INSTRUCTIONS:

- *Use "TEMPLATE PROTOCOL (HRP-503)" to prepare a document with the information from following sections.*
- *Depending on the nature of your study, some sections may not be applicable to your research. If so mark as "NA". For example, research involving a retrospective chart review may have many sections with "NA." For subsections, like 1.x or 8.x, you can delete it if it's not applicable.*
- *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*
- *As you are writing the protocol, remove all instructions in italics so that they are not contained in the final version of your protocol.*
- *Omit starred (*) items if this is the activation of a protocol at a new site or sites that will be overseen by a principal investigator who will take separate and full responsibility for that site or those sites. Complete by describing information specific to the site(s). Do not repeat information in the approved protocol that applies to all site(s).*

PROTOCOL TITLE:

Studying Reward Processing with fMRI, EEG, and TMS

PRINCIPAL INVESTIGATOR:

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VERSION NUMBER/DATE:

Include the version number and date of this protocol.

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	4/19/2022	Added self-report and interview measures, more detailed exclusion criteria. Added protocol for assessing and addressing risk for suicide, and training for basic life support.	Yes
2	6/24/2022	Updated locations in which recruitment flyers can be posted and distributed. Additional self-report survey (DASS-21). Changes are highlighted in red.	No
3	8/12/22	Updated recruitment location to include ResearchMatch	No

4	6/28/2024	Added recruitment site	No

Table of Contents

1.0 Study Summary

Study Title	Studying Reward Processing with fMRI, EEG, and TMS
Study Design	Within-subject Experimental/Control Design
Primary Objective	The purpose of the proposed research is to examine the impact of TMS on brain activity that has been linked to anhedonia using functional magnetic resonance imaging (fMRI) and EEG.
Secondary Objective(s)	
Research Intervention(s)/ Investigational Agent(s)	NA
IND/IDE #	
Study Population	Adults, aged 18-55
Sample Size	80
Study Duration for individual participants	10-15 hours over 4-5 weeks
Study Specific Abbreviations/ Definitions	fMRI – functional magnetic resonance imaging EEG – Electroencephalogram 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 of neural activity that has been linked to anhedonia (i.e., reward-related neural activity) – by examining the impact of multiple TMS sessions on reward-related neural activity. Our goal is to assess whether stimulating medial prefrontal cortex, relative to the inion, produces increases in neural response to rewards using EEG and fMRI. EEG, fMRI, and TMS are well-established, non-invasive techniques used by thousands of labs around the world to study brain function—and this work would begin to suggest specific ways to modulate neural activity that has been implicated in anhedonia and depression.

2.2 State the hypotheses to be tested.

We hypothesize that stimulating the medial prefrontal cortex (MPFC), relative to a control site (i.e., inion), using TMS (i.e., 5 sessions over a week) will result in increases in reward-related EEG and fMRI measures. We additionally examine whether TMS will result in changes in self-report measures.

3.0 Background*

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

We have conducted extensive studies demonstrating hyperactive reward-related neural activity in depression and in relation to anhedonia. In a recent study, we found that a single session of TMS to MPFC potentiated EEG-based reward measures. In the current study, we extend this work to individuals who report high levels of anhedonia—and to multiple TMS sessions and include fMRI measures of reward-related neural activity as an outcome. Finally, we assess whether TMS results in changes of self-report measures of anhedonia and related constructs.

3.2 Describe any relevant preliminary data.

We recently found that a single session of TMS to MPFC increased the RewP; that paper is currently under review and forms the basis for the current paper. We are interested in whether a more protracted TMS protocol to MPFC (5 sessions within a week) would increase reward-related neural measures relative to a control site – and if those changes might be longer lasting and relate to changes in self-report.

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.

We and others have found in multiple studies that depression is associated with reduced reward-related neural activity measured with fMRI and EEG. Both are non-invasive tools that researchers have for studying human brain function, especially in the context of depression. Yet, there have been no causal demonstrations that increasing reward-related neural activity results in changes in depression or related experiences. Here, we focus on anhedonia—the degree to which individuals report day-to-day activities as enjoyable—as individual differences in anhedonia have consistently been linked to reward dysfunction.

