PROTOCOL TITLE:

TMS Studies of Working Memory and Cognitive Control

PRINCIPAL INVESTIGATOR:

Derek Evan Nee
Psychology
850-644-1963
nee@psy.fsu.edu

VERSION NUMBER/DATE:

Include the version number and date of this protocol.

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	9/30/19	Previously approved protocol changed to RAMP	no
2	6/10/20	Added COVID-19 precautions	yes
3	12/15/20	Added follow-up procedures	yes
4	4/30/2021	Revised COVID-19 precautions	no
5	7/26/2021	Added NDA surveys	no
6	8/16/2021	Revised Section 6.0	no
7	8/24/2021	Added New COVID-19 precautions	yes
8	5/16/2022	Added dizziness, lightheadedness, and syncope to risks	yes
9	2/21/2023	Added community recruitment to section 13.1	no
10	6/28/2024	Added recruitment site	no

Table of Contents

1.0 Study Summary

Study Title	TMS Studies of Working Memory and Cognitive Control
Study Design	Experimental/Control Design
Primary Objective	The purpose of the proposed research is to identify brain areas that correlate with working memory and cognitive control using transcranial magnetic stimulation (TMS).
Secondary Objective(s)	
Research Intervention(s)/ Investigational Agent(s)	NA
IND/IDE #	NA
Study Population	Healthy young adults
Sample Size	400
Study Duration for individual participants	1-2 hours
Study Specific Abbreviations/ Definitions	TMS – transcranial magnetic stimulation

2.0 Objectives*

2.1 Describe the purpose, specific aims, or objectives.

The purpose of the proposed research is to further our understanding in the mechanistic operations of working memory and cognitive control. We are interested in the brain mechanisms underlying working memory and cognitive control abilities. Our goal is to identify brain areas that directly correlate with working memory and cognitive control through the use of transcranial magnetic stimulation (TMS). TMS is a well-established, non-invasive technique used by thousands of labs around the world to study causal aspects of brain function.

2.2 State the hypotheses to be tested.

We will test the hypothesis that brain regions that are shown to correlated with a cognitive process are causally relevant to that process such that stimulating those brain regions produces a change in behaviors reflective of the cognitive process.

3.0 Background*

3.1 Describe the relevant prior experience and gaps in current knowledge.

Cognitive control refers to the ability to align behaviors in accordance with goals and contextual circumstances. This ability often depends upon maintaining information (e.g. instructions, goals) when it is no longer available to the senses – referred to as working memory. Cognitive control and working memory are central to higher-level cognition, but their mechanistic operations are poorly understood. In particular, little causal data is available regarding whether and how particular brain regions support cognitive control and working memory. The purpose of the proposed study is to further our understanding of these abilities.

3.2 Describe any relevant preliminary data.

NA

3.3 Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.

TMS is a well-established, non-invasive technique used by hundreds of labs around the world to study causal aspects of brain function. Also, TMS is one of the few non-invasive causal tools that researchers have for studying human brain function. The ability to causally associate brain regions with cognition is of central importance for our understanding of mental and neural function. Furthermore, basic understanding of mental and neural function will

improve our understanding of impairments observed in psychiatric and neurological disorders.

4.0 Study Endpoints*

4.1 Describe the primary and secondary study endpoints.

NA

4.2 Describe any primary or secondary safety endpoints.

NA

5.0 Study Intervention/Investigational Agent

1.1 Description: *Describe the study intervention and/or investigational agent (e.g., drug, device) that is being evaluated.*

NA

5.1 Drug/Device Handling: If the research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

NA

5.2 If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

NA

6.0 Procedures Involved*

6.1 Describe and explain the study design.

In the proposed research, we will used computer-based tasks that engage cognitive control and/or working memory. Typical paradigms will involve presenting stimuli such as words, letters, pictures, or sounds. In tasks involving working memory, participants will be asked to retain in mind some aspect of the stimulus after it is no longer present on the monitor. In tasks involving working memory and/or cognitive control, participants will make decisions on stimuli that are based on previous instruction and previous stimuli. Since cognitive control interacts with the reward system (i.e. to motivate cognitive control), we will also examine reward-related tasks either in tandem with cognitive control, or in isolation.

TMS will be delivered in one of two modes: 1) In "online" studies, TMS will be time-locked to the task (for example, a single pulse may be delivered 20, 60, or 100 ms after the onset of the stimulus) and we will investigate the critical period of involvement of a given region. Such studies will involve either single pulses of TMS or short burst

of pulses. Bursts will contain 5 or fewer pulses with bursts spaced by intervals of 3 seconds or more. All studies will conform to the safety limits established by Rossi et al. (2009). 2) In "offline" studies, longer duration TMS will be administered prior to the task. This TMS will transiently suppress or excite the region resulting in decreased or increased performance on the task. Three types of offline designs may be used: A) Continuous Theta-Burst stimulation (TBS), which is one of the most widely used offline techniques in which 600 pulses are delivered in bursts of 3 pulses (at 50 Hz) repeated at a rate of 5 Hz. This technique was introduced in 2005 by Huang et al. and has been used in hundreds of studies since. B) Intermittent TBS, which is another widely used offline technique introduced by Huang et al., 2005. As in continuous thetaburst stimulation, 600 pulses are delivered in 50 Hz bursts every 5 Hz. However, in intermittent TBS, 2 seconds of stimulation is alternated with 8 seconds of no stimulation. Hence, the entire set of pulses is delivered over 190 seconds. C) 1 Hz stimulation for at most 30 minutes. This technique was considered standard until the invention of TBS and has been used in hundreds of studies too. Again, all procedures will conform to safety limits established by Rossi et al. (2009). It is important to note that these stimulation parameters differ from those that are typically used to treat patients (e.g. depression) in clinical settings. These stimulation parameters are for research purposes designed at producing transient, not chronic, effects and to ensure the safety of the participant. With the exception of TBS, all of our stimulation protocols fall under the heading of either single pulse or low frequency rTMS, for which adverse effects are rare (classified as Class 3, low risk under Rossi et al., 2009). The versions of TBS that we administer are short lasting and have especially low rates of adverse effects (Oberman et al., 2011). In general, analyses will focus on the accuracy and speed with which participants performed the task. The critical analyses will compare these variable as a function of TMS parameters (e.g. timing, location, frequency).

