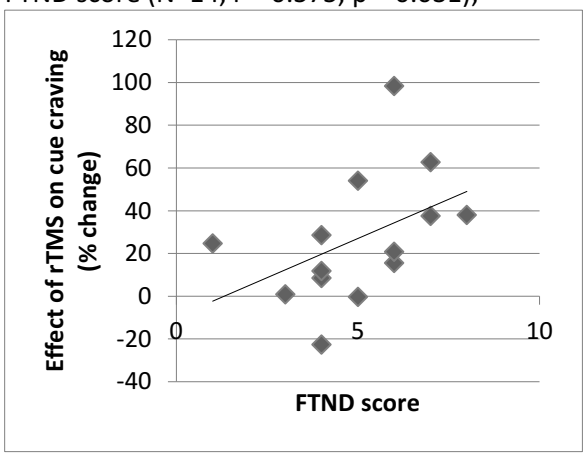


Figure 1. Effects of rTMS of DLPFC on subjective nicotine craving provoked by smoking cue (t = 2.692, n = 14, p = 0.018)

Figure 2. Correlation between Effects of rTMS and FTND score (N=14, r = 0.575, p = 0.031);



TMS research has been ongoing in the Brain Stimulation Laboratory (BSL) at MUSC for the past 15 years. The members of the BSL have been actively researching TMS in depression[41, 50, 65-67], schizophrenia [68], post-

traumatic stress disorder (ongoing), Tourette's syndrome [69], alcohol dependence (unpublished data), methamphetamine (paper in preparation), food craving [70] and cigarette smokers [42] . Dr. Mark S. George is one of the world leaders in refining the use of TMS to treat depression and other neuropsychiatric and substance use disorders. Additionally, we have also studied other minimally invasive brain stimulation technologies such as transcranial direct-current stimulation (tDCS) [71], electroconvulsive therapy (ECT) (ongoing), deep brain stimulation (DBS) [72] and vagus nerve stimulation (VNS) [73] for over a decade. In conclusion, the research group assembled for this project has vast experience in the use of TMS in clinical trials on neuropsychiatric diseases, including substance use disorders.

The treatment of nicotine dependence has been an interest of our research group for many years [74-76]. As one of world leaders in addiction research, Dr. Kathleen T. Brady has been conducting clinical trials and human laboratory research focused on nicotine dependence for decades [12, 76-79]. In an ongoing study, our group is exploring the use of real time fMRI biofeedback to reduce cue-induced craving in smokers [12]. In the pilot TMS study in nicotine dependence, Drs. Li and Hartwell collaborated to recruit 14 nicotine-dependent cigarettte smokers in 6 months. Thus, our research team has experience in recruiting and retaining nicotine dependent participants for clinical trial participation and can easily recruit 42 smoking participants during two years.

Our previous work demonstrates the experience of the investigative team in a number of areas of direct relevance to the proposed project. The investigators have expertise and experience in developing and conducting rTMS protocols. With regard to the study of TMS and nicotine dependence, the team includes world-renowned experts in both TMS and nicotine dependence research. The investigative team has developed a single session rTMS protocol that reduces craving and might lead to a treatment for nicotine dependence with further development as proposed in this R21 proposal. This R21 proposal is designed to ascertain whether repetitive TMS can affect smoking cue-induced craving and consumption of cigarettes over a 3 months period. Additionally, it will provide information on the treatment parameters and dose of rTMS, effects on the longer-term outcomes. The findings of the study can be used to inform the design of a larger, more definitive clinical trial to investigate the use of rTMS in smoking cessation.

