**Study Title:** QuitFast: Evaluating transcranial magnetic stimulation as a tool to reduce smoking directly following a quit attempt

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## Background, Rationale and Context

Significance 1- Developing a novel treatment tool targeted at the first 2 weeks after a smoking quit attempt. Smoking is the leading preventable cause of mortality and morbidity in the United States, contributing to approximately 443,000 deaths annually - more than the deaths attributable to alcohol, illicit-drug use, homicide, AIDS, and suicide combined (14). The combined health and loss-of-productivity costs associated with smoking are substantial, exceeding 300 billion dollars per year, or nearly 10 times NIH's entire 2016 budget (14, 15). In 2015, approximately 36.5 million Americans (15%) were regular smokers ("at least 100 cigarettes total and presently smoking most days of the week"). Of regular smokers 68% would like to quit smoking, and 43% had initiated a smoking quit attempt in the previous year (15.7 million Americans). While these numbers suggest that individuals are motivated to quit smoking, only 6% of smokers who attempt to quit without assistance maintain abstinence for 30 days (14). A Cochrane Review of demonstrated that current smoking cessation treatments (e.g., nicotine replacement therapy, cognitive behavioral therapy [CBT], non-nicotine medications) are 2-3 times more effective than quitting without assistance, however their aggregate success rate is only 30% (70% failure rate) (16).

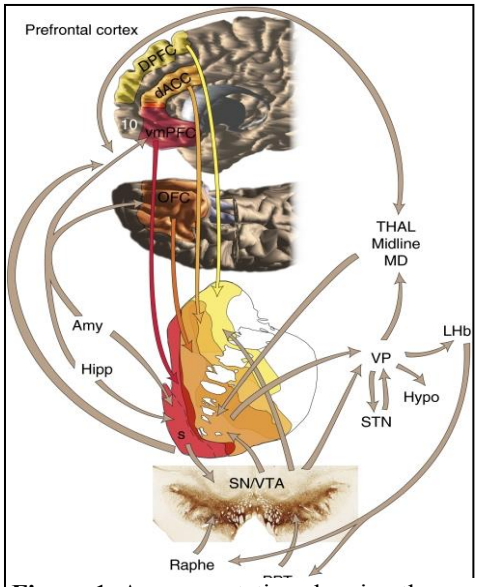


**Figure 1**. A representation showing the separation and unique targets of the fronto-striatal loops in the non-human primate, adapted from Haber and Knutson, 2010, Neuropsychopharmacology (1)

The most critical period for long-term success of smoking cessation appears to be in the first 7 days after the quit date. A metaanalyses of 3 independent pharmacotherapy trials revealed that abstinence during the first 7 days was the strongest predictor of 6-month treatment outcomes (n=1649; Odds ratio: 1.4, P <0.0001; Ashare et al. 2013 (110)). High relapse rates during this first week of smoking cessation are likely facilitated by behavioral and neurobiological factors that contribute to cue-associated craving and loss of executive control. This statement is backed by over 20 years of research. **The long term goal of the research is to develop non-invasive brain stimulation as an evidence-based tool to facilitate abstinence during this critical period after a quit attempt. The scientific premise is that by modulating the neural circuits with govern cue-associated craving and executive control, it may be possible to get people past this vulnerable period for relapse.** Our long term vision is that this early brain stimulation intervention would improve long term outcomes of other pharmacotherapeutic and behavioral training approaches – a topic we will be prepared to explore in a subsequent renewal of this R01 proposal. **The goal of the present proposal is to evaluate 2 promising brain stimulation treatment strategies as innovative new tools which can modulate the neural circuits that contribute to relapse, and enable individuals to get through this critical period.**

Significance 2- Using basic science knowledge to developing an effective, neural-circuit based treatment for tobacco use. Through technical and experimental advances in preclinical neuroscience research over the last 10 years, we have an increasingly sophisticated understanding of the neural circuitry of substance

dependence. Through optogenetics (17, 18) and designer receptors exclusively activated by designer drugs (DREADDs; (19)) it is possible to change drug taking behavior through direct stimulation of frontal-striatal circuits. Specifically, stimulation of the prelimbic cortex (PL) leads to an increase in drug taking, whereas, stimulation of the infralimbic cortex (IL) will decrease drug taking (20). The PL is functionally and anatomically similar to the ventral medial prefrontal cortex (vmPFC) (Fig1. Red), whereas the IL is functionally similar the human dorsal lateral prefrontal cortex (dlPFC) (Fig. 1, yellow) (21, 22).

**Given these promising preclinical data, there is strong momentum to develop a <u>neural circuit-based treatment</u> for clinical substance abuse.** Transcranial magnetic stimulation (TMS) allows researchers to selectively activate or inhibit populations of neurons in humans. Through electromagnetic induction, repetitive pulses of TMS to the scalp will induce long-term potentiation-like (LTP-like) or long-term depression-like (LTD-like) effects in the cortical area beneath the coil in a frequency-dependent manner. Repetitive TMS to the frontal cortex induces a change in dopamine binding (23, 24) in monosynaptic striatal targets. By applying either a single high frequency (> 10 Hz) or intermittent bursting frequency (intermittent theta burst stimulation; iTBS) to the cortex, it is possible to induce an LTP-like effect on both behavior and neural activity (23,25) (26). By applying either a single low frequency (1-5 Hz) or continuous bursting frequency (cTBS), it is possible to induce an LTD like effect on behavior and neural activity (3). In 2013 our group differentially activated these two frontal-striatal circuits in healthy adults using TMS (10). In 2016 this was replicated and extended to cocaine users all of whom were also tobacco users) (27).

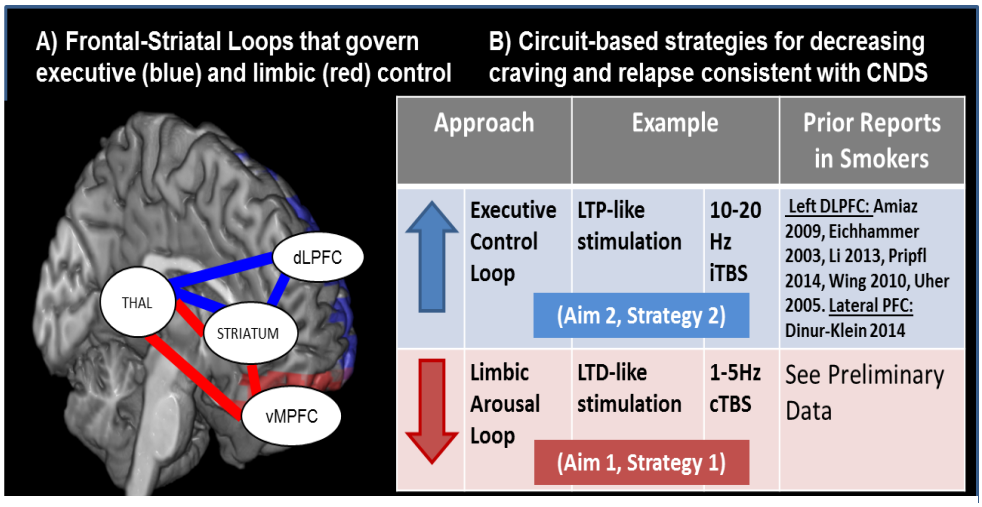


**Figure 2**. Adapted from Hanlon et al 2015, A) The competing neurobehavioral decision systems (CNDS) theory posits that in addiction, *<u>choice</u>* results from imbalance between 2 decision systems (impulsive and executive), which are functionally linked to limbic and executive control circuits in the brain (Bickel et al 2016). B) It follows then, by modulating these competing neural circuits with TMS (e.g. either dampening the limbic/impulsive system or amplifying the executive control system), we may be able to induce a sustainable change in smoking behavior.

