



## Application for Review of Human Research: IRB Protocol (Biomedical Research)

### **Version 6: 1.29.19**

#### **PROTOCOL TITLE**

- 1. Full Title:** A Pilot Study of Repetitive Transcranial Magnetic Stimulation for Adult ADHD
- 2. Brief Title:** TMS for ADHD

#### **STUDY SPONSORSHIP**

- 1. Funding Sponsor:** Brain and Behavior Change Center (BBCC)

#### **PROTOCOL ABSTRACT**

Attention Deficit Hyperactivity Disorder (ADHD) is characterized by symptoms of impulsivity, inattention, and hyperactivity that emerge in childhood and frequently persist into adulthood. These symptoms are accompanied by deficits in cognitive control and risky decision making that can lead to negative psychosocial and health-related outcomes. With advances in the neuroimaging field, we are learning where and how self-control over decisions and behaviors is executed in the brain. This work points to the central role of neural activity in the dorsolateral prefrontal cortices (DLPFC) in self-control processes that contribute to healthy choices. Further, emerging evidence shows that activity in the prefrontal cortices and cognitive control circuits can be modulated using a noninvasive and safe intervention: repetitive transcranial magnetic stimulation (TMS). This within-subject proof of concept study will investigate whether 20 sessions of TMS (versus sham stimulation) can enhance executive cognitive function in adults with ADHD.

#### **OBJECTIVES**

##### **1. Overall Objectives**

**Aim 1:** To assess the effects of TMS (versus sham stimulation) on clinical measures of ADHD symptoms.

**Hypothesis:** Active TMS will reduce symptoms of ADHD as compared to sham treatment.

**Aim 2:** To assess the effects of TMS (versus sham stimulation) on cognitive performance and risk seeking in adults with ADHD.

**Hypothesis:** TMS treatment will improve cognitive performance and reduce risk seeking compared to sham treatment.

#### **BACKGROUND**

Attention Deficit Hyperactivity Disorder is a condition characterized by symptoms of impulsivity, inattention, and hyperactivity that emerge in childhood; in approximately 60% of cases these symptoms persist into adulthood where they may lead to challenges at work and at home (DSM-V, 2012; Faraone et al., 2006; Klein et al., 2012; Volkow and Swanson, 2013). Current pharmacological treatments include stimulants such as methylphenidate and amphetamine as well as atomoxetine, a norepinephrine transporter blocker (Sharma and Couture, 2014; Weyandt et al., 2014). Although these medications can provide relief from symptoms, they are not effective for all participants and require careful dose adjustment to minimize side effects while retaining clinical



benefits (Epstein et al., 2014; Sharma and Couture, 2014). There is a clear need for novel treatments for adult ADHD.

Inattention and impulsivity symptoms in adult ADHD are frequently accompanied by deficits in cognitive control and decision making (Aarts et al., 2015; Matthies et al., 2012; Mowinckel et al., 2014; Rohlf et al., 2012). These deficits are associated with reduced activity in regions subserving the executive control network, including the dorsolateral prefrontal cortex (Bush, 2011) (Bush 2011). Emerging evidence shows that activity in the prefrontal cortices and cognitive control circuits can be modulated using cognitive-enhancing medications (Ashare et al., 2012; Loughhead et al., 2010), computerized cognitive exercise training (Jaeggi et al., 2011; Snowball et al., 2013), and transcranial magnetic stimulation (TMS; (Brevet-Aeby et al., 2016)).

TMS is a non-invasive and relatively safe neuromodulation technique that uses Faradays' principle of electromagnetic induction. With TMS, repetitive magnetic pulses are applied to the scalp to generate electrical currents and depolarization of neurons in the targeted brain cortex with action potentials that propagate to subcortical structures and exert biological effects effect beyond the duration of stimulation. Currently, TMS is FDA approved for treatment of treatment resistant major depression. High frequency TMS delivered to the left dorsolateral prefrontal cortex has been used to treat depression (Garcia-Toro et al., 2001) and a number of other psychiatric disorders (Bystritsky et al., 2008; Clark et al., 2015; Del Felice et al., 2016; Dougall et al., 2015; Slotema et al., 2010; White and Tavakoli, 2015). In addition, a growing body of evidence supports the safety and potential utility of TMS for improving executive cognitive function (e.g. working memory) in healthy adults (Brevet-Aeby et al., 2016; Demirtas-Tatlidede et al., 2013). This has led to increased interest in TMS for improving executive function deficit in ADHD populations. To date, only a few studies have examined TMS protocols for treatment of ADHD, but initial evidence is promising (Bloch et al., 2010; Weaver et al., 2012; Zaman, 2015).

This within-subject proof of concept study will investigate whether repeated sessions of TMS (versus sham stimulation) can attenuate ADHD symptoms in adults.

## **CHARACTERISTICS OF THE STUDY POPULATION**

### ***1. Target Population***

95 healthy adults with ADHD between the ages of 18-65 will be enrolled in order to have 30 participants complete the study. Adults with ADHD are defined as those adults meeting diagnostic criteria for ADHD on the SCID-5 module for adult ADHD.

### ***2. Accrual***

95 male or female participants will be enrolled/sign consent to have 30 complete the study at the University of Pennsylvania Center for Interdisciplinary Research on Nicotine Addiction (CIRNA). Accounting for attrition based upon our previous studies on ADHD & tDCS, we estimate we will need to enroll 95 participants, 75 of which are projected to be eligible at intake, (~4-5 per month over a 22 month period) to have up to 30 participants complete the study. Participants will first be screened over the telephone and then complete an in-person Intake Visit with the Adult ADHD Treatment and Research Program or Center for Interdisciplinary Research on Nicotine Addictions to confirm final eligibility.

### ***3. Key Inclusion Criteria***

Eligible participants will be:

1. Healthy males and females who are between 18 and 65 years of age with an ADHD diagnosis (meet diagnostic criteria for ADHD on the SCID-5 module for adult ADHD).
2. Planning to live in the area for at least the next 6 weeks;



3. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the combined consent and HIPAA form;
4. Able to communicate fluently in English (speaking, writing, and reading).

