TASK AUGMENTATION OF TMS

A pilot proof of concept, within subjects, randomized study of the effects of activation of the DLPFC promotion system on TMS treatment. 25 Healthy volunteer participants will be randomized to one of 3 task conditions and complete 4 sessions of either active rTMS or sham TMS neuromodulation. We will use anatomically guided TMS alone or in combination with tasks to test the hypothesis that cognitive paired associate stimulation results in augmented cortical response.

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List of Abbreviations

For example: LIST OF ABBREVIATIONS-list alphabetically.

AE: Adverse event

DLPFC: Dorsolateral Prefrontal Cortex

DMC: Data Monitoring Committee

DM: Diabetes Mellitus

ECG: Electrocardiogram

IAPS: International Affective Picture System

iTBS: Intermittent Theta-Burst Stimulation

MADRS: Montgomery-Asberg Depression Rating Scale

MRI: Magnetic Resonance Imaging

RMT: Resting Motor Threshold

rTMS: Repetitive Transcranial Magnetic Stimulation

SST: Sternberg Sort Task

TMS: Transcranial Magnetic Stimulation

Study Summary

Title	**Task Augmentation of TMS**
Short Title	**Task TMS**
IRB Number	832232
Protocol Number	N/A
Phase	IND Exempt
Study Duration	2 years
Study Center(s)	Single-center

Objectives

Overall objectives

In this R01 proposal we will determine what neural systems underlie TMS-evoked brain responses and how the addition of a task organizes and augments this response to induce plasticity. We first determine which tasks known to activate DLPFC alone or in combination with TMS have greater activation of the DLPFC and have maximal anti-correlation with the subgenual cingulate. In addition, tasks will be combined with TMS in a sham controlled double-blind experiment to test neuromodulation-induced effects. In a sample of 25 healthy participants we will conduct a series of experiments to examine task effects, task-specific TMS augmentation effects and task-specific augmentation of TMS neuromodulation.

Primary outcome variable(s)

We will determine both an "intensity (difficulty) effect" and an "emotion effect" of task-induced fMRI activity in the scanner, collecting these measures in the same subjects. Participants will receive two working memory tasks:

1a) Sternberg Sorting Task (SST): a cognitive task comparing low-load vs. high-load conditions in which the picture stimuli are letters.

1b) International Affective Picture System (IAPS): an emotional task using IAPS picture that will also compare low load and high load conditions. The number of images will vary by condition load, but for both the high-load & low-load conditions, participants will look at IAPS pictures and answer questions about the images. Further, jittered within this design will be both neutral and negative blocks of IAPS pictures.

Secondary outcome variable(s)

Aim 2: to determine which task provides greater augmentation of the TMS-induced DLPFC activation, participants will receive in randomized order:

1) The cognitive SST working memory task or the IAPS task alone
2) rTMS + the cognitive SST working memory task or rTMS + the IAPS emotional task in randomized order. rTMS and the cognitive tasks will be conducted in the fMRI scanner where brain activation to a TMS probe and connectivity will be obtained.
3) rTMS alone

Aim 3: to determine the effect of neuromodulation on DLPFC activation healthy participants will be randomized to one of the 3 task conditions: high-load cognitive SST, high-load IAPS task, or low-load SST (sham task condition). Following a 4 session course (2 session separated by at least 4 hours on one day, followed by 2 sessions separated by at least 4 hours on a second day) of either active rTMS or sham TMS neuromodulation in combination with the task condition participants will again have probe sessions in the scanner where DLPFC activation and connectivity will be determined. Following a 2-week interval, participants will receive the other stimulation condition (sham TMS if active first and active TMS if sham first).

Number of Subjects	25
Main Inclusion and Exclusion Criteria	**Key inclusion criteria** Gender, inclusive 18 – 60 years of age Right-handed No history of meeting DSM criteria for any diagnosis Normal cognition Patients must be able to read and understand English Participants must be able to provide consent **Key exclusion criteria** Pregnancy (Female participants) Outside age range Meets DSM criteria for any diagnosis Unable to have an MRI scan Medical condition that interferes with the collection or interpretation of MRI data Implanted devices such as: aneurysuym clip or cardiac pacemaker History of stroke, epilepsy, or brain scarring Cognitive impairment Recent use of psychoactive medications, as determined by investigators Otherwise determined by investigator to be unfit for participation: ex) meets DSM criteria for current alcohol or substance use disorder (in last 3 months)
Investigational Product (drug, biologic, device, etc.) **For Device include the planned use** **For Drug, food, cosmetic, etc. include the dose, route of administration and dose regiment**	MagVenture X100 Stimulator - *please refer to the 'Devices in Research Form' attached to this submission* MagVenture Cool B65 Coil - *please refer to the 'Devices in Research Form' attached to this submission* MagVenture MRI B91 Coil - *please refer to the 'Devices in Research Form' attached to this submission*