Experiment Approach

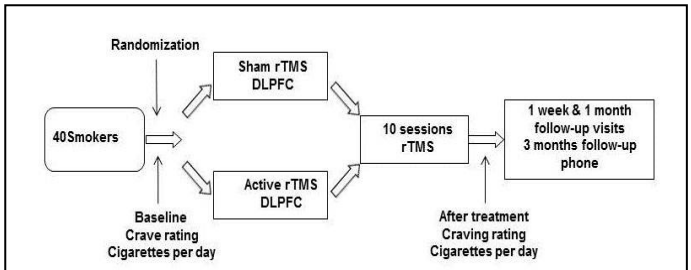


Figure 3. Study Design

1. General Design of the Study. Forty two treatment-seeking nicotine dependent participants between the ages of 18 and 60 will be randomly divided into two groups on a 1:1 basis. One group will receive sham rTMS and the second group will receive active rTMS over DLPFC on a daily basis for 10 sessions (See Figure 3). Treatment is standardized at 100% magnetic field intensity relative to the patient's resting motor threshold (rMT), at 10 pulses per second for 5 seconds, with an intertrain interval of 10 seconds. Treatment sessions last for 15 minutes (60 trains) with 3000 pulses. The masked randomization status will be maintained for the entire enrollment period, until the last subjects have completed the study in the second year. Cue craving rating and cigarette consumption will be assessed before and after active rTMS or sham rTMS for 10 days. All participants will have two follow-up visits at 1 week and 1 month after the last rTMS session and a follow-up phone after 3 months of the last rTMS session. Safety will be assessed by collecting information on all relevant adverse events experienced.

2. Study Subjects and Entry Criteria
Inclusion Criteria:
Subjects will:
(1). Be between the ages of 18 and 60 years old.
(2) Smoke 10 or more cigarettes per day and have a carbon monoxide (CO) level > 10 ppm indicative of recent smoking.

(3) Not received substance abuse treatment within the previous 30 days.
(4) Meet criteria for nicotine dependence as determined by the FTND.
(5) Be in stable mental and physical health.
(6) If female, test non-pregnant and use adequate birth control.
(7) No evidence of focal or diffuse brain lesion on MRI.
(8) Be willing to provide informed consent.
(9) Be able to comply with protocol requirements and likely to complete all study procedures.

Exclusion Criteria:
Subjects with:
(1) Current dependence, defined by DSM-V criteria, on any psychoactive substances other than nicotine or caffeine.
(2) Contraindication to MRI (e.g., presence of metal in the skull, orbits or intracranial cavity, claustrophobia).
(3) Contraindication to rTMS (history of neurological disorder or seizure, increased intracranial pressure, brain surgery, or head trauma with loss of consciousness for > 15 minutes, implanted electronic device, metal in the head, or pregnancy).
(4) History of autoimmune, endocrine, viral, or vascular disorder affecting the brain.
(5) History or MRI evidence of neurological disorder that would lead to local or diffuse brain lesions or significant physical impairment.
(6) Unstable cardiac disease, uncontrolled hypertension, severe renal or liver insufficiency, or sleep apnea.
(7) Life time history of major Axis I disorders such as: Bipolar Affective disorder (BPAD), Schizophrenia, Post-traumatic Stress disorder (PTSD) or Dementia or Major Depression.
(8) Self report of >21 standard alcohol drinks per week in any week in the 30 days prior to screening.
(9) Other forms of nicotine delivery, such as nicotine patch, electronic cigarettes

3. Screening Procedures:
(1) Phone pre-screen: Healthy subjects will be recruited from the greater Charleston area via flyers, Catalyst advertisements, internet and emails. We have used these methods to successfully recruit nicotine-dependent smokers for participation in clinical trials in the past [41]. Prospective subjects will be screened over the phone by trained research staff at MUSC. Subjects that qualify based on the preliminary phone-screen will be invited for an initial assessment to MUSC. Drs. Li and Hartwell and trained study personnel will be assigned to seek and obtain informed consent for all subjects.
(2) Initial assessment: An informed consent procedure will be completed prior to conducting any research procedures. Study personnel will review the consent with the participants and assess participant's understanding of the study. Participants not able to understand the consent after help from the study personnel, and those either excluded or unwilling to participate after the informed consent procedure, will be provided with an appropriate referral for smoking cessation if they are interested.
(3) After the informed consent is obtained, participants will be assessed for study inclusion/exclusion criteria. Participants will complete a battery of assessments listed below.