#### **4. Key Exclusion Criteria**

Subjects who present and/or self-report with the following criteria at any point during study participation will not be eligible to participate in the study:

##### Alcohol/Drugs:

1. History or current diagnosis or treatment for alcohol or drug abuse (as reported during phone screen);
2. Positive breath alcohol concentration test (BrAC greater than or equal to 0.01) at intake;
  - a. Participants testing positive for breath alcohol with a reading equal to or greater than .08 (the legal driving limit) or who are visibly impaired will be instructed not to drive themselves home after the appointment. If a participant needs to use a phone to call for a safe ride home, an office telephone will be made available to the participant.
3. A positive urine drug screen for cocaine, PCP, amphetamines, methamphetamines, benzodiazepines, methadone, and/or barbiturates at Intake, Baseline, or Sessions 5, 10, 15 or 20.
  - a. Participants who are patients of investigators at the Penn Adult ADHD Treatment & Research Program who present a positive urine drug screen for amphetamines or methamphetamines at intake and report use of stimulant medications for the treatment of ADHD will be allowed to continue with participation.

##### Medication:

Current use or recent discontinuation (within the past 6 months at the time of Intake) of:

1. GABAergic medications
2. Glutamatergic medications
3. Any medication for the treatment of ADHD
  - a. Patients seeing investigators at the Penn Adult ADHD Treatment & Research Program for the treatment of ADHD will be given the option to abstain from their ADHD medication for the duration of the study. Since investigators at the Penn Adult ADHD Treatment & Research Program are part of the study team, they are able to oversee the medical aspects of the participant's treatment.
4. Any medication that is known to lower the seizure threshold (e.g., clozapine, bupropion, tramadol, carbapenems, stimulants)
5. Any medication that could compromise participant safety as determined by the Principal Investigator and/or Study Physician

Current use or recent discontinuation (within the last 14 days at the time of Intake) of:

6. Anti-psychotic medications
7. Nicotine replacement therapy (NRT)

Daily use of:

8. Opiate-containing medications for chronic pain
9. Benzodiazepines

##### Medical/Neuropsychiatric:

1. Women who are pregnant, planning a pregnancy, and/or breast feeding. Women of childbearing potential will agree to use a medically accepted method of birth control throughout their participation in the study and will undergo a urine pregnancy test once a week (at intake, Baseline, Session 1, Session 5, Session 10, & Session 15). Women who self-report a condition which renders them unable to become pregnant (i.e.,



hysterectomy, surgical sterility, menopause, etc) will not be required to complete the pregnancy tests. By enrolling in this protocol women of childbearing potential agree to use a method of medically accepted birth control (diaphragm, cervical cap, condom and spermicide, surgical sterility, or birth control pills) for the duration of their participation.

2. History of seizures, epilepsy, or history of epilepsy in first-degree relative
3. History of stroke or transient ischemic attack (warning stroke)
4. History of traumatic brain injury or self-report of brain or spinal tumor
5. History of head injury with unconsciousness lasting more than 5 minutes
6. Previous brain surgery
7. Any additional neurological condition that would likely reduce the safety of study participation, including central nervous system (CNS) vasculitis, intracranial tumor, intracranial aneurysm, multiple sclerosis or arteriovenous malformations
8. History of tinnitus
9. History of diabetes mellitus
10. History of atherosclerotic vascular disease
11. A medically unstable cardiopulmonary or metabolic disorder
12. Increased risk for myocardial infarction or other major cardiopulmonary complications. (Exclusions include, but are not limited to, subjects with unstable angina, decompensated congestive heart failure, severe cardiac valvular disease, a high-grade atrio-ventricular block on EKG, or a symptomatic ventricular arrhythmia or a myocardial infarction within 6 months prior to enrollment.)
13. Any uncorrected visual impairment or abnormality
14. Self-reported history, current diagnosis of psychosis or symptoms consistent with a mood disorder based upon the Structured Clinical Interview for DSM-5 (SCID); including schizophrenia, mania, bipolar disorder, an eating disorder, obsessive compulsive disorder, major depression (subjects with a history of major depression but in remission for past 6 months are eligible). If a participant screens positive for one of the above mentioned mood or depressive disorders they will be excluded from the study and provided with contact information for local treatment programs (mood referrals document).

TMS-related:

1. Subjects with ferromagnetic material in or in close proximity to the head (with the exception of oral dental devices).
2. Implanted devices (including VNS, DBS, pacemakers, spinal cord stimulators, medication pumps, ventriculo peritoneal shunts, defibrillators, intracardiac lines)
3. Self-report of any skull fracture or opening
4. A disturbance in normal sleep patterns/sleep deprivation

Note: Although there is no known risk of TMS to the fetus, the issue has not been fully addressed. Consequently, pregnant women will be excluded. All women of childbearing potential (as described above) will agree to use a medically accepted method of birth control while enrolled in the study and pregnancy status will be monitored throughout participation with the use of pregnancy screens.

General Exclusion:

1. Any medical condition, illness, disorder, or concomitant medication that could compromise participant safety or treatment, or affect clinical or cognitive outcomes, as determined by the Principal Investigator
2. Inability to complete study tasks and provide quality data, as determined by the Principal Investigator



3. Low or borderline intellectual functioning – determined by a score of less than 90 on the Shipley Institute of Living Scale (SILS) (administered at Intake Visit). The SILS correlates with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Estimated IQ Test
4. Inability to provide informed consent

### **5. Vulnerable Populations**

Children (under age 18), pregnant women or prisoners are not included in this research study.

### **6. Populations vulnerable to undue influence or coercion**

Educationally or economically disadvantaged persons are included but not solely targeted for recruitment. Cognitively impaired persons are not included in the current study. Because of our recruitment efforts for this study, it is possible that University of Pennsylvania employees and students may be invited to participate but will be neither targeted nor excluded from participating in this study. Status of participation in the current study will be voluntary and independent of the participants work or school activities. The decision of whether or not to participate in the research study will not impact employee or student standing with the University of Pennsylvania.

