Working Memory Training combined with Transcranial Magnetic Stimulation in Smokers.

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BUTLER HOSPITAL
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PROTOCOL

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1.) TITLE OF PROJECT: Working Memory Training combined with Transcranial Magnetic Stimulation in Smokers: 2x2 Factorial Study

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Other Investigator(s): Noah Philip, MD; Linda Carpenter, MD

2.) Description of Study

A. Specific Aims

The primary objective of the proposed study is to evaluate the potential for improved effects and examine mediating pathways of Working Memory Training (WMT) in combination with Repetitive Transcranial Magnetic Stimulation (rTMS) on a laboratory based smoking task and neuropsychological measures of Working Memory (WM) performance. These aims will be examined in a sample of tobacco dependent adults (N=130) utilizing a 2x2 factorial design including four groups (WMT+rTMS, sham WMT+rTMS, WMT+sham TMS, and sham WMT+sham rTMS) capable of isolating independent and combined effects of WMT and rTMS. The study will include a baseline assessments of neurocognitive, psychological, and smoking related variables, 10 WMT sessions over two weeks, followed by 10 days of WMT immediately preceding and following brain stimulation sessions (10 Hz rTMS, 2000 pulses per session, applied to left DLPFC). Neurocognitive and psychological mediators will be assessed between baseline and final laboratory assessment. Lastly, a follow-up assessment will occur one-month after the final laboratory visit. The proposed study will test the following Specific Aims:

Aim 1: To test the potential for improved effects of combining WMT with rTMS on smoking behaviors as compared to the independent effects of either condition alone. Hypothesis: Single active conditions (WMT+sham rTMS and sham WMT+rTMS) will result in significantly greater time to lapse on a smoking analogue task[1] (a lab based task that measures an individual's ability to resist smoking) as compared to the double sham condition (sham WMT+sham rTMS), and the WMT+rTMS condition will result in significantly greater time to lapse as compared to the single active conditions.

Aim 2: To test the potential for improved effects of combining WMT with rTMS on WM performance. Hypothesis: WMT + rTMS will result in significant increases in WM performance as compared to all other conditions, including the additive increases in conditions outlined in Aim 1.

Aim 3: To test mediating pathways of the effects of rTMS on smoking behaviors including changes in craving, mood, and WM performance. Hypothesis: The direct effect of rTMS on smoking outcomes will be mediated by gains in WM performance, and this effect will be largest in the WMT+rTMS condition.

B. Background

Smoking remains the leading cause of preventable death in the U.S.[2]. Current first line treatments leave approximately 70% of tobacco dependent individuals unsuccessful in their attempt to quit[3, 4]. Specifically, only 5-30% of those who initiate treatment, including intensive first-line interventions, are able to maintain abstinence for one or more years[4, 5]. The inability to quit despite motivation to do so is thought to result, in part, from self-control failure and can be understood within the framework of dual process models of addiction[6]. Dual process models view vulnerability to tobacco dependence as the relative balance between automatic impulses and control processes orchestrated through the interplay of

multiple executive functions[7, 8]. Working memory (WM) is an executive function associated with updating information to solve immediate problems, and achieve current goals[9]. WM is a key cognitive process underlying the regulatory control component of dual process models [6] and is involved in the initiation, maintenance, and relapse stages of tobacco dependence[10-16]. Most notably, deficits in WM performance and activation in associated brain regions predict time to relapse[13, 15] and strong WM has been shown to reduce the effect of craving on the ability to resist smoking[16]. Given this relationship, individuals with tobacco dependence are likely to benefit from interventions that strengthen WM. Recently, several studies have demonstrated that increasing WM capacity through WM training (WMT) is associated with positive outcomes in several populations with substance use or impulse control disorders. Specifically, studies have demonstrated that WMT is associated with decreased: delay discounting in substance users[17], weight re-gain after a weight loss program[18], and alcohol use in heavy drinkers[19].

A second emerging innovation in the treatment of addictions is repetitive Transcranial Magnetic Stimulation (rTMS), a procedure which sends magnetic pulses through the scalp to stimulate neuronal tissue[20] resulting in observed changes in neuronal plasticity[21] and striatal dopamine[22]. rTMS has now demonstrated positive effects in several substance use disorders including nicotine, alcohol, and stimulant dependence[23, 24]. This procedure has been shown to be effective in reducing smoking urges in abstinent as well as satiated smokers[25, 26] and to reduce cigarette consumption[25, 27]. While promising results for this treatment have been demonstrated, the size and durability of the therapeutic effect may be limited[25]. Additionally, the mechanism by which rTMS exerts positive effects on smoking outcomes is unknown. Recently it has been posited that changes in WM performance resulting from rTMS may be the key pathway to its observed effects on smoking related outcomes[28], and furthermore that WMT administered in close temporal precedence to rTMS may result in an additive or supra-additive effect in treating addictive processes[6]. However, these hypotheses have not been tested to date despite their importance for understanding and improving the clinical impact of these emerging therapeutic modalities for treating addictive behaviors. Interventions with the ability to effectively target self-control processes fill in a critical gap in currently available treatment options[6, 29].

C. Experimental Method

C1. Brief Description of Subjects

Smokers endorsing at least moderate dependence[30] (total score > 4), and endorsing no specific plan to quit smoking in the next 3 months, will be randomized to one of 4 groups detailed above. Participants will be recruited from the local community using flyers, newspaper advertisements, and online advertising, including Trialfacts recruiting services. Eligible participants must meet the following inclusion / exclusion conditions: (1) meet safety guidelines for application of rTMS (2) be 18-60 years of age, (3) have smoked cigarettes regularly for at least one year, (4) currently smoke at least 10 to 30 cigarettes per day, (5) have a carbon monoxide (CO) level >10 ppm, and (6) currently be using no other nicotine products. Subjects will be excluded if they: (1) meet criteria for current alcohol or substance dependence as assessed by the (MINI) International Neuropsychiatric Exam[31], (2) have a current affective disorder (depression, dysthymia, or mania) or psychotic symptoms, (3) are currently pregnant or lactating, or intend to become pregnant, (4) have a health condition for which rTMS is contraindicated.