- Psychiatric interview using the Mini International Neuropsychiatric Interview (MINI) will be conducted for the inclusion and exclusionary Axis I psychiatric diagnoses. Baseline CO level will be assessed using a Bedfont microsmokerlyzer (Bedfront Scientific Ltd., Kent, United Kingdom).
- Alcohol breathalyzer test and a urine drug/cotinine/pregnancy tests will be performed. The results from the alcohol breathalyzer and urine drug tests will be used, in conjunction with the MINI, to screen for current substance use disorder.

(4) Each potential subject will be asked about their current height and weight, past medical history focusing on chronic (and current) medical problems, seizure history, medications, psychiatric disorders, and substance use. The research procedures, risks and benefits will be explained. Subjects meeting inclusion/exclusion criteria will be invited to participate in the laboratory investigation.

4. Baseline Evaluation (see schedule of data collection for details)
The baseline evaluation will occur on the same day if the subjects meet the inclusion/exclusion criteria and sign the consent form.

1) Demographic Data: Basic demographic information including age, gender, race, and social history will be collected.
2) Mini International Neuropsychiatric Interview (MINI) [80]: This is a well-standardized structured instrument used to provide quick and accurate DSM-IV psychiatric diagnoses. The MINI will be used to confirm the inclusionary/exclusionary diagnoses in the participants.
3) Tobacco Use History: Detailed history of current and past tobacco use will be obtained, including cigarette smoking. The questions addressed will include the amount, frequency, duration of smoking, preferred brand, reasons for smoking, smokeless tobacco, family history, etc.
4) Fagerstrom Test for Nicotine Dependence (FTND)[81]: This is a self-rating questionnaire for nicotine dependence.
5) Questionnaire of Smoking Urges- Brief (QSU-B) [82]: This is a 10-item self-rating questionnaire for assessment of craving. The questionnaire will be used to track the level of craving during the study. In addition to a total score, the QSU provides scores on two factors: 1) hedonic craving, in anticipation of positive effects, and 2) craving in anticipation of withdrawal relief.
6) Beck Depression Inventory II (BDI) [83]: BDI is a 21-item self-rating scale to assess symptoms of major depression. We will monitor depressive symptoms during the study due to strong association between smoking and depressive disorders.
7) Minnesota Withdrawal Scale - Revised (MNWS-R) [4]: MNWS-R is a DSM-IV based instrument to assess symptoms of nicotine withdrawal.
8) Biomarkers: Urine cotinine levels will be used as biomarkers for cigarette smoking. We will use a dipstick urine cotinine (NicAlert, Nymox Pharmaceuticals). NicAlert is a semi-quantitative enzyme linked immunoassay (Elisa test) dipstick measure of salivary or urine cotinine with ranges of 0 – 10, 10 – 30, 30 – 100 ng/ml, etc. The NicAlert dipstick will be done at each study visit. We will also use carbon monoxide (CO) level in the expired air by a standard CO breathalyzer at each visit.
9) Tobacco diary: This is a daily diary of all tobacco products consumed in the period between visits, including cigarettes. Participants will maintain a daily tobacco diary, which will be collected at each visit. We have piloted a similar diary in our previous studies. Time-Line Follow-Back is not designed for daily prospective monitoring and hence a tobacco diary will be used.
10) Other drug diary: If participant uses marijuana and other drugs, diaries to document other substance use will be provided.
11) Modified Cigarette Evaluation Questionnaire- mCEQ: This questionnaire assesses the reinforcing effects of smoking.
12) Self Assessment Manikin (SAM) [84]. SAM is a graphical picture-oriented instrument that can directly assess the pleasure, arousal, and dominance experienced in response to a cue exposure. SAM ranges from a smiling, happy figure to a frowning, unhappy figure when representing the pleasure dimension, and from an excited, wide-eyed figure to a relaxed, sleepy figure for the arousal dimension. The dominance dimension represents changes in control with changes in the size of SAM: a large figure indicates maximum control in the situation. The participants will rate their subjective “happy”, “excited”, and “control” states.