We have recently demonstrated the LTD-like effects of cTBS on the vmPFC, striatum, and insula in cocaine users (63,111), alcohol users (111), and smokers (Figure 5). **As a significant conceptual advance in the field, this proposal will parametrically evaluate 2 promising neural-circuit based strategies as tools to decrease cigarette use, demand, and brain reactivity to smoking cues. The results from this double blinded proposal will pave a clear pathway for the systematic development of these neural-circuit based strategies as treatments for our participants.**

<u>Significance 3 – Using an established conceptual model in addiction as a foundation for brain stimulation treatment development.</u> Transcranial magnetic stimulation (TMS) is an FDA-approved treatment for depression which is now used in over 650 clinics in all 50 states (Neuronetics Company data), and covered by Medicare in 48 states (Centers for Medicare and Medicaid Services, Local Coverage Determinations). The evolving availability of clinical devices and trained staff represents a latent public health resource with incredible potential. **Through this network of devices, evidence based TMS protocols for substance**

**dependence, including tobacco use, could be swiftly distributed to the public. Currently however, the field of addiction does not have enough data to make a well-informed decision regarding the TMS strategy that is likely best suited for changing smoking behavior.** As of June 2016, there were 12 published studies (including our own) which evaluated TMS as a tool to decrease craving for cigarettes. Of the 12 studies, 9 applied high frequency stimulation (10hz, 20Hz, iTBS) to the left dorsolateral prefrontal cortex (dlPFC) (Strategy 2 in this proposal), the same target used in depression. While this may be valuable, as both diseases share common deficits in executive control (which is largely modulated by the dlPFC), **scientifically, it is not obvious that the standard treatments for depression (e.g. 10Hz and iTBS to the left dlPFC) will be the optimal target sites for tobacco use**. The neurobiological basis for these diseases are not identical. **While these early studies are promising, without a cohesive scientific framework, it is very difficult to reconcile these small studies with one another. To make significant progress in TMS treatment development for tobacco use, we have proposed a large, rigorous, evidence-based study which will prospectively evaluate 2 TMS treatment strategies that logically flow from the Competing Neurobehavioral Decision System (CNDS) theory – an established conceptual model of addiction which unites both behavioral and brain systems involved in tobacco dependence (28-30).**

The CNDS specifies that the frontal-striatal circuits involved in limbic reward and impulsive action are relatively hyperactive, while the executive control circuits are relatively hypoactive. Intervention efforts could be therefore be directed at either decreasing impulsive reward circuit activity to cues or increasing the executive control circuit activity to cues. The primary goal of this proposal is to parametrically evaluate the efficacy of two promising new circuit-based interventions for the treatment of cigarette smoking. Aim 1 will evaluate the efficacy of attenuating activity in the limbic reward system (responsible for reward valuation and craving, Figure 2). Aim 2 will evaluate the efficacy of amplifying activity in the executive control system (responsible for cognitive control, Figure 2). For both interventions we will evaluate the relative efficacy of 5, 10, and 15 sessions of prefrontal cortex (PFC) theta burst stimulation (TBS), as a tool to change cigarette valuation, preference for immediate rewards (delay discounting), cigarette self-administration, and the brain's response to smoking cues.

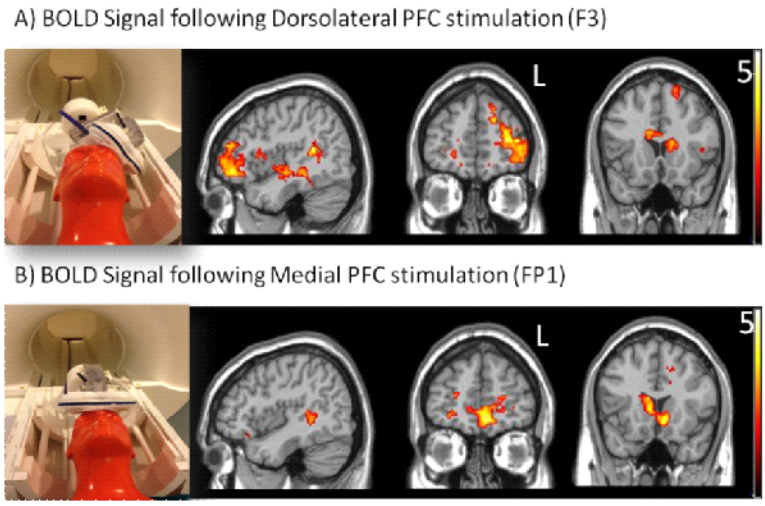


**Figure 3**. Using interleaved TMS/BOLD imaging, we demonstrated that it is possible to differentiate medial and lateral frontal striatal circuits (pillars of the CNDS model) by applying TMS to two prefrontal targets: FP1 & F3 of the EEG 10-20 system (activating MPFC and dlPFC) (Hanlon et al PlosOne 2013).

Significance 4. Logical, outcome-centered investigation of the TMS parameter space on smoking behavior and brain reactivity to cues. Despite the considerable enthusiasm for developing non-invasive brain stimulation treatment protocols for tobacco dependence, many unanswered questions remain. Prominent gaps in our knowledge include 1) the optimal target location [e.g. medial PFC (mPFC) or dlPFC], and 2) the durability of TMS treatment on smoking behavior. **Arguably, these methodologic issues need to be resolved in a reasoned, parametric manner before launching large, expensive, multi-site studies.** We have previously demonstrated that the 2 components of the CNDS theory (Impulsive/Limbic (mPFC & Executive control (dlPFC))) can be differentially stimulated with TMS [(10), Figure 3]. Moreover, activity in these circuits can be attenuated or amplified with human theta burst stimulation (TBS), a biologically-based form of TMS. Continuous TBS (cTBS) results in long-term depression (LTD) of cortical excitability and intermittent TBS (iTBS) results in long term potentiation

(LTP) (3). **The overarching goal of this proposal is to fill these gaps in our knowledge through a 5-year parametric study investigating effects of LTP-like stimulation to the mPFC (Aim 1) and LTP-like stimulation of dlPFC (Aim 2). The significance of this proposal is underscored not only by the innovative neural-circuit based approach to treatment development, but also by the logical, parametric methods we will use to evaluate the efficacy of these two potential interventions, which will inform future treatment studies.**

Significance 5. Use of evidence-based behavioral markers as dependent measures. Delay discounting, cigarette demand, self-administration, and cigarette craving each measure key independent processes related to daily smoking. First, in both cross-sectional and longitudinal studies, excessive discounting of delayed rewards is strongly associated with cigarette smoking and other substance use (31-35); for meta-analyses see (36, 37). In fact, excessive delay discounting is a candidate marker for addiction processes which can be used to identify and predict addiction and its severity, and predict failure in smoking cessation treatment severity (38-40). Moreover, emerging evidence suggests that experimental reductions in delay discounting in the laboratory are associated with reduced cigarette self-administration (41). Second, behavioral economic demand for a commodity, such as cigarettes, is an important indicator for potential harm (42). The interaction of two demand parameters, intensity of demand (i.e., total consumption when the commodity is free) and elasticity (i.e., the sensitivity of consumption to price increases) gleaned from a demand analysis, are measures of the value of cigarettes (43). Importantly, greater demand for cigarettes is associated with greater dependence severity (44) and is predictive of treatment outcome among smokers (greater discounting has worse outcomes) (39). Third, self-administration of cigarettes in the laboratory provides a detailed examination of experiment variables on smoking behavior in controlled environment (41). Fourth, state craving for cigarettes can be measured using the Questionnaire of Smoking Urges-Brief (QSU-Brief). Two factors derived from this questionnaire, relief from smoking and intention to smoke, are validated measures to assess momentary craving (45). These state measures allow for a comparison between self-reported craving and neural responsivity to the MRI cue reactivity task.

Preliminary data demonstrating the systematic Development of Non-Invasive Brain Stimulation for Addiction.

