

## ANCILLARY REVIEWS

| Which ancillary reviews do I need and when do I need them?<br>Refer to <a href="#">HRP-309</a> for more information about these ancillary reviews. |                                                                                                                     |                                                                                                                                                                                                                                                    |                                                                                                                                     |
|----------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Select yes or no                                                                                                                                   | Does your study...                                                                                                  | If yes...                                                                                                                                                                                                                                          | Impact on IRB Review                                                                                                                |
| <input type="checkbox"/> Yes<br><input checked="" type="checkbox"/> No                                                                             | Include Gillette resources, staff or locations                                                                      | Gillette Scientific review and Gillette Research Administration approval is required. Contact: <a href="mailto:research@gillettechildrens.com">research@gillettechildrens.com</a>                                                                  | Required prior to IRB submission                                                                                                    |
| <input type="checkbox"/> Yes<br><input checked="" type="checkbox"/> No                                                                             | Involve Epic, or Fairview patients, staff, locations, or resources?                                                 | The Fairview ancillary review will be assigned to your study by IRB staff<br>Contact: <a href="mailto:ancillaryreview@Fairview.org">ancillaryreview@Fairview.org</a>                                                                               |                                                                                                                                     |
| <input type="checkbox"/> Yes<br><input checked="" type="checkbox"/> 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<br>Contact: <a href="mailto:medreg@umn.edu">medreg@umn.edu</a><br><br>See: <a href="https://policy.umn.edu/research/indide">https://policy.umn.edu/research/indide</a> |                                                                                                                                     |
| <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No                                                                             | Require Scientific Review? Not sure? See guidance on next page.                                                     | Documentation of scientific merit must be provided.<br>Contact: <a href="mailto:hrpp@umn.edu">hrpp@umn.edu</a>                                                                                                                                     |                                                                                                                                     |
| <input type="checkbox"/> Yes<br><input checked="" type="checkbox"/> No                                                                             | Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?                              | Complete the <a href="#">CPRC application process</a> .<br>Contact: <a href="mailto:ccprc@umn.edu">ccprc@umn.edu</a>                                                                                                                               |                                                                                                                                     |
| <input type="checkbox"/> Yes<br><input checked="" type="checkbox"/> No                                                                             | Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)                 | Complete the <a href="#">AURPC Human Use Application</a> and follow instructions on the form for submission to the AURPC committee.<br>Contact: <a href="mailto:barmstro@umn.edu">barmstro@umn.edu</a>                                             | Approval from these committees must be received prior to IRB approval;<br><br>These groups each have their own application process. |
| <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No                                                                             | Use the Center for Magnetic Resonance Research (CMRR) as a study location?                                          | Complete the <a href="#">CMRR pre-IRB ancillary review</a><br>Contact: <a href="mailto:ande2445@umn.edu">ande2445@umn.edu</a>                                                                                                                      |                                                                                                                                     |
| <input type="checkbox"/> Yes<br><input checked="" type="checkbox"/> No                                                                             | Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents?                            | Complete the IBC application via <a href="http://eprotocol.umn.edu">eprotocol.umn.edu</a><br>Contact:                                                                                                                                              |                                                                                                                                     |
| <input type="checkbox"/> Yes<br><input checked="" type="checkbox"/> No                                                                             | Include the use of human fetal tissue, human embryos, or embryonic stem cells?                                      | Contact <a href="#">OBAO</a> for submission instructions and guidance                                                                                                                                                                              |                                                                                                                                     |
| <input type="checkbox"/> Yes<br><input checked="" type="checkbox"/> No                                                                             |                                                                                                                     | If yes, HIPCO will conduct a review of this protocol.                                                                                                                                                                                              |                                                                                                                                     |

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|                                                                        |                                                                               |                                                                                                                                                                                              |                                                                                                                                                                                               |
|------------------------------------------------------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                        | Include PHI or are you requesting a HIPAA waiver?                             | Contact: <a href="mailto:privacy@umn.edu">privacy@umn.edu</a>                                                                                                                                |                                                                                                                                                                                               |
| <input type="checkbox"/> Yes<br><input checked="" type="checkbox"/> No | Use data from the Information Exchange (IE)?                                  | <i>The Information Exchange ancillary review will be assigned to your study by IRB staff</i><br>Contact: <a href="mailto:ics@umn.edu">ics@umn.edu</a>                                        | <b>Approval must be received prior to IRB approval.</b><br><br><b>These groups do not have a separate application process but additional information from the study team may be required.</b> |
| <input type="checkbox"/> Yes<br><input checked="" type="checkbox"/> 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><br>Contact: <a href="mailto:cdrifka@umn.edu">cdrifka@umn.edu</a>                                                |                                                                                                                                                                                               |
| <input type="checkbox"/> Yes<br><input checked="" type="checkbox"/> No | Have a PI or study team member with a conflict of interest?                   | <i>The Col ancillary review will be assigned to your study by IRB staff</i><br>Contact: <a href="mailto:becca002@umn.edu">becca002@umn.edu</a>                                               |                                                                                                                                                                                               |
| <input type="checkbox"/> Yes<br><input checked="" type="checkbox"/> 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><br>Contact: <a href="mailto:kmmccorm@umn.edu">kmmccorm@umn.edu</a>   |                                                                                                                                                                                               |
| <input type="checkbox"/> Yes<br><input checked="" type="checkbox"/> 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><br>Contact: <a href="mailto:oncore@umn.edu">oncore@umn.edu</a> | <b>Does not affect IRB approval.</b>                                                                                                                                                          |