C2. Study Design

Following the initial phone screen, eligible participants will be invited to participate in an eight-week study including a baseline visit, 20 WMT sessions, 10 rTMS stimulation sessions, mid-point and outcome assessments, and a 1-month follow-up assessment. Baseline assessment will include demographic measures and inclusion (including pregnancy testing), measures of smoking and other substance use characteristics, psychological/psychiatric measures, and neuropsychological and behavioral economic tasks. Following baseline assessment participants will be randomized to one of the four conditions detailed previously. Assignment to condition will be conducted using the Urn randomization procedure[32,

[33] to ensure balancing on baseline WM, nicotine dependence, and age. During the baseline assessment participants will be introduced to the WMT software, and instructed on how to access and utilize the software properly from remote locations. WMT/sham WMT will commence immediately following baseline assessment and will include 5 sessions per week for two weeks prior to rTMS/sham rTMS. Participants who do not complete 80% of WMT sessions during this period will be withdrawn from the study prior to initiation of rTMS and not followed further. In week three, participants will initiate rTMS resting motor threshold assessment (detailed below) and immediately begin stimulation sessions on 5 consecutive days each week for two weeks, resulting in 10 sessions in total. WMT or sham will be completed immediately prior to, and immediately after rTMS or sham, in line with experimental designs examining additive effects of motor learning in the motor cortex during rTMS stimulation[34]. Participants will complete measures of craving and mood prior to and after each rTMS session. Participants will also be asked to complete online smoking measures, a behavioral economic task, and an index of WM performance after the first week of rTMS stimulation (mid-point assessment). Participants will be withdrawn if they miss more than one session per week, and primary analyses will focus only those participants completing the rTMS protocol. Partial completers will be included in secondary data analyses, using data up to the point of being withdrawn. Studies utilizing a similar design reported successful completion of 10 sessions of rTMS for 48 out of 52 participants (92%) [24]. In calculating recruitment and sample size needs, we have conservatively assumed an attrition rate of 20%. Following the final rTMS stimulation visit, participants will be asked to return to the laboratory, within 4 days, and complete final outcome measures repeated from baseline. Lastly, four weeks following final assessment day, participants will be asked to complete online measures of mood, craving, cigarette and alcohol use, behavioral economic indices of reward and decision making, and WM performance online or if they do not have access to a computer, they will be able to access computers to complete the assessments at the CAAS study site.

Specific Procedures or Sessions

C.3.1 The Working Memory Training condition: This condition will include 20 sessions across 4 weeks (10 remote sessions prior to initiation of the rTMS stimulation, and 10 in lab sessions on rTMS stimulation days). Participants will be trained on how to remotely access the WMT training tasks during the initial baseline session, and provided with recommendations on when and where to complete the trainings. Remotely accessed WMT has been shown to be effective in previous studies[19]. Participants will be given the option to utilize computers in the laboratory at CAAS if they do not have access to personal computers. Participants will complete three distinct WM tasks in each session: a visuospatial WM task, a backward digit span task, and a letter span task[35] [19]. In the training condition, the difficulty level of all three WM tasks will be automatically adjusted on a trial-by-trial basis. Initially, each task will involve sequences of three items[19]. The length of the sequences will then be increased and decreased according to the participants' performance; highest performance in each session is recorded by the software. In the Sham WMT condition, the difficulty level of the WM tasks will not be adjusted; instead it will remain at the initial easy level throughout each task (i.e., three items in each sequence) [19]. All other aspects of the condition are identical to the true WMT condition. An identical protocol and software have demonstrated efficacy in increasing WM capacity, and this improvement in WM predicts reduction in addictive behavior[19].

C.3.2 The rTMS Condition: rTMS will be delivered with a Magstim Rapid2 system using Magstim Air Film Coils. rTMS pulses will be delivered at 10 Hz (100% resting motor threshold, RMT) in 40, 5 second trains, with 15 second inter-train interval, for a total of 2000 pulses per session, resulting in a total stimulation protocol time of approximately 13 minutes. Active or sham rTMS will be applied over the left DLPFC; corresponding with the standard "F3" location on scalp (F3=left frontal lobe, location #3 for electrode placement using international 10-20 system for scalp measurements). Five consecutive daily sessions will occur on consecutive weeks, for a total of 10 sessions. RMT, defined as the amount of energy required to induce a visible twitch in contralateral hand in at least 50% of stimulations, will be assessed on first day

of application. Sham rTMS will be identical to active treatment, with the exception that mu-metal plates attached to the sham coil block the magnetic field while providing a sensation of stimulation.

Assessments and cognitive tasks include:

C.4 MEASUREMENTS

Assessment measures include 5 domains: (1) baseline demographics; (2) measures of smoking and (3) alcohol; (4) psychological / psychiatric measures; and (5) neuropsychological and behavioral economic tasks. In total, all baseline survey and behavioral measures take approximately 1.5 hours to complete.

C.4.1 Screening and Demographic Measures: will include smoking data related to inclusion criteria, demographics, psychiatric evaluation via the MINI International Neuropsychiatric Exam[31], and safety for rTMS.

C.4.2 Smoking Measures: will include Smoking History/Dependence Questionnaire: Smoking history and life smoking patterns will be assessed as recommended by the National Cancer Institute consensus panel. The Fagerström Test for Cigarette Dependence will be used as a continuous measure of nicotine dependence[36]. The Nicotine Withdrawal Symptoms Scale will be used to assess acute withdrawal from nicotine[37]. The Brief Questionnaire of Smoking Urges will be utilized to measure smoking urges, and also assess urge to drink water, eat candy, and drink caffeine to allow for specificity in measurement[38]. The Importance and Confidence to Quit Scale will be administered to assess participants' perceived importance and confidence for reducing or quitting smoking[39]. Carbon monoxide levels will be assessed using a Bedfont Scientific Smokelyzer®. The Cigarette Purchase Task[40, 41], will be used to assess behavioral economic cigarette demand. The Delay to Smoking Analogue Task[1, 42] is a 50-minute behavioral choice paradigm in which participants earn monetary rewards for delaying initiation of cigarette smoking in 5-minute increments, following a 3-hour smoking deprivation period. Craving for smoking is assessed during the task. This task was chosen for its ability to provide an excellent analogue to smoking relapse in real world settings[43], and demonstrated sensitivity to effects of manipulation and intervention including stress, alcohol use, and medications[42-45].[42-45].

C.4.3 Alcohol Measures: will include The Timeline Follow-back Interview will be used to assess alcohol use over the prior 60 days[46]. Short Inventory of Problems (SIP) will be used to assess the extent to which subjects have experienced problems related to their alcohol use over the past 3 months[47].

C.4.4 Psychological Measures: will include The UPPS-P Impulsive Behavior Scale: a self-report that assesses five subscales that are used to measure distinct dimensions of impulsive behavior[48]. The Positive and Negative Affect Scale will be administered to measure changes in affect[49]. Symptoms of depression, anhedonia, and anxiety will be assessed using the Center for Epidemiologic Studies –Depression Scale[50], SHAPS Anhedonia scale[51], Beck Anxiety Inventory[52], Inventory of Depressive Symptomatology (IDS-SR), and Generalized Anxiety Disorder 7 assessment (GAD-7), respectively.