Duration of administration (if applicable)	The neuromodulation participants will receive is FDA-approved iTBS at 120% RMT stimulation intensity; triplet 50 Hz bursts, repeated at 5 Hz; 2 s on and 8 s off; 600 pulses per session; for a total duration of 3 min 9 s per session to the 'Fitzgerald Target' (identified via MRI imaging). Sham TMS will also be administered at the aforementioned parameters. When in the scanner, participants will receive single pulse TMS probes while completing tasks at 120% RMT with 77 total pulses.
Reference therapy	N/A
Statistical Methodology	Efficacy within subjects: Repeated measures ANOVA will be used to assess changes from baseline to post-stimulation for each task condition. Efficacy between subjects: neuro-response rates and time to response will be compared with published rates within the literature to extrapolate the significance of this modality.
Safety Evaluations	No data or safety monitoring board will be necessary for this protocol. The principal investigator will be responsible for monitoring this protocol.
Data and Safety Monitoring Plan	No data or safety monitoring board will be necessary for this protocol. The principal investigator will be responsible for monitoring this protocol.

BACKGROUND AND STUDY RATIONALE

This study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including [as applicable include the following regulations as they apply 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812 and Good Clinical Practice: Consolidated Guidelines approved by the International Conference on Harmonisation (ICH). Note:Only include ICH compliance if the study will actually comply with these requirements.] All episodes of noncompliance will be documented.

Introduction

This should include a brief paragraph or two that describes rationale for the study.

1.1 Background and Relevant Literature

The standard clinical technique for using repetitive transcranial magnetic stimulation (rTMS) for major depressive disorder (MDD) is associated with limited efficacy to date (Lefaucheur 2014; Berlim 2014). Among the potential causes of limited efficacy are the scalp based targeting technique that is currently the most common targeting method rather than techniques that incorporate fMRI-neuronavigation, which have been shown to have greater efficacy (Fitzgerald 2009a). Image guided TMS can target specific functional brain networks with greater resolution that takes into account individual differences in brain anatomy. Another technique for improving treatment efficacy may be to combine it with cognitive activation of the DLPFC designed to activate the same neural circuitry that is targeted by TMS. Cognitive paired associative stimulation builds on the well-established paradigm of paired associative stimulation (PAS). In that paradigm, co-activation of sensorimotor cortex with afferent stimulation of the median nerve timed to arrive as a TMS pulse is delivered to motor cortex, has been shown to increase cortical response to subsequent stimuli (Ziemann 2008). Analogously, simultaneous activation by 2 neurostimuli (TMS to DLPFC and task activating DLPFC) could result in greater cortical activation and have a greater effect on executive function cognitive control than either stimulus alone. Several studies now suggest that the brain “set” is critical in determining TMS effect (McKinley et al) and that simultaneous task activation can augment TMS efficacy (Li et al). It is not known whether the specific mode of cognitive activation is critical or whether the absolute amplitude of activation is more important. One theory proposes that tasks that activate the DLPFC promotion system via priming will maximally augment TMS treatment (Strauman 2013; Detloff & Strauman 2016), suggesting that the nature of the task is critical in TMS augmentation. Another set of observations (McTeague et al 2018) has found that magnitude but not the valence of emotional arousal predicted TMS augmentation. This suggests that it may not be task type but rather magnitude of emotional arousal that influences maximal TMS treatment augmentation.

Significance: this protocol builds on the RDoC construct of cognitive control to assess the neural substrates involved in TMS activation as well as task-induced TMS augmentation. By using both a passive vs active version of the SST working memory task we can examine the effect of manipulation characteristics of tasks and by using cognitive vs. emotional versions of the task we can probe the contribution of emotional arousal to the effects. Further by randomizing subjects to one of three task conditions (including a task control condition) we can determine the effect of task augmentation on TMS.

