

ANCILLARY REVIEWS

DO NOT DELETE. Submit the completed checklist below with your protocol.

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	Does your study...	If yes...	Impact on IRB Review
☐ Yes ☒ No	Include Gillette resources, staff or locations	<i>Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com</i>	Required prior to IRB submission
☐ Yes ☒ No	Involve Epic, or Fairview patients, staff, locations, or resources?	<i>The Fairview ancillary review will be assigned to your study by IRB staff Contact: ancillaryreview@Fairview.org</i>	Approval must be received prior to IRB
☐ Yes ☒ No	Include an evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	<i>The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreg@umn.edu See: https://policy.umn.edu/research/indide</i>	committee/ designated review. Consider seeking approval prior to IRB submission.
☐ Yes ☒ No	Require Scientific Review? Not sure? See guidance in the Investigator Manual (HRP-103).	<i>Documentation of scientific merit must be provided. Contact: hrpp@umn.edu</i>	

MEDICAL PROTOCOL (HRP-590)

PROTOCOL TITLE: STATE DEPENDENT EFFECTS OF PREFRONTAL
TRANSCRANIAL MAGNETIC STIMULATION

VERSION DATE: 2025.02.28

☐ Yes ☒ No	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	<i>Complete the CPRC application process.</i> <i>Contact: ccprc@umn.edu</i>	Approval from these committees must be received prior to IRB approval; These groups each have their own application process.
☐ Yes ☒ No	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)	<i>Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee.</i> <i>Contact: barmstro@umn.edu</i>	
☐ Yes ☒ No	Use the Center for Magnetic Resonance Research (CMRR) or MR from Masonic Institute for the Developing Brain (MIDB) as a study location?	<i>Complete the CMRR pre-IRB ancillary review</i> <i>Contact: ande2445@umn.edu</i>	
☐ Yes ☒ No	Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents?	<i>Complete the IBC application via eprotocol.umn.edu</i>	
☐ Yes ☒ No	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	<i>Contact OBAO for submission instructions and guidance</i>	
☒ Yes ☐ No	Include PHI or are you requesting a HIPAA waiver?	<i>If yes, HIPCO will conduct a review of this protocol.</i> <i>Contact: privacy@umn.edu</i>	

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TRANSCRANIAL MAGNETIC STIMULATION

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☒ Yes ☐ No	Plan to use CTSI Monitoring services, and/or have an IND, IDE, or designated NSR-IDE by the UMN IRB?	<i>The CTSI monitoring ancillary review will be assigned to your study by IRB staff.</i> <i>Please note eligibility criteria here.</i> <i>Contact: fenc1003@umn.edu</i>	Approval must be received prior to IRB approval. These groups do not have a separate application process but additional information from the study team may be required.
☐ Yes ☒ No	Use data from CTSI Best Practices Integrated Informatics Core? Formerly the AHC Information Exchange (IE)?	<i>The Information Exchange ancillary review will be assigned to your study by IRB staff</i> <i>Contact: bp1c@umn.edu</i>	
☐ Yes ☒ No	Use the Biorepository and Laboratory Services to collect tissue for research?	<i>The BLS ancillary review will be assigned to your study by IRB staff.</i> <i>Contact: Jenny Pham</i> <i>Pham0435@umn.edu</i>	
☐ Yes ☒ No	Have a PI or study team member with a conflict of interest?	<i>The CoI ancillary review will be assigned to your study by IRB staff</i> <i>Contact: becca002@umn.edu</i>	
☐ Yes ☒ No	Need to be registered on clinicaltrials.gov?	<i>If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff</i> <i>Contact: fenc1003@umn.edu</i>	
☐ Yes ☒ No	Require registration in OnCore?	<i>If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff</i>	Does not affect IRB approval.

MEDICAL PROTOCOL (HRP-590)
PROTOCOL TITLE: STATE DEPENDENT EFFECTS OF PREFRONTAL
TRANSCRANIAL MAGNETIC STIMULATION
VERSION DATE: 2025.02.28

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MEDICAL PROTOCOL (HRP-590)

PROTOCOL TITLE: STATE DEPENDENT EFFECTS OF PREFRONTAL
TRANSCRANIAL MAGNETIC STIMULATION

VERSION DATE: 2025.02.28

Protocol Title	State dependent effects of prefrontal transcranial magnetic stimulation
Principal Investigator/Faculty Advisor	Name: Alik Widge, MD, PhD
	Affiliation: ☒ UMN ☐ Fairview ☐ Gillette
	UMN Home Department: Psychiatry
	UMN Home Dept ID: 11961
	Telephone Number: (412) 519 6227
	Email Address: awidge@umn.edu
Scientific Assessment	The funding body, MnDRIVE, has internally reviewed the scientific merit of this protocol
IND/IDE # (if applicable)	N/A
IND/IDE Holder	N/A
Investigational Drug Services # (if applicable)	N/A
Version Number/Date:	2025.02.28

PROTOCOL COVER PAGE

MEDICAL PROTOCOL (HRP-590)
 PROTOCOL TITLE: STATE DEPENDENT EFFECTS OF PREFRONTAL
 TRANSCRANIAL MAGNETIC STIMULATION
 VERSION DATE: 2025.02.28

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	2023.08.29	Update compensation	Yes
2	2024.03.01	Update CTSI monitoring provisions and remove Christi Sullivan from study staff	No
3	2024.09.01	Addition of control experiment procedures (Phase Two)	No
4	2025.02.28	Control study collected online	Yes

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ABBREVIATIONS/DEFINITIONS

Include any abbreviations or definitions for key or technical terms you use in your protocol.

DLPFC – Dorsolateral prefrontal cortex; An area of the brain forming part of the functional hub of cognitive control that is relevant to mental illness. This is the standard target for TMS treatment for mental illness.