### **7. Subject Recruitment**

Participants may be recruited from the Adult ADHD Treatment and Research Program, ADHD discussion boards, study brochure, TV/radio advertisements, patient mailings, Craigslist.org/Internet advertisements, Experiments@penn, flyers, and/or from our database of previous participants who have agreed to be re-contacted for future studies. Interested participants that complete online questionnaires will be given the option to be contacted via email or text message to schedule a time to complete a telephone screen to assess initial eligibility. Interested participants will complete a telephone screen to assess initial eligibility. Those who are initially eligible will be screened against our registration database to confirm that they are not currently participating in another research study at our Center and have not previously reported a condition or circumstance that would make them ineligible for the current study. They will then attend an Intake Visit during which the purpose and procedures of this study will be described to them and final eligibility will be confirmed.

### **8. Real time safety monitoring**

TMS will be administered by appropriately trained personnel and under the supervision of a physician experienced in neuromodulation. Initial motor threshold (MT) determination, targeting for coil placement, and initial determination of treatment parameters will be overseen by the study physician. The study physician will participate in the evaluation of tolerability and response during the TMS course and will be available on site or within a short commute. Subjects will be monitored at all times during TMS for side effects including involuntary motor activity and a protocol for seizure management will be in place. Equipment will also be monitored during sessions with respect to the settings for stimulus intensity (measured in % motor threshold), coil placement, and coil temperature.

## **STUDY DESIGN**

### **1. Phase**

Not applicable

### **2. Design**

This trial will use a between-subject double blind design in which TMS dosage (active or sham) will be randomly assigned. Eligible participants will complete an **Intake Visit (week 0)** for final eligibility determination. Eligible participants will complete an additional 20 study visits



(5 visits per week for 4 consecutive weeks) during which they will receive 26-minute sessions of TMS. Participants will complete a series of computerized cognitive assessments prior to initiating the TMS period (Baseline) and will complete the same series of computerized cognitive assessments after their final TMS session (Session 20).

### **3. Study Duration**

Enrollment will begin in January 2017. Based on the accrual projections described previously, we anticipate enrollment lasting through March 2019. Each participant will be required to be in the study for approximately 4-6 weeks.

## **DRUGS OR DEVICES**

Transcranial magnetic stimulation (TMS) and sham stimulation.

## **STUDY PROCEDURES**

### **1. Procedures**

**Telephone Screening:** Potential participants will be screened by an experienced research technician to determine initial study eligibility. The 6-item Adult ADHD Self-Report Scale (ASRS) will be administered during the phone screen. If the subject meets preliminary telephone eligibility criteria he/she will be invited to attend an Intake visit.

**Visit Reminders:** Participants will receive study visit reminders 24 – 48 hours prior to their scheduled study visits via phone call, email or text (participants who provide a cell phone number for contact). No sensitive information about subjects will be included in electronic reminders.

**Intake (week -1):** (Visit duration 3-3.5hrs) Participants will:

1. Hear a study description where all study procedures will be reviewed. Participant questions will be answered. Following this presentation, the combined informed consent and HIPAA form will be completed;
2. Complete a urine drug screen (at least 30ml [two tablespoons] of urine). The urine drug screen will assess the use of any study-prohibited medications/recreational drugs (See Key Exclusionary Criteria; Alcohol/Drugs). Participants who test positive for any exclusionary medications or recreational drugs will be deemed ineligible.
3. Self-administer a CLIA-approved urine pregnancy test (female participants of child bearing potential only). Participants are advised that we do not recommend participation for pregnant women, and that they may withdraw at any time without penalty;
4. Perform a BrAC assessment to control for alcohol consumption. Participants with a BrAC greater than or equal to 0.01 at Intake Visit will be ineligible;
5. Complete a carbon monoxide (CO) breath assessment (smokers only) to control for smoke exposure;
6. Complete a brief medical history form with a trained staff member;
7. Complete Structured Clinical Interview for DSM-5 (SCID);
8. Complete Shipley Institute of Living Scale (SILS) IQ test. Participants earning less than an estimated WAIS-R IQ score of 90 will be ineligible;
9. Complete demographics and smoking history (smoking rate, nicotine dependence) and paper and pencil questionnaires (mood, QIDS, CAARS:S-L & ASRS).

**Baseline (week 0):** (Visit duration 1.5hrs) Participants will:

1. Urine drug screen. See key exclusionary criteria; Alcohol/Drugs;
2. Pregnancy screen (females of child bearing potential only);
3. BrAC assessment. See breath alcohol concentration under screening/covariates for exclusionary criteria;



4. Provide information regarding recent nicotine and caffeine intake, and any medication changes since the Intake visit;
5. A carbon monoxide (CO) breath sample (smokers only);
6. Complete paper and pencil questionnaires (POMS);
7. Complete computerized cognitive tasks which may include assessments of working memory, sustained attention, risk aversion, delay discounting or reaction time.

**TMS Sessions (Sessions 1 - 20):** (Visit duration ~1-2hrs). The stimulation protocol is adapted from TMS Investigations of Cognition and Motor Function, which was employed in The Laboratory for Cognition and Neural Stimulation (LCNS).

Participants will complete the following during Sessions 1 - 20:

1. Urine drug screen (Sessions 1, 5, 10, 15 & 20). See key exclusionary criteria; Alcohol/Drugs;
2. Pregnancy screen (females of child bearing potential only) (Sessions 1, 5, 10, 15 & 20);
3. BrAC assessment. See breath alcohol concentration under screening/covariates for exclusionary criteria;
4. Assessment of recent nicotine and caffeine intake, and any medication changes since last assessment (Sessions 1, 5, 10, 15 & 20);
5. TMS safety & side effects questionnaire;
6. A carbon monoxide (CO) breath sample (smokers only);
7. Complete paper and pencil questionnaires;
8. Receive 26 minutes of TMS (active or sham);
9. Complete computerized cognitive tasks which may include assessments of working memory, sustained attention, risk aversion, delay discounting or reaction time (Sessions 5, 10, 15 & 20).

**Attendance:** Participants will be asked to attend all study visits. Participants attending less than 4/5 visits during the first two weeks or less than 3/5 sessions in the final two weeks of the study will be excluded.

