PROTOCOL COVER PAGE

Protocol Title	Investigating the causal and phase-dependent role of prefrontal theta oscillations in approach/avoidance behavior
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Scientific Assessment	I believe Scientific Assessment is not required.
IND/IDE # (if applicable)	N/A
IND/IDE Holder	N/A
Investigational Drug Services # (if applicable)	N/A
Version Number/Date:	1.4 from 14/09/2024

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	*Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com*	**Required prior to IRB submission**
☐ **Yes** ☒ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff Contact:* ancillaryreview@Fairview.org	**Approval must be received prior to IRB committee/ designated review.** **Consider seeking approval prior to IRB submission.**
☐ **Yes** ☒ **No**	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreg@umn.edu* *See: https://policy.umn.edu/research/indide*	
☒ **Yes** ☐ **No**	Require Scientific Review? Not sure? See guidance in the Investigator Manual (HRP-103).	*Documentation of scientific merit must be provided. Contact: hrpp@umn.edu*	
☐ **Yes** ☒ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Complete the CPRC application process. Contact: ccprc@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee. Contact: barmstro@umn.edu*	**Approval from these committees must be received prior to IRB approval;** **These groups each have their own**
☒ **Yes** ☐ **No**	Use the Center for Magnetic Resonance Research (CMRR) or MR at Masonic Institute for the Developing Brain (MIDB) as a study location?	*Complete the CMRR pre-IRB ancillary review Contact: ande2445@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of recombinant or synthetic	*Complete the IBC application via eprotocol.umn.edu*	

	nucleic acids, toxins, or infectious agents?		**application process.**
☐ **Yes** ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance*	
☐ **Yes** ☒ **No**	Include PHI or are you requesting a HIPAA waiver?	*If yes, HIPCO will conduct a review of this protocol.* *Contact: privacy@umn.edu*	
☐ **Yes** ☒ **No**	Use data from CTSI Best Practices Integrated Informatics Core (BPIC) Formerly the AHC Information Exchange (IE)?	*The Information Exchange ancillary review will be assigned to your study by IRB staff* *Contact:* bpic@umn.edu	**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 the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff.* *Contact: Jenny Pham* *Pham0435@umn.edu*	
☐ **Yes** ☒ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff* *Contact: becca002@umn.edu*	
☒ **Yes** ☐ **No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff* *Contact:* fencl003@umn.edu	
☐ **Yes** ☒ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff* *Contact: oncore@umn.edu*	**Does not affect IRB approval.**

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1.3	07/18/2023	New study member; two experimental conditions (active and sham) are now performed intermittently in blocks during the same experimental session.	Yes

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ABBREVIATIONS/DEFINITIONS

- (DL)PFC – (dorsolateral) prefrontal cortex
- Ap/Av – approach/avoidance
- EEG – electroencephalography
- MEP – motor evoked potential
- MR(I) – magnetic resonance (imaging)
- TEP – transcranial magnetic stimulation-evoked potential
- TMS – transcranial magnetic stimulation

1. Objectives

1.1. Purpose: 1.1.1. to evaluate the causal link between the phase of ongoing theta oscillations in the prefrontal cortex and approach/avoidance (Ap/Av) behavior in healthy adults using phase-specific transcranial magnetic stimulation (TMS); 1.1.2. to investigate the electroencephalographic (EEG) brain responses during the Ap/Av test to TMS at peak vs. trough phases of ongoing prefrontal theta activity.

2. Background

2.1. Significance of Research Question/Purpose: Approach/avoidance (Ap/Av) behavior is a reliable marker of the emotional processes in the human brain (Corr & McNaughton, 2012; Bramson et al., 2020; Rolle et al., 2021). It presents scientific and clinical interest as a robust predictor of emotional disorders, such as depressive disorder (McDermott et al., 2021; Ironside et al., 2020; Ottenbreit et al., 2014). Ap/Av behavior can be measured in healthy adults using standardized computer tests. Although existing scientific studies found a correlation between the Ap/Av behavior and ongoing theta activity (3-7 Hz) in the left dorsolateral prefrontal cortex (DLPFC), the causal evidence of the phase-dependent role and strength of association between the prefrontal theta oscillations and Ap/Av behavior is missing. Recent advances in probing brain function using closed-loop transcranial magnetic stimulation with concurrent electroencephalography (TMS-EEG) made it possible to monitor the ongoing theta activity during the Ap/Av test and stimulate the theta rhythm at its specific phase (Shirinpour et al., 2020; Gordon et al., 2022). The phase of theta rhythm is important because it tracks the ongoing excitability of the brain region. The peaks of the oscillation indicate the most excitable time and the trough - the least excitable (Anastassiou et al., 2011; Anastassiou et al., 2015). We can monitor the excitability of theta activity in real-time non-invasively using EEG. Thus, we now can use the TMS-EEG system to probe the state of DLPFC during the Ap/Av test at the peaks vs. troughs of theta rhythm and examine the precise causal role and strength of association between the theta oscillations and Ap/Av behavior. These data will provide novel understanding of the mechanisms of emotional processing in human brain and, thus, emotional health.