DPX – Dot pattern expectancy task; A computerized behavioral task that measures cognitive control by requiring participants to respond quickly to target patterns and suppress inappropriate responses to non-target patterns.

EEG – Electroencephalography; used to measure brain activity via electrodes on the scalp.

EMG – Electromyography; used to measure muscle activity via electrodes placed on the surface of the skin above a muscle.

MEP – Motor evoked potential; The response to stimulation of the primary motor cortex, measured with electromyography.

NNL – Non-invasive neuromodulation laboratory; University of Minnesota/MnDRIVE supported laboratory providing support for researchers conducting research involving non-invasive neuromodulation technologies.

RMT – Resting motor threshold; the minimum stimulation intensity (to the nearest 1% of maximum stimulator output) required to evoke a motor evoked potential with peak-to-peak amplitude of 50 uV.

TMS – Transcranial magnetic stimulation; uses electromagnetic pulses to depolarize cortical neurons.

1.0 Objectives

1.1 Purpose:

The first experiment of this project will explore conditions that enhance the effectiveness of transcranial magnetic stimulation (TMS) for improving brain function. Brain stimulation can facilitate or inhibit cortico-cortical functional connectivity, depending on the initial state of targeted brain circuits. This project will assess evidence for this effect in cognitive control brain circuits that are relevant to mental illness. We will test this in a sample of the general population. Our working hypothesis is that the engagement of prefrontal brain networks will depend on the initial state of those targeted circuits. Therefore, if targeted brain circuits are actively engaged by a cognitive task, then the effects of TMS on brain function will be stronger than if those targeted circuits are not actively engaged.

Aim 1: Investigate whether TMS administered during performance of a cognitive task that activates prefrontal brain circuits evokes greater electroencephalography (EEG) metrics of brain function.

Aim 2: Investigate whether TMS-evoked metrics of brain function predict behavioral performance in the cognitive task.

In a second (control) experiment, we will examine how behavior changes over the course of a cognitive task when no TMS is administered. The purpose of this experiment is to measure changes in behavior in the absence of TMS, as a comparison/contrast condition (Phase Two) against the active TMS condition (Phase One). This will involve participants completing the same cognitive tasks as Phase One, but in the absence of TMS and EEG. Those participants may complete an online version of the psychophysical tasks used in Phase One.

2.0 Background

2.1 Significance of Research Question/Purpose:

TMS is used as a noninvasive neuromodulation treatment for mental disorders. Standard FDA approved protocols for depression target the dorsolateral prefrontal cortex (DLPFC), which is part of the functional neural circuitry of cognitive control. However, there is a large amount of heterogeneity in the efficacy of TMS for treatment resistant depression. This heterogeneity may in part be attributable state-dependent effects of TMS on brain function. The effect of brain stimulation is known to be altered by the initial state of targeted brain networks for sensorimotor and visual targets (Silvanto et al., 2008; Silvanto & Pascual-Leone, 2008), but it is not understood whether the same holds true for cognitive control networks that are relevant to mental illness. This has implications for clinical protocols because there are currently no guidelines for patients' behavioral state during treatment. Therefore, by using cognitive tasks, it may be possible to reliably improve the effects of TMS on brain function by having patients engage the targeted brain networks endogenously during treatment.

2.2 Preliminary Data:

There are no direct preliminary data for this project.

2.3 Existing Literature:

The effects of brain stimulation are well known to depend on the initial state of targeted brain circuits for sensorimotor and visual targets. For example, the effects of TMS on visual cortex depends on visual context (Guzmán López et al., 2022; Silvanto et al., 2008; Silvanto & Pascual-Leone, 2008) and effects of brain stimulation on motor cortex are known to depend on the engagement of motor circuits by muscle activation or action preparation prior to movement (Bestmann et al., 2008; Feurra et al., 2013; Marinovic et al., 2014; McInnes et al., 2021). This project will extend knowledge by demonstrating whether similar effects are evident in cognitive control circuits relevant to mental illness.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

We will record electroencephalography (EEG) metrics of brain function (primarily, alpha/theta band power and theta-gamma phase amplitude coupling). We will assess whether TMS-evoked modulations of these metrics are greater when targeted brain circuits are actively engaged by a cognitive task.

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

To assess whether enhanced TMS-evoked brain function is functionally relevant, we will examine whether modulations of brain function by TMS are predictive of behavioral performance (accuracy, reaction time) in the cognitive control task.

We will also examine how behavioral performance (accuracy, reaction time) changes over the course of the cognitive control task in the absence of TMS (Phase Two).

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description:

The devices described here will be used to produce transient modulations of brain function and measure the resulting modulation of brain activity.

Transcranial Magnetic Stimulation

TMS will be administered in Phase One using a MagStim Rapid² magnetic nerve stimulator (MagStim Co. Ltd, Whitland, Wales, UK). The Magstim Rapid² will be used to deliver single and repetitive trains (intermittent theta burst) of pulses to participants. Magnetic stimulation is achieved by discharging the stimulator coil over the scalp, which depolarizes underlying cortical neurons.

The University of Minnesota Non-invasive Neuromodulation Laboratory (NNL) is equipped with a Super Rapid² Plus¹ stimulator, which coordinates the delivery of single or repetitive electromagnetic stimuli at interstimulus intervals as short as 10 ms. To determine the intensity of stimulation required to depolarize cortical neurons, we will determine each participant's resting motor threshold (RMT). This involves finding the minimum stimulation intensity required to evoke a motor evoked potential (MEP) with a peak-to-peak amplitude of 50uv. MEPs will be measured using an electrically isolated bioelectric amplifier with surface EMG electrodes placed over the target muscle belly. Consistency in the localization of the target stimulation site on the scalp will be confirmed for all procedures using the frameless stereotactic BrainSight II neuronavigation system (Rogue Research Inc, Quebec, Canada).