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|                                               |                                                                            |
|-----------------------------------------------|----------------------------------------------------------------------------|
| <b>Protocol Title</b>                         | Phase-dependent evaluation of motor cortex excitability with TMS in stroke |
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|                                                        |                                                                 |
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| <b>IND/IDE # (if applicable)</b>                       | N/A                                                             |
| <b>IND/IDE Holder</b>                                  | N/A                                                             |
| <b>Investigational Drug Services # (if applicable)</b> | Version 2.1                                                     |
| <b>Version Number/Date:</b>                            |                                                                 |

**PROTOCOL COVER PAGE**

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**REVISION HISTORY**

| Revision # | Version Date | Summary of Changes                                                                                                                                         | Consent Change? |
|------------|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| 1          | 7/20/2021    | No changes in protocol;<br>Addition of two paragraphs (notification of FDA inspection and registration in clinicaltrials.gov);<br>Small text change in add | Yes             |
| 2          | 3/9/2022     | Magventure was added as an addition TMS machine;<br>Questionnaire on subjective stroke-related symptoms was added                                          | Yes             |
| 3          | 6/13/2022    | Maximum compensation corrected; Funding source added                                                                                                       | Yes             |
|            |              |                                                                                                                                                            |                 |
|            |              |                                                                                                                                                            |                 |
|            |              |                                                                                                                                                            |                 |
|            |              |                                                                                                                                                            |                 |

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### **ABBREVIATIONS/DEFINITIONS**

- TMS – transcranial magnetic stimulation
- EEG – electroencephalography
- MEP – motor evoked potential
- MRI – magnetic resonance imaging
- RMT – Resting motor threshold
- TEP – TMS-evoked potential

## **1.0 Objectives**

- 1.1* Purpose: (1) to investigate the effects of transcranial magnetic stimulation (TMS) on motor cortex excitability in individuals who have suffered stroke; (2) to study the influence of the phase of the oscillatory rhythm (mu frequency) on motor excitability in stroke individuals.

## **2.0 Background**

- 2.1* Significance of Research Question/Purpose: Neurological disorders, including stroke, are associated with impaired movement leading to significant negative effects on quality of life. Transcranial magnetic stimulation (TMS) is increasingly being explored as a rehabilitation strategy to enhance plasticity in motor regions. However, it is not yet fully understood how TMS acts on motor circuits and what optimal stimulation parameters are. TMS is a noninvasive neuromodulation method which enables in vivo perturbation of neural activity in humans through the application of electromagnetic fields to the brain. TMS has an established safety profile and has been explored extensively in clinical trials for a range of neurological and psychiatric disorders. Particularly, in potential positive effects of TMS have been identified for stroke rehabilitation (Smith & Stinear, 2016). However, significant variability in treatment outcomes across patients has been found, making it necessary to improve current stimulation protocols and to investigate basic mechanism of action (Ovadia-Caro et al., 2019). Here, we plan to study the effects of TMS to the motor cortex in individuals who suffered stroke for movement rehabilitation. We plan to measure motor evoked potentials (MEPs) at different phases of the motor mu-rhythm measured with EEG. Mu rhythms are related to healthy movement execution. By this we characterize phase-dependent cortical excitability differences in stroke.
- 2.2* Preliminary Data: We have developed a closed-loop TMS system which can continuously monitor the mu-rhythm (~10 Hz) with EEG and trigger TMS pulses at specific phases with high accuracy. Our system has been validated in human participants (Shirinpour et al., 2020). Furthermore, pilot data from healthy individuals suggested that MEPs may be modulated by stimulation phase (Figure 1).