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 use computer-based tasks that examine reward processing. Subjects will be screened by the MR technologist, and will be excluded if they meet any exclusion criteria. Subjects will be given instructions about the task and the MRI scanning environment. If there is any concern about claustrophobia, participants will be encouraged to try the mock scanner before entering the MRI scanner. The mock scanner is located next door to the MRI scanner and provides a simulated MRI

environment. If they are uncomfortable with the enclosed environment (at any time), they can exit the study and receive compensation for their time. Otherwise, participants will then be given a short practice session on the task either before entering the scanner, or during collection of preliminary and/or structural images. After being positioned in the scanner by the technologist, the technologist will acquire initial calibration scans. A structural image of the head and brain may be acquired before or after the functional imaging data. The remaining time in the scanner will be used to collect functional imaging data while subjects perform the task. Response time and accuracy data will be recorded during the task. We will relate these measures to the fMRI data from the scanner, in order to understand the relationships between neural activity and behavioral performance.

All TMS studies will conform to the safety limits established by Rossi et al., 2009 and recently updated by Rossi et al., 2021. Two 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 theta burst 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. Again, all procedures will conform to safety limits established by Rossi et al. 2009 and updated by Rossi et al., 2021. The versions of TBS that we administer have especially low rates of adverse effects (Oberman et al., 2011; Rossi et al., 2021).

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 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 cm^2. 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.

TMS will be delivered to multiple sites of interest. Site order will be randomized across participants.

Electroencephalography (EEG) will be used to measure changes in brain activity caused by TMS. 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 will perform. 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
    - 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
  - DARS
    a. Self-reported anhedonia will be measured using the Dimensional Anhedonia Rating Scale (DARS). The DARS is an appealing measure due to its high internal consistency, convergent validity with other measures of anhedonia, divergent validity with depression scores, and ability to capture state levels of anhedonia. This latter property makes it suitable for measuring changes in anhedonia.
  - Screening
    a. Participants will be screened to be fluent in English, between the ages of 18-55, and to have no contraindications for MRI or 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. To be eligible for participation in this study, participants must score 46 or below on the DARS, reflecting increased anhedonia.
  - 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
  - Handedness
    a. Edinburgh Handedness Inventory, which asks about which hand is used in various tasks, will be collected to determine the dominant hand.

- DSM Crosscutting
    a. The DSM-5 Level 1 Cross-Cutting Symptom Measure is a self- or informant-rated measure that assesses mental health domains that are important across psychiatric diagnoses.
- World Health Organization Disability Assessment Schedule (WHODAS)
    a. The WHODAS is a generic assessment instrument developed by WHO to provide a standardized method for measuring health and disabilities across cultures.
- Patient Health Questionnaire (PHQ-9)
    a. The PHQ-9 is a brief depression severity measure.
- Generalized Anxiety Disorder (GAD-7)
    a. The GAD-7 is a brief measure for assessing generalized anxiety disorder.
- Quick Inventory of Depressive Symptomatology (QIDS-SR)
    a. The QIDS-SR is a brief self-report assessment of depressive symptoms.
- Pain scale
    a. Self-reported pain scale.
- Depression Anxiety and Stress Scale (DASS 21)
    a. a 21-item questionnaire to assess symptoms of depression, anxiety and stress.

- Interviews
    - Montgomery-Asperg Depression Rating Scale (MADRS)
        a. The MADRS is a diagnostic questionnaire to measure the severity of depressive episodes.

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

For fMRI, additional risks and preventions include: 1) Magnetic field attracting ferromagnetic objects: Subjects will be screened for metallic objects prior to entering the scan room to minimize this risk and anyone with a questionable history of metal will not be allowed to enter the scanner room. 2) Claustrophobia: Any participant reporting the experience of claustrophobia will be removed from the magnet immediately, debriefed, and given compensation for their time. 3) Noise: All participants will be required to wear ear plugs to shield them from scanner noise while allowing communication from the technician. If the noise is overly bothersome to the subjects, they will be removed from the magnet immediately. Please note: 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 coinvestigators of this study, as well as the scanner technician.

For TMS, 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 updated by Rossi et al., 2021, and 2) Screening and excluding participants with increased seizure risk as indicated by Rossi et al., 2009 and Rossi et al., 2021. As extensively detailed in section 15.1 below, risk for seizure is very low, even for individuals with elevated risk. Due to our interest in individuals with elevated anhedonia, we will not be able to exclude individuals with psychiatric disorders (i.e. major depression) and/or individuals receiving medications to treat psychiatric disorders, both of which increase seizure risks. However, we will screen for other factors that increase seizure

risks and exclude participants accordingly. See section 15.1 for further details of seizure risks.