C.4.5 Neuropsychological and Behavioral Economic Measures: WM Capacity will be measured using the same tasks that are used during WMT. However, the assessment versions of the three tasks will end when participants are unable to reproduce a sequence on two consecutive trials. Additionally, WM capacity will be measured in terms of accuracy, reaction time, and number of errors, using the National Institute of Health Examiner computerized N-back task[53]. The n-back is a well-established index of WM[54]; this paradigm focuses on flexible updating capabilities; the NIH Examiner assessment includes a spatial 1-back and 2-back task requiring maintenance and updating. The Experiential Discounting Task (Delay Discounting) is a behavioral economic measure for assessing state in subjective value of rewards as a function of delay, with greater discounting of value indicative of decreased executive control processes[55]. Lastly, data on participant perception of assigned condition will be collected at final assessment to assess effectiveness of sham.

C**5. Data Analysis**

In order to test Aim 1 and 2 regarding the effects of condition on main outcomes, multiple regression will be utilized to examine the effects of dummy coded condition (WMT + rTMS, sham WMT + rTMS, WMT + sham rTMS, sham WMT + sham rTMS) on outcome measures of smoking as measured by the smoking analogue task and WM performance as measured by the N-back task, controlling for baseline measures of these variables. Secondary analysis will be conducted to examine the durability of effects of condition on WM performance at one month follow up and whether sex moderates the effects of condition at final assessment and follow-up; however, no specific hypotheses are made given the lack of data in the extant literature. In order to test Aim 3, regarding the indirect effects of condition on primary outcomes through WM and craving, mediation analysis with bootstrapping and replacement (Preacher & Hayes, 2008) will be utilized. Bias-corrected bootstrapping with 1000 bootstrap samples will be used for its ability to maximize the power to detect mediation [56-58]. This modeling technique estimates simultaneous regression analyses and generates confidence intervals that correct for bias in estimating the indirect effects. An indirect effect is determined to be statistically significant if the confidence interval does not contain zero.

D. Material Inducements

Participants will be paid up to $540 in total for participating in this study utilizing Clincard© payment technology (confidential debit cards that are loaded with funds electronically after each session) or a similar confidential debit card, or cash. Specifically, participants will be paid $50 for completing the baseline appointment in the lab, $4-8 for each of the 10 online cognitive training sessions, $23-31 for each of the 10 rTMS sessions at Butler, $10 for completing the online midpoint assessment, $70 for the outcome assessment session, and $20 for the final online assessment session.

E. Training of Research Personnel

The Principal Investigator (William Lechner) will work with the co-investigator (Dr. Linda Carpenter) who is Butler Hospital TMS Service Chief. Together they will ensure all research study staff have been trained and are competent in the safe use of the rTMS device for this trial as well as proper administration of the working memory training protocol and all assessments. All research staff are adequately trained for various roles delegated in the conduct of this study (e.g., clinical interviews, diagnosis and symptom assessment, data collection, and communication of clinical information with other care providers).

3) Human Subjects

A. Human Subjects Involvement, Characteristics, and Design: Participants for the proposed study will be 130 adults, aged 18-60, who are currently nicotine dependent and physically eligible to undergo rTMS procedures. Participants will be recruited from the Providence, RI community using flyers, newspaper advertisements, and other advertising methods including online advertisements and social media. Participants will be screened over the phone, or via online survey for major exclusion criteria and eligible participants will then be invited to the lab for a screening and baseline assessment visit. Following instruction from staff, participants will engage in ten remote working memory training sessions for a two-week period, following by 10 sessions of combined working memory and rTMS application over the subsequent two weeks. Participants will then engage in a final outcome session in the laboratory and a follow up session completed online 4 weeks after final outcome.

Inclusion Criteria: Eligible participants must meet the following inclusion / exclusion conditions: (1) to ensure subjects can safely receive rTMS, eligible subjects must meet all established screening criteria for safety during MRI (magnetic resonance imaging), since MRI involves magnetic fields at similar intensity to those emitted from the rTMS stimulation coil. These are conservative measures that require a patient not have following (unless MRI-safe): Cardiac pacemaker; Implanted device (deep brain stimulation) or metal in the brain, cervical spinal cord, or upper thoracic spinal cord (2) be 18-60 years of age, (3) have smoked cigarettes regularly for at least one year, (4) currently smoke at least 10 to 30 cigarettes a day (5) have a carbon monoxide (CO) level >10 ppm at the initial assessment (6) Currently be using no other tobacco products or nicotine replacement therapy.

Exclusion Criteria: Subjects will be excluded if they: (1) meet criteria for current alcohol or substance dependence as assessed by the MINI (2) have a current affective disorder (depression, dysthymia, or mania) or have psychotic symptoms as assessed by the MINI (3) are currently pregnant or lactating, or intend to become pregnant (4) have a health condition or are taking a medication for which Transcranial Magnetic Stimulation is contraindicated including a lifetime history of loss of consciousness due to head injury for greater than 10 minutes, or any lifetime history of loss of consciousness due to a head injury with documented evidence of brain injury (including brain atrophy).

B. Recruitment and Consent Procedures

Participants will be recruited from the local community using flyers, newspaper advertisements, and other advertising methods including Trialfacts recruitment services, which utilizes online advertising and social media advertising to recruit participants. At the start of the baseline session, research staff will review the consent form with potential participants. The purpose and procedures of the study will be fully explained both orally and in writing. The consent form assures participants that they can discontinue their participation at any time without any adverse consequences, that all of the information they provide will remain confidential. Furthermore, they will be informed that the signed consent form will be filed separately from all assessment information and that their data will be marked with a code number and not their name.

C. Potential Risks

Overall, the risks of this study are considered minimal, and include (1) known risks associated with rTMS outlined below (2) possible emotional discomfort from answering sensitive questionnaire items and (3) breaches of confidentiality.

(1) Risk of side effects from rTMS sessions: During sessions, patients may experience a sensation of tapping or painful sensations around the place where the stimulation coil is positioned on the head. Most patients who have had rTMS or TMS therapy usually report these sensations to be mild and find they diminish over time as their body adjusts to the daily stimulation procedure. Other possible side effects associated with rTMS delivered to this standard target on the head are scalp, jaw, face, or neck discomfort or muscle twitching in those area, toothache, and headache. Some stimulation coil adjustments may be possible to make the experience more comfortable. Over-the-counter pain medications such as Tylenol (acetaminophen) or Motrin (ibuprofen) have proven helpful for reducing discomfort from rTMS stimulation. When rTMS has been delivered to areas of the brain outside of the target location where the coil is placed in this study, there have been reports of transient dizziness, fainting, and brief changes in attention and thinking. These are considered extremely rare and highly unlikely to occur in subjects who receive this level of stimulation to the left prefrontal cortex as planned in this study. Assessment of the subjects' well- being and functioning before and after each session, special positioning and targeting procedures to ensure the coil is placed over the target brain region and constant monitoring during each session, will all be done to minimize the risk of experiencing these side effects.