1.2 Name and Description of the Investigational Product

IDE Exempt

2 Study Objectives

3 This protocol aims to determine what neural systems underlie TMS-evoked brain responses and how the addition of a task organizes and augments this response to induce plasticity. We first determine which tasks known to activate DLPFC alone or in combination with TMS have greater activation of the DLPFC and have maximal anti-correlation with the subgenual cingulate. In addition, tasks will be combined with TMS in a sham controlled double-blind experiment to test neuromodulation-induced effects. In a sample of 25 healthy participants we will conduct a series of experiments to examine

task effects, task-specific TMS augmentation effects and task-specific augmentation of TMS neuromodulation.

3.1 Primary Objective

We will determine both an "intensity (difficulty) effect" and an "emotion effect" of task-induced fMRI activity in the scanner, collecting these measures in the same subjects. Participants will receive two working memory tasks:

1a) Sternberg Sorting Task (SST): a cognitive task comparing low-load vs. high-load conditions in which the picture stimuli are letters.

1b) International Affective Picture System (IAPS): an emotional task using IAPS picture that will also compare low load and high load conditions. The number of images will vary by condition load, but for both the high-load & low-load conditions, participants will look at IAPS pictures and answer questions about the images. Further, jittered within this design will be both neutral and negative blocks of IAPS pictures.

We will compare low-load vs. high-load brain activation and connectivity in the cognitive vs. emotional tasks.

Hypothesis 1a: Compared with the maintenance (low-load) SST condition, the high-load cognitive SST condition will produce greater DLPFC activation and dlPFC/sgACC anticorrelation.
Hypothesis 1b: Compared with the low-load IAPS emotional task, the high-load IAPS emotional pictures will produce higher activity in the DLPFC and dlPFC/sgACC anticorrelation.
Hypothesis 1c: The picture rating for arousal will be correlated with the activity in the DLPFC and dlPFC/sgACC anticorrelation.

Secondary Objectives:

Aim 2: to determine which task provides greater augmentation of the TMS-induced DLPFC activation, participants will receive in randomized order:

1) The cognitive SST working memory task or the IAPS task alone
2) rTMS + the cognitive SST working memory task or rTMS + the IAPS emotional task in randomized order. rTMS and the cognitive tasks will be conducted in the fMRI scanner where brain activation to a TMS probe and connectivity will be obtained.
3) rTMS alone

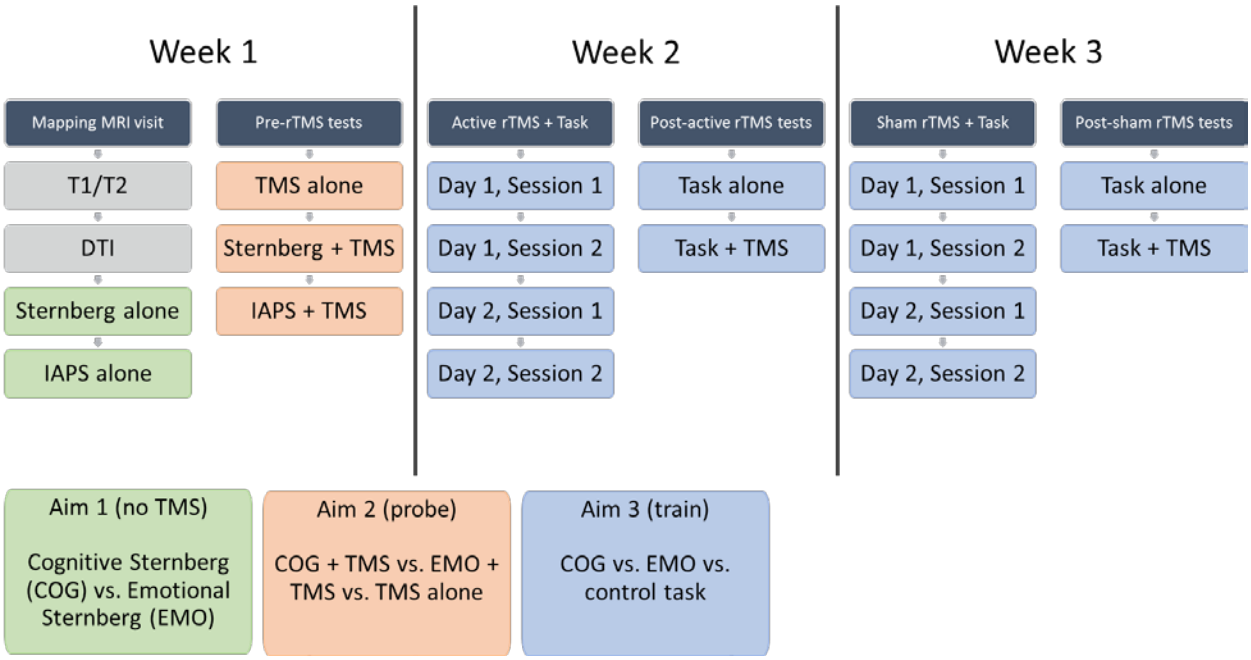
Hypothesis 2a: rTMS + either task will have greater DLPFC activation and greater dlPFC/sgACC anticorrelation than rTMS alone.
Hypothesis 2b: rTMS + the IAPS emotional working memory task will have greater DLPFC activation and greater dlPFC/sgACC anticorrelation than rTMS + cognitive SST (more robust)
Hypothesis 2c: rTMS + IAPS emotional task will have greater signal to noise (more selective).