In order to dose appropriately the TMS stimulation, it is necessary to determine an individual’s sensitivity to TMS. This is done by delivering TMS to the motor cortex to affect muscle activity in the hand in order to record the motor threshold (MT). MT is the standard in the field for determining the intensity of TMS for each individual to ensure participant safety.

MT will be determined in one of two ways: 1) Recording electromyography (EMG) of the first dorsal interosseus muscle of the hand contralateral to TMS to monitor muscle activity. In this case, persistent muscle activity will be elicited by having the participant activate the muscle using the appropriate flexion movement, and the effect of TMS on the muscle will be observed as a brief cessation of EMG activity. This is referred to as the active

motor threshold (AMT). 2) Observing a visually-identified hand twitch in the hand contralateral to TMS (e.g. if applying TMS to the left hemisphere of the brain, a twitch will be observed in the right hand). This is referred to as the resting motor threshold (RMT). In most cases, the AMT will be determined. However, if EMG cannot be recorded due to technical issues (e.g. the participant's hand is too sweaty to record a strong signal), RMT will be recorded. In both cases, the scalp region producing the largest hand twitch will be identified. To identify this region, TMS will be set to 30% of the maximal stimulator output, which is well below the motor threshold for most, if not all, individuals. TMS will be delivered to a scalp location approximating the location of motor cortex based upon surface features using the nose and ears as landmarks. From this initial location, TMS will be delivered. If ineffective to produce a hand twitch, the TMS coil will be moved to a new, nearby site, which will subsequently be tested. This process will continue until a grid of locations has been tested around the starting location, approximating 5 cm2. If a hand twitch has not been produced, this indicates that the stimulation is below threshold and the stimulator output will be raised by 5% of the maximum stimulator output. The process will then repeat until the maximal hand twitch at a given stimulation level is observed, thereby indicating the location of interest. During this process, the participant will be closely monitored and periodically asked whether the stimulation is producing any discomfort or unusual symptoms (e.g. dizziness). At the scalp location of interest, the lowest TMS intensity able to elicit 5 visible cessations of EMG activity in 10 trials (AMT), or 5 visible twitches in 10 trials (RMT) at this site will be determined. Individual MT will be used to determine the intensity of stimulation for each individual, as recommended by safety guidelines. This procedure usually takes about 5 minutes and also serves the purpose of acquainting participants to TMS stimulation. Once MT is determined, TMS will be administered within the limits of the safety guidelines recently updated in Rossi et al., 2021. An additional 12 years of research using TBS ranging between 80% and 100% RMT was examined to determine the continued efficacy of previously established guidelines in Rossi et al., 2009. Since the 2009 publication, the scientific community has gained a better understanding of safety risks and the rarity of adverse events (such as seizure) associated with TMS. To reflect current safety guidelines for offline studies using TBS, TMS will never exceed 100% of RMT or 120% of AMT. For offline studies using 1Hz stimulation, TMS will never exceed 110% of RMT or 130% of AMT. For online studies, TMS will never exceed 110% of RMT or 130% of AMT.

Electroencephalography (EEG) will be used to either guide TMS frequencies and/or targets, measure changes in brain activity

following TMS, or both. The EEG assesses electrical brain activity through surface recording disks (electrodes) which are placed near the participant's head. The electrodes transmit the signals, which are then amplified (via an 8 channel Brain Vision LiveAmp) and stored on a computer. The procedure is entirely non-invasive.

An electrode cap will be placed on the participant's head. In order to record brain activity, these disks need to be filled will a gel which allows the electrodes to better record brain activity at the scalp. Therefore, the participants in this study will need to clean their hair after participation. The gel is completely water soluble, and the procedure is painless. The MRI facility has sinks and towels, and the investigators will help to make sure the participant has thoroughly rinsed all the gel from their hair. After an accurate signal is assured, the signal derived from the electrode cap is then amplified, transmitted to a computer, and stored for later analysis.

In addition to the EEG recording, muscle activity from around the eyes may be recorded from the subjects. Muscle activity from around the eyes is recorded by two small sensors that will be placed below the participant's left eye, as well as behind the ears. These procedures are completely noninvasive and painless.

6.2 Provide a description of all research procedures being performed and when they are performed, including procedures being performed to monitor subjects for safety or minimize risks.

Below is a description of the kinds of tasks that participants may perform in a piecemeal fashion. It is likely that elements from multiple such tasks will be combined into a single task. Hereafter, stimuli will refer to letters, numbers, words, pictures, or sounds. Unless otherwise specified, stimuli will be affectively neutral. In general, tasks will range in duration from 5-10 minutes to 1-2 hours. Breaks will be given every 5-10 minutes. Multiple sessions may be performed. Based upon performance on the tasks, we may contact participants to perform other related tasks. Returning to perform other tasks will be optional and have no bearing upon the tasks the participants have already completed.

- Computer-based Tasks
    - Short-term memory
        a. In this task, participants are presented with a set of stimuli to remember. After a delay, participants will receive a test item. The test item can either be an old/new stimulus requiring a recognition decision (i.e. was the stimulus a member of the set?) or it can be a stimulus to be transformed to match a

stimulus in the set (e.g. rotate a grating until it matches a grating in memory).