Because the device can emit a loud clicking noise during sessions, all subjects will wear protective earplugs or occlusive earbuds during their sessions. Studies done with rTMS therapy delivered by the TMS device has shown that standard applications of the type delivered in this study are not associated with permanent loss of hearing or changes in ability to hear.

Risk of Seizure: It is estimated that in ordinary clinical use, standard rTMS sessions (delivered in the same general location of the brain and with the same strength that will be used in this study) have caused a seizure in approximately 0.1% of patients, representing a risk of seizure in approximately 1 in 30,000 sessions. The rTMS sessions in this study will be given by doctors and staff who have

extensive experience with safe delivery of rTMS and who are trained in steps to prevent and manage seizures. Medical personnel and equipment are available to monitor subjects and apply first-aid procedures if a seizure occurs at Butler Hospital. Most seizures last only a few minutes and spontaneously end, with the patient in a somewhat confused state that resolves over several hours. Management of a seizure during an rTMS application may involve transferring patients to a local emergency room or to another facility for further evaluation, if that is determined to be necessary by the study doctor. Having a seizure may lead to a potential effect on a person's future employability and ability to drive. Should a subject experience a seizure that is related to rTMS application in this research, a study physician will provide him or her with a letter stating that the seizure was produced under specific brain stimulation conditions in this study, and that there is no reason to expect another seizure would occur when not receiving rTMS applications. In case of injury we offer the care needed to treat any injury that results directly from taking part in this research study. We reserve the right to bill insurance company or third parties, if appropriate, for the care related to the injury. We will try to have these costs paid for, but the participant may be responsible for some costs related to injuries incurred during the study.

Risk of Inconvenience and Burden of Required Time/Travel: Subjects may engage in screening procedures and learn they are not eligible for participation in the research session trial. Frequent visits to the research clinic for the rTMS sessions (3 consecutive days) may represent a considerable inconvenience, especially if a subject travels a great distance or has other constraints on their time or transportation. A small payment will be offered to cover part of the subject's expenses related to participation in this research study, but subjects will not be offered reimbursement for all of the expenses they may incur.

(2) Some questionnaire items used may be considered sensitive to some participants (disclosing information about their drinking habits), and as such, may result in distress. However, care has been taken to minimize these risks by making these procedures explicit during the informed consent process, by noting their use in the instructions on specific tasks, and by reminding participants of their right to withdraw from the study at any time. These risks are thought to be minimal.

(3) Breach of confidentiality (judged highly unlikely). The risks of a breach of confidentiality will be addressed by emphasizing that information obtained during assessments is confidential and will be used solely for research. All participant data collection related to surveys and psychological measures will be collected via online assessment surveys (Qualtrics secure data collection program). Additionally, data collected for the working memory training task will be collected through a secured server with no identifying information stored on the server. In addition, all records will be kept in locked or password-protected files, and stored in either locked offices and/or secure servers maintained by Brown University (121 South Main St., Providence, RI) or the Neuromodulation Laboratory at Butler Hospital (345 Blackstone Blvd., Providence, RI). These records will be accessed only by essential study staff who are trained in human subject's protection guidelines; clinical information regarding administration of rTMS will be documented in the Butler Hospital Medical Record according to institutional policy. In addition, all questionnaire data will contain only numeric codes, with identifying information and link codes kept in a separate, password-protected database. All assessment procedures will be closely supervised, and study staff will be trained and reminded of the need to keep all information confidential. No names will be used in presenting data in lectures, seminars, and papers. In order to protect participants confidentiality related to email communication all email links containing any PHI will be sent through CNE secure portal and participants will be asked to sign the consent for email communication in a research project form (in appendix) prior to any email communication. Basic study info (not containing any PHI) will be communicated through the study email account (brownworkingmemory@gmail.com). This email address will be named in the email consent, which participants may opt out of.

E. **Protection of the Subject** *(include: D.1. measures to minimize potential risks; D.2 measures to ensure confidentiality; D.3. data safety monitoring plan)*

B. Protections against risks: Comfort and Safety during TMS procedures: An appropriately trained staff member will administer each session and be present throughout application sessions to observe the participants under the direct supervision of a TMS-credentialed physician at Butler Hospital. Serial assessment of side effects at each TMS session will be used to identify and address any application-emergent adverse effects. Topical anesthetic cream and use of over the counter nonsteroidal analgesics (acetaminophen, ibuprofen, etc.) may be recommended for those who experience significant scalp pain. Risk of seizure and other serious adverse events related to stimulation will be mitigated by careful screening of past health history, identification of underlying risk factors, and application of the study inclusion/ exclusion criteria. The TMS safety screening process, which includes screening for presence of implanted ferromagnetic metal in potential TMS patients, will be documented per Butler Hospital policy and approved procedures for TMS Therapy. Patients will be provided with ear protection (earplugs or earbuds) during sessions to reduce risk of discomfort or harm from loud clicking sounds emitted from the device during stimulation.

All information obtained during the online assessment and laboratory sessions is confidential and will be used solely for research purposes. All digital records will be collected via Qualtrics survey software and FileMaker Server. The FileMaker Server will be hosted on Brown's secure server and will be password-protected to ensure that only essential research staff will have access Qualtrics survey data will be downloaded weekly, and entered into a password protected data file that will be stored on the Brown University servers (121 South Main St., Providence, RI); clinical information regarding administration of rTMS will be documented in the Butler Hospital Medical Record according to institutional policy. Study items and participant contact information will be collected in separate surveys. In a separate database (which is itself password-protected), participants' identifying and contact information will be stored and linked to a unique study code, which will be used to connect this information to their study data during the duration of the study. After all study procedures are complete, the database containing all participant identifying information, as well as their unique study codes, will be destroyed, resulting in a de-identified final dataset.

Informed consent documents will be kept in a locked file that is available only to essential research personnel who have been trained in human subject's protection guidelines. Any study measures that are collected on paper will contain only participants' unique study ID numbers, and no identifying information, and will be kept in a separate, secure location. All research staff will be trained and reminded of the need to keep all information confidential. There are certain limitations to confidentiality relevant to the current study; confidentiality may have to be broken if imminent risk of suicide or homicide is discovered (i.e. imminent risk to self or others), or if legal authorities subpoena information or testimony from the investigators. In order to protect participants confidentiality related to email communication all email links containing any PHI will be sent through CNE secure portal and participants will be asked to sign the consent for email communication in a research project form (in appendix) prior to any email communication. Basic study info (not containing any PHI) will be communicated through the study email account (brownworkingmemory@gmail.com). This email address will be named in the email consent, which participants may opt out of.