Aim 3: to determine the effect of neuromodulation on DLPFC activation healthy participants will be randomized to one of the 3 task conditions: high-load cognitive SST, high-load IAPS task, or low-load SST (sham task condition). Following a 4 session course (2 session separated by at least 4 hours on one day, followed by 2 sessions separated by at least 4 hours on a second day) of either active rTMS or sham TMS neuromodulation in combination with the task condition participants will again have probe sessions in the scanner where DLPFC activation and connectivity will be determined. Following a 2-week interval, participants will receive the other stimulation condition (sham TMS if active first and active TMS if sham first).

Hypothesis 3a: Task (any of the 3) + active rTMS will result in greater DLPFC activation and greater dlPFC/sgACC anticorrelation than task plus sham rTMS
Hypothesis 3b: the IAPS task in combination with active rTMS will produce greater activation than the cognitive SST + active TMS or than control task + active TMS.

4 Investigational Plan

Below is an example of the proposed study flow after screening visit. Please refer to attached task descriptions for further information:



4.1 General Design

A mechanism oriented study, with within subjects design will be used. Healthy volunteer participants who are between 18 – 60 years old and meet basic eligibility criteria, will be offered participation in this study. Consenting participants will then undergo a baseline MRI scan in order to identify the exact location of the "Fitzgerald Target" in their DLPFC. Study staff will use FSL to analyze the images and communicate the coordinates via BrainSight to study coordinators. Participants will complete within subject comparisons and then will be randomized to a 3 arm study.

In the first phase participants will complete:

1) low-load condition vs high-load condition in the (cognitive) SST
2) low-load condition vs high-load condition in the (emotion) IAPS task

They will then complete again (in randomized order) with rTMS:

1) rTMS alone
2) rTMS + SST (cognitive)
3) rTMS + IAPS (emotion)

rTMS and the cognitive tasks will be conducted in the fMRI scanner where brain activation to a TMS probe and connectivity data will be obtained.

Finally they will be assigned to one of 3 groups to determine the effect of neuromodulation on DLPFC activation. Healthy participants will be randomized to one of 3 task conditions: high-load SST, high-load IAPS or low-load SST (sham task). Following a 4 session course of either active rTMS or sham rTMS neuromodulation (both active rTMS & Sham rTMS: at 120% RMT in triplet 50 Hz bursts, repeated at 5 Hz; 2 s on and 8 s off; 600 pulses per session; for a total duration of 3 min. and 9 s) in combination with one of

the 3 task conditions participants will again have single pulse probes (120% RMT; 77 pulses/session) sessions in the scanner where DLPFC activation and connectivity will be determined. In this protocol we will use anatomically guided rTMS alone or in combination with tasks to test the hypothesis that cognitive paired associative stimulation results in augmented cortical response.

5 Study Population and Duration of Participation

25 healthy adults between the ages of 18 – 60 who meet inclusion/exclusion criteria will be asked to participate in approximately 7 study visits over the course of 3 – 4 weeks.