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 Basic Life Support and 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, 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.

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 while being tested in the MRI scanner.

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.

The MRIF contracts with The Mind Research Network (MRN) for screening of all subjects. To this end, subjects electing to partake in the IF program will have their T1 and T2 weighted scan data sent to MRN via encrypted data link. Other scans such as Susceptibility Weighted Images (SWI), Diffusion Weighted Images (DWI), and Fluid-attenuated Inversion Recovery (FLAIR) can also be send to MRN for review, if needed.

The MRN Contracted Radiologists will review images provided to them, and do not have access to additional clinical information. The MRI scans are collected under research protocols and are not obtained for clinical purposes.

The research MRI scans are not a substitute for a clinical scan and might not show problems that may be picked up by a clinical scan. If MRNs find an abnormality that requires follow-up, they may also mail a copy of the report to the subject, or contact them (with their permission), to help answer questions.

All MRN radiology reviews are completed within 30 days and are forwarded as a de-identified report directly to the MRI Technologist. All reports are then printed and mailed via US Postal Service to the subject's mailing address. They are provided with the contact information of the MRI Technologist in case they have questions. Any returned reports will be recorded and the hard copy destroyed.

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 30 minutes 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 and fMRI. Screening will proceed with a combination of e-mail, phone, and in person questions. First, the screening forms will be sent to the participant via e-mail (see Appendix), performed

over the phone, or both. 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. Screening for TMS will be completed again in each experimental session to assess if any changes have occurred prior the last screening. The individuals included in this study will be adults from ages 18 to 55.

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.

Finally, screening for this study will also involve completing the Dimensional Anhedonia Rating Scale (DARS); only participants who score 46 or below (i.e., those who endorse increased anhedonia) are eligible.

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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 18-55. 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. Because of the visual presentation of stimuli, participants will need to have normal or corrected-to-normal vision. Only participants who score 46 or below on the Dimensional Anhedonia Rating Scale (DARS) are eligible.

Exclusion: Left-handed people will be excluded. Many brain functions are lateralized (e.g. language is often processed by the left hemisphere). While such lateralization is typically very consistent in right-handers, brain lateralization is less predictable in left-handers which can confound localization of function. Participants must pass the MRI screening protocol, excluding people who have metal in any portion of the body, have medical complications, cardiac pacemaker cochlear implant, aneurysm clip, IUD shrapnel, history of metal fragments in eyes, neurostimulators, weight over 300 pounds, known problems of claustrophobia, or illicit drug use. Because alcohol has a transient effect on neural activity, subjects will be screened to have not consumed alcohol for the past 24 hours via self-report. 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.

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 and Rossi et al., 2021, 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, 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. A screening form (attached) will be used to assess each subject's eligibility for participation. In addition the above, the following exclusion criteria will be applied:

1. Medical contraindication for neuromodulation and/or MRI (e.g., ferrous metal in head, seizure disorder, brain tumor, stroke, aneurysm, multiple sclerosis, etc.)
2. Active substance use disorder in last 3 months or any current substance use that puts the participant at increased risk or significant impairment

3. Dementia or other cognitive disorder making unable to engage in treatment
4. Any history or diagnosis of Schizophrenia, Schizoaffective Disorder, delusional Disorder or other psychotic illness that precludes safe participation in trial
5. Suicidal risk that precludes safe participation defined as clinical impression that the participant is at significant risk for suicide
6. OCD cannot be the primary disorder but can have OCD symptoms
7. Inability to stop taking any medication that significantly lowers the seizure threshold (e.g., tricyclic antidepressants, clozapine, etc.)
8. Current, planned, or suspected pregnancy
9. Unstable medical conditions or any current medical condition that could preclude being able to safely participate in TMS treatment (e.g., unstable metabolic abnormality, unstable angina, etc.)
10. Severe Traumatic Brain Injury
11. We will exclude non-English speakers because of the need for rapid communication during the delivery of treatments
12. Significant ongoing litigation or claims that impact research activities, as determined by the research study team. (Research may especially be impacted when mental health or pain is being evaluated for litigation or claims, such as civil and criminal cases, disability claims and worker's compensation).

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 150.