Over the last 4 years our laboratories at the Medical University of South Carolina (MUSC) and Virginia Tech Carillion Research Institute (VTCRI) have performed 3 independent studies and 1 joint study which directly contribute to the rationale and design of the present proposal. While both of our research groups have a long history of publications which have contributed to the scientific thoughts that went into this proposal, the most germane studies are summarized below:

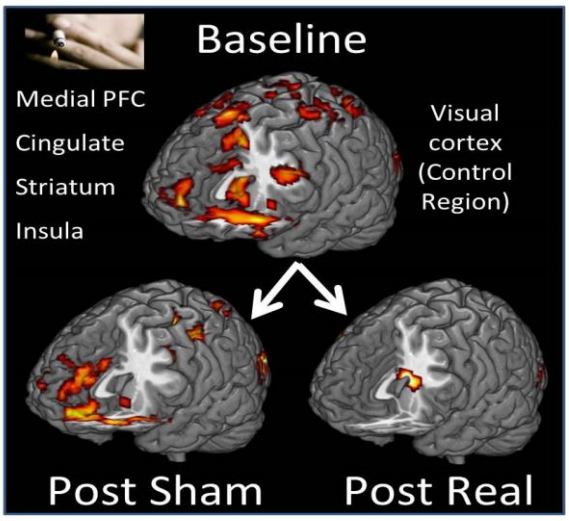


**Figure 5**. In a pilot study by Dr. Hanlon & Bickel, after 5 days of vmPFC cTBS (Strategy 1), individuals that received real TMS had a significant decrease in mPFC, insula and cingulate response to cigarette cues. This was not present in the Sham group. (Data shown are within group contrasts Visit 1 vs Visit 6, Factorial design, k = 25, voxel level p<0.05, uncorrected).

In Study 1, we demonstrated that the frontal-striatal **circuits involved in limbic drive and in executive control can be differentially activated** through TMS in healthy, non-smokers. In this study TMS was applied to a cortical node of the limbic circuit (frontal pole/vmPFC) and to the executive control circuit (dlPFC) while participants were in the MRI environment [(10) Figure 3]. Thus, demonstrating that TMS can selectively modulate limbic regions.

In Study 2, we demonstrated that 6 sessions of LTD-like TMS (cTBS) to the vmPFC **(Strategy 1 in the present proposal)** delivered in a single day caused a specific decrease in orbitofrontal cortex and ventral

striatal/accumbens BOLD signal in cocaine users (all of whom smoked cigarettes) relative to sham stimulation (Hanlon et al 2015). At the time, this was the first study to apply multiple doses of cTBS to the vmPFC.

In Study 3, through a NIDA R21 Dr. Li (a co-investigator on this application), has evaluated the effect of 10 sessions (10 days) of LTP-like TMS to the dlPFC **(Strategy 2 in the present proposal, cigarette smokers)** (10Hz rTMS) on 46 smokers randomized to receive real or sham TMS. These methods built on prior published work demonstrating single session effects on craving (7). The preliminary results of this study suggested that 10 days/10 sessions of standard 10 Hz rTMS is likely not sufficient to generate large quit rates after 1 month. Importantly however, several new reports have demonstrated the power of intermittent TBS (iTBS). iTBS is a biologically based treatment protocol, in which similar effect sizes can be achieved 20x faster relative to standard single frequency stimulation. Moreover, iTBS is as effective as 10 Hz in depression (46), and multiple sessions per day are feasible)

In Study 4, in a collaborative effort with the PI of this proposal (Hanlon) and Dr. Warren Bickel of Virginia Tech, we performed a sham-controlled randomized study evaluating the effects of 5 sessions of LTD-like cTBS TMS to the vmPFC on cigarette demand, delay discounting, and brain reactivity to cues in a cohort of 18 cigarette smokers. We demonstrated that this protocol decreased: (1) cigarette valuation as measured by behavioral economic demand (Figure 4), (2) delay discounting for monetary rewards, (3) the neural response to nicotine cues in the PFC, striatum, and insula (Figure 5), compared to a sham group. As we noted above, the current treatments available to smokers, although somewhat efficacious, are not robust. The 70% failure rate of treatment-as-usual highlights the necessity of exploring novel therapeutic interventions. **Through a systematic and parametric exploration of the effect sizes and durability of two promising TMS treatment strategies, the experiments proposed in this 5-year R01 have the opportunity to begin a new chapter in the development of efficacious treatments for tobacco dependence.**

**INNOVATION.**

Systematic Development of Non-Invasive Brain Stimulation for Addiction. The development of brain stimulation treatments for addiction has garnered significant attention from both the NIH (i.e. recent RFAs) and in the literature [see reviews: (47-51)]. In humans, TMS is the only non-invasive tool currently available in human clinical research which can selectively inhibit limbic reward or potentiate executive control circuits that contribute to addiction. A single pulse of TMS applied over a cortical target induces significant changes in neural activity in the area directly under the coil as well as measurable changes in BOLD signal and dopamine levels in regions monosynaptically connected to the target (24, 25, 52-56). Therefore, a series of repetitive TMS pulses can induce a sustainable potentiation or attenuation in those regions.

Frequency. Nearly all brain stimulation studies published to date in addiction have used a single continuous frequency (often 10 Hz or 1 Hz) of stimulation (rather than a biologically relevant rhythm) in an attempt to modulate craving. While 10 Hz and 1 Hz are the oldest, most established, and most commonly used brain stimulation protocols, newer protocols based on biologically relevant rhythms have emerged (3) and appear to produce comparable effects, but in a more efficient manner than single frequency stimulation (46). The most commonly used form of patterned brain stimulation is TBS. A single session of TBS stimulation (600 total pulses delivered within 2 minutes in 3 pulse bursts with a 5Hz burst frequency) has effects that last up to an hour (3, 57). Modeled from basic science methods (58, 59), human TBS induces a potentiation and depression of cortical excitability when given in an intermittent (LTP-like) and continuous (LTD-like) manner, respectively (3). Given the role of LTP in the acquisition and maintenance of drug use behaviors, and the clinical reality that a more efficient treatment (2 minutes versus 20 minutes) would likely be more manageable for addiction treatment programs, in preliminary studies we have been using cTBS (rather than rTMS at 1 Hz) to induce an LTD-like state in limbic circuitry while nicotine users are viewing nicotine cues (see Figure 3 & 4).

Target. Nearly all of the currently published brain stimulation studies in addiction have focused on the executive control circuit (dlPFC). Although several of these studies have found mixed results for nicotine (4, 6-8), the scientific rationale for targeting the dlPFC in addiction is sound and is typically based on its role in the executive processing system (likely necessary to resist drug cues). However, targeting the limbic reward system may be a more direct and efficacious approach to dampening cigarette valuation and cue-reactivity given that nicotine directly affects dopamine reuptake in the mesolimbic dopamine system (60-62). A recent sham-controlled crossover study in non-treatment seeking nicotine users by our group demonstrated that a single session of frontal pole/vmPFC cTBS led to a significant decrease in evoked BOLD signal in the orbital prefrontal cortex and the ventral striatum (Figure 3, (63)). All participants received real cTBS on one visit and sham cTBS on another visit (randomized) with functional MRI data collected immediately before and after the cTBS stimulation (given that single session effects likely abate after 1 hr). These data have guided this revised R01 proposal design.

Other areas of innovation which have been mentioned include: the conceptual focus on developing a tool to target the first week after a quit attempt which could ultimately be used in conjunction with a comprehensive pharmacotherapy and cognitive behavioral therapy program (Significance 1), and the use of an established conceptual model (CNDS theory) to parametrically explore 2 promising treatment interventions.

## Objectives

Cigarette smoking constitutes the greatest preventable cause of mortality and morbidity in the US. The most critical period for long term success of smoking cessation appears to be in the first 7 days after the quit date. A metaanalysis of 3 pharmacotherapy trials revealed that abstinence during the first 7 days was the strongest predictor of 6 month outcomes (n=1649; Odds ratio: 1.4, P <0.0001; Ashare et al. 2013). Prodigious relapse rates during this first week of smoking cessation are likely due to behavioral and neurobiological factors that contribute to high cue-associated craving and low executive control over smoking. **The long term goal of the research is to develop evidence-based transcranial magnetic stimulation (TMS) protocols to facilitate abstinence during this critical period.**

The **competing neurobehavioral decision systems** (CNDS) theory posits that in addiction, *choice* results from a regulatory imbalance between two decision systems (impulsive and executive). These behavioral systems are functionally linked to two discrete frontal-striatal circuits which regulate limbic and executive control (2). **Modulating these competing neural circuits (e.g. either dampening the limbic/impulsive system or amplifying the executive control system), may render smokers less vulnerable to factors associated with relapse.** The scientific premise for the proposed research is that direct modulation of these neural circuits will induce changes in cigarette valuation and brain reactivity to smoking cues. However, the relative efficacy of targeting one or the other systems is unknown. To address this gap we will target the two components derived from the CNDS.