Table 1. Schedule for data collection

Assessments	Baseline	The 1st Week TMS	The 2nd Week TMS	The 1st Follow-up Visit One Week After TMS	The 2nd Follow-up Visit One Month After TMS	Follow-up Phone Three Months After TMS
Demographic	x					
Medical history	x					
Physical exam	x					
Neuro exam	x					
MINI	x					
Psychiatric evaluation	x					
Tobacco history	x					
FTND	x	x	x	x	x	x

QSU-B	x	x	x	x	x	
BDI	x					
MNWS-R	x					
CO	x	x daily pre	x daily pre	x	x	
Craving rating panel	x	x daily pre post	x daily pre post			
Tobacco diary	x	x	x	x	x	x
Adverse Events	x	x daily pre post	x daily pre post	x	x	x
Drug diary	x					
mCEQ	x	x	x	x	x	
Hematology	x					
Routine urinalysis	x					
Urine cotinine	x	x	x	x	x	
Pregnancy test	x					
Urine drug	x					
MRI scan	x		TMS Day 10			
Best guess	x		x			

5. Randomization. Subjects will be randomized to either sham rTMS over DLPFC or real rTMS over DLPFC with Data Coordination Unit (DCU) at MUSC. Briefly, the subject will be assigned a study number and will then be assigned either a sham or active TMS smart card. An Active Smart Card will only allow TMS treatment with the active TMS head coil. A Sham Smart Card will only work with the sham TMS coil.

6. **MRI Scanning Procedures.** At baseline and at the TMS 10 visit, subjects will have a 3.0 T MRI scan of the head with vitamin E tablets placed over the Abductor Pollicis Brevis (APB) motor cortex. Vitamin E tablets are easily visible on the MRI without artifact. We will acquireT1, T2, and FLAIR images to rule out coincidental pathology. These will be followed by high-resolution 3D SPGR images through the whole head (124 contiguous sagittal 0.9 mm slices) for accurate localization.

7. TMS Procedures

1). All TMS procedures will be performed by a highly trained faculty or staff member of the Brain Stimulation Laboratory at MUSC under the supervision of a licensed M.D. with specialized training in TMS delivery. All participants will be fitted with a white lycra swim cap at the initial setting. This cap will be worn during the 1st TMS sessions and in the MRI scanner in order to insure proper placement of the TMS coil across visits. The motor cortex will be located and the TMS motor threshold will be assessed. With Brainsight™ neuronavigation software (Rogue Research, Montreal, Canada), the TMS coil will then be moved over the left prefrontal cortex. Using a black permanent marker, landmarks will be placed on the cap to allow for proper refitting for following TMS sessions.

2). Treatment parameters and grouping – The time in the chair and the number of pulses on the head will be the same for all subjects. Active or sham TMS will be the only difference. The sham group only receives sham at all treatments. Stimulation frequency for all active subjects: 10 Hertz – Pulse train duration (on time) 5 seconds, Inter-train interval (off time) 10 seconds (15 second cycle time), Power (intensity) level 100% rMT, Total 60 trains, 15 minutes, Total pulses 3000 per day, 3000 x 10 = 30000 pulses for 10 sessions.

Group 1 = Sham treatment over DLPFC

Group 2 = Active treatment over DLPFC

3). Treatment Scheduling - All participants will be treated Monday – Friday for 10 treatments. Ideally, all participants will be treated in the morning, at the same time of day throughout the study, with a note of any time deviation in the case report form (CRF). Each treatment will last about 35 minutes, including 15 minutes of rTMS or sham treatment delivery and 20 minutes pre and post craving rating (10 minutes each). At the end of 5th and 10th rTMS sessions, subjects will be assessed for craving and cigarette consumption.

4). Subject Preparation for TMS delivery - The subject will be asked to remove and store any glasses or earrings, and to remove wallets from their pockets if they contain magnetic media (e.g., credit cards). They will be asked to empty their bladder to avoid treatment interruption. Ear protection will be provided.