We estimate the following amount of time for each visit:

- Screening Visit: 2 hours
- Visit 1 - Baseline MRI Scan: 1 hour
- Visit 2 – Initial Task MRI Scan: 2 hours
- Study Visits 3 – 5: 2 hours each
    - Includes 1 hour MRI scan after Visit 4
- 7 – 14 day break pending participant availability
- Study Visits 6 – 8: 2 hours each
    - Includes 1 hour MRI scans before Visit 6 and after Visit 8

5.1 Inclusion Criteria

- Gender, inclusive
- 18 – 60 years of age
- Right-handed
- No history of meeting DSM criteria for any diagnosis
- Normal cognition
- Patients must be able to read and understand English
- Participants must be able to provide consent

5.2 Exclusion Criteria

- Pregnancy (Female participants)
- Outside age range
- Meets DSM criteria for any diagnosis
- Unable to have an MRI scan
- Medical condition that interferes with the collection or interpretation of MRI data
- Implanted devices such as: aneurysuym clip or cardiac pacemaker
- History of stroke, epilepsy, or brain scarring
- Cognitive impairment
- Recent use of psychoactive medications, as determined by investigators
- Otherwise determined by investigator to be unfit for participation:
  ex) Current alcohol or substance use disorder in last 3 months

5.3 Subject Recruitment

All participants will be recruited through the University of Pennsylvania and surrounding community. All subjects will express interest by initiating contact with the research staff for a center wide phone screening or self-screening procedure. All subjects fitting inclusion criteria will be approached by study staff to continue in the study. All subjects fitting inclusion criteria will be approached by study staff. This study will also be advertised on Facebook. These ads will be posted from the UPenn – Center for Neuromodulation in Depression and Stress Facebook page. They will be posted monthly and/or weekly. Study coordinators in the present study will use the results in REDCap as a source of recruitment, at which point those subjects will undergo the full phone-screen. This phone screen will also be collected and stored in REDCap. All recruitment materials, including but not limited to flyers, brochures, referral letters, online postings, and email templates will be IRB-approved before distribution of any of these material.

5.4 Duration of Study Participation

We anticipate enrolling in the pilot for 6-months, but if the concept is proven after 6 months, for 2 years total. Each participant will be enrolled for 5 – 7 weeks, from the time of consent and screening to study completion. We anticipate this study will begin enrolling participants March 1, 2019.

5.5 Total Number of Subjects and Sites

We plan to initially enroll 25 healthy control patients at the University of Pennsylvania.

5.6 Vulnerable Populations: N/A

6 Study Procedures

A mechanism oriented study, with within subjects design will be used. Healthy volunteer participants who are between 18 – 60 years old and meet basic eligibility criteria, will be offered participation in this study. Consenting participants will then undergo a baseline MRI scan in order to identify the exact location of the "Fitzgerald Target" in their DLPFC. Study staff will use Brain Site to analyze the images and communicate the coordinates to study coordinators. Participants will complete within subject comparisons and then will be randomized to a 3 arm study.

In the first phase participants will receive:

1) a low load condition vs a high load condition in the SST
2) a low load condition vs a high load condition in the IAPS task

They will then receive in randomized order:

1) rTMS alone
2) rTMS + the SST or
3) rTMS + the IAPS task in randomized order.

rTMS and the cognitive tasks will be conducted in the fMRI scanner where brain activation to a TMS probe and connectivity data will be obtained.

Finally they will be assigned to one of 3 groups to determine the effect of neuromodulation on DLPFC activation. Healthy participants will be randomized to one of 3 task conditions: high-load SST, high-load IAPS or low-load SST (sham task). Following a 4 session course of either active iTBS or sham TMS neuromodulation (both iTBS & Sham: at 120% RMT in triplet 50 Hz bursts, repeated at 5 Hz; 2 s on and 8 s off; 600 pulses per session; for a total duration of 3 min. and 9 s) in combination with one of the 3 task conditions participants will again have single pulse probe (120% RMT; 77 pulses/session; 2.4 s each) sessions in the scanner where DLPFC activation and connectivity will be determined. In this protocol we will use anatomically guided TMS alone or in combination with tasks to test the hypothesis that cognitive paired associate stimulation results in augmented cortical response.

Although there are no known risks related to MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no possible benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women. All women of child bearing potential are asked if they are using a reliable method of birth control and are required too attest that they are not pregnant before study visit and on the TMS safety screening form.

Does your study use MRI? (CAMRIS is the appropriate contact for all studies involving MRIs)

☒ Yes ☐ No

Check of all that apply:

☐ 1.5T MRI
☒ 3T MRI
☐ 7TMRI

Does the MRI use investigational sequences and/or coils?
(See Experimental Device Clause)

☐ Yes ☒No ☐ Unsure (if unsure you need to contact CAMRIS)

Does your study include pregnant women?
(See Pregnancy Clause and Justification)

☐ Yes ☒No

Does the MRI require the use of Contrast Agents?
(See Contrast Risks)

☐ Yes ☒No

Does your study involve the exposure to radiation, radiotracers and/or radiological imaging modalities?