Electroencephalography

Brain activity will be recorded in Phase One throughout the experimental protocol using EEG. The NNL is equipped with a BrainProducts actiChamp 64-channel EEG acquisition system, with TMS-compatible active electrodes. The EEG system is battery powered which electrically isolates the participant from mains power. Electrical impedance between the recording electrodes and the scalp will be minimized by applying conductive saline gel.

Cognitive/perceptual tasks

In both Phase One and Phase Two, The Dot Pattern Expectancy (DPX) task will be used both as a measure of cognitive control and to endogenously engage target brain circuits that underly cognitive control. The computerized task requires participants to countermand biased responses (see Figure 1) and is well established as a clinical measure of cognitive control (Henderson et al., 2012; Jones et al., 2010). In each trial of DPX, two consecutive dot patterns appear, and participants must respond as quickly as possible to a target sequence whilst countermanding inappropriate responses to non-target sequences. We have previously analyzed data from the DPX task in patients undergoing TMS for depression and demonstrated that modeled behavioral performance

in this task is strongly predictive of depression symptomology, supporting the task's relevance to DLPFC circuitry.

As a control condition, we will also administer a computerized perceptual task which requires participants to respond as quickly as possible whether two simultaneously presented dot patterns are matching or not.

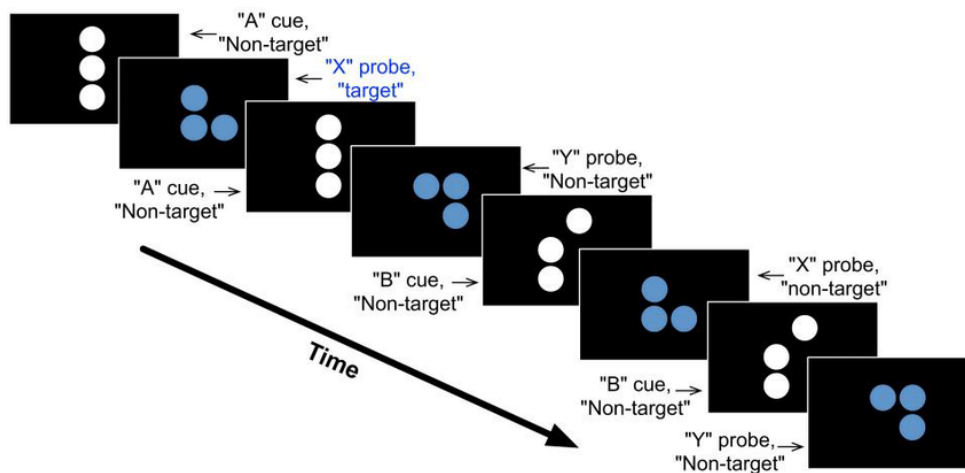


Figure 1. Example of the Dot Pattern Expectancy (DPX) task. In each trial, participants are presented a sequence of two dot patterns – a cue and a probe. The cue and probe can each either be valid or invalid. Participants are asked to respond as quickly as possible to each presented sequence and indicate with a computer keyboard whether the target sequence (valid cue AND valid probe) was presented in that trial. The target sequence is presented more often than not, which produces a response bias which must be countermanded when an invalid probe is presented (cognitive control).

1.1 Drug/Device Handling:

Only IRB approved study personnel who have undergone appropriate training will administer the TMS, EEG, and cognitive/perceptual tasks. The equipment used in this study are located in the UMN Non-invasive Neuromodulation Laboratory (NNL). The laboratory is located in a secured area of the 717 Delaware Building requiring authorized

access (ID badge and/or key), and only laboratory and study personnel will have access to the devices. Those devices will not be used in other locations, and study participants will not be unsupervised in the laboratory at any time.

4.2 Biosafety: N/A

4.3 Stem Cells: N/A

4.4 Fetal Tissue: N/A

5.0 Procedures Involved

5.1 Study Design:

This is a repeated measures experimental study, taking place over two separate sessions, approximately seven days apart. We will recruit a sample from the general population.

5.2 Study Procedures:

All participants in the first phase of the study will complete the same study battery, which includes:

- Pre-screening (15 minutes)
- Consent (30 minutes)
- Research visit one (Up to 2.5 hours)
 - EEG set up (Approximately 30 minutes)
 - RMT determination (Approximately 15 minutes)
 - Single pulses of TMS at rest (Approximately five minutes)

- Cognitive/perceptual task (Approximately 20 minutes)
- Cognitive/perceptual task + TMS (Approximately 20 minutes)
- Cognitive/perceptual task (Approximately 20 minutes)
- Single pulses of TMS at rest (Approximately five minutes)
- Research visit two (Up to 2.5 hours), approximately seven days later, depending on scheduling availability. The same procedures as the first research visit will be conducted, with the exception that the participant will complete the cognitive/perceptual task that was not administered in the previous research visit.

Phase Two will involve similar procedures, but without the administration of TMS or EEG. Thus, participants will complete the cognitive/perceptual task three times.

Specific detail on the above procedures follow:

Pre-screening

Participants will be screened for potential contraindications to TMS using the TMS Safety Screening Questionnaire, adapted from Rossi et al. (2021).

Participants who do not meet screening safety criteria will be ineligible for the study. This questionnaire will be completed by the participant remotely via Qualtrics. If eligible for the study, the participant's email address and/or phone number will be forwarded to the study team to schedule a consent visit. As such, this will involve the collection of identifiable contact information. TMS safety eligibility will be confirmed at both research visits before administering any TMS.

Consent

Participants will be informed of the study protocols, risks, and given the opportunity to ask questions with the study team. If informed consent is provided by the participant, they will be invited to complete the study.