**TMS Training Procedures:** Prior to each TMS session an investigator or trained research assistant will review the procedures, goals, risks, and potential benefits of the study and confirm that no change has occurred affecting study inclusion and exclusion criteria. The TMS sessions will be conducted by a trained TMS clinician using the The MagPro R30 (Magventure, Inc., Copenhagen, Denmark) device with a figure 8 coil. During Sessions 1 - 20 participants will receive 26 minutes of sham or active TMS using the parameters described below. Participants will be blind to condition.

**Active TMS:** A MagPro R30 (Magventure, Inc., Copenhagen, Denmark) device with a Cool-B65 A/P figure 8 coil will be used to deliver TMS. This coil has an active side and a sham side, and can be used to perform double-blinded studies. The MagLink software program is used to define the treatment protocol for each participant. This includes defining whether a given patient is to receive real or sham treatment. When the protocol has been defined it is downloaded to a Patient Key (which must be inserted into the device in order to deliver stimulation. The Cool-B65 A/P coil has a built-in position sensor used to ensure that the correct (active or sham) side of the coil faces towards the participant's head. If the coil position is wrong, a "Flip Coil" prompt will be displayed on the MagPro screen.

We will use a TMS paradigm which has been successfully and safely utilized in other studies of rTMS at the University of Pennsylvania. In this paradigm, brief trains of moderately rapid stimulation are presented for a short period of time. In light of the demonstrated utility of the



brief train technique in conjunction with an excellent safety record, we propose to deliver brief trains of stimulation.

To control for inter-participant variability in sensitivity to TMS, a motor threshold will be established for each participant at the beginning of each week of TMS. Motor threshold is defined as the lowest intensity at which a single pulse of TMS over the contralateral hand representation elicits a visible motor response of the hand. The hand representation is typically identified as the omega or epsilon shaped section of the motor cortex.

TMS will be administered at 10Hz with an intensity of 120% of patient resting motor threshold. Stimulation will be delivered to the left dorsolateral prefrontal cortex using 20 sec cycles (i.e., 5 sec train with 15 sec inter train interval). Subjects will receive 80 trains per session for a total of 4000 pulses per session (~26 min sessions). These settings are considered high dose and we intend to use them to increase the chances of patient clinical benefit and treatment compliance and to reduce the risk of lack of efficacy due to unnecessarily conservative dosing. Although these parameters differ from the set parameters described in Rossi et al., 2009, they are still in line with safety recommendations for motor cortex of healthy subjects including ITI >5 (more than twice as long as the active stimulation time in this case) and are consistent with what has been published as being safe (no induction of seizures) and effective when used to stimulate non-motor cortex (i.e., dorsolateral prefrontal cortex) of patients with major depressive disorder taking medications that may decrease seizure threshold (Connolly et al., 2012; Hadley et al., 2011). The proposed ITI also complies with the 2016 FDA label modification that allows a range of inter-train intervals from 11-26 seconds when using TMS in clinical settings (Food and Drug Administration, 2016). To further increase the margin of safety in this protocol we are excluding patients taking medications known to decrease seizure threshold and we will use ~40% less pulses per session than what is considered safe in the literature (Hadley et al., 2011). The Beam-George EEG F3 system for location of the stimulation target will be used in conjunction with personalized patient caps to increase consistency in coil placement.

Sham TMS: Sham TMS will utilize the same procedures as above, except that the sham side of the coil will be positioned toward the participant's scalp. The sham coil is designed to mimic the appearance and sound of active tDCS stimulation, but is equipped with a magnetic shield that reduces the strength of the field by approximately 80%. This reduction in field strength ensures that no neural stimulation occurs (Duecker and Sack, 2015).



**Table 1. Measures and Time Points**

Activity	Intake	Baseline	TMS Sessions (1 - 20)
Weeks	-1	0	1, 2, 3 & 4
Urine Drug Screen	x	x	x <sup>2</sup>
Urine Pregnancy Screen	x	x	x <sup>3</sup>
BrAC	x	x	x
Carbon Monoxide (CO)	x <sup>1</sup>	x <sup>1</sup>	x <sup>1</sup>
Demographics	x		
ETOH History	x		
Smoking Behavior (FTND)	x <sup>1</sup>		
Caffeine & nicotine use	x	x	x <sup>2</sup>
Height	x		
Weight	x		
Medical History Form	x		
TMS safety checklist	x		x
ShIPLEY Institute of Living Scale (IQ)	x		
SCID-5	x		
<b>Treatment</b>			
TMS (active or sham)			x
<b>Primary Outcomes</b>			
CARRS: S-L	x	x	x <sup>4</sup>
ASRS	x	x	x <sup>4</sup>
<b>Secondary Outcomes</b>			
PASAT		x	x <sup>4</sup>
Continuous performance task		x	x <sup>4</sup>
Risk Task		x	x <sup>4</sup>
QIDS	x	x	x <sup>4</sup>

<sup>1</sup> Smokers reporting having smoked in the past 24hrs.

<sup>2</sup> Administered at sessions 1, 5, 10, 15 & 20.

<sup>3</sup> Administered at sessions 1, 5, 10, & 15.

<sup>4</sup> The cognitive battery & ADHD clinical measures will only be administered at TMS sessions 5, 10, 15 & 20.

**Back-up scheduling for Session 1 visits:** Since we are limited in the number of study tracks we are able to run per week we are also offering the opportunity to become a back-up participant for Session 1 visits. Back-up participants will only be scheduled for a TMS session 1 visit (occurring on Mondays). Participants may only be a back-up if they have not yet initiated a TMS track (have not attended TMS Session 1). Becoming a back-up is completely voluntary and participants will not receive any extra stimulation sessions if they decide to become a back-up participant in this study. In order to be scheduled as a back-up participant the participant must agree to do the following:

- Show up for the scheduled Session 1 appointment at the designated time;
- Be available for all subsequent study track visits in the event that they are promoted to the primary participant (if the primary participant for that date does not attend their session or is deemed ineligible at the visit).

If the participant attends the Session 1 visit as a back-up participant and is not needed on that date they will not undergo any study procedures (will not receive any stimulation), they will be

compensated \$25 for their time and will be free to leave. Back-up participants will then be scheduled for the next available study track as the primary participant.