5). Resting Motor Threshold (rMT): At entry, we will determine each subject's rMT and all rTMS dosing will be given relative to this value. Surface electromyogram (EMG) will be recorded with silver-silver chloride

electrodes with a tendon-belly arrangement from the APB muscle. The signals will be filtered (band-pass 10 Hz to 1 KHz), amplified, displayed, and stored in a laboratory computer for offline analysis using Signal Software (Cambridge Electronic Design Limited, Cambridge, UK). Resting motor threshold (rMT) will be determined using a Neuronetics® Model 3600 with a solid focal coil TMS machine (Neuronetics, Malvern, PA, USA) by starting with 80% of the machine output and 1 Hz stimulus frequency. The coil will be positioned over the area of the skull roughly corresponding to the motor cortex and then systematically moved and adjusted until each pulse results in isolated movement of the right thumb. Once we completed "threshold hunting", we will use a modified PEST algorithm attached EMG to determine rMT.

6). Localizing the TMS Coil over DLPFC: At a visit after providing informed consent, but before the MRI scanning session, participants will be fitted with a white lycra swim cap. This cap will be worn during the MRI scan and during all TMS sessions in order to insure proper placement of the TMS coil across visits. While sitting upright in a comfortable position, the cap will be placed securely over the head, and pulled down to insure an adequate snug fit. Using a black permanent marker, landmarks will be placed on the cap to allow for proper refitting. Localization of the stimulation site in the prefrontal cortex will be performed using Brainsight ™ software along with a brain surface reconstruction. This software allows simultaneous display of high resolution MRIs in the coronal, sagittal and axial planes along with a brain surface reconstruction. Furthermore, after identification of the anterior and posterior commissures, correction for images tilt and limiting the outer brain extension in all planes, the images are normalized to the Talairach coordinate system. First we identify the superior frontal sulcus on the axial images, normally starting with the more superior slices where this sulcus is better displayed. From there, the sulcus is telescoped onto the coronal plane and we select the coronal plane that intercepts the brain 1 cm rostral to the anterior tip of the genu of the corpus callosum. A landmark is picked up on the cortex corresponding to the midpoint of the middle frontal gyrus, and its position is checked on the 3 image planes as well as on the surface reconstruction to confirm that it falls on the middle frontal gyrus. Finally, the Talairach coordinates of the landmark in both the anterior-posterior and dorsal-ventral directions are checked. This landmark, and thus the stimulation site, should lie within the conservative range of Talairach coordinates of Brodmann area 46. Once TMS coil is localized, the location of TMS will be marked on the swim cap and be recorded with the coordinates of Neuronetics chair which will be used for subsequent treatments.

7). Treatment administration: The Neuronetics TMS therapy is an FDA-cleared non-invasive medical treatment for patients with major depression who have not benefited from initial antidepressant medication. The Neuronetics TMS device to be used in this study has several important features for this study. First, the TMS coil is iron-filled, and thus does not overheat during repeated stimulation of multiple subjects, as in this clinical trial. Second, Neuronetics has developed a sham coil that looks and sounds much like the real coil, but has a layer of metal between the coil and the brain which blocks magnetic fields from entering the brain. The device also has a rigid arm-holder for positioning the TMS coil on the person's head. Finally, the generator has smart cards, which can be individualized for each subject. Following randomization, each subject will receive a specific card for the treatment. The TMS machine will not work if the wrong coil (real or sham) is attached to the machine for that person. The treatment parameters for an entire 15-minute session can be flexibly programmed. Thus, the intensity of stimulation can gradually be increased over the first minute, which should help with patient tolerability, especially for higher intensity stimulation. Both active and sham treatments will be delivered as programmed into the Smart Card assigned to each subject at the time of the first treatment. The same card will be used each day that the patient returns for treatment.

8). Active Sham rTMS: Successful patient and operator masking is key to the success of this trial. In one of our previous studies, we have successfully developed an active sham system [41]. The subject and the treatment operator will be masked to the treatment group assignment, as will all research personnel. Randomization information will be controlled and coordinated through operator 'Smart' cards, distributed by the MUSC CDU. Active sham TMS involves the use of a specially designed sham TMS. The sham TMS system will be connected to an electrical generator on a 9 V battery and electrodes will be placed over the prefrontal cortex. The regulator is triggered by the TMS machine to allow brief, microsecond, pulses of the electrical current through to the skin on the subjects' forehead. Electrical stimulation will be triggered by the TMS machine to correspond to the sham TMS pulses. To further assess the adequacy of the mask, TMS administrators, clinical raters, and patients will complete "best guess" questionnaires, assessing their best guess as to treatment condition, and their level of confidence in this guess.