EEG set up

Phase One participants will have their head measured to fit an EEG cap. Conductive saline gel will be applied to the electrodes and scalp with blunt tip syringes to minimize electrical impedance. Data quality will be monitored for the duration of the experiment and the EEG signal will be recorded continuously for the experimental procedures. During the EEG setup, participants will complete a brief demographics questionnaire. EEGs will be administered by IRB-approved study staff who have undergone training to the satisfaction of the PI and NNL staff.

RMT determination

In Phase One, single pulses of TMS will be applied over the motor cortex to first determine the optimal scalp location (hotspot) to elicit a MEP in the first dorsal interosseous (FDI) muscle. MEPs will be measured using an electrically isolated EMG amplifier with electrodes placed on the FDI muscle. Then, pulses will be applied at the hotspot with decreasing intensity to find the minimum intensity required to evoke a MEP with a peak-to-peak amplitude of 50 uV in 50% of test trials, while the target muscle is at rest. Once the RMT has been determined, stimulation during the experiment will be applied at up to 120% of this intensity.

Single pulses at rest

In Phase One, to determine brain reactivity to brain stimulation, up to 30 single pulses will be delivered with the stimulator coil positioned over the F3 electrode site and with a minimum inter-trial interval of three seconds. This procedure will be conducted before and after completing the blocks of the cognitive/perceptual task.

Cognitive/perceptual task

Participants will complete either the DPX task (cognitive task) or perceptual task. Participants will complete up to 200 trials of the task in a given block. In Phase one, these will be administered without TMS before and after the block for which TMS is administered. In Phase Two, all three blocks of the cognitive/perceptual task will be completed without TMS.

Cognitive/perceptual task + TMS

Phase One participants will complete a single block of either the cognitive/perceptual task, with active stimulation applied during task engagement. Theta-burst stimulation will be applied with up to 10 triplet bursts delivered at 50 Hz and with a carrier frequency of 5 Hz. In addition, in up to 50% of trials, a single pulse of TMS will be delivered during the active task epoch to measure cortical reactivity.

Study Duration:

Each participant will complete two research visits, approximately seven days apart, depending on scheduling availability.

The second phase of the experiment will involve a control experiment in which no TMS or EEG is administered. The goal is to observe how behavior changes during cognitive engagement in the absence of TMS. This experiment will involve two

research sessions, approximately one week apart, each one hour in duration. The procedures will follow the same as those outlined under Cognitive/perceptual task above. A second, unique sample will be recruited for the second phase, though participants that completed Phase One will be eligible to participate in Phase Two. Those participants will not be specifically approached, but may self-identify for the study using the recruitment processes described in Section 11. For participants that opt to participate in both phases of the study, participation in Phase Two must take place at least one week after completion of Phase One. The sample will be subject to the same eligibility and screening criteria as Phase One to ensure consistency in sample characteristics.

5.3 Use of radiation: N/A

5.4 Use of Center for Magnetic Resonance Research: N/A

6.0 Data and Specimen Banking

6.1 Storage and Access:

All data will be stored securely using UMN Box storage cloud, including study questionnaires and EEG recordings. Only IRB approved and appropriately trained members of the study team required for data analysis will have access to these data.

6.2 Data:

All data, including study questionnaires and EEG recordings, will be stored in a HIPAA compliant Box storage cloud. Participants' identity will be anonymized and data will be deidentified.

6.3 Release/Sharing:

Deidentified data from this study may be used in the future to compile larger datasets from multiple studies with similar methodologies and populations to conduct additional analyses and publications. Should the investigators pursue this, future studies seeking to compile data acquired from this protocol will obtain IRB approval before doing so. In the event that this occurs, only investigators or study personnel listed in an IRB-approved protocol pertaining to the data compilation will have access to this data.

Appropriately anonymized subject data may also be shared as required by journals or other publication venues. If those journals permit data deposition alongside papers, this will be a further opportunity for data sharing. We will follow the NIH Public Access policy and deposit papers to PMC accordingly.

7.0 Sharing of Results with Participants

We will not be sharing study results with participants. If requested, a summary of the research findings will be emailed to participants at the conclusion of the study.

7.1 Sharing of genetic testing: N/A

8.0 Study Population

8.1 Inclusion Criteria:

- Age 18 to 65

8.2 Exclusion Criteria:

- Refusal to give informed consent, refusal or inability to comply with study procedures. In addition, experiment procedures will be aborted if RMT cannot be determined.
- Diagnosed psychiatric disorder

- Potential contraindications to EEG (e.g. visible scalp abrasions, non-removable hair extensions and/or hair styling that would impede proper EEG recording)
- Potential contraindication to TMS (as identified by the TMS safety screener)
 - Any previous adverse reaction to TMS or MRI
 - Diagnosed epilepsy or previously experienced a seizure
 - Diagnosed neurological condition, such as stroke or tinnitus
 - Experienced a head trauma that was diagnosed as concussion
 - Current use of, or recent withdrawal from, medications that can increase the risk of seizure (Rossi et al. 2021)
 - Currently pregnant
 - Any metal in the head (excluding mouth)
 - Any implanted medical device

8.3 Screening:

Participants will self-identify via posted study advertisements and assessed for basic eligibility in accordance with TMS safety guidelines. Those who are identified as potentially eligible will be scheduled for consent. Participants will be asked to refrain from any extra caffeine consumption (more than their usual intake) or nicotine products, prior to the scheduled study visit. They will be asked to wash their hair prior to the visit and not to use any additional hair product the day of their research visit.

