Causal Role of Frontostriatal Circuitry in Goal-directed Behavior

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Protocol Number: 22-2430

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Summary of Changes from Previous Version:

Version Control	Affected Section(s)	Summary of Revisions Made	Rationale
V2	Adverse events reporting section. Side effects description.	There is no plan for a follow-up 30 days following the completion of study participation. Side effects were expanded to include psychological discomfort from receiving stimulation and rare side effects to mood, concentrating, and sleepiness.	This is now consistent with our previous work using transcranial magnetic stimulation. Side effects are now consistent between post-stimulation questionnaire and description of risks.
V3	Adding EMG and session 1 TMS for tolerability.	An EMG recording is added for session 1, 3, and 4. TMS is added to the end of the first session to screen participants with low tolerability. Inclusion criteria updated to be right-handed only.	Recent findings suggest that recording electrical activity in the hand and forearm might contribute to the mechanistic understanding of our findings. To increase study feasibility, participants will receive two practice blocks of TMS on the first session to screen for tolerability.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Causal role of frontrostriatal circuitry in goal-directed behavior

Study Description: The purpose of this clinical trial is to investigate the causal role that frontrostriatal circuitry plays in goal-directed behavior. The participants will perform a reward-based decision-making task. During the task, cross-frequency patterned rhythmic transcranial magnetic stimulation (rTMS) will be delivered at delta-beta frequency, a control-frequency, or an active sham to either the dorsolateral or medial prefrontal cortex (PFC). Electroencephalography will be collected concurrent with stimulation. Structural and functional magnetic resonance imaging (MRI) will be collected during performance of the reward-based decision-making task to localize the stimulation targets.

Objectives: Primary Objective: To investigate whether delta-beta rTMS to anterior middle frontal gyrus will produce an increase in goal-directed behavior during reward-based decision-making.
Secondary Objective: To investigate whether delta-beta rTMS to anterior middle frontal gyrus will result in a lasting increase in delta-beta coupling during the decision-period of reward-based decision-making.
Exploratory Objective 1: To investigate whether personality traits of motivation explain individual differences in the primary outcome.
Exploratory Objective 2: To investigate whether theta-gamma rTMS to medial prefrontal cortex will produce an increase in reward-evaluation during reward-based decision-making.
Exploratory Objective 3: To investigate whether theta-gamma rTMS to medial prefrontal cortex will result in a lasting increase in theta-gamma coupling during the decision-period of reward-based decision-making.
Exploratory Objective 4: To investigate whether the strength of functional connectivity between dorsal striatum and anterior middle frontal gyrus explains individual differences in the primary outcome.

Outcomes: Primary Outcome: Behavioral metric, percentage of hard trials chosen, during the streamlined version of the Expenditure of Effort for Reward Task (S-EEfRT).
Secondary Outcome: Neural metric, degree of phase-amplitude coupling between prefrontal delta oscillations and left motor beta oscillations, quantified during the decision epoch of the S-EEfRT.
Exploratory Outcome 1: Personality metric, traits of motivation explain individual differences in the primary outcome.
Exploratory Outcome 2: Behavioral metric, percentage of hard trials chosen as a function of incentive during the S-EEfRT.
Exploratory Outcome 3: Neural metric, degree of phase-amplitude coupling between prefrontal theta oscillations and posterior gamma oscillations, quantified during the decision epoch of the S-EEfRT.

	Exploratory Outcome 4: Connectivity metric, strength of task-based functional MRI connectivity between dorsal striatum and dorsolateral prefrontal cortex during the decision-epoch of the S-EEfRT.
Study Population:	We will recruit healthy men and non-pregnant women ages 18-65 without a neurological disorder, free of benzodiazepines and anticonvulsant medications. Participants must also be eligible to receive rTMS and MRI. Participants will be recruited from the Chapel Hill, Durham and Raleigh areas.
Phase:	Pilot Phase
Description of Sites/Facilities Enrolling Participants:	University of North Carolina at Chapel Hill
Description of Study Intervention:	We will use the MagPro X100 or R30 system (MagVenture Inc., Alpharetta, Georgia, USA) for transcranial magnetic stimulation. The MagPro X100 or R30 are an advanced, high performance magnetic stimulator designed primarily for research purposes. It is a high-quality tool for researchers with a large choice of stimulating parameters and has stimulation rates up to 100 pulses per second at high intensities and the possibility to combine waveforms and pulse modes. Patterned rhythmic TMS will be delivered in either cross-frequency delta-beta, cross-frequency theta-gamma, or an arrhythmic pattern that is matched for the number of pulses and duration. Stimulation will be delivered at 80% of motor threshold in the 2 seconds before the decision epoch with 5 triplets of 3 pulses per train per trial.
Study Duration:	2 years
Participant Duration:	Participation for each participant will be 4 weeks. Completion includes four sessions: an EEG session, an MRI session, and two EEG-TMS sessions. The EEG session will take approximately 1.5 hours. The MRI session will take approximated 1.5 hours. The two stimulation sessions will each take approximately 2 hours. We estimate that total participation to be approximately 7 hours.

1.2 SCHEMA

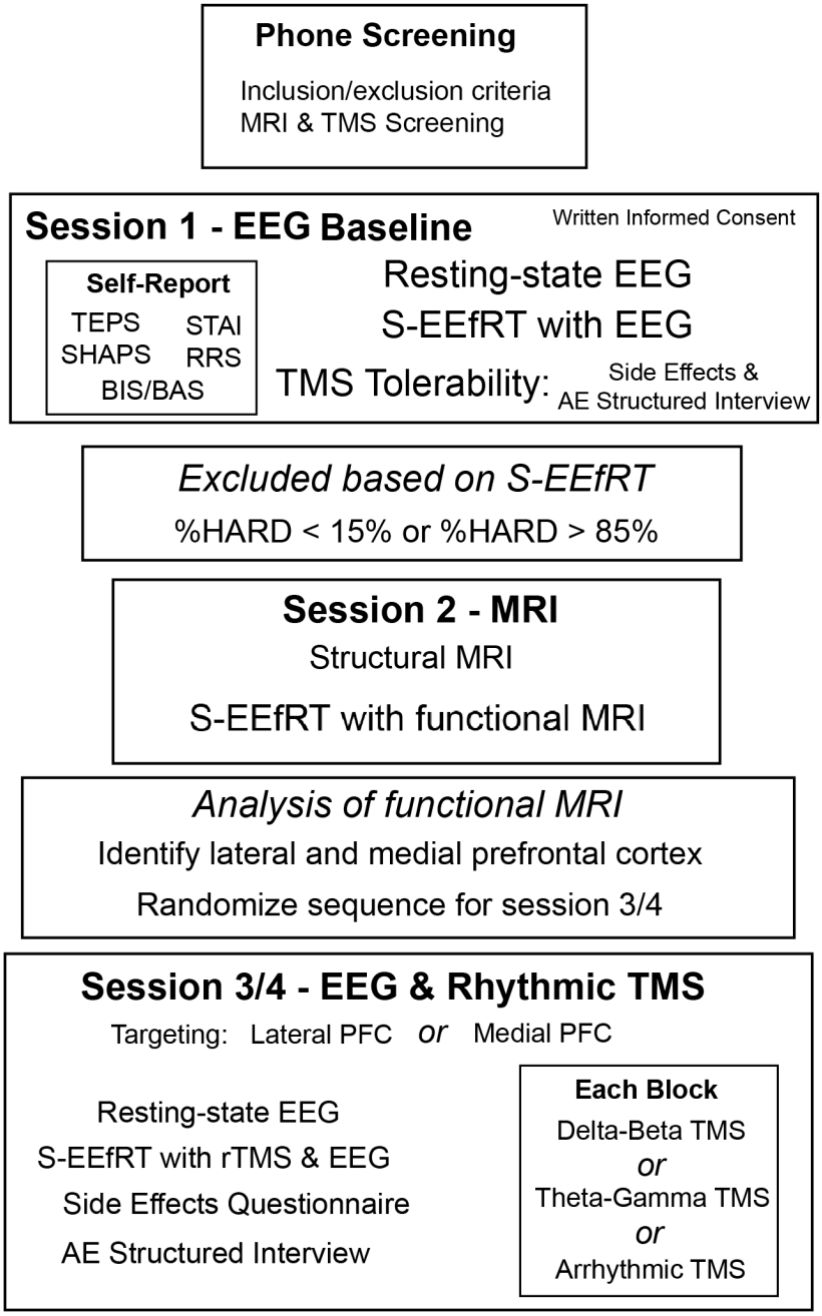

Figure 1. Experimental design depicted as a flow-chart for this protocol. This study is four sessions with a full crossover design. After a phone screening to assess eligibility, an EEG baseline session is conducted to estimate baseline metrics of task performance and task-based neural metrics. Brief session of TMS is delivered to assess tolerability. Participants are then excluded based on task performance. In session 2, participant complete a functional MRI session that is used to localize the stimulation targets that are used in the 3rd and 4th session. In the

3rd & 4th session, stimulation is delivered to lateral prefrontal cortex (PFC) or medial PFC in a counterbalanced and randomized sequence. For each block of the task, rhythmic transcranial magnetic stimulation (TMS) is delivered in the target frequency delta-beta, an active control frequency (theta-gamma), or an arrhythmic pattern (active control condition).

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Phone Screening	Session 1 EEG Only	Session 2 - MRI	Session 3 – EEG and TMS	Session 4 – EEG and TMS
Verbal informed consent	X				
Written informed consent		X			
Determine Eligibility	X	X			
MRI Screening	X		X		
TMS Screening	X	X		X	X
Demographics	X				
SHAPS		X			
RRS		X			
BIS/BAS		X			
TEPS		X			
STAI		X			
Urine Pregnancy Test (if applicable)		X			
Resting-state with EEG		X		X	X
S-EEfRT with EEG		X		X	X
EMG recorded		X		X	X
Structural MRI			X		
S-EEfRT with functional MRI			X		
Motor threshold using single pulse TMS		X			
TMS tolerability test		X			
S-EEfRT with patterned TMS				X	X
Stimulation Questionnaire		X		X	X
AE Structured Interview		*		*	*
AE Review and Evaluation		*		*	*

* when applicable

2. INTRODUCTION

2.1 STUDY RATIONALE

Anhedonia, the inability to seek-out and experience pleasure, remains difficult to treat, with many pharmacological interventions occasionally increasing, or introducing, anhedonia (Husain and Roiser 2018; Lambert et al. 2018; Treadway and Zald 2011). Many proven treatments in psychiatry are less effective in patients with elevated symptoms of anhedonia (Hatzigiakoumis et al. 2011; Landén et al. 2005; McMakin et al. 2012; Nierenberg et al. 1999; Shelton and Tomarken 2001). In affective disorders such as major depressive disorder (MDD), anhedonia is positively correlated with suicidal behavior (Bonanni et al. 2019). Therefore, effective treatment for anhedonia is a critical factor in the ongoing mental health crisis. Symptoms of anhedonia fall within the "Positive Valence System" of the research domain criteria (RDoC) framework (Nusslock and Alloy 2017) and comprise two primary components: "liking" and "wanting" (Gard et al. 2006; Kring and Barch 2014). The "liking," or consummatory, component reflects the experience of rewards as pleasurable. Collectively, reward evaluation is known to critically rely on the orbitofrontal cortex of the medial prefrontal cortex (mPFC) to process the value of the reward (O'Doherty 2004; Padoa-Schioppa and Cai 2011) and the nucleus accumbens of the ventral striatum (vSTR) to evaluate the effortful cost (Sugam et al. 2012). Correlational studies find reduced activation and decreased functional connectivity in mPFC-vSTR during reward-based decision-making tasks in patients with anhedonia (Epstein et al. 2006; Greenberg et al. 2015; Wacker et al. 2009). The second component is the "wanting," or anticipatory, component that reflects the organization of behavior according to a cost-benefit computation – *goal-directed behavior*. The dorsal striatum (dSTR) processes the anticipation of receiving a future reward and orients behavior towards reward-seeking (Pizzagalli et al. 2009; Zhang et al. 2016). The dSTR (caudate and putamen) is guided by the dorsolateral prefrontal cortex (dlPFC; middle frontal gyrus) and together they play a critical role in planning and initiating goal-directed behavior (Badre and Nee 2018). Lesion to the dlPFC results in deficits in planning and initiating goal-directed behavior (Szczepanski and Knight 2014) and lesion to dSTR results in apathy and similar deficits as lesions to dlPFC (Mendez et al. 1989). Thus, the neuropsychological etiology of anhedonia presents two candidate neural circuits tied to two relevant cognitive constructs: mPFC-vSTR for reward-evaluation and dlPFC-dSTR for goal-directed behavior (Höflich et al. 2019; Kring and Barch 2014; Rizvi et al. 2016). Pathology of both circuits is *correlated* with anhedonia (Walsh et al. 2019), and causal investigation may differentiate the relative importance of each circuit.

