QuitFast: Evaluating Transcranial Magnetic Stimulation as a Tool to Reduce Smoking Directly Following a Quit Attempt

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Protocol & Statistical Analysis Plan

Protocol.

Overview. We will parametrically evaluate the efficacy of two promising TMS treatment strategies (LTD-like stimulation to the vmPFC (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 1-2, Aim 2 Years 3-4). 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 Charleston, SC. Current cigarette smokers seeking to quit smoking and willing to set a quit date will be recruited from the tri-county area (Charleston, Berkeley, Colleton County) 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 vmPFC (Aim 1, Years 1-2) or the dlPFC (Aim 2, Years 3-4) via a Central Randomization Core (run by the MUSC Data Coordination Unit (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 be allowed to miss up to 2 TMS visits in a row but all 10 visits must be completed in 14 days.

During the Follow Up Phase, behavioral assessments will be acquired weekly for the first 4 weeks (see Table 1), and daily EMA will be acquired. Additionally weekly EMA assessments will be acquired for 24 weeks (approx. 6 months from quit date).

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 MUSC clinical intake evaluation screen for research (used in other studies by the PI and Co-I), MINI International Neuropsychiatric Interview (88), TLFB (89), Beck Depression Inventory II (90), StateTrait Anxiety Inventory (91) and Profile of Mood States (92). Data will be collected using REDCap™, and entered directly into the online portal to ensure security and prevent data loss. 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. 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).

TMS Procedures. After the MRI scans participants will be escorted into the Brain Stimulation room (30 feet away) where scalp localization will be performed for the TMS procedure. The Cartesian position of the coil (X,Y,Z) will be determined by standardized positions from the EEG 10-20 system: 1) FP1 will be

used for the left 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 beneath FP1 and F3 using the individual's T1 scan for guidance. The locations and coil orientation will be indicated on a nylon cap which will be worn during the TMS sessions. We will then determine the participant's resting motor threshold (RMT, the minimal amount of stimulation required over the hand area of the primary motor cortex to induce contraction of the APB muscle of the hand 50% of the time) via the standardized PEST procedure (106, 107). During each TMS session, we will take a non-identifiable photo of the participants' forehead (eyes covered with an index card) to ensure the coil is correctly placed each time they return to the lab. 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). Experiment 1/Aim 1: cTBS to the vmPFC. For continuous theta burst stimulation (Aim 1), participants will receive stimulation over the left frontal pole (FP1) (each train: 3 pulse bursts presented at 5Hz, 15 pulses/sec, 600 pulses/train, 60 sec intertrain interval; 110% RMT, MagPro) using a figure 8 coil (Coil Cool-B65 A/P). This protocol has been shown to attenuate the mPFC and striatum in cocaine dependent individuals in the past (63) as well as in nicotine users (see Preliminary Data, Study 4). Experiment 2/Aim2: iTBS to the left dlPFC. For intermittent theta burst stimulation (Aim 2), participants will receive 6 trains of stimulation over the dlPFC (F3) (each train: 3 pulse bursts presented at 5Hz, 15 pulses/sec for 2 sec, 8 sec rest, 600 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) from 80% to 110% RMT to enhance tolerability. The coil will be left in position during the 60-second intertrain interval. 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. ACTIVE SHAM system. The MagVenture MagPro system has an integrated active sham that passes current through two surface electrodes placed on the scalp. The electrodes are placed on the left frontalis muscle under the coil for both the real and sham stimulation sessions. To assess the integrity of the blind (active sham) a questionnaire will be given to both the patients and to the research staff at day 1, 6, 10 to evaluate their opinion on whether they received real or sham, their level of confidence (Likert scale 1-10), and their rationale (text entry).

Sample size: 138

Participating enrolling clinics: All participant visits including Informed Consent, screening, TMS, and MRI scanning will take place on the MUSC campus. The TMS visits will be done in the Department of Psychiatry. The MRI scanning procedures will be done at the Center for Biomedical Imaging.

Projected timetable: Retention will be incentivized by escalating remuneration procedures on subsequent visits. Recruitment will commence in Year 1, with all participants enrolled by the end of year 4.

Data management, acquisition, and transmission: The Principal Investigators at each site (MUSC: Hanlon; VTCRI: Bickel) will be the primary parties responsible for management, oversight, and accountability in terms of participant safety and consent. A conflict of interest will be avoided by secondary evaluation of records by a Monitoring Entity (ME) (aka. data safety monitoring board- DSMB) on an annual basis. This Entity's reporting will be supported by the South Carolina Translational Research Institute, MUSC's CTSA. Quality control will include regular data verification (Integrity of the

Consent and HIPPA, scores on the Assessments, MRI scanning information), study progress and subject status, any adverse events, and any protocol deviations. Protocol adherence will be monitored by the MUSC Institutional Review Board and the VTCRI Institutional Review Board, who will also be given access to the reports from the PIs to the ME.

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

Adverse Event Reporting.