9.0 **Vulnerable Populations**

Population / Group	Identify whether any of the following populations will be the focus of the research (targeted), included, but not necessarily the focus or excluded from participation in the study.
Children	Excluded
Pregnant women/fetuses/neonates	Excluded
Prisoners	Excluded
Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	Excluded
Non-English speakers	Excluded
Those unable to read (illiterate)	Excluded
Employees of the researcher	Excluded
Students of the researcher	Excluded
Undervalued or disenfranchised social group	Included but not the focus
Active members of the military (service members), DoD personnel (including civilian employees)	Included but not the focus

Population / Group	Identify whether any of the following populations will be the focus of the research (targeted), included, but not necessarily the focus or excluded from participation in the study.
Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	Excluded
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	Included but not the focus
Individual or group with a serious health condition for which there are no satisfactory standard treatments.	Excluded
Individual or group with a fear of negative consequences for not participating in the Research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	Excluded
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	Excluded

9.1 Additional Safeguards:

Undervalued, disenfranchised and/or disadvantaged social groups and active members of the military and/or DoD personnel are not targeted but may be included in this study. This information may not be known; research staff will not ask direct questions about socioeconomic status or military status to potential participants. We do not anticipate vulnerability for this group being increased by participating in this study.

9.2 If research includes potential for direct benefit to participants, provide rationale for any exclusions indicated in the table above: N/A

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented:

The investigators anticipate enrolling 40 participants for each study phase in order to account for screen failures, drop outs, and individuals who surpass maximum motor threshold levels. Recruitment will be stopped once the target sample size of 25 individuals (having completed all study components) has been reached in each study phase.

11.0 Local Recruitment Methods

11.1 Recruitment Process:

Participants may be recruited via advertisements posted on the university studyfinder website, Discovery Partners website, and various social media platforms. The study will also advertise recruitment in public postings of posters around the metro area, a university research program, other public forums as well as various social media platforms. Participants may also self-identify for participation via the UMN Department of Psychology's research participation pool. We will also utilize word of mouth recruitment.

For participants completing the control experiment (Phase Two) for which no TMS or EEG is administered, participants may also be recruited from online recruitment platforms, such as Prolific. Those participants will complete study components electronically via survey and psychophysical tasks administered online and the same screening criteria will be used. The study will be available to participants who are residents of the United States and that self-reportedly will have access to a desktop computer or laptop with audio capabilities.

11.2 Identification of Potential Participants:

Participants will self-identify and consent to be contacted for potential participation through postings made in the above mentioned platforms. If participants are not recruited for the online control experiment via Prolific, during screening, identifiable contact information will be collected from participants. Those potential participants that opt to communicate with the study team via email will be contacted using the text contained in our protocol email script. Participants will be given the option to authorize unsecure email communication. Participants that opt to communicate with the study team via phone call will be contacted using the study protocol phone script. For participants enrolled for the online control experiment, no identifiable information will be collected. Those participants that self identify for the online control study will immediately be directed to consent information and screening prior to beginning the study procedures.

11.3 Recruitment Materials:

We will utilize brochures, Qualtrics surveys, and digital/print posters. We will also have a phone and email script available.

11.4 Payment:

Participants that enroll for the study via public postings will be compensated with escalating payments to encourage completion of both research visits. \$15 will be given to participants for completion of the first research visit and \$25 will be given for completion of the second research visit. For participants completing the study in-person, payment will be given using Greenphire Clincards, a pre-paid credit card, at the end of the study visit, or a prepaid gift card, depending on participant preference and card availability. The cards will be kept in a locked cabinet in MTRF where part of the study team is housed. Participants that enroll via research experience programs, such as the UMN Department of Psychology REP program, will receive course credit for eligible courses.

For participants completing the online control experiment, payments will be delivered to participants through Prolific's payment system. After completing the experiment, payments will be delivered from the recruitment platform (i.e., Prolific) to the participant's selected payment method. Thus, no personal financial information is required or collected by the study team, as payments are managed directly through Prolific. The online task contains attention checks that automatically detect non-compliance, such as random responses, use of automated tools ("bots"), or failure to follow instructions. Participants are informed in the consent form that failure of those checks will result in them being unable to complete the tasks and potentially ineligible for payment.

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances:

If a participant misses a study visit, they will not be immediately withdrawn, but if they do not make it to the study visit after rescheduling three times, they will be at risk of being withdrawn from the study. Participants will also be withdrawn at their request, if they are non-compliant with study procedures, no longer meet safety criteria for TMS, or have an adverse reaction to study procedures. We also hold the right to withdraw

participant(s) if the study procedures are not suitable for a participant (e.g. unsuitable hairstyle for EEG data acquisition).

1.2 Withdrawal Procedures:

If a participant wishes to withdraw from the study, we will retain data collected up to that point in time. Due to data being deidentified, we will be unable to re-identify data for deletion. Discontinuation information (e.g., date and the reason(s) for discontinuation) will be recorded in the participant study file.

Participants withdrawn from the study due to an adverse event will be followed up for 30 days or until resolution. An effort will be made to determine why a participant does not return for the required visits or is dropped from the study. This information will subsequently be recorded on the participant's study file.

12.2 Termination Procedures:

Any severe adverse effect (e.g., seizure during study procedures) will be reported to the IRB according to reporting requirements. In the very unlikely event that numerous severe adverse events occur, the investigators will pause recruitment, and will consult with the IRB to reassess the balance of risks and benefits and determine whether the study can be continued safely. If it is concluded that it cannot be continued safely, the study will be terminated. Data collected prior to termination may be used for analyses. In the event of study termination, the sponsor/funding source and participants may be notified.

13.0 Risks to Participants

13.1 Foreseeable Risks:

TMS procedures have been used extensively in research protocols over the past three decades, and typically are deemed to constitute nonsignificant risk (NSR) studies.

As the theta burst protocol will be performed in a healthy population, it is a non therapeutic study and constitute a nonsignificant risk (NSR) design (Rossi et al., 2021) The procedures in the proposed protocol are standard in neurophysiologic TMS research and consistent with expert guidelines. Specific safety measures based on expert consensus will be implemented to minimize and mitigate potential risks for study participants (Rossi et al., 2021).