2.2. Preliminary Data: We have developed a real-time TMS-EEG system which can continuously monitor the prefrontal theta rhythm (3-7 Hz) and trigger TMS pulses at specific phases with high accuracy. Our system has been validated in computational simulations and in proof-of-concept study in

healthy adults (Shirinpour et al., 2020). Recently, our real-time TMS-EEG system was used to investigate the phase-specific role of ongoing oscillations in motor cortex in adult participants, demonstrating robust performance and no unexpected side effects (Wischnewski et al., 2022).

2.3. Existing Literature: The combined application of TMS and EEG has established itself as a potent tool to probe and measure the causality of brain activity. It allows to accurate capture brain responses to the perturbation at specific times relative to the ongoing brain processes or cognitive tasks (Rogasch et al., 2016; Rogasch and Fitzgerald, 2013; Zrenner et al., 2016). Further, several recent studies have investigated the brain neurophysiology using real-time TMS-EEG for probing neural oscillations at different phases (Shirinpour et al., 2020; Schaworonkow et al., 2018; Zrenner et al., 2017). Our lab developed a novel closed-loop algorithm with higher accuracy compared to previous methods (Shirinpour et al., 2020). We recently applied the novel system to test the role of ongoing beta and mu oscillations in the motor cortex in healthy adults (Wischnewski et al., 2022). Moreover, the initial efforts to utilize real-time TMS-EEG for probing prefrontal activity and link between the prefrontal theta and cognition showed effectiveness and safety of such approach (Gordon et al., 2022).

3. Study Endpoints/Events/Outcomes

3.1. Primary Endpoint/Event/Outcome: The approach/avoidance test measures (reaction times to positive and negative emotional stimuli) during concurrent probing of ongoing prefrontal theta oscillations at peaks vs. troughs using TMS.

3.2. Secondary Endpoint(s)/Event(s)/Outcome(s): TMS-evoked potentials (TEPs) in concurrent EEG during the approach/avoidance test.

4. Study Intervention(s)/Investigational Agent(s)

4.1. Description: A TMS machine (MagVenture® X100 or MagStim® Rapid2) will be used to noninvasively stimulate the brain via a figure-8 coil. Both machines have FDA 510(k) clearance for several clinical indications, including major depressive disorder. They are developed and manufactured in accordance with Quality System Regulation 21 CFR 820. EEG will be recorded before, after, and during the whole experimental session using a 24-bit, battery-driven, amplifiers actiCHamp/actiCHamp

Plus (BrainProducts®) with the active electrode actiCap or equivalent (BrainProducts®). Electrooculography and heart rhythm will be recorded together with EEG using non-invasive sensors from BrainProducts® or equivalent.

4.2. Drug/Device Handling: The TMS device will be stored in our laboratory in (i) Nils Hasselmo Hall, 312 Church St SE, University of Minnesota or (ii) Phillips-Wangensteen Building, 516 Delaware St SE, University of Minnesota. In addition, (iii) the space of the Non-invasive Neuromodulation Laboratory at the University of Minnesota Twin Cities Campus located at 717 Delaware St SE can be used. Only authorized personal will have accesses to the room. Application of the stimulation will follow the guidelines for TMS from the International Federation of Clinical Neurophysiology (Rossi et al., 2021).

4.3. Biosafety: This study does not involve biological materials.

4.4. Stem Cells: This study does not involve stem cells.

4.5. Fetal Tissue: This study does not involve fetal tissues.

5. Procedures Involved

5.1. Study Design: Up to 26 healthy adult volunteers will be recruited for participation in this randomized crossover study. The study will consist of up to three sessions – the first session using magnetic resonance imaging (MRI) session and subsequent sessions with transcranial magnetic stimulation and concurrent electroencephalography (TMS-EEG). Informed consent for all study procedures and initial questionaries will be obtained before the first session. The 3T MRI scan will provide accurate prefrontal cortex anatomy for using neuronavigation for TMS. During the TMS-EEG sessions, we will first identify individual TMS intensity of motor threshold by recording motor evoked potentials. The stimulation will then be applied with an intensity of up to 120% of the resting motor threshold (which is a safe and common practice; Rossi et al., 2021). The intensity can be decreased for individual participants. Two TMS-EEG conditions – verum and sham, will occur in intermittent blocks in randomized order, and