- Span
    a. In this task, participants will be presented with a list of stimuli to remember. In some cases, they will be asked to make judgments in-between the presentation of memoranda (e.g. assess the validity of a simple arithmetic expression). Upon termination of the list, participants will be asked to reproduce the list.
- Change-detection
    a. In this task, participants will see a collection of stimuli, followed by another collection of stimuli. They will respond with whether the collection changed or not.
- Sequence Memory
    a. In this task, participants will learn a predefined stimulus sequence. Participants will make judgements regarding whether the presented stimuli follow the predefined sequence or not.
- Alternative forced choice
    a. In this task, participants will judge the categorical status of stimuli. Categories include word/non-word judgements, semantic judgements, number judgements (e.g. is the number odd or even), object category judgments (e.g. face, scene), and spatial judgments (e.g. which direction does an arrow point).
- Cued attention
    a. In this task, participants will be directed to attend to a particular stimuli, regions of space, or location of sound. Participants will make either alternative forced choice or memory judgements regarding the attended stimuli.
- Task-switching

a. In this task, participants will switch among two or more tasks of the nature described above.

- Doors Task
    a. Participants will be shown graphics depicting doors, and will be asked to choose a door. After picking a door, participants receive feedback on the screen indicating whether they have won or lost on that trial. The participants' goal is to do their best to win as much money as possible. In this task, participants will receive a monetary bonus for correct guesses, which will total between $0.00 and $10.00 depending on how many correct guesses they make. This task will take approximately 5-10 minutes.
- Motivated Behavior Task
    a. Participants will be given the opportunity to complete a specified number of trials for a specified reward. Trials will entail trials of the tasks described above or other simple cognitive tasks such as arithmetic.

- Written tasks
    - DSM-5 Crosscutting Assessment (Adult)
        a. This is an assessment requested by the NDA for clinical studies. This assessment in particular is used to assess a participant for any psychiatric diagnoses that the study can impact. The version being used asks adult participants if certain symptoms related to psychiatric disorders have been bothering them in the past two weeks.
    - WHODAS 2.0
        a. This is an assessment requested by the NDA for clinical studies. This assessment in particular is used to determine the disability status of a participant. The questionnaire asks the participant about difficulties due to a health condition. Health conditions include injuries, mental/emotional issues, and substance use issues. The questions are answered in the perspective of difficulty

completing a specific task within the past 30 days.

- PHQ-9
    a. This is an assessment requested by the NDA for clinical studies. This assessment in particular is used to determine the severity of Major Depressive Disorder if present in the participant. The questionnaire asks about behavior trends from the past two weeks in the form of a Likert scale.
- GAD-7
    a. This is an assessment requested by the NDA for clinical studies. This assessment in particular is used to determine the severity of anxiety if present in the participant. The questionnaire asks about behavior trends from the past two weeks in the form of a Likert scale.
- Raven's Progressive Matrices
    a. In this standardized measure of intelligence, participants decide which among several images completes a logical matrix of images
- Self-reported tasks
    a. At the end of an experimental session, we may ask participants to answer questions regarding their strategic approach to tasks. Examples of questions include whether participants verbally rehearsed material to themselves, whether they named images, and whether they maintained vigilance. In all cases, questions will be about task performance. No personal information will be requested for these tasks.
- Screening
    a. Participants will be screened to be fluent in English, between the ages of 18-30, and to have no contraindications for TMS. Participants will also be screened such that they do not belong to populations vulnerable to the Coronavirus Disease (COVID-19) and have not been exposed. They will also be asked to indicate whether they have received

a full FDA-authorized COVID-19 vaccination series, the specific vaccine product they received, and the date of complete vaccination.

- Demographics
    a. Demographic information including age, gender, race, and ethnicity will be collected. This information will be used for reporting purposes to demonstrate fair inclusion. Participants will be informed that providing this information will be optional. This information has no direct bearing upon the research to be performed
- Follow-up Form
    a. One month after the last TMS session, participants will be contacted and asked to fill out a follow-up form. This form inquires about possible experiences the participant may have had that may be attributable to TMS. This information will be used to assess any possible risks of TMS.

6.3 Describe:

- *Procedures performed to lessen the probability or magnitude of risks.*
- *All drugs and devices used in the research and the purpose of their use, and their regulatory approval status.*
- *The source records that will be used to collect data about subjects. (Attach all surveys, scripts, and data collection forms.)*

To lessen the probability or magnitude of risks, researchers will stop testing or administer breaks if participants feel frustrated, tired, and/or uncomfortable. Additionally, the occurrence of any adverse events associated with this study and its procedures, as well as any changes in risk level, will be monitored by the principal investigator and co-investigators.

The most severe risk is that of seizure. The risk of seizure will be minimized in two ways 1) Using stimulation parameters that are within the safety guidelines reported by Rossi et al., 2009, and 2) Excluding participants at increased risk for seizure as indicated in the exclusion criteria. Within the stimulation parameters to be used in the present protocol, no seizures have been reported resulting from TMS in the populations that we

will study. Personnel who administer TMS will be trained to recognize a potential seizure event and to act as first responders in order to administer appropriate initial care. In addition, all study personnel will be trained in CPR usage. However, we wish to emphasize that there are no known cases where individuals required the use of CPR during a TMS session. The major physical signs the study personnel will look out for in detecting a potential seizure include chewing movements, convulsions/tremor/shaking, difficulty talking, a blank stare, eyes rolling up, and profuse sweating. If any of these signs are observed, study personnel will stop the research procedure and inquire whether the subject feels okay. If the subject is unresponsive (and therefore likely experiencing a seizure), first-aid will be supplied. The first-aid response consists of making sure the subject is physically safe for the duration of the seizure. This involves moving the subjects out of the TMS chair and onto the floor lying down on their left side. The subject will be kept lying down on their left side, while the staff call emergency medical help, via a 911 call. Resources available in the laboratory include a first-aid kit and immediate phone access. In the extremely unlikely event of an actual occurrence of a seizure, it will be immediately reported to the IRB. To minimize headaches and/or other forms of discomfort, the experimenter will encourage participants to report any form of discomfort during the procedure. The experimenter will periodically directly query the participant regarding whether or not they are experiencing discomfort. In addition, an arm will be used to help support the coil to reduce downward pressure on the subject that could lead to neck discomfort. The experimental procedure will be immediately terminated whenever anyone reports experiencing discomfort. To prevent adverse effects on hearing due to the sound produced by TMS, all experimental participants will wear ear plugs.