In the present study, we propose to test for the causal role of these two frontal-striatal circuits in reward-based decision-making in healthy participants that are not included on the basis of psychiatric illness. A better understanding of the role of these circuits in reward-based decision-making is a critical first step in developing novel treatment targets for intervention for psychiatric illness. In addition to building a neurobehavioral framework for reward-based decision-making, this study will test novel techniques for using non-invasive brain stimulation to increase activity within specific frontal-striatal circuits.

2.2 BACKGROUND

In the past few decades, non-invasive brain stimulation emerged as a promising intervention for treatment-resistant depression that is safe with minimal side-effect (Perera et al. 2016). The most widely available stimulation protocols to treat depression use transcranial magnetic stimulation (TMS) to increase neural activity in the left dlPFC (Perera et al. 2016) or mPFC (Downar et al. 2014; Siddiqi et al. 2020), and recent work from our lab found promising treatment effects using transcranial alternating current stimulation (tACS) to dlPFC (Alexander et al. 2019; Riddle et al. 2020a). With multiple spatial targets emerging for the treatment of depression, researchers are beginning to

understand that heterogeneity in depression symptoms alters which spatial targets are most effective at treating depression (Siddiqi et al. 2020). Inaccurate spatial targeting can render treatment ineffective (Fox et al. 2012). Therefore, improved understanding of the neural circuits that underly specific symptoms of depression is of critical need. One such symptom, anhedonia, is more responsive to stimulation targeting dlPFC than stimulation targeting mPFC (Downar et al. 2014; Drysdale et al. 2017; Duprat et al. 2018; Pettorruso et al. 2018; Siddiqi et al. 2020). Stimulation to left dlPFC in depressed patients with anhedonia only alleviated depression when symptoms of anhedonia decreased (Levkovitz et al. 2011). In contrast, stimulation to mPFC only alleviated depression in patients without symptoms of anhedonia (Downar et al. 2014). Despite recent evidence that dlPFC-dSTR is the optimal target for treating anhedonia in depression, the overall response rate is still lower than depressed patients without anhedonia (Krepel et al. 2020). One explanation is that stimulation efficacy is also critically dependent on the temporal structure of neural activity (Ali et al. 2013). Thus, investigation of the electrophysiology of dlPFC-dSTR during goal-directed behavior in patients with anhedonia is critical to further advance the efficacy of treatment interventions.

Neural oscillations are a critical mechanism for interregional communication (Fries 2015), with low frequency oscillations facilitating long-distance communication and high frequency enhancing local connectivity (Buzsáki et al. 2012). Cognitive control tasks evoke low frequency neural oscillations in prefrontal cortex that couple to high frequency oscillations in posterior cortex (Canolty and Knight 2010; Helfrich et al. 2017; Voytek et al. 2010; Voytek et al. 2015). This *cross-frequency coupling* is proposed to be a mechanism for prefrontal cortex to exert top-down control (Canolty and Knight 2010). One candidate cross-frequency coupling signal for goal-directed behavior is the coupling of delta oscillations (2-4Hz) in prefrontal cortex to beta oscillations (15-30Hz) in motor cortex (Riddle et al. 2021a; Wyart et al. 2012). In the proposed experiment, we investigate the causal role of delta-beta coupling and the dlPFC-dSTR neural circuit in goal-directed behavior in healthy participants. We are convinced that our experiment is of high significance since a mechanistic understanding of the neural circuits that underlie goal-directed behavior will ultimately allow the rational design of novel brain stimulation techniques to more effectively treat depressed patients with anhedonia.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risk of Seizure from TMS: There is a rare, but potential, risk that TMS will produce a seizure in healthy individuals. In order to mitigate this risk, we use multiple strategies. First, we screen participants based from participating in the study that present with any traits that may lower their seizure threshold or pose increased risk of seizure. These contraindications are well documented within the field and updated guidelines are released approximately every 10 years with the latest recommendation released in 2020 (Rossi et al. 2020). Contraindications screening is conducted during phone screening and prior to each of the TMS sessions. Second, we calculate the motor threshold for each participant using electromyography or visible twitches in order to calibrate the intensity of stimulation to the endogenous electrical levels of the brain of the participant. This calculation is performed in the motor cortex which is one of the most excitable regions of the brain and then stimulation is delivered to the prefrontal cortex which is a region with considerably lower excitability. Third, we have chosen our stimulation parameters to be within recommended safety guidelines. We do not exceed the suggested pulse-per-second rate for our given intensity of stimulation (80% of motor threshold). Fourth, we employ a comprehensive monitoring and adverse event assessment in each participant. This includes consultation with our Medical Monitor, Dr.

Clio Rubinos, who is an epileptologist. Fifth, we have created an emergency response plan with our medical monitor in the unlikely event of a seizure.

Risk of Confidentiality Breach: In the unlikely event of a breach of confidentiality, people might discover that an individual was involved in this research study. This is relevant to our study because some might not agree with the principle of participating in research for changing natural brain activity. To avoid breaches in confidentiality, study documents that contain personal information and including the informed consent document are kept in locked filing cabinets in locked rooms separate from any source documents containing participant dummy identifiers. The document that links study ID numbers to personal identifying information is encrypted and protected using a password-protected document on a secure server provided by UNC School of Medicine. All data is stored in locked cabinets inside locked offices; electronic data will be stored only on password-protected computers, and data encryption methods will be used during communication between investigators. Only study personnel will have access to the data. All study staff participate in annual human participant training that includes education about responsibilities to the minimize risk of confidentiality breach.

Risk of Embarrassment: Self-report assessments contain questions regarding sensitive personal information. This risk is necessary in order to assess personality traits that might be relevant to subclinical expression of symptoms that were discovered to explain individual differences in this task in our previous data. Participants will be assured upon intake that self-identifying information will not be collected alongside HIPAA protected information.

Risk of Injury and Discomfort: Transcranial magnetic stimulation has been cleared for use in the USA by the FDA. TMS (the methodology used in this experiment) has nothing to do with electroconvulsive therapy that applies many orders of magnitude higher stimulation current. The level of electrical stimulation produced by TMS is within the range of activity that is endogenous to the brain. Furthermore, the intensity of stimulation is calibrated to the sensitivity of the individual participant such that the level of stimulation is matched to that of naturally occurring activity. In order to monitor side-effects, we will be administering an adverse effects stimulation questionnaire after each stimulation session to determine whether these effects were experienced. Research personnel present during these sessions will also check with the participant periodically during the stimulation to see whether they are comfortable. If any side-effect occurs that is rated by the participant and confirmed by the researcher to be stronger than “moderate,” the stimulation will be immediately stopped.

Risk of Psychological Discomfort: There is a psychological element in that some participants may become claustrophobic upon entering the small space of the MRI bore. To reduce psychological distress, participants are informed that they can withdraw consent and stop participation at any time. Participants are monitored throughout the MRI scans and can terminate the scan at any time by squeezing a ball held in the hand, and will be quickly removed from the MRI bore. There is additionally a risk of psychological discomfort from receiving transcranial magnetic stimulation (TMS). Due to the discomfort from receiving TMS and the proximity of the TMS coil to the face and head of the participant, this can result in psychological discomfort. Similar to MRI, participants are informed that they can withdraw consent and stop participation at any time. Participants are monitored throughout the TMS sessions and can stop receiving stimulation at any time by physically moving away from the TMS coil. The field of stimulation is less than a couple centimeters. Furthermore, researchers monitor the participant throughout stimulation and will check in with the participant approximately every 5 minutes between each task block.

Risk of Injury from MRI: MRI will be conducted within the Biomedical Research Imaging Center (BRIC) at UNC Chapel Hill. The BRIC has a full-time staff that is well trained in the safety involved with MRI. Participants complete a contraindications form for MRI upon enrollment in each study. Any questions or concerns from the researcher can be addressed by the staff at the BRIC. In addition, the participant completes an additional screening form in the presence of the staff at the BRIC to further ensure that all safety concerns are addressed. The specific risks that are presented to the participant are avoided by effective screening. These risks include physical injury from the presence of metal within the body or in the environment when entering the magnetic field of the MRI. The strong magnetic field will pull metal towards the center of the field. Thus, it is imperative that all metal is removed from the body and any participants with metal within the body do not enter the field. The MR technicians at the BRIC maintain strict boundaries and screening via metal detector before entering rooms near to the MRI, adjacent to the MRI room, and the MRI room. This three-staged system is standard practice for MRI. Participants are provided with a medical gown and private changing room within the BRIC. This ensures that there is no chance that participants will enter the room with metallic objects in their pockets (e.g., phones or wallet). In addition, technicians screen participants and walk through a check list. Another risk from the MRI is the chance of a skin burn from clothing that contains metallic microfibers/particles. Thus, participants wear a medical gown to avoid the complication from modern athletic clothing technology. These risks are well-understood by the scientific community and extensive safety procedures are put in place by regulatory oversight that are maintained by the BRIC.

Risk of Transient Psychological Changes from TMS: There is a rare risk that TMS will result in alterations in mood, trouble concentrating, or sleepiness. These side effects are not commonly reported, but given the diversity of cognitive functions that the prefrontal cortex supports, TMS could potentially produce a transient change in the above listed cognitive functions.

2.3.2 KNOWN POTENTIAL BENEFITS

This study has not been designed to benefit the individual participants. However, the knowledge gained from this study will contribute to understanding about the psychological and biological basis of reward-based decision-making. This knowledge is highly relevant to some psychiatric illnesses such as major depressive disorder that shows systematic changes in reward-based decision-making. The results from this study might be used to develop future interventions using non-invasive brain stimulation.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks and benefits presented above are no more serious than for other clinical trials in healthy participants. These techniques are common practice within the field of cognitive neuroscience and are increasingly being applied to the field of psychiatry. Based on the need for complementary and alternative treatments for MDD, the potential risks are worth the potential future benefits as studies like this one are essential for the development of novel treatment targets for non-invasive brain stimulation.

2.3.4 REFERRALS FOR MEDICAL FOLLOW-UP

To ensure participant comfort, a researcher will periodically check in with the participant about any side-effects he/she may be experiencing during each stimulation session. Following the conclusion of any session with TMS, the participant will receive an Adverse Effects Questionnaire to report on any of the side-effects he/she may have experienced. This questionnaire reports side-effects on a Likert scale (0 = Absent, 1=Low, 2=Medium, 3=High, 4=Very high). If the participant reports side-effects of "very high" intensity, the researcher running that session will administer the Structured AE Interview. The majority of studies using TMS do not record or document Adverse Events unless a serious adverse event occurs or an AE of significance occurs, but that threshold is determined by the researchers of that study. For example, two systematic reviews of adverse events for TMS in depression in older participants (Overvliet et al., International Journal of Geriatric Psychiatry 2021) and TMS in Parkinson's disease (VonLoh et al., Parkinsonism and Related Disorders 2013) summarized the frequency of AEs and SAEs across many studies (Overvliet et al. 2021; VonLoh et al. 2013). From a careful read of these studies, it is clear that the threshold for what constitutes an Adverse Event on the mild end of the spectrum is not agreed upon. Thus, by using a Likert scale (0 = absent, 1 = low, 2 = medium, 3 = high, 4 = very high) and considering all instances of "very high" as the threshold to be considered an Adverse Event is a conservative approach that will result in documentation and follow-up interviews at a level greater than 95% of studies. The purpose of the Adverse Events Structured Interview is to acquire more information about the experience of the participant with respect to the onset of symptoms, the time course of the symptoms, presence of symptoms at baseline, and the potential cessation of symptoms at completion of the TMS session. This information is written up in a comprehensive document, the Adverse Events Report Form, that is then communicated to the Principal Investigator, Dr. Flavio Frohlich, and the Medical Monitor, Dr. Clio Rubinos. The PI and Medical Monitor then determine the severity of the Adverse Event and make a plan for follow-up with the participant if necessary. In the rare event that the researcher finds the adverse event to be unexpected, serious, or more than mild, then the researcher will immediately call the Medical Monitor to conduct an immediate assessment with the participant.