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, at the FSU Behavioral Health Clinic at Apalachee Center Clinic, FSU Psychology Clinic, community spots (i.e. coffee shops and restaurants) and responses to approved electronic postings (see Appendix). In addition, subjects may be reached out to via an 'Okay to be Contacted' list that was collected/provided by Dr. F. Andrew Kozel, a member of the FSU College of Medicine (FSU STUDY #STUDY00002548: FSUN Future Contact Registry), via the SONA system at FSU where potential subjects will read about and sign up for the study on the SONA system or via ResearchMatch which is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University (they maintain the IRB approval for the Research Match database creation and recruitment). 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. DARS will be completed electronically to identify eligible participants. Potential subjects that pass initial screening 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 (e.g., having scored 46 or below on the DARS) and "no" responses to TMS and MRI 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, community spots, the FSU Psychology Clinic, and the Apalachee Center Clinic. 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 $20 per hour. 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-$10 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:

- Frustration from poor performance on the task, fatigue, or eye-strain
- Probing for personal or sensitive information in surveys, interviews, or questionnaires.
- Risks from MRI:
    - Magnetic field attracting ferromagnetic objects. There is a potential risk of the main magnet field attracting ferromagnetic/metallic objects towards the magnet.
    - Claustrophobia. The magnet is a small enclosed space that can induce feelings of claustrophobia.
    - Noise. The scanner makes a bothersome/loud noise during the course of data collection. This can damage hearing if measures are not taken to protect the ears.
- Risks from EEG:

  Risks are minimal. The EEG recording is completely non-invasive. The EEG will be recorded with a gel-based system. There is the possibility that some participants will experience mild, temporary itching or tingling sensation in response to the electrode cap or electrode gel. This is neither harmful nor permanent. During the EEG recording, there is a small possibility of mild skin irritation (redness) where the electrode contacts the skin. However, this is rare and temporary. If a participant is afraid of needles, there is a chance that they may become dizzy or lightheaded at the

sight of the plastic syringes that we use to put gel in the EEG cap – they are not sharp, but because they look a little like needles, they might make the participant anxious.

- Risks from TMS:

  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, and has recently been updated (Rossi et al., 2021). 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; Rossi et al., 2021). 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, which were updated in Rossi et al., 2021. 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; Rossi et al., 2021) are included as a supporting document attachment with this IRB application. The PI on this project (Dr. Nee) has extensive experience with TMS during graduate school, post-doctoral studies, and at FSU. 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. 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 updated (Rossi et al., 2009; Rossi et al., 2021). 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; Rossi et al., 2021). In the Rossi et al. (2021) report it was stated that "the risk of rTMS in inducing a seizure is definitely low, even in patient populations taking drugs acting on the central nervous system, at least with the use of traditional stimulation parameters and focal coils." These conclusions were based upon an estimated risk for seizures in single, paired, and low frequency stimulation paradigms to be 8/100,000 sessions across high and low-risk subjects, and 7/100,000 sessions in repetitive TMS (rTMS) paradigms. Individuals at elevated risk (see paragraph below) were reported to have a standardized risk of 27/100,000 in single, paired, and low-frequency TMS, and 67/100,000 in rTMS.

The following are considered factors that place participants at elevated risk for seizures: sleep deprivation, stress/anxiety, metabolic abnormalities, raised blood concentrations of proconvulsant medications, alcohol withdrawl, use of stimulations such as cocaine or MDMA, use of immunosuppressive therapy with agents that can cause the posterior reversible leukeoencephalopathy sundrome, diaysis, systemic infection, and fever. In addition, individuals with epilepsy and other neurological conditions are at elevated risk for seizures. Elevated seizure risk has also been reported in psychiatric conditions including major depression, schizophrenia, autism, bipolar disorder, and alcohol abuse. The presence of any of these factors would cause an individual to be considered at elevated risk of seizure, and therefore, at elevated risk of a TMS-induced seizure. Our TMS screening form is designed to exclude individuals at elevated risk of seizure from these causes with the following exception: since we are interested in individuals with elevated anhedonia, we will not exclude individuals with psychiatric conditions (e.g. major depression) nor individuals who are taking medications to treat psychiatric conditions. With regard to the latter, the safety guidelines of the Rossi et al., 2009 originally advised caution with regard to medication status, but after further study, the Rossi et al., 2021 guidelines state that "the currently available data showing low seizure rate no longer support this recommendation." Therefore, medication

status is not considered to confer undue risk. Although risk may be elevated for individuals with psychiatric conditions, we note that patients with major depression are among the most studied population with TMS and form a large part of the basis of the conclusions of Rossi et al., 2021 that "seizure risk is definitely low." As a result, Rossi et al., 2021 indicate that psychiatric populations are not contraindicated for TMS, but "it remains necessary to be prepared to deal with a seizure that might arise in any experimental protocol." We will thus take steps to be prepared as follows:

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 Basic Life Support and 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. 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.