Data Safety and Monitoring Plan

Entities Conducting Monitoring:

The Institutional Review Board (IRB) at Butler Hospital will review this protocol and all procedures and will provide oversight. Monitoring will be done by the contact Multiple Principal Investigator, Dr. William Lechner, the Butler Hospital IRB, and an independent data and safety monitoring board (DSMB). Drs. Kahler, Philip, and Carpenter (Co-I's) will also participate in the administration of the monitoring plan.

What is Monitored?

Monitoring is done of all procedures to ensure that they conform to the approved protocol; of unforeseen circumstances that might arise and affect safety; of all reports of serious adverse events as defined in 38 CFR 46 and the FDA 312.32 (death, life-threatening experience, new or prolonged hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defect); of other significant adverse events (adverse events that lead to drop out by participant or termination by the investigator); of unexpected adverse events (i.e., an adverse drug experience that has not been previously observed) resulting from the study; and of expected adverse events.

Monitoring is done of all study inclusion and exclusion criteria, specifically ensuring that female subjects who are pregnant, nursing, or not using effective methods of birth control will be excluded from participation. Subjects who test positive for pregnancy will be informed that they have had a positive test result and are not eligible to participate in the study. They will be informed that it is possible to have a false positive and will be given information encouraging them to follow up with a medical provider of their choosing.

During this clinical trial, we will notify officials, as mandated by law, if a participant reports intention to harm him/herself or others, or reports child abuse or abuse of an elder. In the event a participant was to report a need or interest in treatment for alcohol/substance dependence, psychiatric disorder, or distress, an appropriate referral to resources will be provided based on an extensive list of referral resources maintained by the study.

All side effects of mild or greater severity will be reported to the study physician, a licensed physician employed by Butler Hospital who will be ultimately responsible for decisions to stop the application of transcranial magnetic stimulation and who will be available on call (this is an included service in the Butler Hospital Neuromodulation Facility contract). Participants will be encouraged as a first step to use over-the-counter medications to treat mild symptoms such as headache (acetaminophen). Assessment of the subjects' well- being and functioning before and after each session, special positioning and targeting procedures to ensure the coil is placed over the target brain region and constant monitoring during each session, will all be done to minimize the risk of experiencing mild side effects. It is estimated that in ordinary clinical use, standard rTMS sessions (delivered in the same general location of the brain and with the same strength that will be used in this study) have caused a seizure in approximately 0.1% of patients, representing a risk of seizure in approximately 1 in 30,000 sessions. The rTMS sessions in this study will be given by doctors and staff who have extensive experience with safe delivery of rTMS and who are trained in steps to prevent and manage seizures. Medical personnel and equipment are available to monitor subjects and apply first-aid procedures if a seizure occurs at Butler Hospital. Most seizures last only a few minutes and spontaneously end, with the patient in a somewhat confused state that resolves over several hours. Management of a seizure during an rTMS application may involve transferring patients to a local emergency room or to another facility for further evaluation, if that is determined to be necessary by the study doctor. Having a seizure may lead to a potential effect on a person's future employability and ability to drive. Should a subject experience a seizure that is related to rTMS application in this research, a study physician will provide him or her with a letter stating that the seizure was produced under specific brain stimulation conditions in this study, and that there is no reason to

expect another seizure would occur when not receiving rTMS applications. In case of injury we offer the care needed to treat any injury that results directly from taking part in this research study. We reserve the right to bill insurance company or third parties, if appropriate, for the care related to the injury. We will try to have these costs paid for, but the participant may be responsible for some costs related to injuries incurred during the study. Participants will be given a telephone number for calling the physician, and physician office hours will be available as needed. The physician will be responsible for determining whether transcranial magnetic stimulation should be discontinued and will inform the PI of this decision. Those discontinued from medication will continue to participate in the trial and in the follow-up assessments.

Frequency of Monitoring:

All adverse events will be continuously monitored by the PI. Participants will be given contact information so that they can inform us of events that occur in between study visits. Dr. Lechner will conduct daily oversight of participant safety. He will meet weekly with staff to review participant progress and their experiences with the experimental procedures, including adverse events. Any adverse events that are observed and/or reported will be immediately reported to Dr. Lechner. The IRB conducts the monitoring at the continuing reviews as scheduled, whenever modification requests are considered, and upon receiving reports of serious adverse events from the PI or anyone else. NIDA monitors the study upon receipt of annual progress reports and whenever other information is received.

The DSMB will review progress of the trial every six months after enrollment of the first participant until the completion of the study. Additional meetings will be convened quickly if problems arise that require addressing between reviews.

Reporting Plan:

Any serious adverse events that are observed and/or reported will be immediately reported to Dr. Lechner. Serious adverse events are then reported to the Butler Hospital IRB and the NIH. All serious adverse events related to this study will be reported to the Butler Hospital IRB immediately by telephone and by written report within 48 hours of our receipt of information regarding the event. All other adverse events related to the study will be reported at the continuing review. Serious adverse events will also be reported in writing to the NIDA Project Officer and to the DSMB within 48 hours. All serious adverse events **and adverse events** related to the study will be reported annually in the Progress Report sent to the NIDA Project Officer.

Any actions taken by the IRB or DSMB, other than acceptance of the adverse event report, will be reported to NIDA along with any changes or amendments to the protocol requested by the IRB or DSMB in response to these reports. Proposed changes or amendments to the protocol in general must be requested first in writing to the IRB, which will then grant or deny permission to make the requested change or amendment in protocol. NIDA will subsequently be informed of any substantive changes or amendments in approved protocol.

(a) Procedures to ensure the validity and integrity of the data. Several procedures currently in practice in our laboratory will also be utilized for this study to guarantee the validity, integrity, accuracy, and completeness of the data. It will be made clear to all participants that all information obtained during assessments is confidential.

(b) Procedures to guarantee the accuracy and completeness of the data during data collection, transmission, and analysis. First, the Research Assistant will review each file within 2 days of data collection for completeness, accuracy, and validity of responses. All scanned data will be verified by the Research Assistant using a computerized verification program. Data files are accessible only to project

personnel and are password protected. The Research Assistant will review the distributions of all raw data to ensure that data are within range and to check missing data with the hard copy of the data. Finally, the project database (including uploaded data files from the laptop computer and scanner machine) is also password protected and accessible only to the project's Senior Programmer/Analyst and PI.

Members: The DSMB includes behavioral scientists with expertise in addictions who are not involved in the project.

Board Chair: Jen Tidey, Ph.D.

Other Members: Peter Monti, Ph.D., Damaris Rohsenow, Ph.D., Suzanne Colby, Ph.D.

Conflict of interest. DSMB members will be asked to disclose any conflicts of interest prior to DSMB meetings. No DSMB members will have any role on the study.

Meeting format. The meetings may include both open and closed sessions. In the open sessions, the PI presents and discusses information with the DSMB on study progress and adverse events. In closed sessions, the DSMB chairperson leads the meeting with the board members and without participation of the PI or study investigators to discuss any concerns with the progress of the study or with risks to participants. The need for closed meetings are at the discretion of the DSMB chair.