Epileptic Activity Follow-up: There is a theoretical likelihood that stimulation of neuronal circuits can lead to epileptic discharge. To minimize this occurrence, we screen and exclude participants with personal and family history of neurological conditions from the study. We further emphasize that there has never been a single report of a seizure that resulted from transcranial alternating current stimulation or transcranial direct current stimulation. If abnormalities or a seizure is witnessed during the course of the study, a referral will be made to Dr. Clio Rubinos at UNC Department of Neurology for follow-up. In the exceedingly rare event that a seizure is witnessed, researchers will contact Dr. Clio Rubinos by her cell phone who will perform a check on the participant. A follow-up appointment will be scheduled in the Post-Acute Symptomatic Seizure Clinic where Dr. Rubinos is a specialist. Patients that developed a seizure after TMS are candidates for this clinic. In the theoretical event that a seizure is witnessed that involves the loss of consciousness, the participants will be further instructed of seizure precautions as per standard of clinical care.

Neurological Abnormality Follow-up: When imaging the brain there is a chance that the MRI scan will reveal a neurological irregularity that might be of medical importance to the participant. These incidental findings are uncommon and rarely lead to early identification of neurological issues. However, as is

standard practice, we allow participants the option to choose to be alerted to any incidental findings. In the consent form, participant can opt out of being notified about incidental findings. If a researcher notices a neurological abnormality, then they will reach out to our collaborators in the department of neurology to investigate the MRI scan further. If the neurologist considers the abnormality to be of medical importance, then the participant will be contacted for future steps. It should be noted that the research MRI scans used (T1-weighted) are not diagnostic scans and are not sensitive to detecting common neurological problems such as brain cancer. There is no expectation that the participant population studied in this research program will be of greater likelihood for incidental finding.

3. OBJECTIVE AND OUTCOME MEASURES

OBJECTIVES	OUTCOMES	JUSTIFICATION FOR OUTCOMES
Primary		
To investigate whether delta-beta TMS to dlPFC-dSTR will produce an increase in goal-directed behavior during reward-based decision-making.	Behavioral metric, percentage of hard trials chosen, during the Streamlined Expenditure of Effort for Reward Task (S-EEfRT).	Stimulation is delivered prior to the decision epoch and the stimulation parameters were determined based on a previous study that investigated a different cognitive construct.
Secondary		
To investigate whether delta-beta TMS to dlPFC-dSTR will result in a lasting increase in delta-beta coupling during the decision epoch.	Neural metric, degree of phase-amplitude coupling between prefrontal delta oscillations and left motor beta oscillations, quantified during the decision epoch of the S-EEfRT.	Our previous study found increased delta-beta phase-amplitude coupling during the decision-epoch in participants with high goal-directed behavior.
Exploratory		
To investigate the degree to which traits of motivation predict individual differences in the impact of delta-beta TMS on goal-directed behavior.	Two-dimension factor analysis is run on clinical assessments to derive motivation and rumination personality dimensions. These scores are correlated with the impact of TMS on goal-directed behavior.	Our previous study found two symptom dimensions within participants with major depressive disorder that captured individual differences in reward-based decision-making. Here, we utilize personality assessments that might be similar to the clinical analog.
To investigate whether reward-evaluation is increased by theta-gamma TMS to medial PFC.	Behavioral metric of reward-evaluation is the percentage of hard trials chosen as a function of the incentive offered, during the S-EEfRT.	Our previous study found reward-evaluation was related to theta-gamma coupling. This additional behavioral metric allows for the investigation of the circuit- and cognitive-specificity of TMS.

OBJECTIVES	OUTCOMES	JUSTIFICATION FOR OUTCOMES
To investigate whether theta-gamma coupling is increased by theta-gamma TMS to medial PFC.	Neural metric, degree of phase-amplitude coupling between prefrontal theta oscillations and posterior parietal gamma oscillations, quantified during the decision epoch of the S-EEfRT.	Our previous study found increased theta-gamma phase-amplitude coupling during the decision-epoch in participants with high reward-evaluation behavior.
To investigate whether functional connectivity between dorsal striatum and left lateral prefrontal cortex predicts individual differences in the impact of delta-beta TMS on goal-directed behavior.	Functional connectivity analysis of resting-state functional MRI is correlated with the impact of delta-beta TMS on goal-directed behavior.	Previous research has suggested that frontal-striatal connectivity is related to reward-based decision-making. Participants with reduced connectivity within this neural circuit may be predictive of the impact of TMS on reward-based decision-making.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This study is a pilot, four-session, crossover study with transcranial magnetic stimulation (TMS), electroencephalography (EEG), and magnetic resonance imaging (MRI) to understand the causal role of delta-beta coupling in goal-directed behavior in the dorsolateral prefrontal cortex (dlPFC) to dorsal striatum (dSTR) circuit. Participants that request to be in the experiment will provide verbal, documented consent to undergo a phone screening to assess that the participant meets initial exclusion/inclusion criteria. Participants complete an MRI and TMS screening form over the phone to ensure eligibility.

The first session will be an EEG session with the reward-based decision-making task. At the start of the session, we will acquire written informed consent. Then, we will administer a pregnancy test if applicable. Participants will complete a five assessments: the Snaith Hamilton Pleasure Scale (SHAPS) (Snaith et al. 1995), Behavioral Activation System and Behavioral Inhibition System (BIS/BAS) (Carver and White 1994), Temporal Experience of Pleasure Scale (TEPS) (Gard et al. 2006), the State-Trait Anxiety Inventory (STAI) (Spielberger 2010), and Ruminative Responses Scale (RRS) (Nolen-Hoeksema, Larson et al. 1999). Note that our participants are from a convenient sample and are not required to be diagnosed with major depressive disorder. Thus, these assessments were selected as they survey various personality traits that might be relevant to performance in the task. In our previous published study using this task, we discovered a continuum of task performance between the control participants and the participants within a major depressive disorder (Riddle et al. Cerebral Cortex 2022). We speculate that participants with personality traits related to reduced behavioral approach (quantified by the BIS/BAS) could be a precursor to symptoms of anhedonia (quantified by the TEPS and SHAPS). Similarly, increased personality traits of behavioral inhibition (quantified in the BIS/BAS) could be a precursor to symptoms of anxiety (STAI and RRS). Thus, we collect this data in healthy control participants as an exploratory aim of the study.

The scalp dimensions of each participant are calculated and a low-profile EEG net is applied. For each session, muscle activity from the hand and forearm are recorded. Next, the participants complete an eyes-open and eyes-closed resting-state recording of EEG. Then, the streamlined version of the Expenditure of Effort for Reward Task (S-EEfRT) is completed. These data serve as baseline measurement of brain activity without any form of stimulation. This session takes approximately 1.5 hours to complete. After each block of the task, the task difficulty will increase or decrease based on performance. At the end of the session, if the participant chose to perform the HARD task greater than 85% of the time or less than 15% of the time, then the participant will not be invited to the next session of the experiment. The rationale is that we are studying reward-based decision-making and participants that do not dynamically change their response based on the incentive are not engaged with the relevant cognitive constructs under investigation in this study.

Finally, in this first session we will calculate the motor threshold of the participant. In the first, third, and fourth session, participants will complete a TMS contraindications screening form. The same TMS screening form will be administered over the phone and at the start of each of the TMS session. If there is any ambiguity in the contraindications for the TMS form, then the medical monitor, Dr. Clio Rubinos, who is an epileptologist is consulted and final approval is acquired. Similar to the MRI screening form, it is highly unlikely that eligibility will change between sessions. Out of an excess of caution, we administer the TMS screening form at each TMS session to confirm that there is no contraindication, otherwise participation is discontinued. In the third session, the motor threshold of each participant will be calculated using single-pulse TMS to the hand knob of the left primary motor cortex with real-time monitoring of the motor-evoked potential using electrodes on the first dorsal interosseus muscle. Researchers may also use visible twitch to calculate the motor threshold. The motor threshold is defined as the percent stimulator output when a motor-evoked potential or visible twitch is observed approximately 50% of the time. Next, the participant will receive two abbreviated blocks of TMS similar to those that will be delivered during the third and fourth session. One block will deliver stimulation to medial PFC and the other to lateral PFC. These blocks are used as a tolerability test to ensure that the participant is comfortable with receiving TMS and to acclimate them to the experience. After stimulation, a questionnaire is provided with common side effects of TMS. Based on the results of the stimulation side effects questionnaire, a structured adverse events interview is conducted to acquire more information regarding any side effects that were selected to be “very high” by the participant. This session will take approximately 2 hours.

For the second session, participants are instructed to arrive at the Biomedical Research Imaging Center (BRIC) in Marsico Hall on UNC-CH campus. In the 24 hours prior to this session, participants complete an MRI screening form. This screening form is the standard provided by the BRIC. During the phone screening, if there is any ambiguity in the eligibility of the participant, then we consult with the technicians at the BRIC for approval to conduct an MRI. Then, in the 24 hours prior to their MRI session, MR technicians at the center review a new screening form and confirm their eligibility to receive an MRI. Because this is the same form used in the screening for the experiment, the only way that a participant would fail to be eligible at this stage is if there was some change in their eligibility between sessions. While this is highly

unlikely, the participant would be discontinued from participating. Participants are instructed to arrive at the facility 30 minutes before the start of the scheduled MRI block to ensure that they are ready to go into the MRI for the 60-minute allotted timeslot. During the 60 minutes of scanning, a 5-minute structural MR is acquired and the remaining time is used to complete as many blocks of the EEfRT as possible. The minimal number of sessions required to use the data is 5 blocks, which requires approximately 25 minutes to collect. Note that the only other scan of significant length acquired during this time is a 5-minute anatomical scan and the remaining 50 minutes or more is dedicated to acquisition of the task data that is used for localization. Thus, we do not expect to collect less than 5 blocks of data in any given participant. However, if a participant was unable to complete the requisite number of sessions, then they would be excluded from the rest of participation. We expect that this a highly unlikely. Functional MRI data is analyzed before the 3rd and 4th session to localize the regions of dorsolateral PFC and medial PFC for stimulation. In our analysis, we will draw a region of interest mask in the head of the left caudate (dSTR) and in left nucleus accumbens (vSTR) and localize the region in dlPFC and mPFC with peak functional connectivity in task-based functional connectivity to these regions. In our pilot data, we found that the contrast of HARD vs EASY localized the anterior middle frontal gyrus and the contrast of HIGH vs LOW incentive localized the super frontal junction. Thus, we will choose regions in these anatomical areas with maximal connectivity to their respective nucleus in the striatum.

The order of regions (dlPFC then mPFC, or mPFC then dlPFC) targeted by TMS in the third and fourth session will be randomized and counter-balanced. First, the participants will be fitted with a low-profile EEG net and EMG electrodes to the hand and forearm. For the third and fourth session, the same stimulator intensity will be used as in the first session. The structural MRI and regions of interest (dlPFC and mPFC) are imported into Localite neuronavigation software. The participant wears a 3D stereotaxic tracking headband and is registered to their structural MRI. Then, the TMS coil is targeted to either mPFC or dlPFC and the position of the coil relative to the head is recorded throughout the session. The participant performs the S-EEfRT as the patterned trains of TMS are delivered on every trial. Each block of the study is randomized to receive either delta-beta patterned (triplets of TMS pulses at 20 Hz every 3Hz), theta-gamma patterned (triplets of pulses at 50 Hz every 5 Hz), or an arrhythmic pattern (same number of pulses and duration with a random inter-pulse interval). After stimulation, a questionnaire is provided with common side effects of TMS. Based on the results of the stimulation side effects questionnaire, a structured adverse events interview is conducted to acquire more information regarding any side effects that were selected to be “very high” by the participant. This session will take approximately 2 hours.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study is a fully crossed target engagement study. It is not possible to include blinding in the study for either the participant or the experimenter. The difference between the active control pattern of TMS and the targeted pattern of TMS as well as the difference between dorsolateral PFC and medial PFC will not be meaningfully discernible to the participant as there is a difference of only a few centimeters between sites and only a fraction of a second for the stimulation patterns. There is no obvious association between the site of stimulation and the frequency of stimulation and the task itself. Therefore, not only is blinding

not possible, but it is not necessary for the scientific questions under investigation in this study. In a recent review by Duecker and Sack *Frontiers in Psychology* 2015, the authors survey modern approaches to creating a sham form of TMS. These efforts have been unsuccessful despite increasingly sophisticated designs. The authors found that even with moderate success in blinding in a parallel arm study where the participant is naïve to stimulation, when a design is crossover, the participants become aware that the stimulation is placebo. These observations lead to the conclusion that even when sham stimulation is used, the experiment should include an active control condition such as an alternate location of stimulation or an alternate frequency of stimulation: "TMS experiments always require an active TMS control condition, and sham TMS approaches can never be sufficient as they fail to demonstrate such specificity" (Duecker and Sack 2015).