volunteers will be blinded to the conditions. During each session, volunteers will first perform a task training and a short (approx. 5 min) block of the approach/avoidance task (Ap/Av) without TMS to record intrinsic EEG activity and use it for calibrating the real-time TMS-EEG system (Shrinpour et al., 2020). Then, volunteers will perform 8 main blocks of approach/avoidance tasks with TMS (approx. 6 minutes per block) in randomized order: 1. congruent task + TMS at theta peaks, 2. congruent task + TMS at theta troughs, 3. incongruent task + TMS at theta peaks, and 4. incongruent task + TMS at theta troughs. During each task trial, the volunteer will receive a single burst of TMS (up to three pulses) at the peak or trough of ongoing theta rhythm. In the verum TMS-EEG condition/block, we will apply TMS pulses over the left DLPFC based on the left DLPFC theta oscillations. In the sham condition/block, TMS will be applied over the head vertex (which should not induce changes in the prefrontal activity but will induce the same sensory effects). EEG will be recorded throughout the TMS-EEG sessions. In addition, electrooculography and heart rate will be recorded together with EEG using non-invasive sensors for the accurate removal of ocular and cardiac artifacts. There will be 3-5 min breaks in-between the blocks for rest. The total number of TMS pulses per day will not exceed 3,000 pulses, many times lower than the established safety limit of 90,000 pulses per day (Cole et al., 2022, 2020).

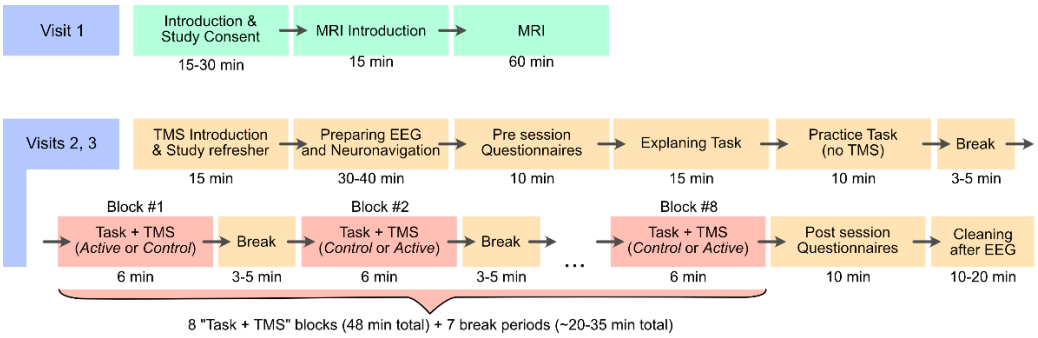

Diagram 1: Experimental pipeline with timing.

5.2. Study Procedures:

5.2.1. Initial questionaries: during the initial visit, each volunteer will fill out standardized self-reported questionaries regarding their demographic data and emotional assessment. These include the Patient Health Questionnaire (PHQ-9), General Anxiety Disorder (GAD-7) tool, and Quick Inventory of Depressive Symptomatology – Self-Rated (QIDS-SR-16). Total time necessary to complete all questionaries is approx. 25 minutes.

5.2.2. MRI: During the first session, 3T MRI scans will be performed at the Center for Magnetic Resonance Research (CMRR). Participants will

lay in the supine position within the scanner and be asked to relax. T1 and T2-weighted images will be collected to provide anatomical models for neural navigation during TMS. In addition, diffusion tensor imaging will be collected to assess structural connectivity of the prefrontal cortex, and BOLD fMRI contrast will be collected during the resting state to assess functional connectivity. All imaging modalities will follow standard Human Connectome Project (HCP) protocols (Harms et al., 2018), as routinely used in CMRR. Overall scanning time will be under one hour.

5.2.3. The approach/avoidance (Ap/Av) test: In the Ap/Av task, during each task trial, the volunteer sees on the screen a human face with either positive emotion (happiness, joy), negative emotion (anger, fear), or neutral emotion (Figure 1). During the congruent condition, the volunteer has to pull a joystick towards themself when they see a face with positive emotions and push away when they see negative emotions. In the incongruent condition, the responses with a joystick are the opposite. Neutral emotional stimuli require no response. When a joystick is pulled, the image become larger on the screen (imitating approach), when a joystick is pushed away – it become smaller (imitating avoidance). The reaction times to the stimuli and reaction time difference between the congruent and incongruent conditions constitute the primary test outcomes. We will perform four task blocks (approx. ten minutes each): two with congruent conditions and two with incongruent. The emotional stimuli are taken from publicly available, scientifically validated databases of emotional facial expressions, including Karolinska Directed Emotional Faces (KDEF; Lundqvist et al., 1998) and AffectNet (Mollahosseini et al., 2017). All stimuli can legally be used and redistributed for research purposes. The task presentation PC will be synchronized with the EEG amplifier and TMS machine using TCP/IP, UDP, and/or TTL protocols. Total time per session is 4 blocks of approx. 10 minutes, with approx. 5 minutes breaks in between.