These two frontal-striatal neural circuits - the limbic loop (ventromedial prefrontal cortex (vmPFC)-ventral striatum), and executive control loop (dorsolateral PFC (dlPFC)-dorsal striatum) can be differentially stimulated by theta burst stimulation (TBS), a patterned form of transcranial magnetic stimulation. Continuous TBS (cTBS) results in long term depression (LTD) of cortical excitability and intermittent TBS (iTBS) results in potentiation (LTP) (3). Recent studies by our group have demonstrated that **LTD-like cTBS to the vmPFC (Aim 1)** attenuates brain activity in the nucleus accumbens (Hanlon et al. 2015) and salience network (2017). In a collaborative MUSC/VTCRI study, 5 days of vmPFC cTBS reduced the value of cigarettes, preference for immediate gratification, and smoking cue-evoked brain activity (see Preliminary data). Alternatively, other groups have demonstrated that **LTP-like stimulation to the dlPFC (Aim 2)** decreases cigarette craving and cigarette use (4,5). These studies support the targets specified by CNDS. We will evaluate the relative efficacy of these 2 strategies as novel tools to change smoking-related behaviors and dampen brain reactivity to cues in two double-blind, sham-controlled neuroimaging studies. Our long-term vision is that TBS would be used as an acute intervention enabling individuals to get through

the first week after a smoking quit attempt without relapsing, and transition to more sustainable mechanisms of behavioral change (e.g., medication, cognitive behavioral therapy).

**Aim 1 (Strategy 1): Modulating the limbic system as an approach to treatment: mPFC iTBS.** Cigarette smokers will be randomized to receive 10 days of real iTBS or sham iTBS directed to the mPFC. Intermittently the desire to smoke, cigarette value using behavioral economic demand, preference for immediate gratification (delay discounting), and cigarette self-administration will be assessed. Smoking cue-evoked brain activity will also be measured when individuals are asked to 'crave' (passive limbic engagement) versus 'resist' the craving (executive engagement)(7,11-13). We hypothesize that iTBS will: 1) decrease the behavioral smoking measures described above, which will be explained by a selective 2) decrease in the neural response to cues when individuals 'allow' themselves to crave, and 3) sustain these changes over a time period sufficient to overcome the initial quit attempt (~7-14 days).

**Aim 2 (Strategy 2): Modulating the executive system as an approach to treatment: dlPFC iTBS.** Aim 2 will follow the design of Aim 1. The procedures will be identical, except iTBS will be delivered to the left dlPFC. We hypothesize that iTBS will: 1) decrease the behavioral smoking measures described above, which will be explained by a selective 2) increase in the neural response to cues when individuals attempt to 'resist' the cues, and again 3) sustain these changes over a similar period as specified in Aim 1.

**Exploratory Aim- Evaluate baseline frontal striatal connectivity and discounting rate as factors to predict an individual's likelihood of responding to Strategy 1 versus Strategy 2.** We will test the hypotheses that individuals with a higher ratio of (mPFC-striatal)/(dlPFC-striatal) connectivity will be more likely to have a behavioral change after Strategy 1. Various demographics (e.g. gender, smoking history, socioeconomic status, subclinical depressive symptoms, self-efficacy, & motivation to quit will be evaluated as explanatory variables.

The outcomes of the present aims will resolve a critical gap in our knowledge regarding the relative efficacy of 2 promising TMS treatment strategies. These outcomes will be directly translated to a larger longitudinal study evaluating a multipronged approach to improving outcomes in traditional pharmacotherapy or behavioral treatments.

## Methods and Measures

### Design

The long term goal of the research is to develop non-invasive brain stimulation as an evidence-based tool to facilitate abstinence during the first week after a quit attempt, as this is a robust predictor of 6-month treatment outcomes with traditional pharmacotherapeutic and behavioral interventions. The next step in pursuit of that goal is to systematically and parametrically evaluate the efficacy of two promising TMS treatment strategies (LTP-like stimulation to the mPFC (Aim 1), LTP-like stimulation to the dlPFC (Aim 2)) as tools to change smoking behavior and brain reactivity to smoking cues. These aims will be addressed in serial (Aim 1 Years 1-3, Aim 2 Years 3-5). A randomized, double-blind, sham-controlled design will be used for each aim. In total, 138 smokers will be recruited from the tri-county area surrounding Winston-Salem, NC. Current cigarette smokers seeking to quit smoking and willing to set a quit date will be recruited from the tri-county area using digital and print advertising in diverse media outlets. Following informed consent and screening, participants will be randomized to receive real or sham TMS to the mPFC (Aim 1, Years 1-3) or the dlPFC (Aim 2, Years 3-5) (see Table 1 and TMS Procedures below for more details regarding sham controls and double blinding procedure). During the Treatment Phase, participants will receive 10 sequential days of TMS (with additional behavioral and MRI scanning (see Table 1). Participants will receive TMS at least 3 times a week for a total of 10 TMS sessions. During the follow-up phase, participants will receive 4 maintenance TMS sessions once a week for 4 weeks. During the Follow Up Phase, behavioral assessments will be acquired weekly for the first 4 weeks (see Table 2), and daily EMA will be acquired. **Consistent with the CNDS model, the primary hypotheses are that LTP-like stimulation to the mPFC and LTP-like stimulation to the dlPFC will both lead to a decrease in**

**smoking cue-reactivity in the salience network (neuroimaging outcome), and cigarette value (behavioral outcome) but that directly targeting the value circuit (mPFC) will be more efficacious. Additionally, we will test the hypothesis that individuals with higher discounting rates and cigarette valuation at baseline will respond more to the stimulation strategies compared to those with lower baseline discounting and valuation (Exploratory Aim).**

**Table 1. Study Design. Aim1&2 will be conducted sequentially.** *Quit date, ^primary goal: evaluate 2 TMS strategies as tools to enhance cessation in the critical first week after a quit date. #secondary goal: durability

Screening

| Group Assignment | | |
|---|---|---|
| Aim 1 | vmPFC | Real |
| | vmPFC | Sham |
| Aim 2 | dlPFC | Real |
| | dlPFC | Sham |

| | Treatment Phase^ | | | | | Follow up Phase# | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1* | 2-5 | 6 | 7-9 | 10 | 1 wk | 2 wk | 3 wk | 4 wk | 8-24 wks |
| Behavior (Lab) | X | | X | | X | X | X | X | X | |
| Neuroimaging | X | | | | X | | | | | |
| TMS | X | X | X | X | X | | | | | |
| EMA (daily, remote) | X | X | X | X | X | X | X | X | X | X |

**Setting**

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

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

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

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

## Subjects selection criteria

We anticipate that we will be able to recruit 138 eligible individuals from the communities surrounding WFUHS. We anticipate that 56% of subjects will be male and 44% female, and that approximately 14% of subjects will be racial and ethnic minorities. The risks of MRI and TMS to the unborn fetus are not well understood. Therefore, to be included, females must not be pregnant as determined by a urine pregnancy test and must be utilizing reliable birth control during the course of the study.

**Inclusion Criteria**

1. Age 18-75 (to maximize participation, and minimize effects of cortical atrophy on neuroimaging data)
2. Current cigarette smoker (at least 10 cigarettes per day)
3. Able to read and understand questionnaires and informed consent.
4. Has accommodations within 50 miles of the study site.
5. Is not at elevated risk of seizure (i.e., does not have a history of seizures, is not currently prescribed medications known to lower seizure threshold)

6. Does not have metal objects in the head/neck.
7. Does not have a history of traumatic brain injury, including a head injury that resulted in hospitalization, loss of consciousness for more than 10 minutes, or having ever been informed that they have an epidural, subdural, or subarachnoid hemorrhage.
8. Does not have a history of claustrophobia leading to significant clinical anxiety symptoms.