Furthermore, the experimenters cannot be blinded to the site of stimulation as this needs to be carefully maintained throughout the experiment using neuronavigation, nor to the frequency of stimulation as these are audible to the experimenter. The primary and secondary outcome of the study include a control condition within each session and within a participant between sessions. Thus, the scientific integrity of the study is provided through multiple control conditions built into the crossover experimental design: spatial variable (dlPFC vs mPFC), temporal variable (delta-beta vs theta-gamma vs arrhythmic), and cognitive variable (goal-directed behavior vs reward evaluation). Our previous study found that goal-directed behavior was positively correlated with delta-beta coupling and reward-evaluation was positively correlated with theta-gamma coupling (Riddle et al. Cerebral Cortex 2022). Thus, this preliminary data provides a strong motivation for the type of stimulation used in this experiment. In addition, our previous study discovered a significant negative relationship between symptoms of anhedonia in major depressive disorder with goal-directed behavior and delta-beta coupling. Thus, this study will serve as a critical target engagement study such that future studies may use these results to develop interventions to treat symptoms of anhedonia in MDD.

Finally, our exploratory outcomes hypothesize that theta-gamma stimulation to medial PFC will increase reward-evaluation during the task. Thus, all conditions of the experiment are of importance to the outcome of the experiment. Therefore, the experimenter will not be unconsciously biased towards one session or another because all of them are important to the success of the project. In addition, the type of stimulation for each block of the task is randomized and not known to the participant or experimenter until the start of the block. Thus, the experimenter will not be able to bias the experiment in any way because they are block to the experimental condition during the slight adjustments that occur during each block. Furthermore, the experimenter does not converse with the participant during the task and the task is computerized such that there are minimal human interactions that could bias the participant one way or another. In addition, the behavioral metrics of interest are patterns of decision-making within the same task condition. Thus, a hypothetical unconscious systematic bias would have to influence a particular pattern of behavior on a particular block of the task but not others within the same session. This type of influence is highly unlikely, if not nearly impossible, given our experimental design.

4.3 JUSTIFICATION FOR DOSE

Transcranial magnetic stimulation (TMS) is a safe, non-invasive, widely-used tool that applies focal electric fields to the brain using magnetic coils placed on the scalp (Rossi et al. 2009). On the first stimulation session of the study, participants will receive a motor thresholding procedure in which electrodes are attached to the first dorsal interosseous muscle of the right hand, or another muscle on the hand or arm that is accessible to be targeted by TMS to the motor cortex. The contralateral motor cortex will be targeted by single pulses of TMS with increased

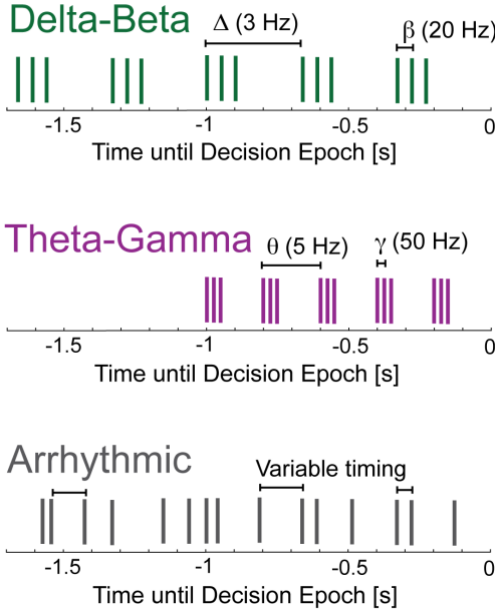

Figure 2. Patterned transcranial magnetic stimulation (TMS) is delivered prior to each trial of the Streamlined Expenditure of Effort for Reward Task (S-EEfRT). Each train comprises 15 pulses. Delta-beta TMS (green) delivers bursts of three pulses at 20 Hz with an inter-burst interval of 3 Hz. Theta-gamma TMS (purple) delivers bursts at 50 Hz every 3 Hz. Arrhythmic TMS is matched for duration and number of pulses but with a random inter-pulse interval.

stimulator output until a motor evoked potential (MEP) is generated: defined as a near-instantaneous increase muscle activity greater than 200 microvolts. Next, the intensity of single pulse TMS will be lowered until a MEP is generated on five out of ten pulses. This is defined as the motor threshold for the participant (Rossi et al. 2009). If the motor threshold cannot be determined via MEP, the experimenter will use visible twitches instead of MEP. Participants will receive 15 pulses of patterned TMS at 80% of their motor threshold during every trial. Patterned TMS takes three different forms (Figure 2). Delta-beta TMS delivers bursts of three pulses at 20 Hz (50 millisecond inter-pulse interval) with an inter-burst interval of 3 Hz (167 milliseconds). Theta-gamma TMS delivers bursts of three pulses at 50 Hz (20 millisecond inter-pulse interval) with an inter-burst interval of 5 Hz (200 milliseconds). As a control for the frequency-specificity of patterned TMS, arrhythmic TMS is delivered with a randomized inter-pulse intervals that are generated for each trial. The duration of arrhythmic TMS is randomly selected from a uniform distribution between the duration of delta-beta and theta-gamma TMS. The minimum inter-pulse interval will be 20 milliseconds. Between every train will be at least 11 seconds. An inter-train-interval of 11 seconds or greater allows for any residual effects of stimulation to return to baseline. This intensity, inter-pulse-interval, and inter-train-interval is well within the safety guidelines set forth for repetitive TMS (Wassermann, 1998; Rossi et al., 2009) and has been used in similar paradigms as the one described here. For example, Hermiller et al. 2020 delivered two seconds of theta-gamma patterned TMS (30 pulses per trial) at 80% of motor threshold (Hermiller et al. 2020). In addition, many other studies have delivered trains of TMS at higher intensities, upwards of 120% of motor threshold, on every trial of a cognitive task (Thut et al. 2011; Hanslmayr et al. 2014; Albouy et al. 2017)(Riddle et al. 2019; Riddle et al. 2020c; Sauseng et al. 2009). During a TMS session, participants will complete six blocks of 30 trials each. The participant will receive stimulation in either delta-beta, theta-gamma, or arrhythmic in a blocked design (the same stimulation is delivered for every trial in a block). The sequence of blocks will be randomized and counterbalanced such that each participant received each condition of TMS for 60 trials total. The third and fourth session of the experiment will be both be TMS sessions, where TMS is delivered to either the dorsolateral prefrontal cortex (dlPFC) or to medial prefrontal cortex (mPFC). The order and TMS sites will be randomized and counterbalanced across participants. Thus, at completion of the full experiment, participants will have received 12 blocks of 30 trials each of stimulation (180 trials per TMS session). In addition, two abbreviated blocks of TMS to mPFC and dlPFC will be administered at the end of the first session to assess for tolerability of TMS.

The evoked electric field from stimulation will be simulated using finite-element modeling of the neuroanatomical MRI for each participant (Gomez, Dannhauer, Peterchev *Neuroimage* 2021). This method ensures that the evoked stimulation strength is within a safe level beyond standard stimulation methodology. The time between each

patterned-train will be a minimum of 11 seconds. These stimulation parameters for individual trains and time between trains fall within the safety guidelines set forth by the Rossi et al., *Clin Neurophysiol* 2009 "The Safety of TMS Consensus Group: Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research", which has guided TMS research the past decade (Rossi et al. 2009). Last year, these guidelines were re-affirmed with an updated safety review (Rossi et al. 2020). The longer the time between each train the better the safety profile from stimulation. Furthermore, patterned stimulation such as the theta-gamma burst pattern, used as a control frequency in this proposal, has been extensively investigated for its safety profile. A meta-analysis conducted by Oberman et al. *J Clin Neurophysiol* 2011 concluded that patterned TMS trains present only a minimal seizure risk with a single case of seizure out of 4,500. The participant was healthy and the protocol used was continuous theta-burst delivered at 100% of motor threshold to motor cortex. Thus, our use of 80% of motor threshold and targeting of dorsolateral and medial prefrontal cortex (less excitable regions of the brain) further reduces the risk. The safety of a TMS train is defined by the inter-pulse interval, with a short inter-pulse interval presenting higher risk (Rossi et al. 2009; Rossi et al. 2020). Thus, the novel delta-beta pattern (3 Hz by 20 Hz) proposed in this study is most likely safer than the theta-gamma pattern (5 Hz by 50 Hz). Finally, we will be delivering 180 trains of 5 bursts each and each train is separated by a considerable amount of time (minimum of 11 seconds) with time for self-paced breaks between every block in the experiment. Thus, this number of pulses exceeds the typical number of bursts in a continuous theta-burst protocol but the overall delivery time is considerably longer. Of note, recent experiments using accelerated-intermittent theta-burst TMS deliver up to 10 trains of intermittent theta-burst per day for many consecutive days. A recent investigation of accelerated-intermittent theta-burst TMS that delivered iTBS 10 times per day with each iTBS train consisting of 1,800 pulses for 5 consecutive days: 18,000 pulses per day at 90% motor threshold, 90,000 pulses in one week (Cole et al. *Am J Psychiatry* 2020). Our proposal to deliver 900 bursts (180 trains of 5 bursts) over the course of 1.5 hours with 11 seconds between train is well within current safety considerations.

To further reduce risk during the stimulation session, the participant will be actively monitored by the researcher and any signs of duress will result in a termination of stimulation and the experimental session. There is a rare likelihood that the participant could undergo a seizure from stimulation. While this is unlikely, all of our researchers are trained in first-aid and CPR with (RedCross certificate). In addition, a collaborator of the Carolina Center for Neurostimulation, Dr. Clio Rubinos, is an epileptologist in the Department of Neurology that is on-call for emergencies and her contact information is posted in our experiment rooms. All researchers are trained in the Carolina Center for Neurostimulation in how to respond in the event of a seizure and are instructed in best monitoring practices to prevent its occurrence. This is a known, unlikely risk of TMS and our screening procedure was developed according to established guidelines (Rossi et al. 2009; Rossi et al. 2020) to prevent participants from receiving TMS that have contraindications.

Finally, there is a theoretical risk that TMS may damage hearing over prolonged exposure given the proximity of the stimulator to the ears (Rossi et al. 2009; Rossi et al. 2020). Thus, we provide participants with ear plugs during motor threshold stimulation and with EEG-compatible ear-buds with an inflatable foam shape during task performance with TMS. These ear buds provide noise protection by making a tight seal and contain a small tube so that we can play white noise to the participant to help mask the noise of the stimulation for analysis purposes. In addition, the experimenter wears ear plugs during TMS to protect their hearing.

EEG and EMG will be collected using the Geodesic 400 system (EGI INC., Eugene, OR, USA). Collecting simultaneous EEG and EMG with TMS does not pose any additional risk over TMS on its own. EEG and EMG do not involve brain stimulation and is used purely for electrophysiology (minimal risk).

4.4 END OF STUDY DEFINITION

The end of this study is defined as when the last participant completes the study (i.e., the 24th participant to complete their final session).

5. STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, a participant must meet all of the following criteria:

- Between the ages of 18 and 65
- Able to provide informed consent
- Have normal to corrected vision
- Right-handed
- Willing to comply with all study procedures and be available for the duration of the study
- Speak and understand English
- Negative pregnancy test for female participants

5.2 EXCLUSION CRITERIA

A potential participant who meets any of the following criteria will be excluded from participation in the study:

- ADHD (currently under treatment)
- Neurological disorders and conditions, including, but not limited to:
    - History of epilepsy
    - Seizures (except childhood febrile seizures)
    - Dementia
    - History of stroke
    - Parkinson's disease
    - Multiple sclerosis
    - Cerebral aneurysm
    - Brain tumors
- Medical or neurological illness or treatment for a medical disorder that could interfere with study participation (e.g., unstable cardiac disease, HIV/AIDS, malignancy, liver or renal impairment)
- Medications that interfere with the EEG signal (e.g., benzodiazepines, anticonvulsants)
- Prior brain surgery
- Any brain devices/implants, including cochlear implants and aneurysm clips
- History of current traumatic brain injury
- (For females) Pregnant or breast feeding
- Anything that, in the opinion of the investigator, would place the participant at increased risk or preclude the participant's full compliance with or completion of the study

- Contraindications for MRI: ferrous metal inside the body, jewelry must be removable, pacemaker or cochlear implant.