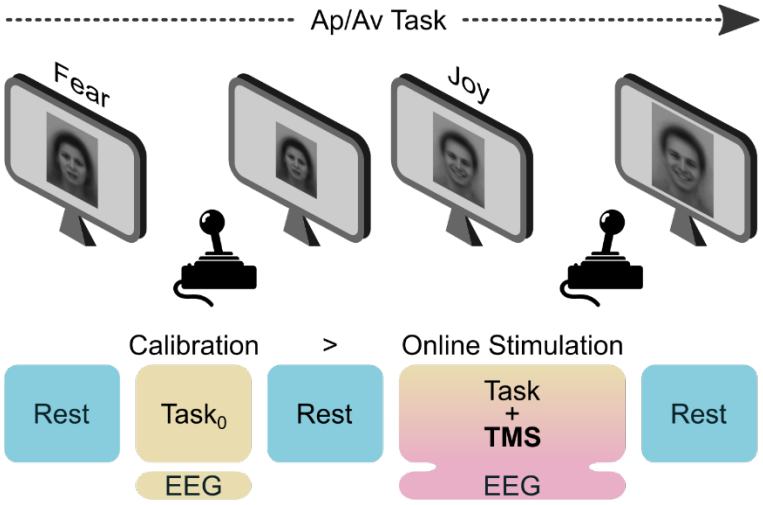

Figure 1. Overview of a single experimental TMS-EEG session.

5.2.4. TMS – motor threshold: To individualize the stimulation intensity before every TMS-EEG session, we will apply single-pulse stimulation to the motor hotspot for the FDI muscle in the left motor cortex (M1). The volunteer will be asked to relax his right hand. The lowest intensity at which 3 out of 6 pulses result in the motor evoked potential will be considered a resting motor threshold. This step will take approx. 15 minutes to perform.

5.2.5. TMS – experiment: During the Ap/Av test, we will apply single bursts of TMS (up to three pulses) every task trial at either peak or trough of prefrontal theta oscillation. The theta signal will be recorded in the frequency band from 3 to 7 Hz from the AF3/F3 electrodes (according to the international 10-10 convention) using a Laplacian electrode-montage. The stimulation will be applied with the intensity of up to 120% of the resting motor threshold (which is a safe and common practice; Rossi et al., 2021). The intensity can be decreased for individual participants. In the verum TMS-EEG condition, we will apply TMS pulses over the left DLPFC based on the left DLPFC theta oscillations (Figure 2). In the sham condition, TMS will be applied over the head vertex (which should not induce changes in the prefrontal activity but will induce the same sensory effects). In total, 8 task/stimulation blocks will be performed per session, each approx. 6 minutes long with 1 burst of TMS every 2-6 seconds (= every task trial). Stimulation will be performed by the investigators listed in the present protocol after safety and application training by the principal investigator and under his oversight. TMS stimulation will follow the guidelines of the International Federation of Clinical Neurophysiology (Rossi et al., 2021).

5.2.6. Physiological recordings: EEG will be recorded throughout the whole experimental session at a high sampling rate (≥ 1,000 Hz) using a 24-bit amplifier with active electrodes and electrode caps of appropriate size. No hardware filtering will be used. Electrooculography and heart rhythm will be recorded together with EEG using non-invasive sensors synchronized with the EEG acquisition.

5.2.7. Post-session questionary: At the end of every session the volunteer will be asked to fill out a written standardized questionnaire regarding the possible adverse effects of the stimulation procedures (Rossi et al., 2021).

5.3. Study Duration: Before the first session, we will have an introductory meeting with volunteers at which point we will schedule sessions. The first session (3T MRI) will last approximately 2 hours, including up to 1 hour of MRI acquisition time. The TMS-EEG session will last up to 3-4 hours, including initial training and 8 blocks of approx. 6 minutes each of task and single-burst TMS. Thus, we anticipate that each volunteer will complete the three sessions in 1-3 weeks. We anticipate that we will complete the study, including data analysis, within two years of the first session.

5.4. Individually Identifiable Health Information: We will collect personal information from volunteers (name, age and date of birth, biological sex at birth, date of enrollment, phone number, and email) as well as biomedical data (EEG, MRI, questionaries). Additionally, records of inclusion and exclusion criteria will be recorded. All biomedical data will be deidentified.