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

Definition and Reporting of AEs/SAEs to the IRB/FDA/NIDA: An AE is defined as any untoward medical occurrence in a participant enrolled in this study. Any unwanted change, physically, psychologically or behaviorally, that occurs in a study participant during the course of the trial is an adverse event. A Serious Adverse Event (SAE) is defined as an adverse event that has one of the following outcomes: death, life threatening, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect.

All unexpected Adverse Events (AEs) will be reported to the MUSC and VTCRI IRB and Committee on Human Research within 48-business hours. Serious AEs will be reported to the MUSC IRB within 24 business hours and to NIDA within 72 business hours. Follow-up of all unexpected and serious AEs will also be reported to these agencies. AEs/SAEs are documented and reported as per IRB requirements. Research staff will identify adverse events and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome and the need for change or discontinuation in the study intervention. Adverse events are generally documented on AE Logs and AE Case Report Forms (CRFs). Additional relevant AE information if available will be documented in a progress note in the research record as appropriate to allow monitoring and evaluating of the AE. If the AE meets the definition for serious, appropriate SAE protocol specific reporting forms are completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization or until the participant is no longer in the study as stated in the protocol. We will report adverse events to the MUSC and VTCRI IRB online per the IRB's guidelines.

Reporting of IRB actions and ME/DSMB reports to NIDA Any adverse events will be immediately reported to both the MUSC and VTCRI IRB and NIDA should this study (R01 proposal) be awarded. All ME/DSMB reports will be submitted to NIH/NIDA annually.

Potential risks/benefits for participants The risks fall into three categories: risks associates with psychological assessment, risks associated with repetitive TMS and risks associated with MRI scanning.

Risks of psychiatric interviewing (minimal risk): 1. Some participants may get emotionally distraught when disclosing sensitive personal stories. Some participants may feel anxiety about disclosing substance use histories and reporting some aspects of their demographics. Risks associated with MRI scanning (minimal risk): 1. The major potential risks for MRI are all subsumed under the risks for TMS and primarily include risks to individuals who have metallic implants, pacemakers, or pregnant women. These individuals will be excluded from the study. 2. Participants may feel restless or uncomfortable when lying in the MRI scanner.

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

Potential Risks of TMS Repetitive TMS has been considered "non-significant risk" by the FDA (2007) when applied at similar intensities, durations, and frequencies to those being used in this protocol. Additionally 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 depedence.

Potential risk of a seizure: In designing this experiment, we have followed the latest safety guidelines for TMS. Despite these precautions, there is a chance of a seizure as a result of rTMS. Eight seizures have been noted in previous studies, with six of them occurring in healthy volunteers without any history of seizures, brain tumors or traumatic brain injuries. All of these seizures have occurred during rTMS with the participant in the treatment chair and a trained operator on hand. All seizures have stopped by themselves without any medication. No participants have had any problems after the seizures. MUSC has a plan for dealing with fainting and seizures, and every TMS researcher involved in providing TMS treatment for this protocol (Key Personnel) will have to attend the MUSC Brain Stimulation Intensive training program wherein they will receive a Certificate of Completion after a written test of TMS didactics and safety measures as well as a skills test associated with collecting an accurate motor threshold (which is one of the largest factors that promotes safety). Additionally, if a participant has a seizure an emergency response team will be called. Most seizures, including those caused by rTMS, last less than 60 seconds and do not require any medication. Participants will be evaluated by a physician associated with the MUSC Brain Stimulation Laboratory following recovery from the seizure. Any participant who has a seizure cannot continue with the study. 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: 1. Potential for scalp discomfort and headaches: Some people report mild discomfort when the magnetic pulses are applied over the scalp. A small number of people (~5%) report headache following rTMS. However, the headaches are temporary and manageable with common over-the-counter pain remedies. 2. Potential hearing loss: The TMS coil generates a high-energy click that may cause hearing damage. Humans exposed to TMS have shown temporary increases in auditory threshold (especially at high frequencies) lasting at least 5 minutes and less than 4 hours. 3. Safety in case of pregnancy: This protocol will exclude pregnant women. The risks of using TMS with pregnant women are currently unknown. Please inform the research team if you are pregnant or think that you might have become pregnant during the study. A pregnancy test will be performed before the experiment begins. 4. Potential for reflex syncopal event: Syncope is defined as a momentary loss of awareness and postural tone. It typically has a rapid onset, short duration, and spontaneous recovery. Although syncopal episodes are very rare with TMS (less than 1%), they typically occur during the motor threshold procedure before the rTMS treatment has begun. Individuals that are sleep deprived and have low or unstable blood pressure are at greater risk. 5. Interaction with electrical or metal implants: Electrically, magnetically or mechanically activated implants (such as cardiac pacemakers), as well as clips on blood vessels in the brain may be affected by rTMS (as well as MRI) and cause pain or abnormal signal propagation. Therefore individuals that have these implants and devices or suspect that they may have pieces of metal in their eyes, head, or body (e.g. bullets, shrapnel, fragments from metallurgy) will be excluded from the study.