5.3 LIFESTYLE CONSIDERATIONS

None.

5.4 SCREEN FAILURES

In the design of this study, initial phone screening procedures will identify the participants who do not qualify for the study. In the phone screening, we ask question to determine eligibility according to our inclusion and exclusion criteria. Then, we conduct a screening for eligibility for magnetic resonance imaging and for transcranial magnetic stimulation. The first session will be used to titrate the difficulty of the task such that participants are engaged with reward-based decision-making. In our previous study using this task, we found that around 30% of participants did not engage with the reward-based decision-making task (Riddle et al. 2021b). In other words, they chose the EASY task almost every time, or they chose the HARD task almost every time. This rate is similar to what other groups have found when using this task (Treadway et al. 2009). As is common practice in cognitive neuroscience studies like this one, the difficulty of the task needs to be titrated to the performance of the individual. While multiple efforts to titrate the difficulty of this task have been employed and are employed here, a high percentage (~30%) of participants still do not use the information about the incentive in their decision process but instead choose the HARD or EASY task almost exclusively. Thus, the cognitive processes under investigation in this study are not engaged in some participants. In addition, we are interested in the impact of stimulation on these performance metrics during stimulation, so a participant that is at “ceiling performance” or “floor performance” is unlikely to show a change in their performance. For these reasons, we expect that up to 30% of participants will be excluded after the first session for a failure to engage the cognitive processes under investigation in this study.

Before the MRI session, we conduct an additional MRI screening to ensure safety. Before each of the TMS sessions, we conduct an additional TMS screening to ensure safety. There is a small and unlikely chance that participants become ineligible at these later sessions as these contraindications are fairly stable over time.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

This clinical trial will utilize multiple recruitment strategies to communicate this opportunity to as many potential participants as possible. We estimate that approximately 40 participants will be enrolled from the Chapel Hill/Carrboro area and 10 between Durham and Raleigh. We will advertise the study directly to the public on websites such as ClinicalTrials.gov, studypages.com, frohlichlab.org and Carolinaneurostimulation.org. We will have contact information and a summary of the clinical trial posted on the Frohlich Lab Facebook and Twitter pages. We may also be launching a Facebook ad to identify potential participants. We will also be using the UNC Mass email listserv to send out an email that has the studypages.com link. All participant identifiers will be stored in REDCap until recruitment is over. When recruitment is over, all participants who do not consent or are not eligible for the study will have their

responses permanently deleted in REDCap. We will also advertise the study through presentations to groups or classrooms.

Retention is primarily achieved through monetary compensation. The payment is $40 for completion of the baseline EEG session for 2 hours. Then, the second MRI session provides $40 for 1.5 hours. Finally, for the 3rd session involved TMS and EEG participants receive $40 for 2 hours, and finally $60 for the 4th session of 2 hours. Thus, completion of all study requirements gives $180 and take 7.5 hours. The escalating compensation per hour with each session incentivizes the participant to finish all sessions. The participant will receive payment at the end of each session on a payment card that can be loaded. The research staff will also give each participant a reminder call or email for upcoming sessions. Each research staff member will be available for the participants to contact via email or phone.

6. STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

We will use the MagPro X100 or R30 system (MagVenture Inc., Alpharetta, Georgia, USA) for transcranial magnetic stimulation. The MagPro X100 and R30 are advanced, high performance magnetic stimulators designed primarily for research purposes. It is a high-quality tool for researchers with a large choice of stimulating parameters and has stimulation rates up to 100 pulses per second at high intensities and the possibility to combine waveforms and pulse modes.

The simulator has several features:

- 3 waveforms: Biphasic, Biphasic Burst and Monophasic.
- Selectable current direction.
- Stimulation rates up to 100 pulses per second.
- Easily connects to external equipment via programmable input/output triggers.
- System operation control via a built-in computer, eliminating the need for an external computer to set up and control the timing of stimulus sequences.
- Controllable from an external device.

In the USA, federal law regulates the sale of Medical Devices through the US Food and Drug Administration (FDA). This is done to ensure safety and effectiveness. Devices which are permitted to be marketed for their intended use must either have a 510(k) or PMA clearance.

MagPro® stimulators R20, R30, R30 with MagOption, X100, and X100 with MagOption are all FDA 510(k) cleared (k160280, k061645, k091940 and k150641).

k150641: The intended use is treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.

k160280, k061645, k091940: The intended use is for stimulation of peripheral nerves for diagnostic purposes.

The use of devices for other than their FDA cleared intended use is considered as investigational. Such use is only permitted if the Investigational Device Exemption (IDE) guidelines have been followed. For full information on this procedure, please consult FDA's website (www.fda.gov).

All investigational devices must be labeled in accordance with the labeling provisions of the IDE regulation (§ 812.5) and must bear a label with this statement:

CAUTION Investigational Device. Limited by Federal (or United States) law to investigational use.

6.1.2 DOSING AND ADMINISTRATION

As described in section 4.3 on justification for dose, the intensity of transcranial magnetic stimulation will be tailored to the sensitivity of the individual using the standardized motor thresholding procedure. This procedure estimates the natural level of electrical activation in the brain that leads to a muscle activation. In the stimulation sessions, we will then deliver trains of TMS at 80% of the motor threshold of the individual. Thus, the electric current generated within the brain from transcranial magnetic stimulation will be within the range of endogenous electrical activity. Personnel will be thoroughly trained and have trainings documented on the transcranial stimulation device and will be present during all stimulation sessions. To monitor side effects of stimulation, a stimulation effects questionnaire will be administered after each stimulation session. In the event that common side effects are experienced, then these will be documented using an adverse event structured interview.

6.3 MEASURES TO MINIMIZE BIAS: CONTROL CONDITIONS, RANDOMIZATION, AND PREREGISTRATION

Control Conditions
As discussed in section 4.2, it is not possible for the researchers to be blinded to the form of stimulation that is being used. However, the outcomes of the study are a comparison between experimental conditions with subtle temporal and spatial differences on the order of centimeters and milliseconds respectively. In brief, we will compare stimulation to dorsolateral prefrontal cortex to medial prefrontal cortex. The proximity of these regions is only a few centimeters and the associations of these regions to aspects of the task is under active investigation. In addition, we are comparing delta-beta patterned stimulation to theta-gamma patterned stimulation to an arrhythmic stimulation condition. The difference between delta-beta and theta-gamma stimulation is only a small difference in frequency, on the order of 100s of milliseconds. Similar to the stimulation site, the association of these frequencies of stimulation to task parameters is under active investigation and there are no online resources to draw these associations. Finally, we will use this task to calculate two distinct behavioral metrics: goal-directed behavior and reward-evaluation. These behavioral metrics are calculated from the same decision-making data and reflect different patterns of performance. In our previous study, we found that these two behavioral metrics were dissociable from each other (low correlation between these metrics across individuals). Thus, the paired association under investigation of delta-beta patterned TMS to goal-directed behavior during stimulation of dlPFC is fundamentally complex and none of these comparisons will be explained to the participant. Two of these three control conditions are included within each session and the site of stimulation is controlled between the third and fourth session. Thus, any systematic differences between sessions will be controlled by a within-session contrast of conditions. Finally, we prevent against unconscious experimenter bias in many ways that are described in section 4.2. To reiterate, conditions of

interest are controlled within session, upcoming blocks are not known to experimenter or participant, behavioral metrics are different patterns of decision-making within the same epoch of the task, all task sessions are meaningful to the outcomes of the study, and experimenter-participant interactions are kept to a minimum within the task.

Randomization
We will use computer code to randomize and counterbalance the sequence of blocks within each session. Each session includes six blocks of 30 trials each. Every trial within a block will be either delta-beta stimulation, theta-gamma stimulation, or arrhythmic patterned stimulation. The order of blocks will be randomized for each participant. We will enforce that the first three blocks and last three blocks include each stimulation condition and participants will not receive the same form of stimulation two blocks in a row. This randomization scheme ensures that each type of stimulation is delivered at various temporal phases across the overall session. Within each session, the incentive that is offered for each trial will be randomized and counterbalanced such that an equal number of low ($2.50, $3.00, $3.50, $4.00) and high ($4.50, $5.00, $5.50, $6.00) value incentives are offered. Finally, the sequence of receiving stimulation to dlPFC and mPFC over the 3rd and 4th session will be randomized and counterbalanced across participants. In addition, both of the stimulation sessions include conditions of active interest to the investigators and so there will be no systematic bias to devalue one of the sessions. These methods for randomization and counterbalancing will reduce the chances that some unforeseen pattern of TMS or task parameters will systematically bias behavior. Thus, the experimental design has been selected to rigorously support scientific integrity.

Preregistration
The hypotheses of this study that are explicitly described in this protocol will be pre-registered on ClinicalTrials.gov. This ensures that the write-up of all manuscripts that result from this project will be clear to define what was a hypothesized outcome and what findings are unexpected. Furthermore, this process prevents any exploratory findings to be framed as hypothesized findings. By clearly defining these planned analyses, bias is minimized in the analysis of these data.

6.4 STUDY INTERVENTION COMPLIANCE

Full compliance with the intervention is defined as completing the four sessions of the experiment. The intervention is applied and monitored by researchers. Thus, compliance can be directly observed.

6.5 CONCOMITANT THERAPY

This clinical trial is conducted in a convenience sample of the population. The exclusion criteria were chosen to ensure the safety of participants and to reduce known sources of electrophysiological confound like neurological disorders or ADHD medications. We will not query, monitor, or change any concomitant therapy in the participants.

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation of stimulation during session 3 or session 4 means that study participation is halted and no other sessions are completed. If a clinically significant finding is identified after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The study intervention (i.e., patterned transcranial magnetic stimulation) will be discontinued for the following reasons:

- Any clinical adverse event (AE), laboratory abnormality, intercurrent illness or other medical condition, or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets any exclusion criteria (either newly developed or not previously recognized).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Any clinical adverse event (AE), laboratory abnormality, intercurrent illness or other medical condition, or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets any exclusion criteria (either newly developed or not previously recognized).

The reason for participant discontinuation or withdrawal from the study will be recorded with the participant files. Participants who sign the informed consent form and are not randomized will be replaced. Participants who sign the informed consent form, are randomized, and receive the full or part of the study intervention, and subsequently withdraw from the study, are withdrawn from the study, or discontinue the study will not be replaced. However, participants who sign the informed consent form, and are not randomized will be replaced. In the event that 24 participants have not completed the experiment but all randomization slots are taken, then we will create an additional 10 slots for randomization. In the unlikely event that those are also filled, then we will create an additional 10 slots.

The reason for drop-out will be documented and reported in the write-up of the manuscripts that results from this study. This study involves stimulation during task performance and the stimulation is spread out over the course of an hour or more. During clinical intervention, TMS is condensed into a 2- to 10-minute period of time. Thus, tolerability of the manner of TMS in this study likely does not generalize into the clinical setting. Nonetheless, this information may be relevant to other researchers or to clinicians using a similar spatial targeting scheme or similar pattern of stimulation.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 1 scheduled visit and is unable to be contacted by the study site staff. All efforts will be made to ensure participants are not lost

to follow-up, including developing rapport and ensuring enrolled participants are reminded of their session dates. Research personnel will be flexible in timing, including offering this session later in the day as well as some weekends.

Every effort will be made to contact participants who are lost to follow-up, including contacting via email and phone. However, if a participant is lost to follow-up, the missed session will be labeled as missing data and our pre-determined analysis plan takes into consideration missing data. Of note, we will continue data collection until the specified number of participants complete the full study. Thus, the statistical analysis plan will not be impacted by those participants that are lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Inclusion and exclusion criteria will be determined during the phone screening.