Although we do not expect it to occur frequently, some subjects may endorse suicidality or increased risk for suicidality; in this event, we will implement the following protocol:

Participants will have a clinical interview performed, and as part of that clinical interview, we will assess suicidality. If participants endorse any suicidal ideation, the severity of suicidality will be assessed using the structured interview on the following pages, and the Joiner method. This procedure is adopted from the FSU Psychology Clinic using the clinic's suicide decision tree, which is an empirically validated structured interview.

Joiner et al. (1999) use the following method to designate risk severity:

1. An individual's risk for suicide is designated nonexistent if he or she has no current suicidal symptoms, no history of suicide, and no or few other risk factors.

2. Risk for suicide is considered mild if the individual is a multiple attempter with no other risk factors or is a non-multiple attempter experiencing suicidal ideation of limited intensity and duration, no or mild Resolved Plans and Preparation, and no or few other risk factors.

3. An individual is designated at moderate risk if he or she is a multiple attempter with any other significant risk factor. A non-multiple attempter with moderate to severe Resolved Plans and Preparations or moderate to severe Suicidal Desire and Ideation accompanied by at least two other risk factors is also considered to be at moderate risk for suicide.

4. A multiple attempter with two or more risk factors or a non-multiple attempter with moderate to severe symptoms of Resolved Plans and Preparations accompanied by one other risk factor is designated at severe risk for suicide.

5. An individual is at extreme risk for suicide if he

or she is a multiple attempter with severe Resolved Plans and Preparation or is a non-multiple attempter with Resolved Plans and Preparations and two or more other risk factors.

Once an individual has been assessed for suicide risk, we will take the following actions, as suggested by Joiner et al. (1999):

For any participant with suicidal ideation, phone numbers for mental health resources will be provided. At their request, participants will be referred to clinicians from the FSU Psychology Clinic, with whom they may speak about their discomfort or distress.

1. If an individual is considered to be at mild risk, he or she will be instructed to use self-control strategies and to seek out social support in the event that he or she becomes suicidal (Safety Card). If these strategies fail, he or she will be instructed to contact an emergency mental health resource or go to the emergency room, the phone numbers for which will be provided.

2. A person who is at moderate risk for suicide will be given a card with a list of steps to follow in case of emergency (Safety Card), which will also contain phone numbers for emergency: 911, 211 (Tallahassee's crisis line), 1800273TALK (National Suicide Prevention Lifeline). He or she will also be given an offer to go to the FSU Psychology Clinic with the interviewer for further care, if desired. Dr. Hajcak (Associate Investigator) will be consulted with immediately for any risk greater than minimal.

3. Someone who is at severe or extreme risk for suicide will be given an offer to go to the FSU Psychology Clinic with the interviewer for further care. If the risk is imminent and serious, then the University's Crisis Management Unit (appropriate mental health providers for suicidal crisis) will be contacted. If he or she refuses such hospitalization (or further care at the FSU Psychology Clinic), the experimenter will call 911 so that the police can escort the participant to further care.

For additional details, see the accompanying interview and safety plan card in the appendix.

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.

NA

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.*

NA

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. An exception is if the participant's responses indicate that they may be at imminent risk for suicide or harming oneself or others. In these cases, one of the trainee clinicians will be notified and will contact the participant with beneficial information and further resources. Resources include self-help plans, crisis line numbers, referral information to mental health clinics, and if necessary for their safety, notification of emergency services.

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 reward. The participants will also be informed of the duration of the experiment, use of fMRI, use of TMS, use of EEG, and inclusion and exclusion criteria.
- Additionally, participants will be screened in order to minimize risks associated with fMRI and TMS. 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. Steps that will be taken to minimize the possibility of coercion or undue influence.
- 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 fMRI 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 MRI scanner is 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?*
  Many students of Florida State University and community members of the Tallahassee area 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 MRI scanner eye tracker, TMS, and EEG equipment where participants will perform experiments.
- *Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.*
  A first aid kit is 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 and shadowing trained researchers.

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