5.5. Use of radiation: The participants of this study will not be exposed to radiation.

5.6. Use of Center for Magnetic Resonance Research*:* During the first session of this study, we will collect anatomical and resting-state functional images in a 3T MRI scanner at the CMRR. These images will provide a precise location of the left dorsolateral prefrontal cortex (DLPFC) and allow us to use neuronavigation during our TMS experiments.

6. Data and Specimen Banking

6.1. Storage and Access: Informed consent and paper questionaries will be safely secured under lock and key, and a backup copy will be saved on Box (box.umn.edu). Experimental data (MRI, EEG, questionaries, test measures) will be saved on Box and used for data analysis; additionally, backup copies will be stored on an encrypted external hard drive (also stored under lock and key). Access to Box is limited to the researchers involved in this study. These data will be destroyed after 6 years. In line with recent requirements of scientific journals and the National Institute of Health, preprocessed and anonymized data will be made available for the research community using a community-supported public repository. Data can be put in open repositories Zenodo (zenodo.org) and National Institute of Mental Health Data Archive (NDA), where it can remain for up to 20 years.

6.2. Data: The MR images, EEG, questionaries, and task data will be preprocessed to comply with Health Information Privacy & Compliance Office (HIPCO) standards for a de-identified dataset. We will remove all information about volunteers except their age (in years), handedness, and biological sex.

6.3. Release/Sharing: Full or partial access to the raw data will be provided upon the request to the faculty / research staff of recognized research, medical, and educational institutions for educational and scientific purposes. The request should be sent via an institutional email and will be stored with the study materials. The request should include a short description of the scientific or educational aims. Access is the subject of approval by the principal investigator. De-identified data related to the scientific publications can be stored in a public repository.

7. Sharing of Results with Participants

7.1. Sharing Results: The data collected in this study (MRI, EEG, task measures, and questionaries) will not be shared with participants. In the case of concerning results, the volunteer will be advised to contact their physician.

7.2. Sharing Genetic Results: N/A

8. Study Population

8.1. Inclusion Criteria:

- Age between 18 and 65 years old.
- Stated willingness to participate and comply with all study procedures.

- Stated availability for the duration of the study.
- Confident level of English language proficiency.

8.2. Exclusion Criteria:

- Chronic health condition that requires pharmacological treatment over the course of study participation.
- History or evidence of seizures, chronic neurological or mental disorder.
- Pregnancy or breastfeeding.
- History or evidence of alcohol or drug addiction.
- Metallic or electric implant in the head, neck, or chest area, or otherwise MRI-noncompatible implants.
- History of metalwork.

8.3. Screening: Initial screening will be conducted prior the study by the investigator who will ensure that the volunteer read and understood the consent and study forms. The investigator will explain the study protocol, inclusion and exclusion criteria, foreseeable risks, withdraw process, and compensation scheme. The volunteers will be asked to fill out the standardized questionnaire to assess that they meet the study criteria.

8.4. Lifestyle Considerations: Participants will be asked to abstain from alcohol for 24 hours prior to every visit. Additionally, participants will be asked to abstain from nicotine-, caffeine-, and xanthine-containing products for 4 hours prior to every visit.

9. Vulnerable Populations

9.1. Vulnerable Populations:

Population / Group	Identify whether any of the following populations will be the focus of the research (targeted), included but not the focus of the research 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
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.	Excluded

institutionalization, deportation, disclosure of stigmatizing behavior).	
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

9.2. Additional safeguards, if any, to ensure inclusion is appropriate: Students and others who directly work in the Principal Investigator's lab will be excluded from participation.

9.3. If research holds prospect for direct benefit to participants, provide justification for any exclusions indicated in the table above: N/A

10. Local Number of Participants

10.1. Local Number of Participants to be Consented: We estimate that a sample size of 26 volunteers will allow us to reach the primary endpoints of this study, corresponding to medium effect size, based on previous research (Shirinpour et al., 2020; Gordon et al., 2022).

11. Local Recruitment Methods

11.1. Recruitment Process: Recruitment poster will be posted publicly throughout the Twin Cities campus of the University of Minnesota.

11.2. Identification of Potential Participants: The potential participant will contact the investigators in this study via the institutional email provided in the recruitment poster.

11.3. Recruitment Materials: An advertisement will be posted on advertisement boards in numerous buildings on the Twin Cities campus. The flyer will include a brief description of the study, experimental procedures, monetary compensation, summary of inclusion/exclusion criteria, and an institutional contact email.

11.4. Payment: The volunteers will receive a monetary compensation at the end of the session. The base rate of compensation is $15 per hour. We will use the Greenphire ClinCard system to process and track payments.