8.1.1 ELECTROPHYSIOLOGY

1. Resting-state EEG (RSEEG) recordings will be completed during the first, third, and fourth session. Eyes-open and eyes-closed RSEEG will be collected before any task are performed or stimulation is delivered. This is collected for exploratory purposes.
2. Phase-amplitude coupling between delta-beta and theta-gamma oscillations will be acquired during the decision epoch of the Streamlined Expenditure of Effort for Reward Task (S-EEfRT) as measured in our previous study (Riddle et al. 2021a; Riddle et al. 2021b). Delta-beta coupling is calculated between the prefrontal cortex and motor cortex. Theta-gamma coupling is calculated between the prefrontal cortex and posterior parietal cortex.

8.1.2 TASK PERFORMANCE

1. Goal-directed behavior: In the Streamlined Expenditure of Effort for Reward Task (S-EEfRT), goal-directed behavior is quantified as the percentage of trials in which the participant chose the HARD task instead of the EASY task. In our previous experiment, goal-directed behavior positively and significantly correlated with delta-beta coupling. Goal-directed behavior ranges from 0 to 100% and task difficulty is titrated to push goal-directed behavior down to <85%. In our previous use of this task, minimum goal-directed behavior was 23%. To ensure that task performance is properly titrated during the baseline session, we will increase the difficulty of both tasks (EASY and HARD) when the HARD task is chosen greater than 85% of the time, and decrease the difficulty of tasks when the HARD task is chosen less than 15% of the time. At the end of the baseline session, if that participant has selected to perform the HARD task greater than 85% of the time or less than 15% of the time, then this will be considered a screening failure and their participation will be discontinued.
2. Reward-evaluation: In the EEfRT, reward-evaluation is quantified as the slope of the linear fit of percentage HARD trials for each incentive level ($2.50 to $6 in $0.50 increments), dependent variable, to the incentive level, independent variable. In our previous experiment, reward-evaluation positively and significantly correlated with theta-gamma coupling. In our previous experiment, the average reward evaluation was 15% per $1. Participants are informed at the

beginning of task performance that the S-EEfRT is a game and that no additional monetary compensation will be provided.

8.1.3 SELF-REPORT ASSESSMENTS

1. The Behavioral Inhibition and Behavioral Activation Self Report Scales (BIS/BAS) (Carver and White 1994) will be completed during the first session. These scales are used to monitor the perceived sensitivity to reward and punishment. BIS/BAS is broken into four sub-scores: BIS (7 to 28), BAS drive (4-16), BAS fun-seeking (4-16), and BAS reward (7-20).
2. The State-Trait Anxiety Inventory (STAI) (Spielberger et al. 1983) for trait anxiety will be completed during each session. These 40 items are used to quantify frequencies of feelings of anxiety. STAI has two subscores, state and trait anxiety, range 20 to 80.
3. The Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al. 1995) will be completed online during the first session to stratify randomization. This scale is acquired at each session. This scale is used to assess anhedonia, range 14 to 56.
4. Temporal Experience of Pleasure Scale (TEPS) is an 18-item assessment that quantifies symptoms of anhedonia along two sub-dimensions: consummatory (8 to 48) and anticipatory (10 to 60) (Gard et al. 2006). This assessment may provide additional insight into subtypes of anhedonia symptoms and is acquired during the first session.
5. Ruminative Responses Scale (RRS) is a 22-item assessment that quantifies the degree to which participants engage in depressive rumination, range 31 to 155 (Nolen-Hoeksema et al. 1999). This assessment is completed at the first session.

8.2 SAFETY AND OTHER ASSESSMENTS

1. A stimulation side effects questionnaire will be administered at the end of each stimulation session. This tool will be used as a safety measure and to collect data on the experience of the participant. The side effects questionnaire was adapted from studies in our group that used a different form of stimulation (transcranial electric stimulation), and was updated to remove questions that are not relevant to transcranial magnetic stimulation.
2. An MRI screening form will be administered over the phone during the phone screening and within 24 hours prior to the MRI session. This screening form is the standard provided by the Brain Research Imaging Center (BRIC) at UNC. During the phone screening, if there is any ambiguity in the eligibility of the participant, then we consult with the technicians at the BRIC for approval to conduct an MRI. Then, in the 24 hours prior to their MRI session, MR technicians at the center review a new screening form and confirm their eligibility to receive an MRI. Because this is the same form used in the screening for the experiment, the only way that a participant would fail to be eligible at this stage is if there was some change in their eligibility between sessions. While this is highly unlikely, the participant would be discontinued from participating.
3. A TMS screening form will be administered over the phone and at the start of each of the TMS session. If there is any ambiguity in the contraindications for the TMS form, then the medical monitor, Dr. Clio Rubinos, who is an epileptologist is consulted and final approval is acquired. Similar to the MRI screening form, it is highly unlikely that eligibility will change between sessions. Out of an excess of caution, we administer the TMS screening form at each TMS session to confirm that there is no contraindication, otherwise participation is discontinued.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

All adverse events (AEs) will be assessed by the principal investigator and/or co-investigator(s) using the following guidelines:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the principal investigator and co-investigator(s) who examines and evaluates the participant based on temporal relationship and their clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test

result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The principal investigator (Dr. Frohlich), with input from the medical monitor (Dr. Clio Rubinos) when necessary, will determine whether an adverse event (AE) is expected or unexpected in this population. The principal investigator (Dr. Flavio Frohlich) is an expert in non-invasive brain stimulation and the medical monitor (Dr. Clio Rubinos) is an epileptologist in the department of neurology at UNC. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits, or the study participant may report AE or SAEs outside of a scheduled study visit.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to

adequate resolution. Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Research personnel will record all reportable events with start dates occurring any time after informed consent is obtained until the last day of study participation. At each study visit, research personnel will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

8.3.5 ADVERSE EVENT REPORTING

We will be adopting the following reporting procedures:

What event is reported	When is event reported	By whom is event reported	To whom is event reported
Fatal or life-threatening unexpected, suspected serious adverse reactions	Within 24 hours of initial receipt of information	Investigator	• Local/internal IRB
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	Within 48 hours of initial receipt of information	Research Personnel	• Local/internal IRB
Unanticipated adverse device effects	Within 10 working days of investigator first learning of effect	Investigator	• Local/internal IRB
Unanticipated Problem that is not an SAE	Within 7 days of the investigator becoming aware of the problem	Investigator	• Local/internal IRB

8.3.6 REPORTING OF PREGNANCY

There have been scientific studies using transcranial magnetic stimulation in pregnancy (see (Damar et al. 2020; Konstantinou et al. 2020) for review). None of these studies reported side-effects specific to pregnancy or fetal development. Nonetheless, pregnant women will be excluded from this study because they are a protected group. Female participants will be asked if there is a possibility that they are pregnant at each session. If the participant says yes or is unsure, then we will verify pregnancy status via a urine pregnancy test. Only upon a verbal confirmation that pregnancy is not possible or a negative finding from a pregnancy test will we proceed with the experiment.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

If a UE occurs, the IRB will be notified, and the study will be adjusted as needed to protect the health and safety of the participants. Depending on the nature of the UE, the research protocol, inclusion/exclusion criteria, and informed consent will be changed to reflect the possibility of this event reoccurring. During this time, no new participants will be recruited and the research procedures for currently enrolled participants will be stopped. Each UE will be recorded and reported throughout the study.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Any new information gained during the study that may affect a participant's willingness to continue in the study will be reported to all currently enrolled participant.

9. STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by Dr. Justin Riddle.

9.1 STATISTICAL HYPOTHESES

- Primary Outcome hypothesis:
    - Null: There is no difference in goal-directed behavior between baseline S-EEfRT and S-EEfRT during stimulation to dlPFC as a function of stimulation type (delta-beta TMS, theta-gamma TMS, or arrhythmic).
    - Alternate: There is a difference in goal-directed behavior between baseline S-EEfRT and S-EEfRT during stimulation to dlPFC as a function of stimulation type (delta-beta tACS, theta-gamma tACS, or active-sham).

- Secondary Outcome hypothesis:
    - Null: There is no difference in delta-beta phase-amplitude coupling strength between prefrontal electrodes and left motor electrodes for the decision period of the S-EEfRT as a function of stimulation type to dlPFC (delta-beta TMS, theta-gamma TMS, or arrhythmic TMS).
    - Alternate: There is a difference in delta-beta phase-amplitude coupling strength between prefrontal electrodes and left motor electrodes the decision period of the S-EEfRT as a function of stimulation type to dlPFC (delta-beta TMS, theta-gamma TMS, or arrhythmic TMS).

- Exploratory Outcome hypothesis 1:
    - Null: The impact of delta-beta TMS to dlPFC on goal-directed behavior is not correlated with personality traits related to motivation.
    - Alternative: The impact of delta-beta TMS to dlPFC on goal-directed behavior is correlated with personality traits related to motivation.

- Exploratory Outcome hypothesis 2:
    - Null: There is no difference in reward-evaluation between baseline S-EEfRT and S-EEfRT during stimulation to mPFC as a function of stimulation type (delta-beta TMS, theta-gamma TMS, or arrhythmic).
    - Alternate: There is a difference in reward-evaluation behavior between baseline S-EEfRT and S-EEfRT during stimulation to mPFC as a function of stimulation type (delta-beta tACS, theta-gamma tACS, or active-sham).

- Exploratory Outcome hypothesis 3:
    - Null: There is no difference in theta-gamma phase-amplitude coupling strength between prefrontal electrodes and posterior parietal electrodes for the decision period of the S-EEfRT as a function of stimulation type to mPFC (delta-beta TMS, theta-gamma TMS, or arrhythmic TMS).
    - Alternate: There is a difference in theta-gamma phase-amplitude coupling strength between prefrontal electrodes and posterior parietal electrodes the decision period of the S-EEfRT as a function of stimulation type to mPFCs (delta-beta TMS, theta-gamma TMS, or arrhythmic TMS).

- Exploratory Outcome hypothesis 4:
    - Null: Functional connectivity during the S-EEfRT between dorsal striatum and lateral prefrontal cortex is not predictive of the impact of delta-beta TMS to dlPFC on goal-directed behavior.

- Alternative: Functional connectivity during the S-EEfRT between dorsal striatum and lateral prefrontal cortex is predictive of the impact of delta-beta TMS to dlPFC on goal-directed behavior.

9.2 SAMPLE SIZE DETERMINATION

The sample size is 24 participants in the final dataset to be used in analysis. However, to ensure that 24 participants complete the experiment, we conservatively estimate to enroll 50 participants as a ceiling for the sake of IRB approval. The motivation for the sample size of 24 participants in the analysis is explained below. The sample size is determined based on previous experiments from our group: the effect size of previous findings and the reliability of our estimates. Our estimators are precise due to sufficient number of trials per condition with each participant and that the tasks are titrated to the individual.

Primary outcome: Rhythmic TMS to lateral frontal cortex at delta-beta frequency will increase goal-directed behavior relative to arrhythmic TMS.

Previous Data: The planning and refinement of the proposed study was informed by our previous experiments that serve as preliminary data for the proposal. In our previous experiment, we delivered rhythmic TMS to lateral frontal cortex to increase performance in a cognitive control task (Riddle et al. 2020b). In our previous study, there was a significant interaction between TMS site and TMS frequency in a two-way repeated-measures ANOVA such that the improvement in performance in the cognitive control task was site and frequency-specific. The effect size from the partial-eta square was 0.23, and the effect from a dependent t-test was 0.532, with 20 participants. The experimental design of this previous study is similar to the current study in that there are two sites for stimulation (lateral frontal and medial frontal) with two different stimulation frequencies (delta-beta and theta-gamma). Both studies used an arrhythmic condition to control for non-specific effects of TMS.

Sample Size Determination and Power Calculation: Based on this previous effect size, we estimated that our participant count at 24 participants is powered at >95%.