Members of the study team and the NNL have extensive experience with TMS procedures and at least two members of the study team who have completed training on response to TMS adverse events (including basic life support training) will be present at all research visits.

List of Anticipated TMS risks

- Localized scalp discomfort
- Tingling/dullness sensation
- Headache
- Nausea/vomiting
- Loss of appetite
- Hearing changes/tinnitus
- Neurocardiogenic syncope
- Seizure

Seizures

With any neuromodulatory procedure there exists the possibility of unanticipated propagation of the stimulatory effect resulting in a clinical seizure. This theoretical risk for seizure is largely based on case reports involving repetitive TMS. For our proposed study, participants with elevated risk for seizure (e.g., intracranial pathology, prior seizure history) will not be eligible.

All personnel involved in research visits will be provided with training in the identification of potential prodromal signs or symptoms of a seizure, particularly the identification of more subtle behavioral events which may herald the occurrence of a

frontal lobe seizure, such as changes in level of consciousness or inattention. All TMS testing will be conducted at the NNL, with access to nearby emergency medical facilities in the event a seizure should occur. Seizure monitoring during treatment sessions will be by visual observation.

In the unlikely event of a seizure, any immediate hazards (such as items the participant may hit their head on) will be removed. Because seizures induced by TMS are typically brief (<60 seconds) and without serious physical sequelae or risk of recurrence, efforts will be focused on preventing complications of the seizure rather than initiating any specific medication that is not required, unless a seizure is prolonged. If a prolonged seizure (>60 seconds) occurs during a research session, appropriate response measures will be initiated, which may include notifying emergency medical services (Rossi et al. 2021). If an adverse response occurs, TMS will be discontinued. Any seizure occurring during TMS will be reported to the IRB and the FDA as required per agreements, regulations, and policies.

Hearing Changes/Tinnitus

TMS produces a loud clicking sound as the coil discharges. This sound pressure level depends on stimulator output and the type of coil used for stimulation. Risk for auditory impairment by TMS is low, given that the brief (~ 320 us) pulse width of the stimulation results in a low accumulated exposure to sound, below occupational safety and health thresholds (Dhamne et al., 2014). As a precaution, during administration of TMS, participants will wear hearing protection.

Other risks

Other potential risks related to the application of EEG are minimal and easily reversible (itchy scalp, slight discomfort, etc.). Administering the cognitive tasks presents no meaningful risk to participants other than mild fatigue or boredom.

13.2 Reproduction Risks:

The risk of TMS procedures to a fetus is likely minimal. There are no known reproductive risks from TMS procedures to males who wish to have children. Magnetic fields attenuate rapidly with distance, so it is unlikely that the fetus might be directly affected by TMS. TMS is routinely administered to pregnant women and several studies have demonstrated the safety of such application during pregnancy (Burton et al., 2014; Eryılmaz et al., 2015; Hızlı Sayar et al., 2014; Kim et al., 2011; Klirva et al., 2008; Lee et al., 2021; Nahas et al., 1999; Pridmore et al., 2021; Shah et al., 2019; Sylvén et al., 2020; Tan et al., 2008; Trevizol et al., 2019; Zhang & Hu, 2009). Specifically, a systematic review of TMS during pregnancy indicates there is no evidence that TMS during any trimester of pregnancy can have adverse effects on the mother or baby (Pridmore et al., 2021). However, given that this is a non-clinical study, as a precaution to mitigate any potential risk, we will screen participants using our TMS safety questionnaire for the chance that participants are pregnant (Rossi et al., 2021). If participants receiving TMS in the experimental study (Phase 1) report that there is a chance that they are pregnant, we will confirm their pregnancy status by asking participants to complete a urine test at their research visit before conducting any experimental procedures. Any participants that return a positive test result will be withdrawn from the study. To reiterate, even if participants falsely report their pregnancy status on the self-report screening item, there is no evidence that suggests this could have any negative consequences (Rossi et al., 2021; Pridmore et al., 2021). Urine tests will not be administered to participants in the control group who are not receiving TMS.

13.3 Risks to Others: N/A

14.0 Potential Benefits to Participants

14.1 Potential Benefits:

There are no anticipated benefits to the individual for participating in this study.

15.0 Statistical Considerations

15.1 Data Analysis Plan:

TMS (and other physiological) artifacts will be removed from the EEG data during pre-processing. We will calculate EEG metrics of brain function, including theta-gamma phase amplitude coupling and alpha/theta power, during both the ITI and the stimulus-locked and response-locked trial periods. We will also compare single-pulse TMS-evoked potentials during the cognitive/perceptual task and during rest. Change in EEG metrics of brain function, and behavioral performance, across experimental blocks and across tasks will be analyzed using generalized linear models to assess our hypotheses. We will also examine how behavioral performance (e.g., accuracy, reaction time) in the behavioral task changes over repeated administrations in the presence (Phase One) and absence (Phase Two) of TMS. Thus, we will analyze behavioral performance using linear mixed models with block number (1, 2, or 3), and condition (TMS, Control) as fixed effects and subject IDs as random effects.

15.2 Power Analysis:

The number of participants we plan to recruit is based on recruitment feasibility, i.e. it is the number we believe we can recruit given the available funding, project timeline, and personnel. A specific *a-priori* power analysis for this study is not feasible given that the effect size of TMS-evoked modulations of brain function are likely to differ for motor-based responses measured with EMG, as opposed to cortical responses measured with EEG. In our previous analyses of similar cognitive tasks (including DPX), we have observed statistically significant changes in behavioral performance with a similar sample size ($n = 25$). Furthermore, we have observed modulations of TMS-evoked potentials with as few as ten participants. Therefore, we expect to have sufficient statistical power for this study.