12. Withdrawal of Participants

12.1. Withdrawal Circumstances: The participant will be removed from the study in the following cases: (1) repeated non-appearance for experimental session; (2) repeated violation of the lifestyle considerations; (3) disrespectful behavior towards the investigators and university staff; (4) stated willingness of the volunteer to discontinue participation; (5) any legal or medical reasons for the volunteer to discontinue participation.

12.2. Withdrawal Procedures: Following participant withdrawal, the volunteer will receive payment for their participation at the rate described in point 11.4 according to the time spent in the study, if any. The incomplete data will be retained. Separately, a dedicated document with the description of withdrawal circumstance will be added by the principal investigator to the folder with study materials. No partial withdrawal is stipulated by this study protocol.

12.3. Termination Procedures: Following the final study procedures, the volunteer will receive payment (point 11.4) and the data will enter the dataset for further analysis.

13. Risks to Participants

13.1. Foreseeable Risks:

13.1.1. MRI machines use a strong magnet and radiofrequency magnetic fields to take images of your body. The scanning process is similar to an x-ray or CT scan, but MRI does not use ionizing radiation (high-energy radiation that can potentially cause damage to DNA) like x-rays or CT scans. The risks associated with MRI scans are:

Projectiles: Objects with magnetic properties can be pulled into the magnet and turn into projectiles. To minimize this risk, we ask that subjects remove all metallic items (watches, cell phones, hair pins, etc.) prior to entering the scanner and by controlling access to the scanner.

Claustrophobia: The scanner is a long narrow tube that may cause some people to feel claustrophobic.

Hearing damage: The noise generated by the operation of the scanner during a study is loud enough to cause hearing damage if you do not wear hearing protection. Hearing protection is required and is provided by the investigator.

Nerve stimulation: Some people experience localized tingling, twitching, or muscle contractions during MRI scans. This is expected, but if it is uncomfortable, participants will be asked to notify the investigator.

Disruption of devices: Some devices can be damaged by magnetic fields and should not be brought into the scanner room. This includes some implanted devices such as pacemakers, cochlear implants, insulin pumps, nerve stimulators, etc. Participants will be screened for implanted devices per the CMRR procedures.

Heating of devices: The radiofrequency waves used in MRI can heat conductive materials such as metal implants (screws, plates, rods, wires, artificial joints, etc.), certain tattoo inks, certain clothing fabrics, jewelry, medication patches, wigs, etc. Participants will be asked to remove these items if possible. If they cannot be removed, they will be asked to provide more information to allow MRI staff to be able to make determination on the safety of proceeding with the scan.

A thorough pre-scan questionnaire will allow us to minimize the risk of device disruption and heating. Subjects will be in constant contact with the investigator and should notify the investigator immediately, via the squeeze ball, if they notice anything unusual, become claustrophobic, think that the hearing protection is not adequate, or if nerve stimulation becomes uncomfortable. In addition, there is a risk of unknown effects related to participation in MRI research. Long-term effects of exposure to high magnetic fields are unknown. Most people experience no short-term ill effects from the strong magnetic field, but some people report dizziness, mild nausea, headache, a metallic taste in their mouth, or sensations of flashing lights. These symptoms, if present, subside shortly after leaving the magnet. If any sensations experienced during participation cause discomfort or pain, subjects will be instructed to notify the researcher immediately and the subject will be taken out of the magnetic field.

13.1.2. TMS is FDA approved for drug-resistant depression, obsessive-compulsive disorder, and smoking addiction. It is a widely used technique with minimal risk, and there is no evidence that the procedure is harmful if

appropriate guidelines are followed. To protect participants from possible risks, we will do as follows:

Head and neck aches: Minimize TMS intensity and avoid sensitive areas of scalp muscles and nerves to avoid head and neck aches.

Transient hearing changes: Earplugs will be offered to subjects and investigators during TMS to prevent transient hearing shifts caused by TMS.

Seizures: Screening and enrollment procedures will exclude subjects for whom TMS is contraindicated, those who are at increased risk of seizure, or those for whom the potential consequences of a seizure are increased. The informed consent process will note the potential risk of seizures. There is no evidence that a TMS-induced seizure increases the risk of having a second seizure in an otherwise healthy individual. In all lab spaces, we have a plan of action in place in the case of a seizure (based on NIH recommendations) as follows:

1. Roll the person on their side to prevent them from choking on fluids or vomit.
2. Cushion the individual's head.
3. Loosen any tight clothing around the neck.
4. Do not restrict the person from moving or wandering unless they are in danger.
5. Do not put anything in the person's mouth – it can cause choking and trauma.
6. Remove any dangerous objects the person might hit or walk into during the seizure.
7. Call 911.
8. Note how long the seizure lasts and what symptoms occurred then report this information to emergency personnel.
9. Stay with the person until the seizure ends and emergency personnel arrive and take over.