What is monitored. The DSMB will evaluate the progress of the trial, recruitment rates, retention rates, adverse events, unanticipated problems, and other factors affecting safety or outcomes. The DSMB will review rates of adverse events in the study (in an unblinded manner if they wish) to evaluate any changes in participant risk. The DSMB also will review major proposed modifications to the study prior to their implementation. Once 50% of our desired sample size has completed the on month follow-up, interim outcome analyses will be run and presented to the DSMB. Differences in adverse events between the active and sham transcranial magnetic stimulation conditions will be compared to determine whether there are significant risks to participation that warrant altering the protocol or stopping the study.

Confidentiality. The DSMB will not have access to personally identifiable information of participants. DSMB members agree not to disclose the results of the data except as agreed by the PI. The report to the DSMB includes actual vs. projected recruitment rates (number screened, consents, randomized, etc.), summary of serious adverse events and any modifications to the protocol. After interim efficacy analyses are conducted, these will also be included in the reports.

Frequency of meetings. The DSMB will review progress of the trial every six months after enrollment of the first participant until the completion of the study. Additional meetings will be convened quickly if problems arise that require addressing between reviews.

Communication plan. At the end of each DSMB meeting, the chair will provide the study leadership with written information concerning findings for the trial as a whole related to problems or adverse events observed and any relevant recommendations related to continuing, changing, or terminating the study. The chair will prepare a summary of the meeting along with any recommendations for changes to the protocol based on the meeting. The draft report will be reviewed and edited by all Board members prior to issuing the final report. The PI will send the report to the IRB and to NIDA.

E. Potential Benefits

Participants will be told that they should expect no personal benefit from participating in the study. Participants will be involved in research that has potential to inform interventions for smoking and benefit the scientific community.

F. Risk-Benefit Ratio

The risk-benefit ratio of this study is favorable. Risks of adverse events associated with the use of the rTMS device and other study procedures are minimal. Patients will be under the care and supervision of experienced research psychiatrists and will be seen by research staff for session assessment.

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5) CRITERIA FOR WAIVER OF AUTHORIZATION FOR USE OF PROTECTED HEALTH INFORMATION (PHI)

5A. Does the requested use of PHI involve more than minimal risk to privacy?

☐ **YES** ***[if " YES," project is not eligible for PHI Waiver]***

☒ **NO** ***[if "NO," address 1-3 below]***

Plan to Protect Patient Identifiers from Improper Use and Disclosure:

PHI collected from callers during preliminary phone screening will be kept in protected research records that are accessible only by research staff directly involved in conducting this research study.

Plan to Destroy Identifiers or Justification for Retaining Identifiers:

PHI collected from subjects who do not go on to sign consent for study participation will be kept in de-identified manner or destroyed.

Assurances that the PHI will not be Re-used or Disclosed:

PHI collected solely for screening and prior to informed consent will not become part of the hospital medical record or be available for re-use of disclosure.

5B. Could the research be practicably conducted without a waiver?

☐ **YES** ☒ **NO**

5C. Could the research be practicably conducted without access to and use of the PHI?

☐ **YES** ☒ **NO**

5D. PHI is only needed for activities preparatory to research

☐ **YES** ☒ **NO**

6) DESCRIPTION OF PHI TO BE COLLECTED UNDER WAIVER

Demographics (Name, age, address), clinical characteristics, medical health/ history

7) ADVERTISEMENTS

See attached.

8) INFORMED CONSENT FORM (ICF)

See attached.

BUTLER HOSPITAL CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

Working Memory Training combined with Transcranial Magnetic Stimulation in Smokers: 2x2 Factorial.

Sponsorship

This study is being paid for by an external grant from The National Institute on Drug Abuse.

Research Project Summary

You are being invited to participate in a study designed to investigate how people respond to a cognitive training exercise in addition to repetitive transcranial magnetic stimulation (abbreviated "TMS" or "rTMS") in terms of their smoking behaviors. The cognitive training exercise is a computerized task which will exercise your thinking and memory skills. TMS is a non-invasive therapy that has been studied for over a decade. It uses magnetic coils to deliver pulses of magnetic energy through the scalp to stimulate nerve cells in the brain (called neurons). TMS has been used in several studies examining its effects on cigarette smoking behavior and now we will examine the effects of TMS when it is delivered together with cognitive training, to see if there is any additional effect on the dependent variables of interest.

You have been invited to participate because you indicated that you smoke between 10 and 30 cigarettes a day and have been a smoker for at least one year. Your participation in the study will last approximately 2 months during which time you will complete online training sessions, and 12 sessions in our offices. It will require approximately 5 hours per week of your time. In order to decide whether or not you wish to be a part of this research study, you should know enough about its risks and benefits to make an informed judgment. This consent form gives you detailed information about the research study which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, risks associated with the procedures, possible benefits of participation and possible alternatives. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form. This consent may contain words that you do not understand. Please ask the investigator or the study staff to explain any words or information that you do not clearly understand.

Description of Procedures

If you decide to participate you will complete the following sessions:

- **Screening and Baseline Session (approximately 1.5 hours):**

You will be asked to complete several brief questionnaires about your nicotine, alcohol, and other drug use as well as your mood and symptoms of psychological disorders (such as depression). You will be asked to breathe into a tube that will measure the amount of alcohol and carbon monoxide on your breath. If you have any alcohol on your breath for today's session, we will need to re-schedule your appointment. You will be asked to complete a computerized task that will measure your thinking performance including your memory, and you will complete two other computerized tasks assessing (1) how much money you would spend in different situations, and (2) how much you would spend on a cigarette in different situations. If all inclusion / exclusion criteria is confirmed, you will be eligible to participate in the rest of the study.

- **Online Training Sessions (approximately 15 minutes each):**

You will log in to our training program at home on your computer, or if you don't have access to a computer with internet, in the lab at Brown. We will ask you to complete 5 cognitive training sessions each week (you can choose which 5 days out of 7 you complete the online training), over the course of two weeks, lasting about 15 minutes each. During these tasks your thinking capacity and memory will be exercised to various degrees.