☐ Yes ☒No (If No, no RRSC review is needed)

Ultrasound

☐ Yes ☒No

Will your study be using CT Scans? (CACTIS is the appropriate contact for studies involving CT scans)

☐ Yes ☒No

Below is a table that outlines what assessments and procedures will be completed at each visit:

Procedure	Screening Visit	Visit 1 Baseline MRI	Visit 2 Initial Task MRI	Visits 3 & 4	Visit 5	Visits 6 & 7	Visit 8
Clinical Assessments	X						
Self-Report Questionnaires	X			X		X	
MRI Scan		X	X		X		X
Behavioral Tasks		X	X	X	X	X	X
TMS *(test pulse at Screening)*	X		X	X	X	X	X

6.1 Screening

- Informed Consent
- Complete MRI Safety Screening Form & TSS form
- Medical History – patient self-report
- Clinician administered measures of mood, behavior and prior treatment history
  - MADRS
  - SCID

- Test TMS with participant to ensure tolerability

6.2 Study Intervention Phase

6.2.1 MRI Visits

- Verify & sign MRI Safety Screening Form
- Undergo MRI with tasks
  - Baseline MRI – tasks in the scanner, no TMS probe
  - Visit 1 – tasks in the scanner with TMS

6.2.2 Prior to Baseline MRI – Randomized order of learning all 3 study tasks (SST, IAPS, and Sham) in the scanner without TMS.

6.2.3 Visit 1 – in the scanner participant completes all 3 tasks, in previously randomized order with TMS.

6.2.4 After Visit 1 – Randomized to SST task only, IAPS task only, or Sham task only & either Active rTMS + task or Sham rTMS + task

5.2.5 Neuromodulation & MRI Probe Visits:

- Visits 2 & 3: Complete randomized task alone & again with randomized rTMS group
  - Confidence rating
- Visits 4 & 5: Complete randomized task alone & again with opposite rTMS group
  - Confidence rating
- MRI probes: in the scanner, participant completes randomized task alone & then with TMS probe.

6.3 Follow Up Phase of the Study – N/A

6.4 Unscheduled Visits

Unscheduled visits will be handled only if deemed necessary by study staff, for instance a participant presented to the ER during study participation, study staff may request the patient come in between visits for evaluation.

6.5 Subject Withdrawal

Participants may be withdrawn from the study by staff if deemed necessary for their health or safety. We anticipate that some participants may withdraw. We do not expect early termination of participation due to patient or investigator withdrawal to have any impact on safety or well-being of participants.

6.5.1 Data Collection and Follow-up for Withdrawn Subjects

N/A

6.6 Early Termination Visits

If deemed necessary to terminate a patient's participation in the study, they will be contacted by study staff to communicate this and the reason why. No other information will be collected from the terminated participant.

7 Study Evaluations and Measurements

7.1 Medical Record Review

N/A

7.2 Physical Examination
N/A

7.3 Vital Signs
N/A

7.4 Laboratory Evaluations
N/A

7.5 Pregnancy Testing
Although there are no known risks related to MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no possible benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women. All women of child bearing potential are asked if they are using a reliable method of birth control and are required too attest that they are not pregnant before study visit and on the TMS safety screening form: 2018.12.07_TASS_832232

7.6 Efficacy Evaluations
- Single pulse TMS probes in the MRI scanner at 120% RMT, 77 pulses at 2.4 second each

7.7 Safety Evaluations

The primary investigator will routinely monitor and evaluate study procedures for potential increased risk.

8 Statistical Plan

Efficacy within subjects: Repeated measures ANOVA will be used to assess changes from baseline to post-stimulation for each task condition.

Efficacy between subjects: neuro-response rates and time to response will be compared with published rates within the literature to extrapolate the significance of this modality.

9 Safety and Adverse Events

9.1 Definitions

9.1.1 Adverse Event
An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:
- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

9.1.2 Serious Adverse Event
Serious Adverse Event
Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:
- fatal
- life-threatening
- requires or prolongs hospital stay

- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

For additional information on definitions and clarifications which may be helpful in creating the safety monitoring portion refer to Appendix 17.7

9.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

9.3 Relationship of AE to Study

The relationship of each adverse event to the study procedures will be determined by the PI and co-PI and relationships will be classified as either: definitely related, probably related, possibly related, unlikely or unrelated.