13.2. Reproduction Risks: No reproduction risks of TMS have been previously reported or suggested in the literature.

13.3. Risks to Others: No risks to others during or after TMS have been previously reported or suggested in the literature.

14. Potential Benefits to Participants

14.1. Potential Benefits: There are no direct benefits for the participant in this study.

15. Statistical Considerations

15.1. Data Analysis Plan: We will analyze reaction times from the Ap/Av test using Hierarchical Bayesian Drift Diffusion Models (HDDM). This model is optimal for two alternative forced-choice cognitive tasks. It estimates single-trial performance in the presence of various sources of noise and trial-by-trial variations. The model will take reaction times as inputs and recover the variables of interest – speed of evidence accumulation (drift rate) and the decision thresholds for responding to the stimuli of positive and negative valence.

EEG from the stimulation and task periods will first be preprocessed. We will exclude noisy trials and interpolate noise channels, bandpass filter the signals (0.2-80 Hz) using Butterworth noncausal filters, suppress the line noise, and clean the data with extended InfoMax ICA. After preprocessing and artifact suppression, we will epoch the data around the TMS pulses, and calculate the TMS-evoked potentials in the left DLPFC caused by the stimulation at the peak and trough of theta oscillations.

15.2. Power Analysis: We estimated that medium effect size of Cohen's d = 0.5, which was observed in comparable studies (Shirinpour et al., 2020; Gordon et al., 2022), will be reached with a sample size of 26 volunteers.

15.3. Statistical Analysis: The HDDM parameters will be compared between the conditions using Generalized Linear Mixed-Effect Models (GLMM) with model outcomes as dependent variables, stimulation conditions (real vs control and peaks vs trough) as categorical independent variables, and participant IDs as a nuance variable. Further, post-hoc pairwise nonparametric tests will be applied between the conditions. Latency and magnitude of TMS-evoked potentials (TEPs) will be comparted between the conditions using nonparametric cluster-based permutation test with false discovery rate correction for number of comparisons. Outcomes of TEPs and behavioral analysis will be correlated using Spearman statistics.

15.4. Data Integrity: Raw data and corresponding log files will be examined by the principal investigator on a regular basis during the data collection stage. The automatic log files will be generated automatically by the software which runs the EEG amplifier. The log files will be cross-checked

with the experimental lab journal. We will control the integrity of EEG data by checking the input impedance on the recording electrodes before and after each session, and by analyzing the signal-to-noise ratio in the raw data.

16. 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.

☐ 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.

Appropriate Use for Research:

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: N/A

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.

We will use email communications for scheduling purposes. The recruitment materials, which will solicit participants, include our institutional email address. A prospective volunteer will write to us on this email, and we will continue communications using the email from which we were contacted. No health information will be shared via email.

16.6. Explain how the research team has legitimate access to patients/potential participants: No medical records will be reviewed. Other personal information will be collected directly from the participants in the laboratory room. Screening questionnaires will be administered in person during enrollment to assess eligibility as a volunteer. 3T MRI scans will be collected to obtain structural brain images using the University facilities. EEG, questionaries, and Ap/Av test data are collected during the main experiment in the laboratory room, and these will be the primary outcome measure.

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 Information Exchange (IE)

☐ Store ☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☐ In REDCap (recap.ahc.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In OnCore (oncore.umn.edu)

☐ Store ☐ Analyze ☐ Share

☑ In the University's Box Secure Storage (box.umn.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 UMN device numbers of all devices:

1. Product model: Dell Inc. - xps, asset id: bme-opitz-112

☐ Store ☑ Analyze ☐ Share

☐ Other:

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 smartform (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. Consultants. Vendors. Third Parties: No information will be collected, stored, analyzed or shared using a consultant, vendor, or third-party software application, system, device or technology (other than University of Minnesota provided REDCap or OnCore).

16.9. Links to identifiable data: Identifiable data sharing, if necessary, will happen only through Box Secure Storage (box.umn.edu). No links will be used.

16.10. Sharing of Data with Research Team Members: Research data, that is, EEG, MRI, questionaries, and task data will be stored on University's Box Secure Storage (box.umn.edu) and shared with relevant team members if necessary.

16.11. Storage of Documents: Screening forms, questionaries, and informed consents will be stored under lock and key for 6 years in accordance with the HIPAA guidelines.