In order to ensure that personnel are qualified to administer TMS, all personnel to be added to this protocol will receive a minimum of 10 hours of training with an experienced TMS administrator. In addition to training, personnel will be required to read safety documentation consisting of Rossi et al., 2009, and Oberman et al., 2011. Prior to being permitted to administer TMS, all personnel will meet with Dr. Derek Nee to ensure understanding of the TMS procedure and all potential contraindications. All personnel will receive CPR training and CITI training. Additionally, all personnel will be instructed on how to deal with a seizure.

The source records that will be used to collect data about subjects will be retained in digital format. Digital information will be stored on password protected local machines, or on secure cloud-based services such as Google Docs, also requiring a password.

Due to the COVID-19 national emergency and pandemic, in cases where participants or study staff have not completed a full FDA-authorized vaccination series at least 14 days before the study session, researchers will also apply the following precautions in conducting this research:

- No persons deemed as higher risk by the CDC will be included in the study. Participants will be screened such that they meet these requirements.
- COVID-19 related risks will be mitigated as much as possible. This will be done through screening for exposure to COVID-19, regular cleaning and disinfecting study areas, reducing in-person interactions, and use of personal protection equipment.
- To prevent the spread of pathogens during TMS, participants may be given a disposable face mask. Administered masks will contain no metal so as to be compatible with TMS.
- Unvaccinated participants will be unable to participate in this study if they have tested positive or if they were in close contact with a positive COVID-19 case within the last ten days.

For in-person study activities involving prospective subjects and study staff, we will as part of our screening and eligibility procedures implement the option of informing subjects and staff that their voluntary disclosure of their full COVID-19 vaccination status is an alternative to the requirement for COVID-19 precautions such as social distancing, use of masks, and other safety precautions. In doing so, we will use the following language: “In order to protect against COVID-19 or Coronavirus, if you come to the lab we are required to follow certain precautions like social distancing and use of masks. However, we don’t have to do this for persons who have completed a full COVID-19 vaccination. You may if you’d like share with us information about your COVID-19 vaccination, but this is your decision and is not required. You can still come to the lab and we will follow our usual COVID-19 precautions."

To implement this COVID-19 vaccination option, we will make a note in our study records for each prospective subjects and staff who choose to disclose their COVID-19 vaccination information.

6.4 What data will be collected during the study and how that data will be obtained.

The data that will be collected during the study includes identifying information. Additionally, brain activations, accuracies and reaction times to tasks will be collected. The data will be obtained using computerized-based tasks or written tasks.

6.5 If there are plans for long-term follow-up (once all research related procedures are complete), what data will be collected during this period.

In some cases, performance in some tasks will trigger eligibility for other tasks. In these cases, procedures will be identical to those described above.

6.6 For Humanitarian Use Device (HUD) uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

NA

7.0 Data and Specimen Banking*

7.1 If data or specimens will be banked for future use, describe where the specimens will be stored, how long they will be stored, how the specimens will be accessed, and who will have access to the specimens.

NA

7.2 List the data to be stored or associated with each specimen.

NA

7.3 Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

NA

8.0 Sharing of Results with Subjects*

8.1 Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how the results will be shared.

9.0 Study Timelines*

9.1 Describe:

- *The duration of an individual subject's participation in the study.*
- *The duration anticipated to enroll all study subjects.*
- *The estimated date for the investigators to complete this study (complete primary analyses)*

The duration for each individual's participation will be between 1 and 2 hours per session. Participants will participate in at least 1, and potentially several sessions. It may take up to several weeks to complete an entire task. The duration anticipated to enroll all study subjects is 72 months.

10.0 Inclusion and Exclusion Criteria*

10.1 Describe how individuals will be screened for eligibility.

Participants will be screened in order to minimize risks associated with TMS. Screening will proceed in two phases. First, the screening form will be sent to the participant via e-mail (see Appendix). The participant will be asked to respond with whether the answer to any question on the screening form is "yes." At this phase, the participant does not need to indicate to which question the answer is "yes." If the response is "yes" to any question, the participant will be excluded. If the participant passes the first phase of screening and remains interested in participating, the participant will be invited to perform the study. Participants will read the consent form and any questions will be answered. After answering questions, the participant will once again be presented with the screening form. In this case, the participant will fill-out the screening form. If the answer is "yes" to a given question, the participant may be asked to elaborate. A "yes" response may occur in the second screening, but not the first, if circumstances changed since the initial screening. The individuals included in this study will be adults from ages 18 to 30.

We will also exclude from study individuals who are vulnerable to or may have come in contact with COVID-19. We will include individuals who have completed a full FDA-authorized vaccination series at least 14 days before the study session, and individuals who have not been fully vaccinated provided that they pass the screening process. As with the other screening forms, the COVID-19 screening

form will be sent to the participant via e-mail (see Appendix). The participant will be asked to respond with whether the answer to question #1 on the form is "yes" or if, alternatively the answer to #1 is "no" and the answer to any other question on the screening form (#2 through #8) is "yes." Question #1 asks participants to indicate if they have received a complete vaccination series, the specific FDA-approved vaccine product they received, and the date of vaccination. At this phase, the participant does not need to indicate which to which of the other questions the answer is "yes." If the response is "yes" to any questions including #2 through #8, the participant will be excluded. If the participant passes the first phase of screening and remains interested in participating, the participant will be invited to perform the study. Participants will read the consent form and any questions will be answered. After answering questions, the participant will once again be presented with the screening form. In this case, the participant will fill-out the screening form. If the answer is "no" to #1 and "yes" to any of the other questions (#2 through #8), the participant may be asked to elaborate. A "yes" response may occur in the second screening, but not the first, if circumstances changed since the initial screening.