9.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

Unexpected and related Adverse Events will be reported to the IRB by study staff within 72 hours of knowledge of the event; all other adverse events will be reported at the time of continuing review. Reporting of Serious Adverse Events will occur within 24 hours of knowledge of the event.

9.4.1 Follow-up report

If an SAE has not resolved at the time of the initial report, follow-up reports with all relevant new, or reassessed, information will be submitted to the IRB until the SAE resolves or stabilizes.

9.5 Medical Monitoring

The documentation and reporting of adverse and serious adverse events will be overseen by the PI and Co-PI for this study.

9.5.1 Data and Safety Monitoring Plan

The Primary Investigator will monitor this study bi-annually to ensure the safety and protection of study participants.

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality, Data Collection/Management, & Records Retention

We will collect the following PHI: name, address, social security number (for compensation purposes) visit dates, telephone number, and email address. Patients entering the study will be given a unique identifying code. This code will be used on all data obtained from scans or study visits. Only one password protected document connecting the code with the participant name (in the form of first two letters of the first name, first three letters of the last name) will exist. Everything will be immediately coded and this coded information will be stored in secure cabinets inside locked rooms or in password protected, IRB compliant online databases, such as REDCap. PHI will be stored separately in secure cabinets inside locked rooms. Coded data will be stored on a secure server at the University of Pennsylvania through the Neuroscience Neuroimaging Group computing cluster. MRI data are securely copied on the uphs network directly from the MRI machine at Stellar Chance to this computing cluster without separate physical storage. Coded data are directly uploaded to the computing cluster from the computers on which the data are collected. The Penn computers are in our secured lab space and connected directly to the uphs encrypted network. None of these data will contain personal identifiers such as name, social security number, address, or phone number. We will be using Neuroflow software for recording participants heart rate during each TMS treatment session. NeuroFlow's software platform analyzes data from a commercially available, third-heart rate monitor. NeuroFlow follows strict HIPAA guidelines with respect to patient privacy and data security, both from a technical and administrative respective. The heart rate data will be recorded using an online, password protected software, Neuroflow. Only deidentified data will be recorded using this platform, no identifiers will be entered on the platform. At the conclusion of the study, coded copies of the data may be maintained at the University of Pennsylvania in its de-identified form for future analyses.

Computer-based files containing electronic PHI, that are not part of the EMR, will be kept on the Penn Network server.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan attached by the investigator bi-annually.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

12.1 Risks

Clinical interview and assessment: Some discomfort may be associated with the clinical assessments conducted in this study. Participants may experience emotional discomfort when answering some questions in the questionnaires or when talking about personal information. Participants may choose not to answer any of the questions and to terminate your participation.

MRI Scan:

- **Claustrophobia**: participants may experience claustrophobia within the MRI scanner. A MRI scan requires participants lay in a partially enclosed space inside the scanner. Some people may find this to be uncomfortable and claustrophobic. Participants will be given an emergency call button in the scan and reminded to notify study staff if they suffer from claustrophobia.
- **Magnetic Fields:** There are no known health risk associated with exposure to magnetic fields during an MRI. There are minimal risks from the loud noise associated with the MRI scanner and from the discomfort of lying on a hard surface. We shall provide participants with protective earplugs as necessary and make every attempt to ensure their comfort with blankets, etc. during their time in the scanner.
- **Flying Objects**: The known risks associated with this study are minimal. Implanted medical devices and metallic foreign fragments inside a participant's body may pose a risk if they were to enter the MRI magnet room. Therefore, each participant will complete an MRI safety screening form at screening and prior to each scan. The greatest risk is a magnetic object flying through the air toward the magnet and hitting a participant. To reduce this risk we require that all people involved with the study remove all magnetic metal from their clothing and all magnetic metal objects from their pockets. No magnetic metal objects are allowed to be brought into the magnet room at any time except by approved personnel. In addition, once participants are in the magnet, the door to the room will be closed so that no one inadvertently walks into the room.
- **Incidental Findings Clause**: it is possible that during the course of the research study, the research staff may notice unexpected finding(s) on a participant's images. Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will inform participants if necessary for medical follow-up. These possible finding(s) will not be disclosed to the participant unless deemed necessary by the PI and reviewing radiologist in order to avoid unnecessary anxiety for participants.
- **Pregnancy**: although there are no known risks related to MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no possible benefit from participating in this protocol for a pregnant woman, we will exclude pregnantwomen.