9) Potential problems: (1) *Missed treatment:* Every attempt shall be made to complete each treatment session as per the protocol. Interruptions during the treatment are allowed as needed for patient comfort or

convenience by using the "pause" selection on the device. However, in the event that an incomplete treatment is given, this information will be recorded. In the event that a treatment is missed, the following procedure will be followed: 1 day missed, or 2 days missed in a row—continue into the subsequent week to complete the missed days. Evaluation will still occur after every 5 treatments. 3 or more days in a row—treatment must be aborted and the subject discontinued from their current phase and likely dropped from the study. *(2)Monitoring for seizure activity:* During the treatment procedure, the treatment administrator must observe the subject closely for any sign of imminent seizure activity or muscle twitching. The administrator must be an individual trained to be perceive to warning signs, and will be familiar with the emergency management of seizure activity. Emergency equipment (oxygen, suction, CPR equipment) will be readily available in the treatment suite. *(3)Recording of adverse events:* During the treatment procedure, the administrator will assess for and record any adverse events. Prior to leaving the facility following each treatment, the subject will be assessed for the occurrence of adverse events by a qualified individual who is masked to the subject's assigned treatment group. Immediately prior to, and following each TMS treatment session, all patients will complete a Visual Analog Scale to assess within session changes in side effects.

8. Assessments and Instruments (Specific Aim 1 & 3)
1). Craving Assessment: Upon arrival at the laboratory, participants will be observed smoking their last cigarette before beginning to complete questionnaires. Immediately prior to, and following each TMS treatment session, all patients will complete a Likert Visual Analog Cue Craving Scale to assess within session changes in subjective craving.
2). QSU – Brief: Cue presentation and Craving Assessment: Scenic images, neutral control images and cigarette smoking cue images are presented in four blocks. Immediately after viewing each block of cue images, subjects will completed an adapted QSU-B utilizing a computerized visual analog scale (CVAS) designed to assess craving. Each question is followed by a CVAS (the range of 0 and 100).
3). Carbon Monoxide: Subjects will be measured CO before TMS daily and at 1 week and 1 month follow-up visits.
4). Weekly Assessments: At the end of the 5th and the 10th treatment and 1 week and 1 month follow-up visits, subjects will complete FTND, MNWS-R, Tobacco diary, mCEQ and adverse events.
5). At the end of the experiment, subjects will be asked what treatment (active or sham) he/she believes was completed.

9. Follow-up (Specific Aim 2). The treatment period of the study will conclude on the end of two weeks. Participants will then enter the follow-up phase of the study. The two follow-up visits will be scheduled one 1 week and 1 month after the 10th rTMS session. Data will include craving ratings, tobacco diary, CO, QSU-B and FTND. We will conduct a follow-up phone survey of participants 3 months after the 10th treatment. Cigarette consumption will be evaluated by asking: 'How many cigarettes do you now smoke on an average day?'. Craving will be assessed by asking: 'How much do you want to smoke a cigarette right now on a scale from 1 to 10?' and "When was your last cigarette?'. Nicotine dependence will be assessed by the FTND.

10. Data Analyses. All data will be analyzed in consultation with Data Coordination Unit (DCU) at MUSC. Quantitative measures of nicotine dependence: Craving rating panel, Tobacco diary, CO, QSU-B and FTND. Side effects: Following standard procedures, frequency and severity measures of side effects will be constructed from the clinical measures. Significance testing: All tests will be two-sided, performed at significance α=0.05, except where noted. The statistical approach will use an ANOVA for each outcome variable. Some data may be longitudinal as well as cross-sectional and we will include random effects to account for within-subject correlation.