10.2 Describe the criteria that define who will be included or excluded in your final study sample.

Inclusion: Because we are interested in the mental function of adults prior to any age-related decline, participants will be between the ages of 18-30. Participants will also need to be fluent in English and have acquired fluency prior to the age of 6 since English is required to understand the instructions and some tasks will use English words/letters as stimuli.

Exclusion: Left-handed people will be excluded. Many brain functions are lateralized (e.g. language is often processed by the left hemisphere).

Based on recommendations of the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation (reported in Wassermann, 1998), as well as the recommendations of Rossi et al., 2009, we will exclude subjects on any of the following grounds: Metal anywhere in the head, excluding the mouth, History of seizures, Family history of epilepsy, Vascular, traumatic, tumoral, infectious, or metabolic lesion of the brain, Stroke, Chronic, or transient insomnia (e.g. jet lag), Alcoholism, Severe headaches, Cardiac pacemakers, Current use of medication for neurological or psychiatric conditions, Tinnitus, and Pregnancy. While the health risks to the fetus are unknown, magnetic field strength decreases approximately with the cube-root of the distance from the magnetic

coil. Therefore, a coil located on the scalp will have little direct effect on the abdomen, though changes in neural firing or emotional stress levels could in theory have distal impact. Nevertheless, any person who is pregnant will be excluded from the study. Additionally, people with the following will be excluded: hearing impairments and permanent retainers on the top portion of their jaw. A screening form (attached) will be used to assess each subject's eligibility for participation.

10.3 *Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of the above populations as subjects in your research unless you indicate this in your inclusion criteria.)*

- *Adults unable to consent*
- *Individuals who are not yet adults (infants, children, teenagers)*
- *Pregnant women*
- *Prisoners*

Special populations will not be studied.

11.0 Vulnerable Populations*

11.1 If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

NA

12.0 Local Number of Subjects

12.1 Indicate the total number of subjects to be accrued locally.

The total number of subjects to be accrued locally is 400.

12.2 If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

NA

13.0 Recruitment Methods

13.1 Describe when, where, and how potential subjects will be recruited.

Recruitment will be conducted at Florida State University at least one hour before testing. Potential subjects will be recruited via voluntary responses to flyers posted around campus and responses to approved electronic postings (see Appendix). Flyers will also be posted around local areas (e.g. coffee shops, restaurants). Additionally, flyers will be given to participants who have

volunteered for similar studies. (A paper flyer will be given to participants who have volunteered for similar studies after they have completed the study. These participants will have completed a study in a lab at Florida State University that uses similar methods to us and has agreed to hand out flyers for our studies to their participants). Volunteers will email or call a trained research technician who will screen the subject by the stated criteria. Potential subjects will be instructed to meet either in the Nee lab in the Psychology Building, Hajcak lab in the Psychology Building, or the MRI facility at the College of Medicine. All of these are private and secure locations requiring key card access.

13.2 Describe the source of subjects.

The source of subjects will be from Florida State University or the local community as long as subjects are eligible based on inclusion and exclusion criteria.

13.3 Describe the methods that will be used to identify potential subjects.

The methods used to identify potential subjects include the inclusion criteria and "no" responses to TMS screening questions.

13.4 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Materials to recruit subjects include an online advertisement and recruitment advertisements posted throughout Florida State University. These documents are attached, along with a sample recruitment email response from a researcher.

13.5 Describe the amount and timing of any payments to subjects.

Participants will receive $15 per hour or credit hours associated with the undergraduate Psychology course. Paid participants may also receive a performance-based bonus as incentive to perform the task to the best of their ability. Such incentives will only be available to paid participants and will be based upon accuracy and speed on the tasks and will tend to total $0-$5 per hour. In the event of a multisession study, paid participants may also receive a completion bonus. Participants that withdraw from the study prior to completion will receive prorated compensation (either monetary or credit hours) commensurate with the duration of participation. Lastly, monetary compensation or credit hours will be awarded once the study is complete, or after the subject withdraws from the study.

14.0 Withdrawal of Subjects*

14.1 Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.

Anticipated circumstances under which subjects will be withdrawn from the research without their consent include inattentiveness, damage to research equipment, clear misunderstanding of task instructions, and inappropriate behavior such as yelling or swearing.

14.2 Describe any procedures for orderly termination.

NA

14.3 Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.

Procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection, include appropriate compensation for their time and safekeeping of their data in appropriate records. Identifying information will be retained in digital format. Digital information will be stored on password protected local machines, or on secure cloud based services such as Google Docs also requiring a password.

15.0 Risks to Subjects*

15.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.

Risks for the study include:

GENERAL INFORMATION TMS is applied through a magnetic stimulator. This device consists of a set of electrical capacitors which can store and rapidly discharge electricity into a coil of electrical wire that is encased in shielded plastic. We will use MagPro X100 Magnetic Stimulator equipped for a figure 8 (i.e. butterfly) coil (MCF-B65) and a flex arm for coil positioning. The stimulator is manufactured by MagVenture, which is one of the most established manufacturers of TMS equipment with arguably the best currently available products and an excellent safety record. The coil is placed adjacent to the scalp above the targeted region. As the electrical current flows through the coil, a magnetic field is generated. The field passes through the skin and skull, inducing a brief change in the electrical flow of current in the brain. The magnetic pulse briefly alters neural activity in brain areas lying directly beneath the coil, presumably by causing discharge of neurons to a depth of 1.5 to 2.0