- **<u>Laboratory Sessions at Butler Hospital</u> (approximately 1.5 hours each):**

You will be asked to fill out a few brief questionnaires about your smoking and your mood, perform another thinking and memory exercise, and receive a 30-minute session of transcranial magnetic stimulation, which may include active or sham (no active stimulation). During the first session we will measure your "motor threshold" which is the minimum amount of energy from a single coil that will produce a slight movement in your hand half of the time. You will hear a clicking sound and feel a tapping sensation on your scalp during this procedure. Once you are seated comfortably in the TMS chair, you will be given ear plugs to wear since the TMS machine makes loud clicking noises. The TMS application coils will be placed on your scalp, over your hair, on the left side of your head just above your forehead. We will take a few measurements of your head to make sure we place the coil in the correct location. You will remain awake and alert throughout the session and a research staff member will be present with you in the room. You will receive 25 short series of stimulation, that last 8 seconds each; the stimulator will send 10 pulses per second during these series. You will hear a clicking noise and you might feel a tapping sensation on your scalp where the coil is placed. These sessions may include active TMS stimulation in which magnetic pulses are transmitted through your scalp to stimulate neuronal tissue, or a sham procedure in which all study procedures are identical with the exception that no magnetic pulses will be transmitted through you scalp. All study staff and procedures are over seen by a doctor who is trained specifically in TMS and TMS safety, to make sure that you are safe at all times. It is possible that you might experience mild discomfort at the place on your scalp where a coil is place. If it is too uncomfortable, you can ask the staff to pause or stop during application at any time. Over-the-counter pain medications such as Tylenol (acetaminophen) or Motrin (ibuprofen) have proven helpful for reducing discomfort from rTMS applications. The application sessions will last about 20-30 minutes. At the end, you will fill out a few more brief questionnaires and complete another thinking and memory exercise. You will be asked to come in for 5 sessions on consecutive days, for the course of two weeks (10 sessions in total). It is important that you come in for all ten sessions in a row.

- **<u>Final Outcome Assessment Session</u> (approximately 4 hours):**

This will be scheduled once you have completed the week of computerized cognitive training, and the week of 3 TMS sessions. During this session we will ask you to complete more smoking, alcohol, and mood questionnaires, a thinking and memory performance task, and to take part in a task that will measure how long you can resist smoking. As part of this task, there will be a time when you can choose to smoke your own cigarettes. Therefore, it is important that you bring a pack of your own cigarettes on this day. During this time, you will have an opportunity to earn money (up to $10) for delaying smoking for up to 50 minutes.

- **<u>Online Survey Sessions</u> (approximately 20 minutes):**

This will be administered twenty-one days after you complete the initial working memory training session, and one month after the final laboratory-based outcome assessment. These surveys will be sent in an email with a link to an online survey. These surveys can be completed on your own using any computer to connect to the internet or at the research office if you prefer. We will protect your confidentiality by using a secure CNE Portal to email you all information related to this session; we will also ask you to sign a separate email consent in addition to this consent. If you choose to not use email you can complete these forms at our Brown offices (121 South Main St., Providence, RI). The surveys should take about 15-20 minutes to complete.

<u>Risks and Inconveniences</u>

The questionnaires used in this study have been used in other similar research studies. Some of the questions may be of an embarrassing or sensitive nature and may make you uncomfortable. Therefore, you are free not to answer any questions you do not wish to answer. Additionally, rTMS is associated with some risks outlined below:

- **Risk of Side Effects from TMS Sessions:**

During sessions, you may experience a sensation of tapping or painful sensations around the place where the application coil is positioned on your head. Most patients who have had TMS therapy usually report these sensations to be mild and find they diminish over time as their body adjusts to the daily stimulation procedure. Other possible side effects associated with TMS applied to this area of the head are scalp, jaw, face, or neck discomfort or muscle twitching in those areas, or toothache, or headache. Over the counter pain medications such as Tylenol (acetaminophen) may be helpful for reducing discomfort from TMS. When TMS has been delivered to other parts of the brain, there have been reports of temporary dizziness, fainting, and brief changes in attention and thinking. These are considered extremely rare and highly unlikely to occur with the type of TMS protocol being used in the current study. Assessment of your well-being will occur before and after each session to ensure your safety and minimize your risk of experiencing these side effects.

- **Risk of Seizure:**

It is estimated that in ordinary clinical use, standard TMS applications (delivered in the same general location of the brain and with the approximate strength that will be used in this study) have caused a seizure in approximately .1% of patients, representing a risk of seizure in approximately 1 in 30,000 applications. The TMS applications in this study will be given by doctors and staff who have extensive experience with the safe delivery of TMS and who are trained in steps to prevent and manage seizures. Medical personnel and equipment are available to monitor subjects and apply first-aid procedures if a seizure occurs at Butler Hospital. Most seizures last only a few minutes and spontaneously end, with the patient in a somewhat confused state that resolves over several hours. Management of a seizure during a TMS session may involve transferring patients to a local emergency room or to another facility for further evaluation, if that is determined to be necessary by the study doctor. Having a seizure may lead to a potential effect on a person's future employability and ability to drive. Should you experience a seizure that is related to TMS application in this research, a doctor will provide you with a letter stating that the seizure was produced under specific brain stimulation condition in this study, and that there is no reason to expect another seizure would occur when you are not receiving TMS application.

- **Risk of Inconvenience and Burden for Time / Travel:**

You may engage in screening procedures and then learn you are not eligible for participation in the research trial. Emotional discomfort may be associated with completing the assessments and questionnaires. Frequent visits to Butler Hospital for 5 days in a row may represent an inconvenience, especially if you travel a great distance or have other constraints on your time or transportation. A small payment will be offered to cover part of your expenses related to participation in this research study, but you will not be offered reimbursement for all of the expenses you may incur.

There may be other risks that are currently unknown. Although TMS has been used for many years, the long-term effect of TMS on individuals are not completely known. If you have any medical issues you should first contact your primary care physician, psychiatrist, or another mental health professional. A TMS-trained physician will oversee all TMS research sessions and is available immediately for urgent medical issues. You will be given information about how to contact the TMS medical staff outside of regular work hours.

Benefits

We cannot and do not guarantee or promise that you will receive any benefits from this study. We are testing for changes in your thinking (working memory ability) after the computer tasks and rTMS, which might relate to improvement in smoking. Additionally, you will have a chance to contribute to a scientific study that may help people in the future.

Any medical treatment or procedure may have unforeseen side effects. You should know that the prediction of effects from a treatment or procedure for any individual cannot be done with certainty, and unexpected potentially harmful effects occasionally occur with the administration of any type of treatment. If you have questions about investigational procedures or treatments, or if you experience any disturbing side effects during participation in the study, inform study personnel. In the event of any unexpected, potentially harmful effects of any treatment or procedure administered in this study, we will monitor your condition closely and institute appropriate treatment. If significant new knowledge is obtained through the course of the research which may impact your willingness to continue participation, you will be informed of this knowledge.

Women Please Note: Repetitive Transcranial Magnetic Stimulation (rTMS) is not recommended for use during pregnancy. rTMS may be harmful to a developing fetus. Therefore, you may be tested for pregnancy at the time of your admission to the study. Prior to your beginning the study we will discuss with you in more detail the importance of avoiding pregnancy. We will specifically ask you to let us know if you change your mind and decide to become pregnant during the study.

Confidentiality

Information about you collected as part of this research will not be used or distributed for future research studies, even if personal identifiers are removed.