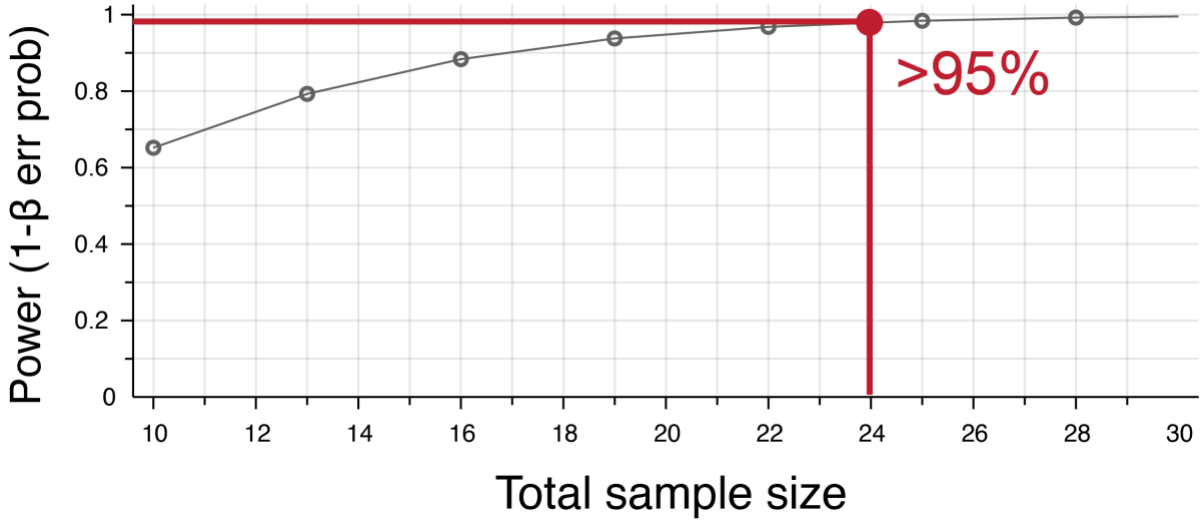

Figure 3. Power calculation for the interaction effect in two-way repeated-measures ANOVA modeled as within factors interaction in a two-way ANOVA with partial-eta square of 0.23, and a correlation between variables of 0.77 based on Riddle, Scimeca et al. 2021. Power calculation run using the G*Power software. Proposed number of participants is 24 and is depicted in red.

Data will be collected until we reach 24 participants. Given the similarity with our previous experiment (Riddle, Scimeca, et al., 2020), we are confident that our current analysis will be sufficiently powered.

Secondary outcome: Rhythmic TMS to lateral frontal cortex at delta-beta frequency will increase frontal delta-beta coupling strength.

Previous Data: The planning and refinement of the proposed study was informed by our previous experiments. In our previous experiment, we delivered rhythmic TMS to lateral frontal cortex and found an increase in oscillatory power and an increase in phase entrainment specific to the targeted frequency band (Riddle, McPherson, et al.). In our previous experiment that delivered theta frequency TMS (4-8Hz) to lateral frontal cortex, we found an increase in oscillatory power in theta frequency (effect size of 0.540) and a robust increase in phase alignment across trials (effect size of 1.01). We use the phase alignment metric (inter-trial phase coherence) to estimate the required power to find a similar impact of delta-beta stimulation to align the phase of delta oscillations to task-modulated beta amplitude. The analysis of our previous experiment used 47 participants. Based on our previous effect size for entrainment, we would need 15 participants to reach 95% statistical power for this comparison. A more conservative estimate of a large effect size (0.60), we would need 24 participants to reach 80% statistical power.

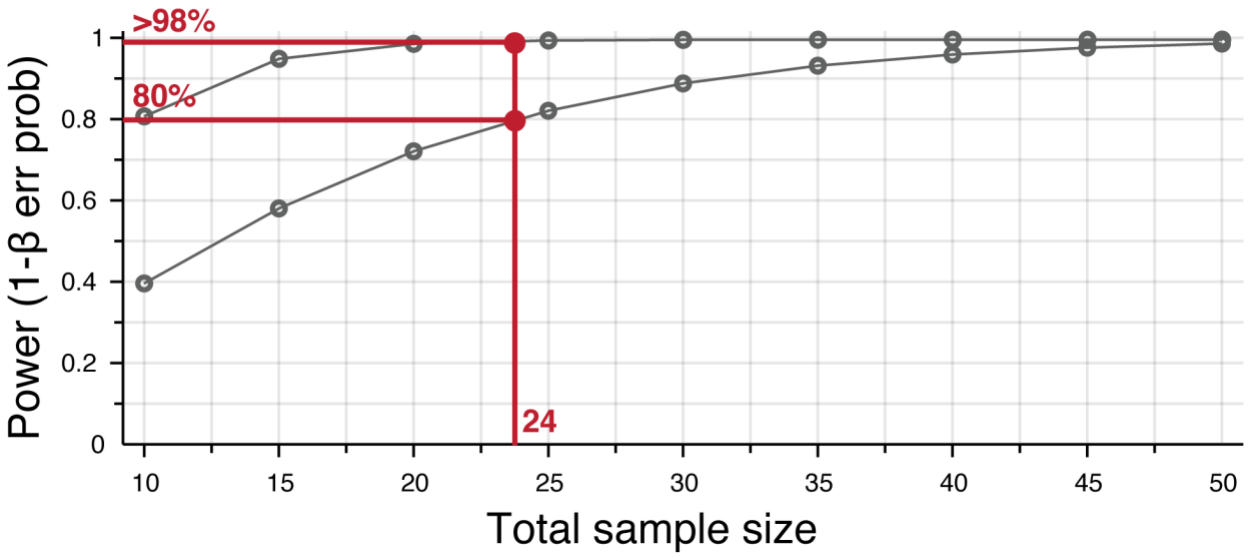

Figure 4. Power calculation for increased phase alignment of delta oscillations to beta power from delta-beta TMS. The effect size estimate is based on phase entrainment in EEG from rhythmic TMS (larger effect, above). A more conservative effect size estimate would be to use the impact of rhythmic TMS on oscillatory amplitude (large effect, below). Both effect sizes were modeled as a dependent t-test using the G*Power software. The proposed number of participants is 24 and is depicted in red.

Data will be collected until we reach 24 participants. Given the similarity in methodology between the current experiment and our previous experiment (Riddle, McPherson, et al.), we are confident that we are sufficiently powered with 24 participants.

9.3 POPULATIONS FOR ANALYSES

Every effort will be made to ensure all enrolled and randomized participants complete all study sessions as described in this protocol. For this study, enrolled eligible healthy participants will be randomized to receive stimulation to frontal and parietal cortex in a randomized sequence. If a participant completes session 4, then they will be included in all analyses moving forward.

As previously stated in ***Section 7 Study Intervention Discontinuation and Participant Discontinuation/Withdrawal***, enrolled participants who do not get randomized will be replaced. If required, then we will create additional blocks of 10 randomized sequences. Therefore, we will collect data until 24 participants complete the study and are eligible for analysis.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

All testing described below assumes a significance threshold of $p = 0.05$. Analyses will be deemed to be statistically significant if the p-value is less than this threshold. An analysis that does not exceed this threshold will be considered inconclusive. Continuous data will be described using means, standard deviations, and confidence intervals, while categorical data will be described using counts/percentages.

There may be additional covariates included in the analysis. Data will be assessed for normality and, if deemed necessary, corrective procedures will be applied (e.g., log normalization). Based on our previous dataset, we expect that the variables used here will be approximately Gaussian. However, if the distribution of a variable displays a skewed tail and a test for normality fails, then it is justified to use a corrective procedure. This correction will be applied upon consideration of the variables themselves, and not based on the result of the intended analysis.

Data will be collected until 24 participants complete the study and all data is usable. Given that recruitment will be feasible in a convenience sample, we expect to have complete data and all analyses will include the full participant pool. However, if there are technical errors that are not caught in time, then the affected analyses may have less participants. In this scenario, the data for a participant is then completely removed from the analysis.

The effects of stimulation are expected to be transitory, lasting for only a second or two after stimulation. For this reason, stimulation is delivered “online” immediately preceding the time at which the cognitive processes of interest are engaged. During each session, we include a control condition (arrhythmic TMS) that will be subtracted from the conditions of interest (delta-beta TMS and theta-gamma TMS). Therefore, we control for any effects of sequence or time within each session by subtracting each metric of interest from the condition-matched arrhythmic TMS metric. Furthermore, any learning effects from performing the reward-based decision-making task should be stabilized by the 3rd session. These methods are typical

in cognitive neuroscience paradigms. For the reasons listed above, it is unlikely that there will be any effect of sequence or carryover effects between sessions.

9.4.2 ANALYSIS OF THE PRIMARY OUTCOME (BEHAVIOR)

Goal-directed behavior will be calculated as the average decision to perform the HARD task. The average of the two blocks for each stimulation conditions will be calculated (three stimulation types by two stimulation sites). A two-way repeated-measures analysis of variance (ANOVA) will be performed using within-participant factor of stimulation type (delta-beta TMS versus theta-gamma TMS; each subtracted by session-matched arrhythmic TMS) and within-participant factor stimulation site (dlPFC TMS versus mPFC TMS). We control for the effect of time with a subtraction of delta-beta TMS versus arrhythmic TMS and theta-gamma TMS versus arrhythmic TMS. In other words, four values are submitted to the ANOVA for each participant.

1. Delta-beta TMS to dlPFC minus arrhythmic TMS to dlPFC
2. Theta-gamma TMS to dlPFC minus arrhythmic TMS to dlPFC
3. Delta-beta TMS to mPFC minus arrhythmic TMS to mPFC
4. Theta-gamma TMS to mPFC minus arrhythmic TMS to mPFC

Thus, only differences from our active control, arrhythmic TMS, are considered meaningfully worth interpretation. We hypothesize to find an interaction between stimulation site and stimulation type in the ANOVA. Post-hoc differences will be investigated using Tukey's method to address multiple comparisons. We hypothesize that the predicted interaction will be driven by an increase in goal-directed behavior for delta-beta TMS to dlPFC. Sensitivity analyses will be conducted to evaluate the specificity of these effects: a similar analysis with reward-evaluation as the dependent variable and we do not expect that delta-beta TMS will have any effect on reward-evaluation.

9.4.3 ANALYSIS OF THE SECONDARY OUTCOME (ELECTROPHYSIOLOGY)

Delta-beta phase amplitude coupling will be calculated between the phase of delta oscillations (2-3 Hz) in prefrontal electrodes (FCz and surrounding electrodes) and the amplitude of beta oscillations (15- 25 Hz) in left motor electrodes (C3 and surrounding electrodes). The instantaneous phase and amplitude of these oscillations will be calculated by averaging the signal in these two regions of interest, band-filtering the signal to the specified range, and then performing the Hilbert transform on the signal. Phase-amplitude coupling (PAC) is then calculated by creating a hybrid signal using the amplitude of beta oscillations in left motor electrodes and the phase of delta oscillations in prefrontal electrodes:

$PAC = \left|\frac{\sum_{t=1}^{N} M*e^{i\theta}}{N}\right|$, M is magnitude of beta oscillations, θ is angle of delta oscillations, N is number of time points

The PAC value is normalized by creating a null distribution by randomly shifting the beta timeseries by at least 10% of the number of time points. Then, PAC is calculated between the delta-phase timeseries and each of these randomly shifted beta-amplitude timeseries. Finally, PAC_Z is calculated as the z-transformed true PAC value relative to the null distribution.

The average during the decision epoch of each trial of the task during stimulation will be calculated. The average of the two blocks for each stimulation conditions will be calculated (three stimulation types by two stimulation sites). A two-way repeated-measures analysis of variance (ANOVA) will be performed using within-participant factor of stimulation type (delta-beta TMS versus theta-gamma TMS; each subtracted by session-matched arrhythmic TMS) and within-participant factor stimulation site (dlPFC TMS versus mPFC TMS). We control for the effect of time with a subtraction of delta-beta TMS versus arrhythmic TMS and theta-gamma TMS versus arrhythmic TMS. In other words, four values are submitted to the ANOVA for each participant.

1. Delta-beta TMS to dlPFC minus arrhythmic TMS to dlPFC
2. Theta-gamma TMS to dlPFC minus arrhythmic TMS to dlPFC
3. Delta-beta TMS to mPFC minus arrhythmic TMS to mPFC
4. Theta-gamma TMS to mPFC minus arrhythmic TMS to mPFC

Thus, only differences from our active control, arrhythmic TMS, are considered meaningfully worth interpretation. We hypothesize to find an interaction between stimulation site and stimulation type in the ANOVA. Post-hoc differences will be investigated using Tukey's method to address multiple comparisons. We hypothesize that the predicted interaction will be driven by an increase in delta-beta coupling for delta-beta TMS to dlPFC. Sensitivity analyses will be conducted to evaluate the specificity of these effects: a similar analysis with theta-gamma coupling as the dependent variable and we do not expect that delta-beta TMS will have any effect on theta-gamma coupling.