16.12. Disposal of Documents: After 6 years screening and informed consents will be destroyed.

17. Confidentiality

17.1. Data Security: The consent and study forms, as well as any other documents that contain Protected Health Information, will be stored in the office of the principal investigator at the Department of Biomedical Engineering, University of Minnesota. We will assign a new study identifier to every participant. This identifier will be used during the data collection and for the purpose of any other documentation. Thus, all datasets will be pseudo-anonymized. The data will be recorded and temporarily stored on the computers at the research sites (see point 16), all of which have restricted access by the authorized personal only. The data will be transferred from the research sites to the computers of the investigators by using an encrypted hard drive. All computers are encrypted and password protected. A copy of the data will be deposited to a secured Box account of the laboratory which was organized in accordance with HIPCO regulations. We will not supply a copy of the consent form or any other documentation that contains PHI to any third party, and will not place it in the participants' medical, employment, or educational records.

18. Provisions to Monitor the Data to Ensure the Safety of Participants

18.1. Data Integrity Monitoring: The principal investigator will be responsible for the data integrity monitoring in this study. The principal investigator will biweekly oversee the collected data, equipment log files, laboratory journal, consent forms, and standardized questionnaires to ensure that all procedures are executed on time and according to the present regulation.

18.2. Data Safety Monitoring: The principal investigator in the study will biweekly monitor (1) the original standardized questionnaires for possible adverse effects, which will be filled out by the volunteers at the end of the experimental session; and (2) aggregated data on the volunteers' reports regarding potential adverse effects. The investigators will inform IRB within 24 hours if a volunteer reports side effects during the experimental procedure or will otherwise inform the investigators about the potential adverse effect.

18.3. Unblinding procedures: This study follows a crossover design, with verum and sham conditions administered in intermittent blocks in randomized order. Thus, each participant will experience all study procedures. The exact sequence of procedures is stored in a computer file. In an unlikely case of adverse events, the study's principal investigator will access the specific file and reveal the sequence of procedures preceding the event to the response team and overseeing bodies.

19. Provisions to Protect the Privacy Interests of Participants

19.1. Protecting Privacy: We will obtain personal information about the volunteer necessary for the study (day of enrollment, name, age and date of birth, biological sex at birth, handedness, phone number, email, screening results regarding study criteria) and store it in paper form and in an encrypted electronic form in the Department of Biomedical Engineering separately from other data. This information will not be shared with any 3rd party, and the volunteers' enrollment in the study will not be disclosed to anyone outside the investigation group. The investigators in the study will contact volunteers through the course of the study to arrange the experimental session via the volunteers' phone or email. The volunteers will be informed prior to their participation that the application of physiological recordings and transcranial magnetic stimulation will require an investigator to touch their head, face, arms, and hands while setting up the equipment.

19.2. Access to Participants: We will not collect PHI about the volunteers from their medical records or any other sources outside this study. The information that is necessary for the study will be obtained by the investigators directly from the participants during the initial meeting and the experimental sessions.

20. Compensation for Research-Related Injury

20.1. Compensation for Research-Related Injury: No specific compensation scheme for research-related injury is planned.

20.2. Contract Language: N/A

21. Consent Process

21.1. Consent Process (when consent will be obtained): The consent process will take place at the research sites (see point 22.1) in the presence of the investigator who is involved in this study. The investigator will be responsible to ensure that the volunteer understands the content of the consent and study forms, and all study procedures. After that, written informed consent will be obtained. The volunteer will be asked to fill out the standardized questionnaire at every session. At this point, the volunteer will verbally indicate the ongoing consent to participate in the study.

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): N/A

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. Setting

22.1. Research Sites: All research procedures will be conducted in the laboratories of the Department of Biomedical Engineering at the University of Minnesota Twin Cities Campus: (1) at Nils Hasselmo Hall, 312 Church St SE and/or (2) Phillips-Wangensteen Building, 516 Delaware St SE. Besides, research can be performed at (3) the Non-invasive Neuromodulation Laboratory at the University of Minnesota Twin Cities Campus located at 717 Delaware St SE. Only authorized personnel have access to the laboratories.

22.2. International Research: N/A

23. Multi-Site Research

23.1. Study-Wide Number of Participants: N/A

23.2. Study-Wide Recruitment Methods: N/A

23.3. Study-Wide Recruitment Materials: N/A

23.4. Communication Among Sites: N/A

23.5. Communication to Sites: N/A

24. Coordinating Center Research

24.1. Role: N/A

24.2. Responsibilities: N/A

24.3. Oversight: N/A

24.4. Collection and Management of Data: N/A

25. Resources Available

25.1. Resources Available: MRI and TMS-EEG experiment will be conducted by the (co-)investigators. 3T MRI scans will be measured at the Center for

Magnetic Resonance Research (CMRR). The TMS-EEG main experiment will be performed at our lab in the Nils Hasselmo Hall, 312 Church St SE, University of Minnesota or Phillips-Wangensteen Building, 516 Delaware St SE, University of Minnesota. This facility is fully equipped for the TMS-EEG experiment. Co-investigators will primarily dedicate their work efforts in completing the study.

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