cm below the scalp. TMS has been used in a large number of laboratories worldwide for over 30 years. When administered within documented safety guidelines, adverse effects associated with TMS are rare. The risk of such adverse effects depends greatly on the form of stimulation employed. Below, various risks and side effects are described with an account of the likelihood of each effect under the proposed stimulation conditions. The primary sources for this information come from the recommendations of the International Workshop on the Safety of Repetitive Magnetic Stimulation, June 57, 1996 (reported in Wassermann, 1998). A new set of guidelines was published in 2009 (Rossi et al., 2009) based on a consensus conference which took place in Certosa di Pontignano, Siena (Italy) in 2008. Our proposed studies fall firmly within these established safety guidelines. There are no known long-term health risks to the use of TMS per se when operated within consensus safety guidelines (Rossi et al., 2009). In 2008, the FDA approved the use of high frequency TMS in the treatment of depression. Also in 2008, an international consensus conference on safety guidelines for TMS met. Their report (Rossi et al., 2009) systematically reviewed the thousands of healthy subjects and patients who have undergone TMS in order to allow for a better assessment of relative risks. The relative infrequency of adverse events using TMS was noted. They concluded that in the case of Class 3 studies (studies involving indirect benefit and low risk in normal subjects and patients that are expected to yield important data on brain physiology or safety, but have no immediate relevance to clinical problems), normal volunteers should be permitted to participate in TMS research. They also concluded that this research can be performed in a nonmedical setting (i.e., psychology labs, robotics labs, research institutions, etc. as opposed to a hospital or appropriately equipped outpatient clinic). The Rossi et al. (2009) consensus report went on to suggest safety guidelines based on the now rather extensive international experience with TMS. These guidelines include the TMS intensity and timing parameters considered safe, training, and planning for and managing emergencies. We will follow these guidelines, and have incorporated them into our screening and session procedures. The consensus safety guidelines (Rossi et al., 2009) are included as a supporting document attachment with this IRB application.

The PI on this project (Dr. Nee) has extensive experience with TMS during both graduate school and post-doctoral studies. He received formal training in the administration of TMS through an intensive course offered by Harvard Medical School (http://tmslab.org/educationintensive.php) lead by Dr. Alvaro Pascual-Leone, a world leader in non-invasive brain stimulation. He has delivered or directly supervised over 100 sessions of TMS with no serious adverse effects. Over the course of these sessions, one

participant withdrew from the study due to discomfort in a muscle near the stimulation site, and another withdrew due to dizziness. No other side effects have been reported. It is important to note that TMS protocols in the literature differ with respect to stimulation intensity, frequency, and duration. Adverse effects increase as each of these variables increases. The TMS protocols to be used in this study are reflective of the PI's previous studies and are suggestive of a low incidence of adverse effects with the planned stimulation parameters. Here I list the documented risks associated with TMS: Seizure. Seizure is a theoretical risk with TMS. In a workshop convened by the National Institute for Neurological Disorders and Stroke (NINDS) in 1996, researchers in the field agreed upon a set of TMS consensus safety guidelines, including recommended stimulation parameters and contraindications (Wasserman, 1998), and these consensus guidelines have been recently updated (Rossi et al., 2009). Widespread adherence to the 1996 guidelines has resulted in the virtual elimination of inadvertent seizures in TMS studies (Rossi et al., 2009). The levels of stimulation used in this protocol are well within safety guidelines (Rossi et al., 2009; Wassermann et al. 1998). In the Rossi et al. (2009) report it was stated that "the occurrence of seizures has been extremely rare, with most of the few new cases receiving rTMS protocols exceeding previous guidelines, often in patients under treatment with drugs which potentially lowered the seizure threshold. A total of 16 seizure cases have been identified to date (from tens of thousands on participants tested). Seven of these cases were included in the previous 1998 safety guidelines and 9 had been reported subsequent to the 1996 report. The majority of the seizures were induced in studies 1) using parameters outside the safety guidelines 2) examining patients with neurological or psychiatric conditions taking pro-epileptogenic medications, or 3) both. Our protocol excludes patients taking pro-epileptogenic medications and uses stimulation parameters that are well within the safety guidelines (Rossi et al., 2009). Four of the new seizures (two following single-pulse and two following repetitive TMS, rTMS) appear to have been induced in studies using "safe" stimulation parameters. The two rTMS incidents involved patients with either major depression (Figiel et al., 1998) or tinnitus (Nowak et al., 2006). The single-pulse incidents involved a patient with multiple sclerosis (Haupts et al., 2004) and a patient with bipolar depression (Tharayil et al., 2005). In summary, all of the new seizure incidents involved patients that would be excluded by our protocol, and in three of the cases, the patients were TAKING proepileptogenic medications. Since 2009, only one more seizure has been reported (Katz et al., 2011). This occurred in a healthy subject who developed symptoms of a seizure after single pulse TMS during initial motor threshold estimation. The initial stimulation setting was

at 50% of the maximum stimulator output (MSO) and produced a very large motor evoked potential signal (peak-to-peak amplitude 9.2 mV), with observable movement of the whole right hand. The stimulation was lowered until the movements were restricted to the fingers. The subject then reported nausea and became unresponsive with involuntary limb movements and loud breathing. These reactions persisted for about 90 s. Given the unusual nature of this case, it has been questioned whether this reaction should be considered a seizure (Alonso-Alonso et al., 2011). The event lacks unequivocal features to be diagnosed as a seizure, and may be better considered as convulsive syncope. In summary, with over 30 years of data, it is clear that the risk of seizure in protocols similar to the one used by us is exceedingly low. Moreover, the few cases that have been reported involve patients with neurological or psychiatric conditions taking proepileptogenic. The stimulation parameters to be used in the proposed studies have never been reported to induce a seizure and are well within the limits recommended by the guidelines established at the consensus conference (Rossi et al., 2009). Personnel who administer TMS will be trained to recognize a potential seizure event and to act as first responders in order to administer appropriate initial care. In addition, all study personnel will be trained in CPR usage. However, we wish to emphasize that there are no known cases where individuals required the use of CPR during a TMS session. The major physical signs the study personnel will look out for in detecting a potential seizure include chewing movements, convulsions/tremor/shaking, difficulty talking, a blank stare, eyes rolling up, and profuse sweating. If any of these signs are observed, study personnel will stop the research procedure and inquire whether the subject feels okay. If the subject is unresponsive (and therefore likely experiencing a seizure), first-aid will be supplied. The first-aid response consists of making sure the subject is physically safe for the duration of the seizure. This involves moving the subjects out of the TMS chair and onto the floor lying down on their left side. The subject will be kept lying down on their left side, while the staff call emergency medical help, via a 911 call. Resources available in the laboratory include a first-aid kit and immediate phone access. In the extremely unlikely event of an actual occurrence of a seizure, it will be immediately reported to the IRB.