9.4.4 ANALYSIS OF THE EXPLORATORY OUTCOMES

First exploratory outcome: personality traits of motivation

In our previous study and found that goal-directed behavior positively correlated with traits of motivation. Thus, we hypothesize that personality traits of motivation will positively correlate with the degree to which delta-beta TMS will increase goal-directed behavior. The analysis will be run as a Pearson correlation between the impact of delta-beta TMS to dlPFC on goal-directed behavior and individual differences in traits of motivation. To control for the specificity of this effect, this correlation will be compared to arrhythmic TMS, personality traits of anxious rumination, and reward-evaluation.

Second exploratory outcome: reward-evaluation

As described in section 8.1.2, we will calculate reward-evaluation to quantify the specificity of TMS on specific behavioral metrics of reward-based decision-making. We will run an ANOVA as described in in the description of our primary outcome, but with the dependent variable as reward-evaluation instead of goal-directed behavior. We hypothesize based on our previous study that theta-gamma TMS to mPFC will increase reward-evaluation.

Third exploratory outcome: theta-gamma coupling

Using the method for calculating phase-amplitude coupling in section 9.4.3, we will calculate the coupling between the phase of theta oscillations in prefrontal electrodes (Fz and surrounding) with the amplitude of gamma oscillations in posterior parietal electrodes (PO4 and surrounding). We will run an ANOVA as described in in the description of our secondary outcome, but with the dependent variable as theta-gamma coupling instead of delta-

beta coupling. We hypothesize based on our previous study that theta-gamma TMS to mPFC will increase theta-gamma coupling.

Fourth exploratory outcome: functional connectivity in frontal-striatal circuity

Using the task-driven functional magnetic resonance imaging data, we will calculate the strength of functional connectivity between the dorsal striatum and the lateral prefrontal cortex. We hypothesize that that individual differences in this functional connectivity strength will be predictive of the change in goal-directed behavior with delta-beta TMS. The analysis will be run as a Pearson correlation between the impact of delta-beta TMS to dlPFC on goal-directed behavior and individual differences in functional connectivity between dorsal striatum and dlPFC. To control for the specificity of this effect, this correlation will be compared to arrhythmic TMS, reward-evaluation, and functional connectivity between mPFC and ventral striatum.

9.4.5 SAFETY ANALYSES

The stimulation questionnaire will be administered for the third and fourth session after stimulation. This questionnaire solicits ratings of 10 possible adverse effects associated with non-invasive brain stimulation, on a scale of 0 (absent), 1 (low), 2(medium), 3(high), 4 (very high). The side effects include that are expected to occur in some participants are headache, neck pain, scalp pain, muscle stiffness, skin tingling, skin itching, ringing noise, trouble concentrating, improved mood, and dizziness. Paired t-tests with random effect "participant" will be calculated per adverse effect to determine if there are any differences in adverse effect severity between sessions (delta-beta TMS, theta-gamma TMS, and arrhythmic TMS to dlPFC versus mPFC). Subjective severity per adverse effect will be described with mean and standard deviation. In addition, we will analyze the severity of each adverse event as determined by the Medical Monitor and PI. The process for determining the severity an adverse event is detailed in Section 2.3.4.

A linear model with random effect "participant" will be calculated per adverse effect to determine if there are any differences in adverse effect severity between sessions (dlPFC and mPFC as categorical independent variables) and adverse effect severity as the continuous dependent variable. Subjective severity per adverse effect will be described with mean and standard deviation. In addition, we will analyze the severity of each adverse event as determined by the Medical Monitor and PI.

9.4.6 BASELINE DESCRIPTIVE STATISTICS

All baseline descriptive statistics will be presented as a mean and standard deviation or count, e.g., age, sex, and personality traits.

9.4.7 PLANNED INTERIM ANALYSES

If there is an unexpected event that is related to TMS, then an interim descriptive analyses on the safety measures will be performed. Because the study is not blinded to the researchers, the analysis can be run by any research personnel. In addition, if the participant has a seizure, then an interim analysis will be performed to assess symptom severity between stimulation sites and evaluate whether stimulation side effects exceed those of other TMS studies.

There are no other planned interim analyses.

9.4.8 SUB-GROUP ANALYSES

Sub-group analyses will not be used in this study, as the sample size is too small to conduct analyses based on age, sex, race/ethnicity, or other demographic characteristic(s).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of TMS will be provided to the participants and their families. Consent forms describing, in detail, the study intervention, device, procedures, and risks are given to the participant and written documentation of informed consent is required prior to the administration of any treatment. All consent forms will be IRB-approved and updated with any new information as modifications are made throughout the study.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

During a phone call, the researcher and potential participants will review the clinical trial in its entirety. At several intervals during the consent review, the researcher will ask questions that will assess the comprehension of the information in the consent. If the participant is unsure or does not know, the researcher will return to that section and more carefully explain the information. Participants will not need a surrogate and will be able to provided consent for themselves or will not be included in the study. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice.

At the beginning of the first visit to the lab, participants will sign a physical copy of the consent document witnessed by research personnel. A copy of the signed informed consent document will then be given to the participant for their records. The rights and welfare of the participant will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly

inform research staff, study participants, and the IRB and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the research team. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

All research activities will be conducted in as private a setting as possible.

All data will only be referenced by dummy identifier code. Data will be stored on a password protected computer. A key connecting names and identifier code numbers will be kept in a locked cabinet, accessible only by research personnel. All data will be stored and analyzed on password protected computers, also only accessible by research personnel. Participants will not be identified in any report or publication about this study and there is no risk of deductive disclosure. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the IRB.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be entered into TraCS Clinical Research Data Management Service (REDCap). The database system provides secure web-based data entry with the data stored on servers that are maintained by TrACS. The data is encrypted during transmission. The servers are located in a secure campus area with all appropriate physical security measures in place. The web and database servers are monitored by the TraCS IT staff, patched frequently, and scanned by a third-party vendor to ensure that they are protected against known vulnerabilities. The scanning application is the standard service for the entire campus. Access is by individual user id and is restricted to the forms and/or functions that the user needs to have.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored within the Carolina Center for Neurostimulation/Frohlich Lab. After the study is completed, the data will be fully de-identified and archived within a locked file cabinet or an encrypted server maintained by the Carolina Center for Neurostimulation.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**	**Study Coordinator, Statistical Analyst**
Flavio Frohlich, PhD The University of North Carolina at Chapel Hill - Department of Psychiatry 919-966-4584 Flavio_Frohlich@med.unc.edu	Clio Rubinos, MD The University of North Carolina at Chapel Hill - Department of Neurology (984) 974-1000 CRubinos@unc.edu	Justin Riddle, PhD The University of North Carolina at Chapel Hill - Department of Psychiatry 984-974-6239 Justin_Riddle@med.unc.edu

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the principal investigator, medical monitor, and study coordinator composed of three researchers. The PI will review AEs in real time and make decisions as of participant's continuation of the clinical trial. The PI will review AEs as appropriate, every three months, with the research team. The PI may request additional review by the medical monitor on a case-by-case basis.

10.1.7 CLINICAL MONITORING

The purpose of the monitoring plan is to present the approach of the Carolina Center for Neurostimulaton to monitoring clinical trials. The plan facilitates compliance with good clinical practice.

(a) The rights and well-being of human participants are protected.
(b) The reported trial data are accurate, complete, and verifiable from source documents.
(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

This section identifies key monitoring activities and specifies the data to be reviewed over the course of a clinical trial. This is a single site, investigator initiated, clinical trial so there will be no site monitoring plan in place.

10.1.7.1 THE CAROLINA CENTER FOR NEUROSTIMULATION MONITORING PLAN

The latest version of the approved IRB application for this clinical trial will be followed at all times. This responsibility falls in the hands of the trained research personnel. If at any time there is a deviation from protocol, the deviation from protocol log will be filled out. All team members will be trained on how and when to use this log. Deviations will be sent to IRB every 4-6 weeks (if necessary).

Data will be verified for completeness following every study session and all data will be entered into REDCap, a secure online database. After a participant has completed their participation (full completion of the study or because they withdrew prior to completion), data will be rereviewed for completeness

and accuracy. After all data has been collected, data will be re-reviewed by another lab member who was not involved with the data collection process.

AE and SAE are clearly defined in the Master Protocol. Documents of AE and SAE can be found in the study binder on file within 77 Vilcom Center, Room 111. It is the responsibility of trained research personnel to report all events to the PI. Reporting of AEs and SAEs is described within ***Section 8.3***.

The PI will have access to the REDCap database. This allows the PI to view reports that provide information on any missing data on an individual participant basis, but does not allow them to add, change or input any data.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The Carolina Center for Neurostimulation will conduct internal quality management of study conduct, data and biological specimen collection, documentation and completion. Following written Standard Operating Procedures (SOPs), research personnel will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Trained research personnel will be responsible for the informed consent process, review for eligibility, questionnaire administration, data entry, device administration, EEG administration, and CRF entries. Research personnel will be responsible for AE/SAE documentation and reporting, while the PI will be responsible for the AE assessment, review of the AE documentation forms and overview of the research staff.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) will be entered into a data capture system provided by TraCS Clinical Research Data Management Service (REDCap). The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Trained research personnel will have complete access to the REDCap system. This will enable the researchers to enter the data and the PI review. The REDCap data management system will be programmed and overseen by Justin Riddle.

As discussed in ***Section 10.1.3***, data entered into REDCap is stored on servers that are maintained by TrACS. The data is encrypted during transmission. The servers are located in a secure campus area with all appropriate physical security measures in place. The web and database servers are monitored by the TraCS IT staff, patched frequently, and scanned by a third-party vendor to ensure that they are protected against known vulnerabilities. The scanning application is the standard service for the entire campus.

10.1.9.2 STUDY RECORDS RETENTION

According to the University of North Carolina at Chapel Hill's Archives and Record Management Services schedule for General Records Retention and Disposition Schedule, records will be kept for 5 years after the completion of the study or grant end date, whichever is later.

10.1.10 PROTOCOL DEVIATIONS

All deviations from the protocol will be addressed in study participant source documents. The researcher will complete a Protocol Deviation Log using the participant code as the identifier. This form will collect information such as the date the deviation occurred, details of what the deviation consisted of, any corrective and preventative actions that were taken as a result of the deviation, and the date that the PI and IRB were notified. The PI will review the information and initial once approved. A completed copy of the Protocol Deviation Form will be maintained in the regulatory file, as well as in the participant's source document. Protocol deviations will be sent to the IRB per their guidelines. The site PI/study staff will be responsible for knowing and adhering to their IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Any conflict of interest for any persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed by the UNC Conflict of Interest Office. If necessary, for persons who have a perceived conflict of interest, management will be provided again by the UNC Conflict of Interest office.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ANOVA	Analysis of Variance
BIS/BAS	Behavioral Inhibition System / Behavioral Approach System
BRIC	Biomedical Research Imaging Center
CFR	Code of Federal Regulations
Co-I	Co-Investigator
CRF	Case Report Form
DHHS	Department of Health and Human Services
dlPFC	Dorsolateral prefrontal cortex
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
dSTR	Dorsal striatum
EEfRT	Expenditure of Effort for Reward Task
EEG	Electroencephalogram
EMG	Electromyography
FDA	Food and Drug Administration
FDI	First dorsal interosseous
fMRI	Functional magnetic resonance imaging
GCP	Good Clinical Practice
HD-EEG	High-density electroencephalography
Hz	Hertz
ICF	Informed Consent Form
IDE	Investigational Device Exemption
LAR	Legally Authorized Representative
MEP	Motor evoked potential
mPFC	Medial prefrontal cortex
MRI	Magnetic Resonance Imaging
MT	Motor threshold
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NSR	Non-significant risk
OHRE	Office of Human Research Ethics
OHRP	Office for Human Research Protections
PAC	Phase-amplitude coupling
PACz	Z-transformed phase amplitude coupling
PHI	Protected Health Information
PI	Principal Investigator
RDoC	Research domain criteria
rTMS	Rhythmic transcranial magnetic stimulation
RRS	Ruminative responses scale
SAE	Serious Adverse Event/Serious Adverse Experience
SHAPS	Snaith-Hamilton Pleasure Scale
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
STAI	State-Trait Anxiety Inventory
S-EEfRT	Streamlined Expenditure of Effort for Reward Task
TEPS	Temporal Experience of Pleasure Scale
TMS	Transcranial magnetic stimulation

UE	Unexpected Event
UNC	University of North Carolina
UNC-CH	University of North Carolina at Chapel Hill
US	United States
vSTR	Ventral striatum

10.4 PROTOCOL AMENDMENT HISTORY

MAINTAINED AT THE TOP OF THIS DOCUMENT

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