A power analysis of results observed during Phase 1 of the study indicated an effect in behavior can be observed in a repeated measures ANOVA with 9 participants. Thus, to ensure adequate power, we plan to recruit up to 25 participants, to account for study drop out or significant outliers.

15.3 Data Integrity:

Monitoring will be conducted by the PI and designated members of the study team to ensure quality and integrity of the data.

16.0 Health Information and Privacy Compliance

16.1 Select which of the following is applicable to your research:

☐ My research does not require access to individual health information and therefore assert HIPAA does not apply.

☒ I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

☐ An external IRB (Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the university stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

16.2 Identify the source of Private Health Information you will be using for your research (Check all that apply)

- ☐ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me
- ☒ I will collect information directly from research participants.
- ☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.
- ☐ I will pull records directly from EPIC.
- ☐ I will retrieve record directly from axiUm / MiPACS
- ☐ I will receive data from the Center for Medicare/Medicaid Services
- ☐ I will receive a limited data set from another institution .
- ☐ Other. Describe:

16.3 Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed.

Only data collected from individuals who have consented to participate will be utilized for this study.

16.4 Approximate number of records required for review: N/A

16.5 Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes

- ☐ This research involves record review only. There will be no communication with research participants.

- ☐ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.
- ☐ Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants:

■ Participants will be contacted by telephone; if preferred by participants, encrypted email communication with the study coordinator and investigators may be used. Participants may also complete the screening and/or consent/assent process via video conferencing if desired. In the case that the consent interview is conducted remotely, the participant will be asked to sign the consent form at their arrival to the research visit, prior to proceeding with any experimental procedures.

16.6 Explain how the research team has legitimate access to patients/potential participants:

Study staff will have access to these participants because they have signed up for the registry which explains the potential for screening for studies. Individuals who self identify for the study via recruitment materials can be accessed by study staff because they have expressed interest in being contacted and screened for the study.

16.7 Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

- ☐ In the data shelter of the
 - ☐ Store ☐ Analyze ☐ Share
- ☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

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☐ Store ☐ Analyze ☐ Share

☐ In REDCap (recap.ahc.edu)

☐ Store ☐ Analyze ☐ Share

☐ In Amazon Web Services (AWS)

☐ Store ☐ Analyze ☐ Share

☒ In Qualtrics (qualtrics.edu)

☒ Store ☒ Analyze ☒ Share

☐ In OnCore (oncore.edu)

☐ Store ☐ Analyze ☐ Share

☒ In the University's Box Secure Storage (box.edu)

☒ Store ☐ Analyze ☒ Share

☐ In an AHC-IS supported server. Provide folder path, location of server and IT
Support Contact:

☐ Store ☐ Analyze ☐ Share

☒ In an AHC-IS supported desktop or laptop.

Provide university/organization device numbers of all devices: Device #

20220723; Device # 20170931

☒ Store ☒ Analyze ☒ Share

☒ Other. Describe:

We will utilize a computer that connects to the EEG system. Due to the nature of the software needed by the EEG system, the computer cannot be connected to HST. This computer will be located at the NNL.

Indicate if data will be collected, downloaded, accessed, shared, or stored using a server, desktop, laptop, external drive, or mobile device (including a tablet computer such as an iPad or a smartphone (iPhone or Android devices) that you have not already identified in the preceding questions

☐ I will use a server not previously listed to collect/download research data:

☐ I will use a desktop or laptop not previously listed

☐ I will use an external hard drive or USB drive (“flash” or “thumb” drives) not previously listed

☐ I will use a mobile device such as an tablet or smartphone not previously listed

☐ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

Provide university device numbers of all devices:

Indicate if data will be collected, downloaded, accessed, shared, or stored using a server, desktop, laptop, external drive, or mobile device (including a tablet computer such as an iPad or a smartphone (iPhone or Android devices) that you have not already identified in the preceding questions

☐ I will use a server not previously listed to collect/download research data

☐ I will use a desktop or laptop not previously listed

☐ I will use an external hard drive or USB drive (“flash” or “thumb” drives) not previously listed

☐ I will use a mobile device such as an tablet or smartphone not previously listed

16.8 Links to identifiable data:

All data will be de-identified and there will be no way to link a participant's identity with their data. Data will be labeled with an anonymous identification code. Any internal data reports will use only these codes and will not use any identifiable information. Any external data reports, abstracts, publications, presentations, etc. will present de-identified, grouped, and/or aggregate data. Any reports to the University of Minnesota IRB (such as Adverse Event reporting and annual renewal reports) will be kept confidential; they will not include participant-identifiable information, and only the anonymous identification code will be used.

16.9 Sharing of Data with Research Team Members.

Only de-identified data will be shared within the study team. These data will be shared via secure Box storage or stored local on university computers or HIPAA compliant systems.

16.10 Storage of Documents:

Only the research team will have access to the study documents and data. We will keep records of informed consent documents, which include the participants' names and date of visits. These will be kept in locked, secured file cabinets (for paper). All other items, such as self-report questionnaires and study data will be kept secure electronically (mainly UMN Box) and only be identified by a subject code that is not in any way related to the participant's PHI.

16.11 Disposal of Documents:

Research data and documents will be destroyed based on the Department of Psychiatry's record retention policies (this has generally been 6 years after the study has been closed).

17.0 Confidentiality

1.3 Data Security:

Protected health information that is obtained as part of the study protocol will be stored in locked file drawers in locked offices; case report forms will have identifying information removed to prevent loss of confidentiality, all computers and databases will be password protected, with passwords available only to limited study personnel

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

18.1 Data Integrity Monitoring:

Independent monitoring of the study will be conducted by the University of Minnesota's Clinical and Translational Science Institute (CTSI) clinical trial monitoring service. The CTSI monitors will confirm that study activities are in compliance with the approved protocol and applicable regulatory authorities (FDA, IRB, local and state regulations). The investigator will give the study monitors direct access to source documentation, study data, and relevant regulatory documentation. Monitoring visits will occur approximately every six months.