Local pain, headache, or discomfort. The most commonly reported side effect of TMS is headache. This headache is typically of a muscle-tension type. It usually develops during or immediately after the stimulation and may last for minutes to hours following the end of the stimulation. It is typically limited to the day of stimulation. Neck pain or scalp pain may also occur. Both are usually managed easily with over-the-counter analgesics. The experimental procedure will be immediately terminated whenever anyone reports

experiencing discomfort. There are no reports of any such effects recurring. For many scalp locations, TMS feels only like a sudden tap on the scalp accompanied by a clicking sound. For other scalp locations, TMS can cause face or limb twitches. These twitches are not painful, but can feel odd or disquieting when first experienced. On some occasions, TMS might cross the threshold to the point where it would actually be described as producing a slightly painful scalp sensation. We will closely monitor subjects' comfort and will request them to tell us if the stimulation ever feels painful. If this occurs, we will immediately decrease TMS intensity to a level that is not painful. It is important to note that the likelihood of headache and other discomfort depends upon the stimulation parameters. Parameters for clinical applications for depression note a rate of 28% for pain, which is greater than the 16% observed for sham (i.e. no true stimulation; Loo et al., 2008). However, for TBS, the rate is less than 3% (Oberman et al., 2011). In many cases, discomfort can be due to neck pain resulting from holding one's head still against the coil. The figure 8 coil (MCF-B65) is lightweight compared to most coils and will be supported by an arm for positioning that alleviates downward pressure on the subject. Therefore, we anticipate rates of adverse effects due to pain and discomfort will be low and in accordance with the PI's previous history with the technique.
Transient hearing changes. TMS produces an audible clicking noise when the current passes through the coil. This click can result in tinnitus and transient decreased hearing if no protection is used. To prevent this adverse effect, all experimental participants will wear ear plugs. Animal and human studies have demonstrated that earplugs can effectively prevent the risk of hearing disturbances or discomfort due to TMS.

Participants may experience lightheadedness or dizziness. In rare cases, a syncope may occur (Rossi et al., 2021). Participants will be verbally queried for any feelings of lightheadedness or dizziness immediately after stimulation. Since these symptoms typically result from cerebral hypoperfusion (i.e. reduced blood flow to the brain), steps will be taken to facilitate cerebral perfusion including hydration (offering the participant water), cold compress to reduce vasodilation, and lowering the head of the participant. The procedure chair can recline to facilitate the latter. In the event of dizziness, experimental procedures will be paused until symptoms resolve. In the rare event of a syncope, participants will be monitored until they regain consciousness. Experimental procedures will be terminated, and the IRB will be informed.

The experimenters will also be provided with ear protection devices to minimize any discomfort they might experience from the clicks.
Transient cognitive/neuropsychological changes. Some repetitive TMS protocols have been shown to affect cognitive processing for

up to one hour following stimulation. Specifically, this is the case for "offline" techniques such as 1 Hz stimulation and theta-burst stimulation (TBS; Huang et al., 2005). These changes are small, but could in theory affect the subject's ability to drive home safely. However, our use of offline TMS always precedes the actual experimental task that subjects are performing. Since the effects of the TMS parameters we are proposing to use have never been observed to last more than 1 hour, the potential cognitive effects of TMS are expected to have worn off by the time the testing session is concluded. Participants may experience frustration from poor performance on the task. Another potential risk is probing for personal or sensitive information in surveys, interviews, or questionnaire.

15.2 If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.

NA

15.3 If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.

While the health risks to the fetus are unknown, magnetic field strength decreases approximately with the cube-root of the distance from the magnetic coil. Therefore, a coil located on the scalp will have little direct effect on the abdomen, though changes in neural firing or emotional stress levels could in theory have distal impact.

15.4 If applicable, describe risks to others who are not subjects.

NA

16.0 Potential Benefits to Subjects*

16.1 Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits.

No direct benefit.

16.2 Indicate if there is no direct benefit. Do not include benefits to society or others.

No direct benefit.

17.0 Data Management* and Confidentiality

17.1 Describe the data analysis plan, including any statistical procedures or power analysis.

Data analysis will follow standard procedures detailed in the relevant literature including frequentist tests and Bayesian statistics when applicable. Power analyses will be performed on relevant past and/or

preliminary data to inform planned sample sizes. If such data are no available, power analyses will be performed based on anticipated effect sizes.

17.2 Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

The steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission include retaining information in digital format. Digital information will be stored on password protected local machines, or on secure cloud based services such as Google Docs also requiring a password.

17.3 Describe any procedures that will be used for quality control of collected data.

NA

17.4 Describe how data or specimens will be handled study-wide:

- *What information will be included in that data or associated with the specimens?*
- *Where and how data or specimens will be stored?*
- *How long the data or specimens will be stored?*
- *Who will have access to the data or specimens?*
- *Who is responsible for receipt or transmission of the data or specimens?*
- *How data or specimens will be transported?*

NA

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

This section is required when research involves more than Minimal Risk to subjects.