Participation in this study and information gathered from the study, including online assessments, will be kept confidential. A cross-index of your name (with address and telephone number) and your code number will be kept in a separate locked location, available only to the Brown University investigators and employees on this project. Specifically, these records will be kept in locked or password-protected files, and stored in either locked offices and/or secure servers maintained by Brown University (121 South Main St., Providence, RI) or the Neuromodulation Laboratory at Butler Hospital (345 Blackstone Blvd., Providence, RI). These records will be accessed only by essential study staff who are trained in human subject's protection guidelines. This cross-index will be destroyed once the final study data set is completed. In addition, all questionnaire data will contain only numeric codes. Clinical information regarding administration of rTMS will be documented in the Butler Hospital Medical Record according to institutional policy. To further protect your confidentiality, we will refer to ourselves during all telephone calls as "Brown University" and will not use any other identifying information. The findings of the study may be published but individual participants will not be identified. Any reports related to child abuse/neglect or elder abuse will be reported by us to the appropriate authorities. There are other limitations to confidentiality relevant to the current study; confidentiality may have to be broken if imminent risk of suicide or homicide is discovered (i.e. imminent risk to self or others), or if legal authorities subpoena information or testimony from the investigators. In order to protect your confidentiality related to email communication all email links containing any PHI will be sent through a secure portal and participants will be asked to sign a separate consent for email communication in a research project form prior to any email communication.

You will not be personally identified in any reports or publications that may result from this study. The confidentiality of the information you provide to us will be maintained in accordance with state and federal laws. If you tell us something that makes us believe that you or others have been or may be physically harmed, we may report that information to the appropriate agencies.

Clinically relevant research results, including individual research results, will not be disclosed to you.

The U.S. Food and Drug Administration (FDA) may inspect all study records to ensure that the study is being conducted in accordance with FDA regulations. General information about this study has been or

will be submitted to the federal clinical trial registry databank, which can be accessed on the Internet at www.ClinicalTrials.gov."

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see above); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

Authorization for use/disclosure of your Identifying Health Information, to Conduct this Research Study

If you sign this document, you give permission to research staff in the Transcranial Magnetic Stimulation Clinic at Butler Hospital to use your health information that identifies you, for the purpose of conducting the research study described above.

The health information that we may use or share with others for research purposes includes information in your medical record, results of physical examinations, and medical history as needed to determine your eligibility and safety to receive repetitive transcranial magnetic stimulation.

Your health information may also be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, and conducting public health surveillance, investigations, or interventions. The U.S. Food and Drug Administration (FDA) may inspect all study records to ensure that the study is being conducted in accordance with FDA regulations.

Butler Hospital is required by law to protect your health information. Individuals outside of Butler that receive your health information may not be required by Federal privacy laws (such as the HIPAA Privacy Rule) to protect it, so we cannot guarantee that they will not share it without your permission.

Please note that:

- You do not have to sign this consent form, but if you do not, you may not participate in or receive research-related treatment in this study.
- Butler Hospital may not withhold treatment or refuse to treat you, based on whether you sign this consent form.
- You may change your mind and revoke (take back) this consent and authorization at any time. If you no longer want to give us permission to use your health information for this research study, you must contact the Principal Investigator, [William Lechner, contact information listed next to the signature line of this form], and you will be instructed to provide a written statement. You may need to write a separate statement to other institutions or organizations if health information about you related to this study is maintained in records outside of Butler.
- Even if you revoke (take back) this consent and authorization, Butler researchers may still use or share health information about you that they already have obtained, when doing so is necessary to maintain the integrity or reliability of the current research.
- You generally will not have access to your personal health information related to this research until the study is completed. At the conclusion of the research and at your request, you will have access to your health information that Butler Hospital maintains in a designated record set, according to the Notice of Privacy Practices provided to you by Butler Hospital. The designated record set

includes medical information or billing records used by doctors or other health care providers at Butler Hospital to make decisions about individuals.
- Your health information will be provided to you or to your physician if it is necessary for your care.
- If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

This Authorization will expire when all the activities associated with this research study have concluded.

Economic Considerations

You will be paid up to $540 in total for participating in this study. Specifically, you will be paid $50 for completing the baseline appointment in the lab, $4-8 for each of the 10 online cognitive training sessions, $23-31 for each of the 10 rTMS sessions at Butler, $10 for completing the online midpoint assessment, $70 for the outcome assessment session, and $20 for the final online assessment session.

Depending on the amount of payment you might receive for your participation in this study you might have to provide your name, address, and taxpayer ID or Social Security number to the Butler/CNE Research Accounting Department or Brown University Accounting Department. In order to receive payment of $300 or more for participation in research, you will have to complete and sign a W-9 form. If you are paid $600 or more in any calendar year for research participation, the IRS will be notified of the total amount you were paid, in accordance with federal regulations. You should ask the researcher for more information if you have questions about this process.

In Case of Injury

We will offer you services in Care New England facilities as needed to treat any injury that results directly from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for any injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed on the last page of this consent form.

Alternative Treatments/Alternative to Participation

This research study is not intended to provide treatment. Standard care for smoking cessation or mental health problems is available from doctors or clinics. Your care at Butler Hospital will not be affected in any way if you decide not to participate in this research study.

Financial Disclosure

None.

Voluntary Participation

You are free to decide whether or not to participate in this study, and you are free to withdraw from the study at any time. A decision not to participate or to withdraw from the study will not adversely affect your current or future interactions with Butler Hospital or Care New England. Your participation in the

study may be terminated by the researchers without regard to your consent; in that case, you are entitled to an explanation of the circumstances leading to that decision.

Questions

Taking part in this study is entirely voluntary. We urge you to discuss any questions about this study with our staff members. You should take as much time as you need to make your decision. If you decide to participate, you must sign this form to show that you want to take part.

Authorization: I have read this form and decided that _____
(printed name of participant)
will participate in the project described above. Its general purposes, the nature of my involvement, and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

_____ _____
Signature of Participant Date

_____ _____
Signature of Principal Investigator Date

or

_____ _____
Signature of Person Obtaining Consent Date

Telephone Number of Principal Investigator or Person Obtaining Consent:_____

If you have further questions about this project or about research-related injuries, please contact William Lechner, PhD at 814-450-1093. If you have questions about your rights as a research subject, please contact Paul Malloy, PhD., Vice Chair, Butler Hospital Institutional Review Board, at 401-455-6355.

THIS FORM IS NOT VALID UNLESS THE FOLLOWING BOX HAS BEEN COMPLETED BY THE IRB OFFICE

THIS FORM IS VALID UNTIL

DATE: April 30, 2021

IRBNET ID# 1054787

BUTLER IRB REFERENCE# 1705-003

BY (ADMINISTRATOR): CCordeiro