If the primary participant for that session does not attend the visit or is otherwise deemed ineligible the back-up participant will be promoted to the primary participant and will start their study track. They will be compensated for their time in accordance with the usual payment plan.

### **1. Screening/Covariates:**

Adult ADHD Self-Report Scale (ASRS) – Screening version: The screening version of the Adult ADHD Self-Report Scale (ASRS) Version 1.1 is a 6-question scale designed to screen for adult ADHD in community samples. The ASRS was developed by a World Health Organization (WHO) work group in conjunction with the creation of the WHO World Mental Health (WMH) Survey Initiative version of the WHO Composite International Diagnostic Interview (WMH-CIDI). This will be administered at phone screen.

Urine Drug Screen: A urine sample will be collected at Intake, Baseline and Sessions 1, 5, 10, 15 and 20 to conduct a urine drug screen. The urine drug screen indicates whether the subject has recently taken any of the following drugs or medications: cocaine, PCP, amphetamines, methamphetamines, opiates, methadone, THC, and/or barbiturates. Participants with a positive urine drug screen for any substance listed above other than THC will be deemed ineligible. In an effort to remain CLIA-compliant, results from urine drug screening will not be shared with participants. Participants will be informed that the testing is for research purposes only and that they will be informed of their eligibility status, but not of the specific testing results.

Urine Pregnancy Test: At the Intake and once a week during the study (Baseline & TMS Sessions 1, 5, 10, & 15), participants will be supplied with a simple, CLIA-waived urine pregnancy screen and informed that pregnant women are not advised to participate in this research study. Participants will then be instructed to administer the pregnancy test independently and will inform study staff if they would like to continue participation after they have administered the pregnancy screen. Participants will be informed that there is no penalty for discontinuing participation at this point in the visit and that they will still receive travel reimbursement for the visit.

Breath Alcohol Concentration: The BrAC assessment will be administered at all sessions. The breath alcohol monitor is a handheld device that uses a disposable mouthpiece and reports the concentration of alcohol in exhaled breath. Any reading greater than 0.000 indicates alcohol consumption within the last 14 hours. Participants with a BrAC greater than or equal to 0.01 at the Intake Visit will be ineligible. Participants who have a BrAC reading greater than or equal to 0.01 at any visit listed above may be ineligible to continue with the visit and will only be rescheduled/allowed to proceed with the study at the discretion of the Principal Investigator.

ETOH History: ETOH history will be administered at the Intake Visit and will ask subjects about their alcohol consumption over the past 7 days.

Demographics: Standard surveys will collect demographics (e.g., age, education, race, and gender).

Smoking Behavior: Participants reporting having smoked in the past 24 hours will complete the 6-item Fagerstrom test for nicotine dependence (FTND; (Heatherton et al., 1991) and a smoking history assessment which includes age at first cigarette, age at regular (daily) smoking, and

current smoking rate. Number of cigarettes smoked in past 24 hours and time of last cigarette will be recorded at each visit.

*Caffeine and Nicotine use:* At intake, baseline and TMS visits 1, 5, 10, 15 & 20 recent caffeine and nicotine use data will be collected to monitor use of these stimulant substances.

*Carbon Monoxide (CO):* The CO monitor is a handheld device that uses a disposable mouthpiece, reports CO in parts per million (ppm), and takes about 5 minutes to administer. Carbon monoxide measurements will be collected from smokers at each visit as a biochemical verification of smoking exposure.

*Medical:* Height and weight will be measured and recorded. All participants will complete a medical history form with a trained staff member to review for all contraindications listed previously.

*Shipley Institute of Living Scale:* All participants will complete the Shipley Institute of Living Scale (SILS) at the Intake Visit. The scale consists of two subtests: a 40-item vocabulary test and a 20-item test of abstract thinking. The total administration time is 20 minutes (10 minutes per subtest). A trained member of the study staff will score the test. The SILS correlates with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Estimated IQ Test; those participants earning less than an estimated WAIS-R IQ of 90 will be ineligible. The SILS is considered a highly reliable assessment tool, with a good total score internal consistency (Cronbach's alpha=.92).

*TMS Safety Checklist:* This checklist will be administered at all Intake and all TMS sessions. The purpose of this checklist is to verify that participants are eligible to receive TMS and that there have been no changes to eligibility status throughout participation.

*Structured Clinical Interview for DSM-5 (SCID):* Diagnostic and Statistical Manual of Mental Disorders (DSM) is the standard classification of mental disorders used by mental health professionals in the United States and contains a listing of diagnostic criteria for every psychiatric disorder recognized by the U.S. healthcare system. This interview will be administered at Intake to help determine eligibility for the study (see exclusion criteria above: medical/neuropsychiatric).

**Treatment:** See description above under TMS.

### **Primary Outcomes:**

*Conners Adult ADHD Rating Scale-Self Report – Long Version (CAARS-S:L):* The CAARS-S:L is a 66-item rating scale designed to assess ADHD symptoms in adults. The scale contains multiple subscales to assess DSM-IV specified ADHD criteria as well as other facets of ADHD such as inattention/memory problems, hyperactivity/restlessness, impulsivity/emotionality, and problems with self-concept. The scale has good internal consistency (Cronbach's alpha .86-.92) and test-retest reliability (Pearson's  $r = 0.89$ ) (Erhardt et al., 1999).

*Adult ADHD Self-Report Scale (ASRS):* The Adult ADHD Self-Report Scale (ASRS) Version 1.1 is an 18-item scale designed to screen for adult ADHD in community samples. The ASRS was developed by a World Health Organization (WHO) work group in conjunction with the creation of the WHO World Mental Health (WMH) Survey Initiative version of the WHO Composite International Diagnostic Interview (WMH-CIDI).



## **Secondary Outcomes:**

**Risk Task:** The risk aversion task is designed to probe different aspects of reward valuation and decision-making. The task involves making hypothetical binary decisions regarding reward contingencies. Variables in these choices will include probability of reward (uncertainty/ambiguity discounting) and the risk of losing previously earned rewards (risk discounting) (task duration: ~10 min).