Power Analysis. The primary efficacy of rTMS for this study will be the abstinence rate and the number of cigarettes smoked per day at the end of treatment. One previous study of rTMS reported that 10 sessions of rTMS significantly reduced the number of cigarettes per day by the 10th treatment (18.11 ± 2.61 vs. 10.71 ± 2.19) [19]. A power analysis was conducted based upon this two group design, a power of 0.8, and an alpha level of 0.05; a significant difference is anticipated with 18 subjects in each group. The attrition rate in the above mentioned study was 8%. The attrition rate for our previous study was 12% [31]. According to the attrition

rate from our study (which is more conservative), we will randomize 21 subjects per group (total N=42) to have ample power to detect a clinically meaningful difference. We will use 1 week, 1 month and 3 months follow-up data to calculate power for future R01 studies.

HUMAN SUBJECTS RESEARCH
Protection of Human Subjects

1. Human Subjects Involvement and Characteristics. Subjects will be women and men aged 18 to 60 years. Subjects meeting inclusion/exclusion criteria (see detail in Study Plan) will be offered participation, regardless of racial/ethnic group. The sample composition will reflect the Charleston-area population distribution of healthy adult smokers.

2. Sources of Materials. Research material obtained from the individual subjects will include psychiatric examination results, drug (including nicotine) use assessment results, urine for cotinine levels, expired air breathalyzer alcohol and CO tests, blood samples, heart rate, skin conductance, and subjective ratings (e.g., craving). Urine samples for the urine drug screen and pregnancy will also be obtained. Research data will be obtained specifically for research purposes. We will not use existing specimens, records or data.

3. Potential Risks. Investigational Device Exemption: Transcranial Magnetic Stimulation is an investigational device. The IRB at MUSC (in cooperation with the FDA) has determined repetitive TMS to be a non-significant risk intervention.

1). *Potential Risks of TMS:* The major risk using repetitive TMS subjects is the possibility of inducing a seizure. We have now studied and given rTMS to more than several hundred subjects over past 15 years. None of these patients has developed a seizure. We will exclude patients with a prior history of seizures. We have reported that single session doses of 12,960 stimulations were safely given to volunteers with inducing seizures [85]. We will carefully adjust each person's stimulus intensity to his or her motor threshold, before beginning treatment.

2). *Potential hearing loss:* The discharge of the rTMS coil generates a high-energy click that may cause cochlear damage. Foam earplugs can protect against these changes and will be worn by the subjects and the researchers present during TMS sessions.

3) *Potential risks of active Sham TMS:* When subjects receive sham TMS they may experience mild discomfort on their scalp.

4) Potential loss of confidentiality: Despite efforts to maintain subjects' anonymity and confidentiality, there is always some minimal risk of people other than the study investigators gaining access to subjects' information. Every effort will be made to ensure that subject information will be collected and stored in a manner that ensures the highest level of protection of confidentiality.

4. Adequacy Of Protection Against Risks.

1). *Recruitment and Informed Consent:* Healthy subjects will be recruited from the greater Charleston area via flyers, Catalyst advertisements, internet and emails. Drs. Li and Hartwell and trained study personnel will be assigned to seek and obtain informed consent for all subjects. All prospective subjects will be judged clinically competent to give written informed consent. The informed consent form will detail the procedures, the time commitment, potential risks, confidentiality (HIPAA), and compensation for participation. The subjects will always have the right to discontinue participation in the study at any time without penalty and will be informed of this. If a subject is judged to be having any ill-effects from the experimental procedures, they will be withdrawn from the study by the PI and appropriate medical care will be arranged by available nurses, physicians and/or psychologists at MUSC hospital at no charge to the subject.

2). *Confidentiality of Subjects' Responses:* In the informed consent form, subjects will be told that the information they provide and all findings will be kept strictly confidential, with access limited to the research staff and the possible exception of state or federal regulatory personnel. No one but the project staff has access to the master list linking subjects' names to code numbers, and all information obtained is coded. The respective master lists are kept under strict lock and key.