iTBS & TMS: this study utilizes two forms of Transcranial Magnetic Stimulation (TMS): intermittent Theta Burst Stimulation (iTBS) & single pulse TMS. TMS is a FDA-approved non-invasive brain stimulation technique for a variety of diagnoses. As with any technique, there may be long-term risks due to TMS that are currently unknown. The most common side effect of TMS (approximately 25% of patients) is a mild headache. There are no known long-term adverse effects reported with the use of this device. Rarely, device malfunction could result in a scalp burn (less than 1% of patients). There may be long-term risks that are currently unknown

- **Magnetic Fields**: are produced during TMS treatment. The stimulation intensities used are thought to be without harm. The exception is if participants have a cardiac pacemaker, or a certain type of metallic clip in their body (i.e., an aneurysm clip). In addition to responding to questions about potential MRI risks prior to scheduling a screening visit, participants will also be asked to complete a 'TMS treatment screening (TTS)' form at the screening visit prior to receiving any stimulation so participants with these devices are excluded from the study, as any form of TMS could cause these object to heat up, move, or malfunction. Objects such as watches and credit cards should also be removed as these could be damaged.
- **Certain Medical Diagnoses**: for patients with epilepsy, activation of the brain by forms of TMS could also activate a seizure. Patients with stroke may be at increased risk for a seizure due to the brain scar. Therefore, in addition to responding to questions about medical history and

diagnosis prior to scheduling a screening visit, participants will be asked to respond to questions about their medical history at their screening visit prior to receiving any stimulation so participants with these diagnoses are excluded from the study. For a typical physically healthy person, a TMS-induced seizure in this experiment is very unlikely.

- **Noise**: TMS devices produce clicking sounds. To minimize this possibility, participants will be given protective earplugs or headphones.
- **Nausea**: although it is uncommon, approximately 5% of subjects have experienced nausea during the experiment. Participants can discontinue the experiment at any time if they experience any discomfort during the study.
- **Mild Swelling or Bruising**: participants may also experience temporary and local bruising, swelling, or pain from the swim cap and/or muscle activation by TMS.

TMS & fMRI scans: There is no added risk by performing TMS and fMRI together.

Risk to confidentiality: As with any research, there is a rare risk that confidentiality could be breached in this study. Breaches in confidentiality could impact a participant's future insurability and/or employability. In compliance with HIPAA and GCP guidelines, we will protect participant information and PHI to the extent permitted by law with the following measures:

All study materials (with the exception of informed consent, financial, and safety forms) will only be identified with a randomly generated research identification number. All study documents with identifiable information (i.e. informed consent, financial, and safety forms) will be stored separately from the participant file in a double-locked environment. As hard copy source documents are collected, they will be kept in a double-locked environment. Data collected during the study will be entered and stored in a password-protected database, accessible only to engaged study members. All electronic data will be coded and identified only with a randomly generated research identification number.

12.2 Benefits

This study will provide no direct benefit to individual participants.

12.3 Risk Benefit Assessment

This study is minimal risk. There is essentially zero risk of harm from the research procedures (MRI, TMS, assessments of symptoms). The potential benefit to society through the increased understanding of the mechanisms of neuromodulation via TMS far outweighs the potential risk from the MRI and TMS procedures. Additionally, those who would be unable to tolerate TMS or an MRI scan will be screened out.

Alternatives to Participation: the alternative to participation is to not participate.

12.4 Informed Consent Process / HIPAA Authorization

Consent will be obtained by research coordinators or the PI. Because this study does not involve treatment, coercion is not a concern. Consent will be obtained in a private room where the coordinator and investigator(s) can explain the purpose of the study procedures and aims. Furthermore, they will explain that participating is completely voluntary and that not participating will not impact them negatively. The potential participant will be given the option to consider study enrollment and will not be forced to make a decision the same day. If they decide to participate, a combined consent and HIPAA form will be signed by research staff and the patient. The patient will be reminded before and after enrolling, and before any research procedure that their participation is optional and has no impact on the care they can expect.

13 Study Finances

13.1 Funding Source

Investigator Initiated Trial.

13.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

13.3 Subject Stipends or Payments

Participants will receive compensation for their time and participation, up to $200.00 if they complete the entire study. Compensated will be dispensed via Greenphire ClinCard at the end of Visit 8 once all study procedures are complete.