**Continuous Performance Task (CPT):** The CPT is a measure of sustained attention. In this task, participants are shown a series of stimuli (letters, numbers, or pictures) on a computer screen and are asked to press the spacebar in response to certain stimuli, but to withhold responding to other stimuli. (task duration: ~15-20min).

**Paced Auditory Serial Addition Task (PASAT):** The PASAT is a validated measure of attention, working memory, and information processing. Subjects are presented aurally with single digit numbers and instructed to respond verbally with the sum of the two most recently presented numbers. The PASAT has been used to assess cognitive impairment in patients with a wide range of neuropsychological conditions and shows a high level of internal consistency and test-retest reliability (Tombaugh, 2006); improvements in performance on the PASAT have been demonstrated following tDCS with working memory training in healthy subjects (Gill et al., 2015).

**Quick Inventory of Depressive Symptomatology (QIDS):** The 16 item QIDS – Self Rated Version (QIDS-SR) (Rush et al., 2003) will be used to assess the severity of depressive symptoms. The QIDS-SR assesses nine diagnostic symptom domains used to characterize a major depressive episode and is sensitive to change resulting from medications, psychotherapy, or somatic treatments.

## **2. Statistical Analysis**

**General Issues:** Prior to performing analyses, standard data screening/cleaning procedures will be applied. These procedures will (a) screen the data for data-entry errors, (b) check for outliers, (c) assess the extent and pattern of missing data, (d) create all summary scores needed for analysis, and (e) check that appropriate distributional assumptions are met. In all analyses, the assumptions underlying the application of all the statistical methods that are used will be examined, principally through the use of standardized residuals, influence diagnostics, and graphical displays. All analyses will be conducted using Stata software (STATA Corporation, College Station, Texas).

**Hypothesis Testing:** The primary outcomes will be cognitive performance on the tasks administered before and after TMS. All of these outcome measures are continuous, and hypotheses will be tested using mixed effects modeling. A sample size of 30 individuals will provide ~80% power to detect a moderate to large effect size, similar to the effect size seen for TMS treatment of depression.

## **3. Confidentiality**

Confidentiality of the data generated in this study shall be maintained in the following ways:

1. All participant information will be kept in a secure filing cabinet that is accessible only to authorized study personnel.
2. All databases containing participant information will be password protected, and again, accessible only to authorized study personnel.



3. Any study communications made by e-mail will use ID numbers only and never include names or any other personal information.
4. All data sets will use ID numbers only. A separate data set subject map table linking names with ID numbers will be accessible only by authorized personnel.

Since self-report and biological data will be collected and stored as part of this study, it is possible that subject privacy or confidentiality can be threatened. To address this concern, the data management system has set up several safeguards to prevent unauthorized access to participant data. In the subject map table, an automatically generated index number is assigned to a subject's study identification number. A linked subject identification table is created to store subject name, address, and telephone contact information. This table uses the automatically generated index number rather than the study identification number. The master subject map and subject identification information are maintained in separate locations. Using this method, no identifying subject information is directly linked to bio-samples or results. All electronic data are stored on institutionally secured and managed network drives. Any publication of data will not identify participants by name or with an identifier that could be used to reveal identity.

All subject data that can be linked to the study ID will be stored in the secure data management system, which has limited, password-required access. The aforementioned precautions and procedures will be applied to protecting subject privacy and the protected health information detailed in Section 4 below.

#### **4. Subject Privacy/Protected Health Information**

The following protected health information (PHI) may be collected as part of this study:

1. Name
2. Street address, city, county, zip code
3. All elements of dates (except year) for dates directly related to an individual and all ages over 89
4. Date of birth
5. Social Security Number
6. Telephone number, email address
7. Results from all questionnaires, tests, and procedures
8. Any other unique identifying number, characteristic, or code

Potential participants will be contacted over the phone after responding to recruitment efforts. Only individuals who have responded to recruitment efforts or who have agreed to be contacted regarding research studies at our Center will be contacted. If an individual cannot be reached immediately, staff members will identify themselves only as calling from the University of Pennsylvania; no mention will be made of the inquiry regarding study participation. Participants will undergo an initial phone screening where preliminary eligibility for the research study will be determined. Only if a participant is initially eligible, will they attend an in-person Intake Visit to confirm eligibility. All data collected over the phone and during in-person visits will be collected by research staff that have completed the CITI-Protection of Human Subjects Research Training as well as HIPAA Compliance Training. Information will never be recorded with identifiers other than study ID. A separate list of names with ID numbers will be accessible only by authorized personnel. All testing, TMS sessions, medical and psychiatric interviews will be conducted individually in dedicated testing and evaluation rooms to protect participant privacy. All records will be kept in locked filing cabinets to maintain confidentiality. Results will not be communicated to other personnel or to the subjects. All analyses will be conducted on de-identified data. Data will be accessible to the Study Investigators, Study Physician, study staff, UPenn IRB, Office of Clinical Research and authorized UPenn staff (e.g. accounting and billing matters, provide treatment, etc.).



## **5. Tissue Specimens**

Urine: Urine (~30ml) will be collected to conduct a urine drug screen and urine pregnancy screen (females only). These samples will be disposed of following the conclusion of every study visit.

## **6. Genetic Testing**

Not Applicable.

## **RISK/BENEFIT ASSESSMENT**

### **1. Potential Study Risks**

The potential risks to participants, and their likelihood and seriousness, are described below. Participants can choose, as an alternative, to not enroll in this study. Overall, there is minimal risk for serious adverse reactions as a consequence of enrolling in this study. Adverse reactions will be assessed and reported as required by Federal law and UPenn regulations.

TMS: The most common adverse effect from TMS is brief and mild muscle contraction headache. This occurs in approximately 10% of subjects. The most significant risk is a seizure. Using single pulse and 1 Hz repetitive TMS no seizures have been reported when stimulus parameters of intensity and duration were within the guidelines described by Wassermann (1998). Similarly, there have been no seizures reported using the brief train at 10 Hz paradigm. These TMS paradigms have been employed at the University of Pennsylvania without any adverse effects. It is also of note that seizures induced by TMS have typically been focal motor seizures. There have been no episodes of status epilepticus; there have been no reports of a TMS associated seizure leading to the development of epilepsy.