18.1 Describe:

- *The plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.*
- *What data are reviewed, including safety data, untoward events, and efficacy data.*

- *How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).*
- *The frequency of data collection, including when safety data collection starts.*
- *Who will review the data.*
- *The frequency or periodicity of review of cumulative data.*
- *The statistical tests for analyzing the safety data to determine whether harm is occurring.*
- *Any conditions that trigger an immediate suspension of the research.*

The primary safety risk of TMS is seizure. Any seizures resulting from TMS will be reported to the IRB. The incidences of seizures will be monitored. If it appears that the incidences of seizures observed in the study are statistically higher than those reported in the literature (e.g. through the use of a chi-square test), the IRB will be alerted and the safety protocol will be revisited.

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.

The steps taken to protect subjects' privacy interests include testing in a private and secure location requiring keycard access. Subjects will be consented and screened individually in a testing room, where he or she will have contact with trained personnel identified in this application. During the consenting process, the participant will only have contact with trained personnel identified in this application.

19.2 Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.

Subjects will be able to stop or leave at any moment. Additionally, trained personnel will deliver instructions and provide information regarding where to go if they have questions.

19.3 Indicate how the research team is permitted to access any sources of information about the subjects.

The research team is permitted to access any sources of information about the subjects using the digital formats storing subject information. Researchers will need to know the passwords or have access to view the information.

20.0 Compensation for Research-Related Injury

20.1 If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

None

20.2 Provide a copy of contract language, if any, relevant to compensation for research-related injury.

Routinely, FSU, its agents, or its employees do not compensate for or provide free care for human subjects in the event that any injury results from participation in a research project. If you become ill or injured as a direct result of participating in this study, contact your regular medical provider. If you have insurance, your insurance company may or may not pay for these costs. If you do not have insurance, or if your insurance company refuses to pay, you will be billed. Funds to compensate for pain, expenses, lost wages and other damages caused by injury are not routinely available.

21.0 Economic Burden to Subjects

21.1 Describe any costs that subjects may be responsible for because of participation in the research.

NA

22.0 Consent Process

22.1 Consent will be obtained:

- In person, onsite in the Nee lab or Hajcak lab, prior to the collection of data.
- There will be no waiting period available between informing the prospective subject and obtaining consent.
- There will be no process to ensure ongoing consent
- HRP-090 consent will not be used.
- The individuals listed in the application will tell subjects that the purpose of the study is to understand the mental processes involved in retaining information in mind when it is no longer available to the senses, and using retained information to guide behavior. The participants will also be informed of the duration of the experiment, use of TMS, use of EEG, and inclusion and exclusion criteria.
- Additionally, participants will be screened in order to minimize risks associated with fMRI. Screening will proceed in two phases. First, the screening form will be sent to the participant via email (see Appendix). The participant will be asked to respond with whether the answer to any question on the screening form is “yes”. If the response is “yes” to any question, the participant will be excluded. If the participant

passes the first phase of screening and remains interested in participating, the participant will be invited to perform the study. Participants will read the consent form and any questions will be answered. After answering questions, the participant will once again be presented with the screening form. If the answer is "yes" to a given question, the participant may be asked to elaborate. A "yes" response may occur in the second screening, but not the first, if circumstances changed since the initial screening.

- Consent discussion will occur prior to data collection. Data collection will not occur until subjects understand the study outlines and protocol.
- Researchers will inform subjects that participation is voluntary and they can leave at any moment.
- Researchers will ask participants questions regarding understanding of the study before proceeding.
- The consenting process will take as long as any subject needs to understand the experiment.
- Steps that will be taken to minimize the possibility of coercion or undue influence include understanding the task and a formal signature on the consent document before proceeding with data collection.

Non-English Speaking Subjects

- NA

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

- *NA*

Subjects who are not yet adults (infants, children, teenagers)

- *NA*

Cognitively Impaired Adults

- *NA*

Adults Unable to Consent

- NA

Adults Unable to Consent

- NA

23.0 Process to Document Consent in Writing

23.1 Describe whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not, describe whether and how consent of the subject will be documented in writing.

Yes, written consent will be obtained.

23.2 If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent.

23.3 (If you will document consent in writing, attach a consent document. If you will obtain consent, but not document consent in writing, attach a consent script. Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)"to create the consent document or script.)

A consent document is attached.

24.0 Setting

24.1 Describe the sites or locations where your research team will conduct the research.

- *Identify where your research team will identify and recruit potential subjects.*
- *Identify where research procedures will be performed.*
- *Describe the composition and involvement of any community advisory board.*
- *For research conducted outside of the organization and its affiliates describe:*
  - *Site-specific regulations or customs affecting the research for research outside the organization.*
  - *Local scientific and ethical review structure outside the organization.*

The research team will identify and recruit potential subjects in the Nee lab or Hajcak lab in the Psychology Building at Florida State University. Consent and TMS screening will occur in the Nee lab or Hajcak lab in the Psychology building at Florida State University. The research procedures will be performed in the College of Medicine at Florida State University. This is where the

TMS and EEG equipment are housed. There will be no composition and involvement of any community advisory board.

25.0 Resources Available

25.1 Describe the resources available to conduct the research: For example, as appropriate:

- *Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?*
  Much of the student population of Florida State University will be eligible for our studies. This is a large pool from which to draw which will ensure the ability to recruit and test the required number of participants.
- *Describe the time that you will devote to conducting and completing the research.*
  The research will be conducted over the next several years
- *Describe your facilities.*
  The Nee lab and Hajcak lab are equipped with testing rooms with computers designated for testing subjects and privacy for consenting and screening participants. The College of Medicine houses the TMS equipment where TMS studies will be performed.
- *Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.*
  A CPR kit and AED are available at the TMS suite. Emergent medical care is available through standard sources (e.g. 911).
- *Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.*
  All persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions by completing the Human Subjects Research training offered by CITI, shadowing trained researchers, and training in seizures and CPR.

26.0 Multi-Site Research*

*26.1 Study-Wide Number of Subjects**
If this is a multicenter study, indicate the total number of subjects to be accrued across all sites.

NA