3). *Research Procedures:* We have described above the potential risks of the research procedures. If the subject can't continue the treatment, further participation will be terminated. We will minimize the risk of

seizure by prescreening subjects for a seizure history, getting a detailed medication history and by tailoring each person's TMS intensity to their own motor (and indirectly seizure) threshold. We will exclude subjects if they are taking medications that are associated with lowering of seizure threshold including stimulants (except for caffeine). We will minimize hearing damage by having all subjects wear earplugs to protect their hearing during the TMS sessions. Subjects will be stimulated with TMS in private clinical settings. A resuscitation cart including an Ambu bag and oxygen will be available. A licensed MD will be readily available during all TMS procedures to quickly respond to medical emergencies if they should arise.

5. Potential Benefits Of The Proposed Research To The Subjects And Others

For the proposed studies, the risks are minimal with very little chance of long-term or serious harm. Participants may experience a reduction in the number of cigarettes smoked per day and cigarette craving as benefit from study participation. Subjects will be compensated $70 for the screening visit which includes $20 for drug screen, $25 for physical examination and assessments, and $25 for the baseline MRI. Subjects will be compensated $40 per visit for each visit attended during the treatment. Subjects will be compensated $25 for MRI scanning. During the follow-up phase of the study, subjects will be compensated $50 at the 1 week and 1 month visits. Thus, the total compensation could potentially equal $595 over 3 months, depending on the number of visits. Subjects will be paid in cash.

Payments subjects receive from MUSC for participating in a research study are considered taxable income per IRS regulations. Payment types may include, but are not limited to: checks, cash, gift, certificates/cards, personal property, and other items of value. If the total amount of payment you receive from MUSC reaches or exceeds $600.00 in a calendar year, you will be issued a form 1099.

6. Subject Safety And Minimizing Risks (Data And Safety Monitoring Plan)

1). *Trial Management:* The study will be managed from the Brain Stimulation Lab within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina.

2). *Data Management and Analysis:* Data will be entered by research assistants directly into a computer using standard database software. The data analysis plan is outlined in the Data Analysis Plan section.

3). *Quality Assurance:* The PI will have weekly meetings with the research assistants to discuss qualitative comments received during data collection and any problems in data collection. The statistician will periodically examine the database to look for irregularities. 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 above.

4). *Regulatory Issues:* 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.

5). *Definition of AE and SAE:* An AE is defined as any untoward medical occurrence in a study subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment (ICH GCP). Any unwanted change, physically, psychologically or behaviorally, that occurs in a study participant during the course of the trial is an adverse event. A Serious Adverse Event (SAE) is defined as an adverse event that has one of the following outcomes: death, life-threatening, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect.

6). *Documentation and Reporting:* 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.

7). *Inclusion of Women and Minorities:* Both men and women who meet study criteria will be eligible to participate. Since this study is designed to examine adult smokers, children will not be included. Our minority enrollment is limited by the demographics of our county and state. At MUSC, the population of our county (Charleston , South Carolina) includes 0.3% Native American, 1.1% Asian American, 34.5% African-American, 0.1% Native Hawaiian or other Pacific Islander, and 2.4% Hispanic. We anticipate a recruitment and participation of minorities lower than what the Census 2000 reports for Charleston County since a large portion of Charleston County is rural and suffers from similar 'barriers for mental health treatment' identified by the Surgeon General's 2001 report and African Americans smoke at lower rates than Caucasians. In addition, MUSC is centrally located and in proximity of both major African-American and Hispanic communities in Charleston. We will take advantage of several intensive out-reach programs already in place at MUSC to enhance minority recruitment. For the reasons listed above we expect our enrollment to include 2% of Hispanics, 15% African-Americans or Blacks and 1.4% of Asians. Other minorities are almost non-existent in our catchments area.

Targeted/Planned Enrollment Table-Total Planned Enrollment: 42			
Targeted/Planned Enrollment: Number of Subjects			
	Sex/Gender		
Ethnic Category	**Females**	**Male**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	20	20	40
Ethnic Category Total of All Subjects*	21	21	42
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	3	6
White	18	18	36
Racial Categories: Total of All Subjects*	21	21	42
*The "Ethnic Category Total of All Subjects" must be equal to the "Racial Categories Total of All Subjects."			

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