18.2 Data Safety Monitoring.

The degree of risk for this study can be classified as non-high-risk with very little chance of an SAE. We believe that the method of monitoring described above is commensurate with the degree of risk to subjects, the size and complexity of this study. As such, regular intervals of PI and institutional monitoring should be sufficient.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy:

Every effort will be made by research staff to conduct the consent process and study visits in as private a space as possible. Additionally, we will ensure that participants understand how their data will be stored and who has access to their data so they can communicate concerns or limits they would like to place on their data. Stored data will be de-identified and there will be no way to link an individual's identity with their data collected from this study.

19.2 Access to Participants:

We will only approach individuals who have expressed interest in the study via our recruitment methods outlined in section 11.

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury:

In the unlikely event that research-related activities result in an injury, treatment will be provided to the participant (e.g., first aid, emergency treatment called). Expenses related to such injuries will be billed in the ordinary manner to the participant or the participant's insurance company.

20.2 Contract Language: N/A

21.0 Consent Process

21.1 Consent Process (when consent will be obtained):

Consent will take place either in person at the study site or over the phone/secure Zoom, whichever one is more convenient for the participant. Potential participants will be given (in person, or via mail or secure email) a consent form to read and consider. They will be instructed to read the consent and ask any questions they may have. It will be stressed to the subjects that this is voluntary. The participant and study personnel will review and discuss the consent form and answer any questions. If the candidate is interested, meets eligibility criteria, and has read and reviewed the consent form with all questions and concerns answered to their satisfaction, then the candidate will be able to sign the consent form as witnessed by study personnel. If consent is conducted virtually, a verbal consent will be collected and documented in the consent log and the physical signature will be collected at the first in person visit.

21.2 Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

21.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained):

Screening procedures will take place prior to the consent discussion and obtaining written consent. For the purposes of screening, participants will imply consent to providing that information to the study team by submitting their screening items to the study team.

For participants enrolled in the online control experiment, we will be unable to obtain written consent and the online nature of the experiment makes a waiver of written/signed documentation necessary. The consent will contain a detailed description of all study procedures as well as risks, benefits, and other relevant information. Participants will have a choice whether or not to proceed to complete self-report questions and computer tasks and choose to proceed after reading the consent and explicitly “clicking” the option to acknowledge understanding and willingness to participate. Participants will not be able to complete study activities unless they have acknowledged the online consent. The online nature of this study requires a waiver of written documentation of consent. The experiment is a minimal risk study and is not FDA-regulated. We are not collecting personally identifiable information making the consent form the only document linking their identity to their participation. Participants will be provided a consent form online which they must electronically acknowledge before they are allowed to complete the assigned tasks, so completion of the task indicates that the participant is willing to participate in the study. This is consistent with procedures in place throughout the UMN Psychiatry department.

21.4 Non-English Speaking Participants: N/A

21.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): N/A

21.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A

21.7 Adults Unable to Consent: N/A

22.0 Setting

22.1 Research Sites:

Local Research:

Research procedures for Phase One and/or Phase Two will be performed in the following locations:

- MnDRIVE Non-invasive Neuromodulation Laboratory (NNL), 717 Delaware St SE, Minneapolis, MN 55414

For Phase Two of the study (but not Phase One), given that EEG and TMS equipment are not required, study procedures may be conducted within dedicated research space in the University of Minnesota Department of Psychiatry:

- Department of Psychiatry, Room F226, 2450 Riverside Ave, Minneapolis, MN 55454

Participants completing the online version of the Phase Two control experiment will complete all research activities electronically. The experiment will take place online through the platform Prolific. This data will be shared and collected electronically without interaction with the research participants.

22.2 International Research: N/A

23.0 Multi-Site Research

N/A

24.0 Coordinating Center Research

N/A

25.0 Resources Available

25.1 Resources Available:

All study personnel will be trained for their individual roles appropriately before engaging in the study. In particular, study personnel administering procedures will undergo training to the satisfaction of the PI and NNL staff. The following research infrastructure is available to be utilized in the implementation of the study:

- MnDRIVE Non-invasive Neuromodulation Laboratory: The laboratory provides support for researchers conducting clinical research projects involving non-invasive neuromodulation technologies. The laboratory's administrative home is in the Department of Psychiatry and Behavioral Sciences and is directed by Kelvin O. Lim, MD, Professor of Psychiatry and Vice Chair for Research. The laboratory has two locations in the 717 Delaware St. Building: an adult facility located on the second floor, and a pediatric facility located on the third floor in the Center for Neurobehavioral Development. Equipment includes: two transcranial magnetic stimulation (TMS)/repetitive TMS systems (Magstim Co. Ltd., Carmarthenshire, UK); 64-channel electroencephalography (EEG) systems (Brain Products GmbH, Gilching, Germany; Electrical Geodesics, Inc., Eugene, OR, USA); Neuroelectronics StarStim transcranial

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current stimulation system (Neuroelectronics, Inc. Barcelona, Spain); custom electromyography (EMG) system (built with Y03-2, Motion Lab Systems, Inc., Baton Rouge, LA, USA); TMS neuronavigation system (Rogue Research Inc, Montréal, Québec, Canada). There are two full time staff available to assist with experiments, including a doctoral-level manager (Mo Chen, PhD) available for scientific and protocol consultation, as well as a bachelor-level trained research coordinator. The location of the study is adjacent to the University of Minnesota Medical Center and emergency medical facilities are located within that facility if required.

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