A report by Zangen et al. (2005) describes a subject who developed permanent hearing loss after 1 Hz TMS at 120% of the motor threshold; the subject's ear protection had become displaced during the session. This event is of clear concern and relevance to our participants. We will ask participants to immediately report any loosening or detachment of their earplugs or change in the subjective loudness of the coil noise during TMS. Should participants report a change in the sound intensity or feeling that their earplug is displaced, TMS will be immediately terminated until the earplug is repositioned. Additionally, research staff administering TMS will monitor the status of the participant's earplugs and will terminate TMS if the earplugs appear to be displaced on the basis of visual inspection.

There is no need for routine follow-up after a TMS session as side-effects typically occur during the stimulation period. All participants will be given a copy of their signed consent form on which contact information is provided, and will be encouraged to call the project manager, PI or study physician should they have any questions.

Withdrawal Syndrome: Some individuals who discontinue use of stimulant medications (such as Ritalin or Adderall) exhibit a pattern of symptoms related to withdrawal (Ashton et al., 2006; Godfrey 2009; Kutcher et al., 2004). These symptoms include: poor sleep, irritability, fatigue, headaches, depression, and/or return of ADHD symptoms. Eliminating the risk for these would not be possible, although in most cases these events are short-lived and have low intensity. Study personnel will be trained to recognize these symptoms and educate the participants about them (e.g., their duration, methods for reducing them).

Email Communications: In this research study participants may prefer to receive appointment reminders via email or submit questions related participation via email. Email is not a secure means of communication. Email messages travel across the Internet passing through multiple



computers before reaching their final destination. It is not possible to know whether an email a participant sends will be viewed along the way. Additionally, if sent messages are not deleted, an email provider may have an archive of everything that is sent. If someone gets access to an email account (for example, a participant's family member), they could see archived messages. There are many other ways in which emails are not secure—these are only selected examples. To manage this risk the informed consent form will include specific language to educate research participants on the privacy risks involved in email communications. Participants will also be explicitly instructed to only use email communications for routine matters and never for personal or confidential messages or questions.

Threats to Privacy/Confidentiality: See description in Section 3 (Confidentiality) and 4 (Subject Privacy/Protected Health Information) above.

## **2. Potential Study Benefits**

There is no direct benefit from participation in this study. Participants enrolled in this study will be contributing to research that may lead to novel treatments for ADHD symptoms.

## **3. Alternatives to Participation**

The alternative to participation is to decide not to enroll in this study.

## **4. Data and Safety Monitoring**

During the course of the study, data and safety monitoring will be performed on an ongoing basis by the Principal Investigator, project staff, and the IRB. The project staff are responsible for collecting and recording all clinical data. This includes ensuring that all source documents exist for the data on the case report forms, ensuring all fields are completed appropriately, and all corrections are done according to Good Clinical Practice (GCP's). Any inconsistencies/deviations will be documented. Project staff will perform regular chart reviews to verify data integrity. Project staff will meet on a regular basis to reconcile data queries. The IRB will review the trial on an on-going basis.

## **Unanticipated Problems, AE, and SAE Definitions.**

### Unanticipated Problems Involving Risk to Subjects or Others:

Any incident, experience, or outcome that meets all of the following criteria will be considered an unanticipated problem in the current study:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, FDA approved labeling, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

### Adverse Event:

An **adverse event** (AE) is a subcategory of the broader category of “Unanticipated problems Posing Risk to Participants or Others” and is defined as any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal



- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Any event that could be characterized by the definitions above is an AE **whether or not considered related to the study.**

*Serious Adverse Event:*

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but based upon appropriate medical judgment may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious. All adverse events that do not meet any of the criteria for serious will be regarded as **non-serious adverse events**.

**Collection and Recording of AEs and SAEs.**

Adverse Events and SAEs will be assessed throughout the study and will be collected at the time of self-report.

Research staff are trained to inquire (time of onset, nature of issue reported, possible relation to TMS, medications, severity/intensity, etc.) about any notable side effects or medical concern reported by participants. Any notable medical concern will be reported to the Project Manager, Study Physician, and Principal Investigator to determine a course of action and relationship (causality) to the study procedures. This consultation, including all relevant information will be documented via email. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Information surrounding AEs and SAEs are recorded and secured within the appropriate source documents (i.e. subject chart), Case Report Forms (e.g. SEC form, etc.) when applicable, an AE note or SAE report, and the AE/SAE log within the Study Administrative File.

Documentation of AEs will include the following information:

- Protocol name
- Subject identifier
- Description of the event
- Date and time of onset and outcome
- Intensity/Severity
- Action taken
- Relationship (causality) to the study
- Outcome



Documentation of SAEs will include the following information:

- Protocol name
- Subject identifier
- Description of the event
- Date and time of onset
- Current status
- The reason why the event is classified as serious
- Action taken
- Investigator assessment of the association between the event and study treatment
- Welfare of subjects/Outcome
- Follow-Up Plan (if applicable)

### **Management of SAEs or Other Study Risks.**

The Study Physician will oversee the management of all SAEs and other study risks. SAEs will be monitored closely until the event has been stabilized and/or the subject has been referred to the care of their primary care physician. The Study Physician will also review data collected during the medical history portion of the Intake Visit for all subjects who experience a SAE and, when required, will provide follow-up consultation with the participant. All instances of consultation will be recorded.

### **AE, SAE, and Unanticipated Problems Reporting.**

The procedures for unanticipated problem, adverse event, and serious adverse event reporting are consistent with NIH and UPenn-specific guidelines and are as follows:

1. Alert the IRB of any and all reports of unanticipated problems involving risk to subjects or others, AEs, and SAEs when appropriate (i.e. within 10 business days, summary at continuing review, etc.). AEs and SAEs meeting reportable event/unanticipated problem guidelines (unexpected and related) will be submitted to the appropriate IRB within 10 business days of occurrence using the on-line system. If an AE/SAE involved a death and indicates that participants and others are at an increased risk of harm, the event will be reported to the IRB within 3 days.
2. Inform applicable members of the study team of any and all reports of adverse events.