**Exclusion Criteria**

1. Any psychoactive illicit substance use (except marijuana, alcohol, and nicotine) within the last 30 days by self-report and urine drug screen. For marijuana, no use within the last seven days by verbal report and negative (or decreasing) urine THC levels. Participation will be discontinued if participants use psychoactive illicit substances (except nicotine and alcohol) after study initiation.
2. Meets DSM-V criteria for current axis I disorders of major depression, panic disorder, obsessive-compulsive disorder, post-traumatic stress syndrome, bipolar affective disorder, schizophrenia, dissociate disorders, eating disorders, and any other psychotic disorder or organic mental disorder.
3. Has current suicidal ideation or homicidal ideation.
4. Has the need for acute treatment with any psychoactive medication including anti-seizure medications and medications for ADHD.
5. Females of childbearing potential who are pregnant (by urine HCG), nursing, or who are not using a reliable form of birth control.
6. Has current charges pending for a violent crime (not including DUI related offenses).
7. Does not have a stable living situation.
8. Suffers from chronic migraines.
9. Does not have a stable phone number for contact through calling and/or texting.
10. Does not have a stable means of using WebEx (e.g. personal computer, Internet) for interaction with study personnel during COVID-19.

**Sample Size**

**Power.** Aims 1& 2 are powered to detect a quantifiable and clinically meaningful difference in several primary outcome measures (neuroimaging and behavioral). The hypothesis for the sample size calculations corresponded to the treatment phase for the behavioral outcomes. Based on data from our preliminary study of cTBS to the vmPFC (see Significance) and our previously published study on dlPFC TMS a sample size of 28 individuals per group will yield at 80% power will be adequate to detect a minimum effect size d=0.8. For all sample size calculations, we used a repeated measures design with 4 time points using the observed AR (1) correlations. Aim 2 will be evaluated in a manner identical to Aim 1. **Retention**. Based on published data (5) and prior studies in this population (NIH R21 PI: Li), we anticipate an overall retention rate of 78% for the treatment phase, wherein the dropout rate declines as the study progresses (retention: first week (0.80 V1-V6), 2nd week (0.85 V6-V10; (0.89 V11-4wk follow up). Allowing for a 10% data loss associated with excessive movement during neuroimaging, this recruitment protocol will lead to a final sample size of 36 individuals that received mPFC TMS (Aim 1), dlPFC TMS (Aim 2), and Sham TMS to each site (Aim 1&2). We do not expect a difference in attrition between the real and sham groups, nor the mPFC (Aim 1) versus dlPFC (Aim 2) location. Thus an initial sample of 138 individuals, randomized to 4 groups, will yield a final sample of 108 usable data sets at V11 providing 80% power with a type 1 error rate of 5% to detect a minimum effect size of d=0.8 in the Behavioral and Brain Measures. **Primary data analysis will be done on the Intent to Treat sample (n=138; 69 per Aim: 46 active, 23 sham).**

**In our experience retention rates do not differ during 10 days of real or sham TMS, nor mPFC versus dlPFC stimulation,** based on ongoing studies in Dr. Hanlon's laboratory and Dr. Li's laboratory in which individuals with cocaine, alcohol, and/or nicotine dependence are receiving 10 days of TMS (R21 (Hanlon); (R21 (Li)). All individuals will be enrolled at WFUHS.

Due to several COVID related factors, including challenges with scheduling and some hesitation participants may have wearing a mask in the MRI scanner, some individuals will not receive the MRI portion of this experiment. This will neither affect our total enrollment goals, nor compromise the scientific integrity of the study. Moreover, it will lower the risk associated with MRIs to these participants.

## Interventions and Interactions

**Participants and Procedure.** A total of 138 non-treatment-seeking nicotine-dependent men and women, 18-75 years old will be recruited from the local community using flyers, as well as traditional and social media outlets (radio, television, Facebook, Craigslist, local newspapers). Following initial contact, and informed consent, participants will be scheduled for a screening visit at WFUHS (inclusion/exclusion criteria described above). Participants must be motivated to quit and willing to make a quit attempt with the use of TMS and educational booklets for smoking alone ("Forever Free – A Guide To Remaining Smoke Free" Tobacco Research and Intervention Program). {Note: In the interest of experimental rigor, in this study we wanted to directly evaluate the efficacy of these 2 TMS strategies of smoking cessation without the confound of pharmacologic manipulation. Therefore, participants that would prefer to use pharmacotherapy immediately after the quit date will be referred to the WFUHS Smoking Cessation Treatment program and will not be eligible to enroll. Following the 4 week follow up, interested participants will be referred to a WFUHS Smoking Cessation Treatment program wherein they will have the opportunity to receive additional pharmacotherapies for smoking cessation}. Eligible participants will work with the clinical research team to set a quit date (within 2 weeks of the screening visit). They will be encouraged to set "Monday" as their quit date given prior studies that have shown higher motivation to quit on Mondays (120). They will be introduced to the Forever Free booklets at the first TMS visit. One aspect of these educational booklets will be discussed with the participants on each TMS visit. Although this program has low to moderate efficacy on its own (especially in the first 7 days), it is unlikely that TMS alone will be sufficient for smoking cessation. Therefore, all participants will also be exposed to these booklets by the Tobacco Research and Intervention Program.

Study Visit 1 (Behavior, MRI, TMS) will begin 1 week prior to the quit date. **Inclusion/Exclusion criteria:** To participate in the present study, participants must: 1) be 18-75 years of age, (2) smoke at least 10 cigarettes a day (on average; as measured by 1 month timeline follow-back (TLFB), (3) not have a history of or current psychiatric or neurologic disease, or traumatic brain injury (4) not be pregnant, , (5) not currently use psychoactive substances other than alcohol, nicotine, or marijuana; nor have current or recent (e.g. within the past 5 years) moderate/severe substance use disorder (DSM-V) (6) not have any barriers to making contact between the TMS coil and the skin (e.g. braids that cannot be removed), and 7) meet all criteria on a standardized MRI/TMS safety screen (TASS) (including but not limited to implanted electronic devices, bullets or metallic fragments, hair clips and piercings that cannot be removed). These inclusion/exclusion criteria are those used in Study 4 described in Preliminary Research. **Randomization.** Participants will be individually randomized and assigned to treatment or control conditions using stratified block randomization (with blocks of randomly varying sizes) prior to the study.

**Experimental Procedure (Aim 1 and 2): Screening Visit – Consent.** Participants will receive a series of assessments designed to evaluate nicotine dependence and use, psychiatric conditions, and mood. These include a standard clinical intake evaluation screen for research (used in other studies by the PI), MINI International Neuropsychiatric Interview (MINI 5 P) (88), Timeline Follow-Back (TLFB) (89), Beck Depression Inventory II (BDI) (90), State-Trait Anxiety Inventory (STAI) (91) and Profile of Mood States (POMS) (92). Data will be collected using REDCap™, and entered directly into the online portal to ensure security and prevent data loss.

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

**Study Visit Procedures:** At all visits, individuals will provide a urine screen to detect recent use of drugs of abuse and pregnancy, a breath carbon monoxide (CO) sample to detect recent cigarette smoking, and a breath sample to test for recent alcohol use. During the consent visit, visits 1, 6, 10 and follow up visits samples will be collected to determine cotinine (nicotine metabolites) levels in the urine. Samples will be taken from the urine sample provided for the drugs of abuse screen, no additional samples will be required from the participant. At visits 1, 6, 10 and follow up visits (Assessment visits), participants will complete a battery of behavioral assessments following active TMS or sham (see Table 2). MRI scanning (at visits 1 and 10) will occur prior to TMS in order to isolate cumulative, rather than acute, effects of TMS. At all visits participants will be required to provide a CO reading at least 50% of their baseline CO measure to ensure they are at least 6 hours deprived from cigarettes. Cigarette deprivation will be use to increase craving and responding for cigarettes. Short term cigarette deprivation has known amplification effects on the brain response to smoking cues (93, 94). Moreover, we have extensive experience with successfully using this deprivation procedure (33, 41).