Adequacy of protection against risks

Recruitment and Informed Consent Identification of Subjects, Recruitment of Subjects and Informed Consent Process. Subjects for this study will be recruited through the community. At the initial contact, potential study participants will be given a detailed description of the study requirements and the informed consent form. This will describe the study requirements, risks, and benefits. Individuals will have the opportunity to meet with the study personnel privately to ask questions. Interested individuals will be contacted via telephone and scheduled for screening and Visit 1. 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 provides a layer of protection for the privacy of health information for individuals that engage in federally funded medical research (b) Security of Participant Information For individuals that are enrolled in the study (invited for a screening visit) there will be three documents that contain their first and last names: the informed consent, the HIPPA document, 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 patient ID number (starting sequentially from '100'). A folder will be created for each of these participants and labeled with their Patient ID number. The folder will contain the results of all of the testing for each individual. The patients will only be identified by number, not by name, on these documents. All information stored digitally for the enrolled participants will be labeled with the Patient ID number. As above all of the participant folders, along with the binders will be stored in a locked cabinet in Dr. Hanlon's data storage office at MUSC.

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

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.

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 either of 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 MUSC PI in all aspects of the study interventions. Personnel listed in this protocol (as well as any rotating medical students, graduate students, psychiatry residents or fellows that may be exposed to this investigation as part of their reseaerch training exposure) will be required to maintain their certification of HIPPA training and Protection of Human Participants in Research training on an annual basis. Any new personnel without experience in human clinical research will be encouraged to attend the MUSC Core Clinical Research Training Course, which is offered live and online throughout the year. Through these measures we will ensure that all study staff will be trained and will maintain ongoing understanding of research ethics and the rights of the participant during the consenting process and throughout an individual's participation in the study.

In the event of a medical emergency, a research participant will be transported to the Emergency Department at Medical University of South Carolina (MUSC hospital) which is within two blocks of the Brain Stimulation Laboratory in the Institute of Psychiatry. If a psychiatric crisis occurs, the Department of Psychiatry at MUSC will be contacted to arrange for either an emergency outpatient appointment or an in house psychiatric consult.

Potential benefits of proposed research

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

2. The risks to subjects are reasonable in relation to the anticipated benefits they will gain. Risks to subjects can be satisfactorily minimized to keep the risk to benefit ratio acceptably low. The potential to modulate addiction circuitry has profound scientific as well as health care cost implications.

19) Importance of the knowledge to be gained The proposed research is innovative in several ways. First, we are developing an alternative treatment strategy for nicotine dependence, which involves non-pharmacologic modulation of circuits responsible for the perception of craving. This is a significant conceptual advance for the field of addiction. The knowledge gained from these aims would hasten the pipeline through which TMS could be developed as a *neural circuit, evidence based* treatment option for physicians and providers of treatment for nicotine dependent individuals. Second, while most TMS investigations focus on the relative efficacy of stimulation at a single site (or a single functional network), by evaluating 2 Strategies in this proposal we will be uniquely positioned to advance the field. Through these Aims we will determine if the effects of TMS on nicotine craving are greater when the limbic reward circuit is dampened (Strategy 1, vmPFC) or the executive control circuit is amplified (Strategy 2, dlPFC). Third, we are using a novel stimulation profile, theta burst stimulation (supported by our preliminary data). This stimulation profile will reduce the total time of active stimulation relative to standard 10 Hz rTMS, thus reducing patient burden.

Frequency of DSMB reviews. Annually (every 12 months)

Content of DSM report Number of individuals consented, number of individuals enrolled, gender and race distribution of participants, discussion and listing of all amendments to the proposal, any publications of scientific presentations related to the proposal, review of any AE or SAEs, review of any new scientific literature related to the safety and efficacy of this protocol. 26) DSM Board Plan Meet every 12 months with the PIs (facilitated by videoconferencing) to discuss the information listed in "Content of DSM report". The content of this meeting will be formalized in a report which will be circulated by email and digitally approved by the PI and DSMB. It will be sent to the MUSC IRB, and to NIDA. The DSMB will be composed of individuals with content-specific expertise in brain stimulation and smoking treatment trials.

Statistical Analysis Plan.

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

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.

Behavioral Outcomes: For the treatment phase (10 days of real/sham TBS), the 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.

Statistical review of the study, will be conducted by a faculty member from the MUSC Provost-sponsored Biostatistical Collaborative Unit (including enrollment, retention, assessment inventories) annually. Data collected in previous studies by our research group have demonstrated that after extended use in the MRI scanner environment (likely more than 5000 pulses) the strength of the induced magnetic field from the Magstim biphasic coil begins to drop in a non-linear fashion. Consequently, the intensity of the induced magnetic field from the Magstim coil will be assessed by study personnel and logged weekly (alongside with use records from that week, number of pulses, intensity of pulses). This cumulative record of coil performance will be monitored and, when the intensity of the induced field had degraded 10%, we will switch to a new, identical Magventure coil. We do not anticipate this will occur within the 2-year period of this project.