In addition to unanticipated problems (including applicable AEs and SAEs), the following events will be promptly reported to the IRB within 10 business days:

1. Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
2. Any adverse event that would modify the protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
3. Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that subjects have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.



- A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- 4. Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- 5. Breach of confidentiality.
- 6. Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
- 7. Incarceration of a subject when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- 8. Complaint of a subject when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- 9. Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more subjects at increased risk, or affects the rights or welfare of subjects.

**5. Management of Information for Multi-center Research where a Penn Investigator is the Lead Investigator of a multi- center study, or Penn is the lead site in a multi-site study.**

Not applicable.

**6. Risk/Benefit Assessment**

Research staff will monitor participants closely during the TMS sessions. Thus, the risk to benefit ratio for this project is perceived to be low and justifies its implementation.

**SUBJECT COMPENSATION**

Participants will be compensated for the time and effort required to complete study procedures and for travel to the Center for in-person assessments. Participants will be eligible for compensation only if they complete the visits/assessments listed below (Table 2). Participants who are found ineligible for any reason during the Intake Visit will only receive travel reimbursement for that session. Through participation in this research study participants are estimated to earn up to \$955.

Participants will be paid in cash for intake visits. At the baseline visit participants will be issued a Greenphire ClinCard, which is a reloadable, pre-paid card for the purposes of compensation. Compensation will be loaded onto the ClinCard at the end of successfully completed visits.



**Table 2. Study Compensation**

Time Point	Study Week	Session Length	Visit Compensation	Bonus <sup>1</sup>	Travel Reimbursement	Total Estimated
Intake	-1	~3-3.5hrs	\$15		\$10	\$25
Baseline	0	~1.5hrs	\$15		\$10	\$25
Session 1	1	~1.5hrs	\$20		\$10	\$30
Back-up Participant*	1	30 min	\$15		\$10	\$25
Session 2	1	~1hr	\$20		\$10	\$30
Session 3	1	~1hr	\$20		\$10	\$30
Session 4	1	~1hr	\$20		\$10	\$30
Session 5	1	~2hrs	\$30	\$60 <sup>1</sup>	\$10	\$100
Session 6	2	~1.5hrs	\$20		\$10	\$30
Session 7	2	~1hr	\$20		\$10	\$30
Session 8	2	~1hr	\$20		\$10	\$30
Session 9	2	~1hr	\$20		\$10	\$30
Session 10	2	~2hrs	\$30	\$60 <sup>1</sup>	\$10	\$100
Session 11	3	~1.5hrs	\$20		\$10	\$30
Session 12	3	~1hr	\$20		\$10	\$30
Session 13	3	~1hr	\$20		\$10	\$30
Session 14	3	~1hr	\$20		\$10	\$30
Session 15	3	~2hrs	\$30	\$60 <sup>1</sup>	\$10	\$100
Session 16	4	~1.5hrs	\$20		\$10	\$30
Session 17	4	~1hr	\$20		\$10	\$30
Session 18	4	~1hr	\$20		\$10	\$30
Session 19	4	~1hr	\$20		\$10	\$30
Session 20	4	~2hrs	\$30	\$60 <sup>1</sup>	\$10	\$100
<b>TOTALS</b>			<b>\$485</b>	<b>\$240</b>	<b>\$230</b>	<b>\$955</b>

\*Back-up participants are eligible for this compensation when they are eligible and attend this visit but are not needed (because the primary participant was compliant).

<sup>1</sup>Participants who attend 5/5 TMS sessions per week will be eligible for a \$60 adherence bonus.

## **INFORMED CONSENT**

### **1. Consent Process**

Participants will complete an initial eligibility assessment by phone, reducing the likelihood that participants attend an Intake Visit only to learn that they are ineligible. The phone screen poses no more than minimal risk and involves no procedures for which written consent is normally required outside of the research context. All participants who are contacted for the phone screen will have been recruited through the Adult ADHD Treatment and Research Program or responded to an advertisement for the research study, and have therefore requested the initial phone screening call. Those interested/eligible at phone screen will be scheduled for an in-person Intake Visit (Week 0). At this Intake Visit, participants will provide written study consent



and HIPAA documents (combined) before completing additional survey measures and undergoing any study related activities. Participants will receive a copy of the combined consent/HIPAA form. Hard copies of Intake Visit data and a copy of the signed combined consent/HIPAA forms will be stored in a subject's study folder. The original signed combined consents/HIPAA will be centrally stored in Regulatory Consent Binders.

**2. Waiver of Authorization.**

Not applicable

**RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION**

**2. Staff Training**

The Principal Investigator and the Project Managers will oversee the development of protocols for laboratory related tasks and training of staff in these protocols. The Principal Investigator and/or the Project Managers will be responsible for the development of procedures pertaining to all study visits and implementing and monitoring ongoing staff training procedures accordingly. An initial, intensive training period will be implemented followed by periodic in-service trainings that will be coordinated by the Project Managers. They will also oversee study progress as part of regular study meetings. All research staff will undergo training on research practices involving human subjects, including the protection of subject confidentiality, and will maintain current certification in patient oriented research. Moreover, all research staff who administer TMS are required to undergo a TMS administration and safety training course.

**3. Study Facilities**

This project will be conducted at and through the Center for Interdisciplinary Research on Nicotine Addiction (CIRNA) and the Adult ADHD Treatment and Research Program at the University of Pennsylvania. The above mentioned centers have numerous similar protocols and well-developed procedures for staff training, data collection and storage, and study completion. The facilities available for this project include a large conference room, individual consulting rooms with computer/internet access, storage rooms, office space for study personnel, and data management facilities.

The MagPro R30 device with a Cool-B65 A/P figure 8 coil was purchased from Magventure, Inc., and is stored in a locked treatment room at the the UPENN TMS clinical service. All TMS administration will be conducted by trained personnel. The stimulation protocols are programmed into the software and controlled by the Patient Key generated for each participant; they are not alterable by the research staff administering the stimulation.



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