**Table 2**

| Measure | Time (Min.) | Visits | Description |
|---|---|---|---|
| 1. Biochemical and self-report assessment of tobacco use and dependence | | | |
| Carbon monoxide (CO Level) | 1 | 1-10, and follow-ups | Breath CO provides an accurate measure of **recent exposure to CO**, including from smoking combustible tobacco products (95). The CO measurement will be used to determine recency of smoking. |
| Timeline Follow-Back (TLFB) interview | 5 | 1, 6, 10, and follow-ups | This **self-reported tobacco product use interview** asks participants to retrospectively estimate the number of tobacco products they've used each day for the past 30 days or since the previous assessment, whichever is fewer (89). |
| Fagerström (FTND) | 3 | 1, 6, 10, and follow-ups | This 6-item questionnaire quickly assesses degree of **cigarette dependence** (96, 97). Test for Cigarette Dependence. |
| 2. Measures of tobacco product value and sensitivity (**PRIMARY DEPENDENT MEASURES) | | | |
| Questionnaire on Smoking Urges-Brief (QSU) | 2 | 1 - 10 and follow-ups | This 10-item questionnaire assesses **cigarette craving**. Participants will be asked to rate from 1 (strongly disagree) to 100 (strongly agree) their agreement with several statements (e.g., "I have a desire for a cigarette right now," and "Nothing would be better than smoking a cigarette right now."). Factor analyses support two factors: one that reflects a strong desire and intention to smoke and one that reflects relief from negative affect associated with an urgent desire to smoke (45). |
| Hypothetical Purchase Task (**Demand Alpha, Q0) (HPT Cigarettes) | 5 | 1, 6, 10, and follow-ups | The hypothetical purchase task (HPT), a validated measure for cigarette demand, (98, 99) will assess cigarette purchases at various price conditions. Participants will hypothetically purchase quantities of cigarettes to use over a 24-hour period across ascending prices (e.g., $0, 0.12, $0.25, $0.50, $1.00, and $2.00 per cigarette). The HPT has been shown to be predictive of treatment outcomes (100). |
| 3. Cognitive/behavioral task (** PRIMARY DEPENDENT MEASURE) | | | |
| Delay-discounting tasks (*discounting rate, $1K) | 5 | 1, 6, 10, and follow-ups | 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]. Monetary delay discounting has been documented to be predictive to treatment success for smokers (39). |
| 1. Brain Reactivity to Smoking Cues (**PRIMARY DEPENDENT MEASURE) | | | |
| Functional MRI Smoking Cue Reactivity Task (acquired after behavioral assessments) | 15 | 1, 10 | This task has been used in 4 original research publications by our group and reliably activates orbitofrontal and medial prefrontal regions (7, 11-13). We will give participants an unlit cigarette to hold in their hand while they are in the MRI scanner. They will receive two 12m runs of the task (fixed within subject, counterbalanced within groups). During one run they will be instructed to 'allow' themselves to crave (passive limbic engagement) and in the other run they will be told to 'resist' the cues (executive engagement). When the task begins participants are shown pseudorandomly interspersed blocks of images: 1) cigarette images (e.g., cigarettes, lighters, people smoking) (CIG), 2) neutral images, |

| | | | |
|---|---|---|---|
| | | | chromatically matched to the CIG images (NEU), and 3) blurry non-images (BLUR). Stimuli are presented in six 120-s epochs, each consisting of four 24-s blocks of an image type (one block each of CIG, NEU, BLUR). Each block is followed by a 6-s washout period, allowing the hemodynamic response from the previous block to decline before the next is presented. Scanning parameters: Multislice gradient-echo echo planar imaging (TR=2200, TE=35 msec, field of view of 192 mm, voxel size 3.0 x 3.0 x 3.0 mm, 36 slices, 3 mm thickness, no skip). |
| 2. Other Assessments | | | |
| Confidence in Active or Sham TMS Assignment (Active vs Sham) | 1 | 1, 6, 10 | Participants will complete a form indicating their confidence (scale 1-10) in whether they are receiving active or sham treatment. Pooled accuracy from prior work in our collaborator's laboratory was 47.6% suggesting that individuals were not aware of the stimulation being received. |
| Minnesota Nicotine Withdrawal Scale (MNWS) | 2 | 1 - 10 and follow-ups | Participants will be asked to rate a variety of mood and physiological symptoms associated with **nicotine withdrawal** (e.g., anxiety, attention, hunger). Total withdrawal scores will be measured using the 8-item MNWS originally adapted from Hughes and Hatsukami 1986 (102) and Hughes 1992 (103). The 8-item scale is a validated measure and the most frequently used (104, 105). |
| Beck Depression Inventory (BDI) | 10 | 1,6,10,and follow-ups | Given that iTBS to the left dlPFC improves depression scores, we will perform a mediation analysis to determine if any effects observed on smoking behavior and the brain response to smoking cues is related to changes in depression |
| Generalized Self-efficacy scale (GSF) | 10 | 1,6,10,and follow ups | This scale was designed to assess self-efficacy, i.e., the belief that one's actions are responsible for successful outcomes. The scaled score for each question ranges from 1 to 4. Higher scores indicate stronger participant's belief in self-efficacy. Previous studies have demonstrated predictive validity of self-efficacy as baseline predictor of smoking treatment outcome (112). |
| 3. Other neuroimaging sequences | | | |
| T1 MPRAGE | 5 | 1,10 | High-resolution structural scans will be obtained using an inversion recovery 3D spoiled gradient echo (3DSPGR) sequence, 192 slices, voxel size: 1.0 x 1.0 x 1.0, field of view: 256 mm, section thickness:1.0 mm with no gap, giving an in-plane resolution of 256. This sequence will be used for anatomic overlays of the functional data and spatial normalization to a standard atlas, TMS coil positioning, and subsequent voxel-based morphometry. |
| Field Map | 1 | 1,10 | Field Map calculations allow for offline correction of imaging distortion during post-processing. Field map configurations will include: flip angle (FA)= 60 degrees, field of view (FOV) = 192 mm; voxel size = 3.0 x 3.0 x 3.0 mm, 36 contiguous slices 3.0 mm thick. |

**TMS Treatment – 10 days (Experiment 1/Strategy 1: iTBS to the mPFC; Experiment 2/Strategy 2: iTBS to the dlPFC)**

After the MRI scanning visits participants will be escorted into the Brain Stimulation Research Laboratory (Dr. Hanlon's research suite) where scalp localization will be performed for the TMS procedure. The Cartesian position of the coil (X,Y,Z) will be determined by standardized positions from the EEG 10-20 system: 1) AFZ will be used for the mPFC stimulation (Aim 1), 2) F3 will be used for the left dlPFC stimulation (Aim 2). The angular position of the coil (pitch, yaw, roll) will be determined by the individual's cortical geography using the individual's T1 scan for guidance. The locations and coil orientation will be indicated on a nylon cap which will be worn during the TMS sessions. We will then determine the participant's resting motor threshold (RMT, the minimal amount of stimulation required over the hand area of the primary motor cortex to induce contraction of the APB muscle of the hand 50% of the time) via the standardized PEST procedure (106, 107). The procedures for acquiring the motor threshold, performing cortical localization, standardized procedures, blinding, establishing standardized paradigms and training regimens for all staff, as well as safety and ring the experimental procedures are consistent with our prior publications (7,27, 54, 63, 69, 78, 111). We will also publish a Standard Operating Procedure document and video file as supplementary material with any publications that arise from this project (as in 111, supplement).

For Aim1 (Strategy 1) stimulation will be over mPFC. For Aim 2 (Strategy 2) stimulation will be over the left dlPFC. The Aims will be pursued in serial, with a 2:1 active versus sham randomization for each Aim. Participants will receive 20 trains of stimulation (1200 pulses total; each train: 3 pulse bursts presented at 5Hz, 15 pulses/sec for 2 sec, 8 sec rest, 10 pulses/train; 110% RMT, MagPro) using a figure 8 coil (Coil Cool-B65 A/P). This is the iTBS sequence initially published (3) which has been used in clinical depression treatment (46). During each real and sham TBS session each day the amplifier output will be escalated ("ramping" in 5% increments over 30 seconds) up to 80% to 110% RMT to enhance tolerability. The time between the end of the TBS procedures and the beginning of the behavioral assessments will be compiled and used as covariates in subsequent analyses.

TMS ACTIVE SHAM system and strategies to promote rigor of the blind: : The MagVenture MagPro system has an integrated active sham that used two surface electrodes placed on the scalp to mimic the sensation of active TMS. The coil is visually identical on both sides, but only one side will direct an electric field on the participants head. At each TMS visit, the coordinator will place 2 surface electrodes on the scalp near the TMS stimulation site. Once the electrodes are in place and the TMS coil is in position, the coordinator enters a 6 digit number assigned to that participant into the MagPro capacitor. Each number is coded to be either active or sham TMS, but the classification is unknown to the coordinator or the participant. The capacitor can sense whether the TMS coil is positioned in a direction wherein the active or the sham side is facing the participant's head. The capacitor will instruct the coordinator that is either "Ready" or to "Flip Coil" based upon the participants group assignment. This enables both the participant and the coordinator to be blind.

For the initial TMS visit, during the motor threshold procedure, the active side is always down in order to determine an appropriate dose To ensure that the coordinator (who both finds the motor threshold and then delivers the treatment) does not learn the relationship, on Visit 1 after the motor threshold procedure is done, the coordinator will leave the room and a second individual will unplug the coil, flip it 1 or more times, and leave the room. The coordinator will return to the room, plug it in, place the TMS coil in the proper position, and commence the treatment.

Further strategies to promote blinding: The TMS coil will be visually inspected by the PI or lab manager on a regular basis to be sure that no marks have occurred on the surface of the coil. If marks have occurred they will be either washed off or covered in a manner that is symmetrical to both sides of the coil. Additionally all staff will be trained on the importance of blinding when they join the laboratory and encouraged to contact the lab manager or the PI if they ever feel they may have "figured out" the blind. A

questionnaire will be given to the participants to evaluate their opinion on whether they received active or sham, their level of confidence (Likert scale 1-10), and their rationale (text entry).

## Outcome Measure(s)

**Behavioral Outcomes: For the treatment phase (10 days of real/sham TBS)**, the primary behavioral outcomes include Cigarette demand (Q0 and alpha), Craving (QSU Intention, QSU Relief), and Delay Discounting ($100 and $1000). For the treatment phase the analysis will be performed using repeated measures ANOVA on change scores from baseline for each visit. The main independent variable in the ANOVA will be time (visits on day 1, 6, 10), group (real or sham) and their interaction. For correlations of observations across visits an AR(1) structure will be considered and compared with other structures such as compound symmetry and a general structure. The primary hypothesis is the interaction. If the interaction effect for an outcome is significant, we will conclude there is statistical evidence of overall treatment effect. If the spaghetti plots suggest trends (e.g., linear, quadratic, or piecewise changes) we will treat time as a continuous variable and fit repeated measures regression models along with group and its interaction with continuous time as independent variables.

**Neuroimaging Outcomes: For the treatment phase, primary analysis**. Image pre-processing will be conducted with FSL v. 5.0: (FMRIB Analysis Group, Oxford, UK) (108) realignment to the first volume, smoothing with an anisotropic 8-mm Gaussian kernel, high-pass filtering, resampling to 2-mm isotropic voxels, and stereotactic registration to the Montreal Neurological Institute 152-subject average template. Subjects with >3 mm movement (total mean frame displacement across the entire task) will be excluded from analysis.

Hypothesis Aim 1: Based on the framework predicted by CNDS theory, and preliminary work (see Study 4), we anticipate that mPFC stimulation will lead to *a decrease in brain reactivity to cues* during the "allow" condition (passive limbic engagement). We will analyze the neuroimaging data in concert with the behavioral data, evaluating the hypotheses that 1) mPFC iTBS will decrease the brain reactivity to cues in the 'allow' condition (with no consistent link to the 'resist' condition) and that 2) this will be related to the behavioral change in a dose-dependent manner. This will be achieved by extracting the average BOLD signal timecourse and the percent signal change during the CIG versus NEU blocks from *a priori* anatomically defined regions of interest (ROIs), including the striatum (ventral striatum and dorsal striatum), insula, inferior frontal gyrus, and anterior cingulate cortex. Ventral striatal and dorsal striatal ROIs are derived from the FSL Oxford-GSK-Imanova striatal atlas, mapped via probabilistic diffusion tractography (109) in agreement with anatomical projection zones from the frontal cortex (1). Hypothesis Aim 2: Based on the framework predicted by CNDS theory, and prior studies of dlPFC stimulation in smokers (4-9), we anticipate that dlPFC stimulation will lead to *an increase in executive control circuitry (left dlPFC, posterior parietal cortex)* during the "resist" condition (executive engagement). As in Aim 1, we will analyze the neuroimaging data in concert with the behavioral data, evaluating the hypotheses that 1) dlPFC iTBS will decrease the brain reactivity to cues in the "resist" condition (with no consistent link to the "allow" condition) and that 2) this will be related to the behavioral change in a dose-dependent manner. **The ROI based outcomes of Aim 2 will be compared with the outcomes of Aim 1 using standard general linear modeling as well as a data-driven hierarchical model (see Integration below).** As an experimental control, for both Aims we will also calculate the percent signal change from the primary motor cortex, a region which should not be differentially modulated by mPFC or dlPFC stimulation. Although some studies have used the visual cortex as a control region a recent meta-analysis by our group demonstrated that the visual cortex is typically activated more to drug cues than neutral cues (78). Secondary functional connectivity analysis: Additionally, an exploratory seed-based functional connectivity analysis using psychophysiological interactions (PPIs) will be performed using the TMS stimulated ROIs (mPFC and dlPFC) and the striatal target regions (ventral striatum, dorsal striatum- defined above) as seed regions. These data will be compiled across participants and compared between the mPFC and dlPFC stimulation days. Group analyses will be performed using a random effects model limiting significant clusters to those that meet $p<0.05$ family-wise error corrected.

**For the follow-up phase:** We will test the hypotheses that behavioral change related to Strategy 1 and 2 will be based on an individual's baseline brain cue reactivity data. We will generate Kaplan-Meier curves of behavioral change for the four groups and compare these with cue-reactivity in the MPFC, insula, cingulate (salience network nodes) and striatum using log-rank tests and consider Cox's proportional hazards model to include covariates. Diagnostics will be performed to verify the assumptions such as homoscedasticity and normality. If it is merited, transformations on the outcomes will be considered. Linear contrasts will be utilized to test the hypothesis of equal effects in the two groups at any given time point. Covariates, such as gender and depression that were used to stratify, will be included.

**Exploratory Aim: Evaluate baseline frontal striatal connectivity and discounting rate as factors to predict an individual's likelihood of responding to Strategy 1 versus Strategy 2.** Finally, will compare the relative efficacy of Strategy 1 versus Strategy 2 on the behavioral change by constructing a computational model. We will test the hypotheses that individuals with a higher ratio of (mPFC-striatal)/(dlPFC-striatal) connectivity will be more likely to have a behavioral change after Strategy 1. Various demographics (e.g. gender, smoking history, socioeconomic status, subclinical depressive symptoms, self-efficacy, & motivation to quit will be evaluated as explanatory variables. This will be achieved by hierarchical linear modeling (HLM v. 7.0, Scientific Software International, Skokie, IL) of the behavioral variables of interest as well as the BOLD signal change in the striatum (caudate) between smoking and image blocks (e.g., CIG vs. NEU) in 'allow' and 'resist' (behavioral change variables nested within treatment (cTBS, iTBS)).

## Analytical Plan

**Primary data analysis will be done on the Intent to Treat sample (n=138; 69 per Aim: 46 active, 23 sham).** Prior to formal statistical analysis, summary statistics for all variables will be obtained and spaghetti plots will be generated. All behavioral outcome measures will be based on standardized composite scores from the literature. We will also use data reduction techniques (such as factor analysis or principle component analysis) to confirm the applicability of the composite scores in our population. Analyses will be performed for each phase separately.
Results will be analyzed initially using descriptive statistics. Comparison between groups will be done using chi square tests for proportions, and t-tests or ANOVA procedures for continuous variables. Regression analysis will be performed to identify independent outcome predictors. Other inferential statistical analysis will be conducted as appropriate.

## Human Subjects Protection

### Potential Risks

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

**Risks of psychiatric interviewing (minimal risk):**

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

**Risks associated with MRI scanning (minimal risk):**

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

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

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

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

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

Other potential risks:

2. Potential for scalp discomfort and headaches: Some people report mild discomfort when the magnetic pulses are applied over the scalp. A small number of people (~5%) report headache following rTMS. However, the headaches are temporary and manageable with common over-the-counter pain remedies.
3. Potential hearing loss: The TMS coil generates a high-energy click that may cause hearing damage. Humans exposed to TMS have shown temporary increases in auditory threshold (especially at high frequencies) lasting at least 5 minutes and less than 4 hours.
4. Safety in case of pregnancy: This protocol will exclude pregnant women. The risks of using TMS with pregnant women are currently unknown. Please inform the research team if you are pregnant or think that you might have become pregnant during the study. A pregnancy test will be performed before the experiment begins.
5. Potential for reflex syncopal event: Syncope is defined as a momentary loss of awareness and postural tone. It typically has a rapid onset, short duration, and spontaneous recovery. Although syncopal episodes are very rare with TMS (less than 1%), they typically occur during the motor

threshold procedure before the rTMS treatment has begun. Individuals that are sleep deprived and have low or unstable blood pressure are at greater risk.

6. Interaction with electrical or metal implants: Electrically, magnetically or mechanically activated implants (such as cardiac pacemakers), as well as clips on blood vessels in the brain may be affected by rTMS (as well as MRI) and cause pain or abnormal signal propagation. Therefore individuals that have these implants and devices or suspect that they may have pieces of metal in their eyes, head, or body (e.g. bullets, shrapnel, fragments from metallurgy) will be excluded from the study.

**Adequacy of protection against risks**

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

**(b) Security of Participant Information**

For individuals that are enrolled in the study (invited for a screening visit) there will be two documents that contain their first and last names: the informed consent containing the HIPAA authorization and a receipt for their compensation kept for tax purposes. Each of these documents will be kept in a separate 3-ring binder.

Each individual enrolled in the study will be assigned a unique participant ID number (starting sequentially). A folder will be created for each of these participants and labeled with their Participant ID number. The folder will contain the results of all of the testing for each individual. The participants 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 Participant ID number. As above all of the participant folders, along with the binders will be stored in a locked cabinet in Dr. Hanlon's research laboratory.

**Protection Against Risks**

**Risks of psychiatric assessments:**

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

**Risks associated with MRI and TMS (minimal risk):**

1. Although the TMS protocol that we are using has never been associated with causing a seizure, individuals that have a history of seizures, stroke, or other neurological impairment that might lower their seizure threshold will be excluded from the study. All study personnel will have received a formal education course in seizure detection, care, and treatment and a physician will be available to immidiately assist in stabilizing the participants in the event of a seizure Any participant who has a seizure cannot continue with the study.
2. We will exclude individuals with claustrophobia such that they are not exposed to this risk. Additionally participants will be given a pressure sensitive squeeze ball that they can use to indicate at any time that they would like to leave the scanner.
3. To protect against hearing loss concerns, participants will wear high fidelity earplugs throughout the scanning session.

4. Participants will be informed of potential risk of scalp discomfort and headache before they consent and will be told that they should feel free to take non-steroidal antiinflammatory agents after the TMS session if they have a headache.We will also exclude individuals with chronic migraines such that they are not exposed to this risk.
5. We will exclude pregnant females such that they are not exposed to this risk.
6. All participants that enroll in this study will complete a written MRI saftey screen. We will also use a handheld metal detector to ensure the participant has no metal in or on is/her body before entering the MRI scanning room.

Participants may withdraw from the study at any time or may be withdrawn from the study if the PIs feel it is in the best interest of the participant. All key personnel will undergo appropriate IRB training for dealing with human participants and will be trained by the PI at their site in all aspects of the study interventions. Personnel listed in this protocol (as well as any rotating medical students, graduate students, psychiatry residents or fellows that may be exposed to this investigation as part of their reseaerch training exposre) will be required to maintain their certification of HIPAA training and Protection of Human Participants in Research training on an annual basis. Any new personnel without experience in human clinical research will be encouraged to attend the WFUHS Core Clinical Research Training Course, which is offered live and online throughout the year. Through these measures we will ensure that all study staff will be trained and will maintain ongoing understanding of research ethics and the rights of the participant during the consenting process and throughout an individual's participation in the study.

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

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

**Subject Recruitment Methods**

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

MRI center and the TMS sessions will be done in the TMS laboratory located in Dr. Hanlon's research lab.

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

**Informed Consent**

Individuals that have previously consented to be contacted about future research studies will be contacted and phone screened to determine preliminary eligibility. They will be scheduled for their screening visit, which will take place in a private, quiet screening room in the Clinical Neuromodulation Laboratory space in Dr. Hanlon's research suite. Informed consent will be reviewed with the potential participant by a member of the key personnel on this proposal. The consent will be signed by the participant as well as one of the Key Personnel on the proposal. A copy of the consent will be given to the subject and the original placed in the research record. All records will be stored in locked departmental files. Section 301(d) of the Public Health Service Act of November 4, 1988 also protects a layer of protection for the privacy of health information for individuals that engage in federally funded medical research.

**Confidentiality and Privacy**

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

**Data and Safety Monitoring**

The principal investigator (PI) will be the primary party responsible for data management, oversight, and accountability in terms of participant safety and consent.
The DSMB member holing the unblinding key (Elizabeth Shilling) will have the following responsibilities:
1) Storing the unblinding spreadsheet on a secure server that is not accessible by members of the study team that are blinded
2) In the event of a safety event (and at the conclusion of the year), she will have the ability to look up the condition the participant was receiving (active/placebo)
3) A conflict of interest will be avoided by secondary evaluation of records by a Monitoring Entity (ME) (aka. data safety monitoring board- DSMB) on an annual basis. Quality control will include regular data verification (Integrity of the Consent and HIPAA, scores on assessments, MRI scanning information), study progress, subject status, adverse events, and protocol deviations. Protocol adherence will be monitored by the Wake Forest IRB, who will also be given access to the reports from the PI to the ME.

**Provisions to Monitor the Data to Ensure the Safety of Subjects**

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

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

**Plans for Interim Analysis of Efficacy Data:** Data from this study will be analyzed when 20% increments of the recruitment goal have been obtained(e.g. 20% (n=27), 40% (n=55), 60% (n=83), 80% (n=110), 100% of the total enrolled sample (n=138)). A member of the DSMB that holds a copy of the unblinding key will provide the PI with the unblinding codes for individuals that have completed enrollment. Data analysis will be performed by trainees for educational purposes (e.g. graduate students, postdoctoral fellows) as well as the laboratory manager for preparation of DSMB reports and assessment of any disparities in the demographic distribution between the active and placebo groups. Final analysis will occur when all participants have finished the final follow-up phase of the study.

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

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

**Data Analysis Plan:** Data for this study (behavioral assessments, functional MRI measurements) will be acquired by protocol-approved members of the research team, including graduate students and research specialists. These individuals will also perform data management and analysis under the guidance of the PI. Deidentified data will be shared per NIH requirements. 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.

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

**Definition and Reporting of AEs/SAEs to the IRB/NIDA:** 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, inparticipant 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, ME/DSBM, and NIH. 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, ME/DSMB and to the sponsor, the NIH.

**Management of SAEs or Other Study Risks:** As described above, SAEs will be immediately reported, within 24 business hours, to the ME/DSBM, sponsor 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, ME/DSBM, and NIH.

**Reporting of IRB Actions and ME/DSMB Reports to NIAAA:** Any IRB actions and ME/DSMB reports will be reported to both the Wake Forest IRB and the NIH Institute supporting the study following the sponsor's report submission guidelines, should this study be awarded.

**Report of Changes or Amendments to the Protocol:** Any changes to the proposal/protocol must be approved by the NIH Institute supporting the study. Any amendments to the IRB protocol associated with the proposed work will be reported to NIH should this proposal be awarded funding.

**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. SAEs will be reported to NIH within 72 hours. Should the reported SAE be confirmed as directly related to the protocol, the trial will be terminated. The device manufacturer will be notified within 72 business hours. Of note, according to the literature associated with the MagVenture device, there have been no clinical trials stopped or SAEs reported.

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

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