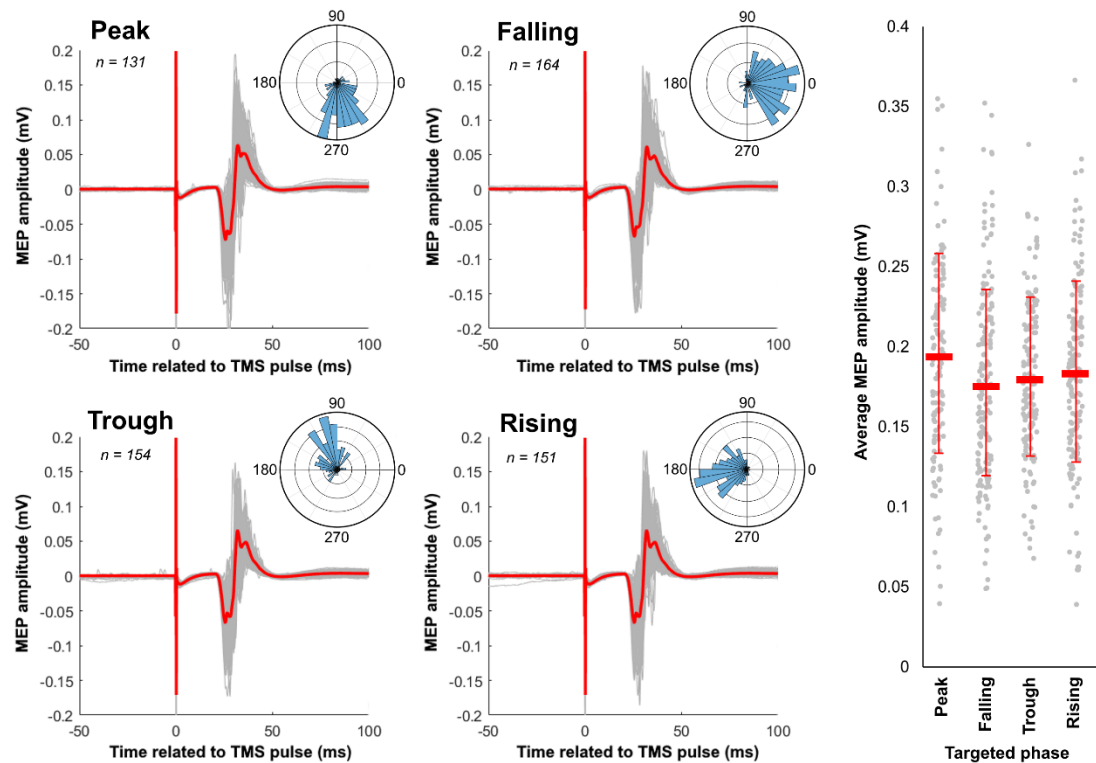


**Figure 1.** Pilot data from a single healthy volunteer. MEP recordings at the four different stimulation phases (peak, falling phase, trough, and rising phase) of the Mu rhythm. Polar plots indicate that the four phases are targeted reliably and distinctly. Average MEP amplitudes during TMS at the peak of the Mu oscillation were largest, compared to other conditions.

- 2.3 Existing Literature: A large number of studies have used TMS to study the motor cortex. (Groppa et al., 2012; Opitz et al., 2014, 2013; Siebner and Rothwell, 2003; Stokes et al., 2013). However, only few recent studies have investigated the effect of applying TMS in a closed-loop fashion with respect to the underlying mu-rhythm (Shirinpour et al., 2020; Schaworonkow et al., 2018; Zrenner et al., 2017) measured with EEG. The combined application of TMS and EEG has established itself as a potent tool to more accurately time and measure the effects of TMS with millisecond temporal resolution (Rogasch et al., 2016; Rogasch and Fitzgerald, 2013; Siebner et al., 2009; Zrenner et al., 2016). Our lab developed a novel closed-loop algorithm with higher accuracy compared to previous methods (Shirinpour et al., 2020).

### 3.0 Study Endpoints/Events/Outcomes

- 3.1 Primary Endpoint/Event/Outcome: To evaluate the effect of TMS on motor excitability relative to the ongoing mu rhythm measured with MEPs.

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

- 4.1 Description: TMS will be administered with a Magstim or Magventure 70mm figure-8 coil allowing for focal stimulation. The Magstim and Magventure stimulator are developed and manufactured in accordance with Quality System Regulation 21 CFR 820 and have received FDA 510(k) clearance for the treatment of drug resistant Major Depressive Disorder.
- 4.2 Drug/Device Handling: The TMS devices will be stored in our laboratory in Nils Hasselmo Hall, 312 Church St SE, University of Minnesota. Only authorized personnel will have access to the room. We will also use the noninvasive neuromodulation laboratory (NNL) at 717 Delaware St SE, University of Minnesota, which has identical set-up. Application of the stimulation will follow the guidelines for TMS (Rossi et al., 2009) from the International Federation of Clinical Neurophysiology.
- 4.3 Biosafety: This study does not involve biological materials.
- 4.4 Stem Cells: This study does not involve stem cells.

#### **5.0 Procedures Involved**

- 5.1 Study Design: Up to 36 stroke adult volunteers and 36 healthy adult volunteers will be recruited. Participants will be recruited based on self-reported symptomatic unilateral stroke. All of them will start with an initial session in which informed consent will be obtained and the volunteers will be introduced to the study procedure. Each volunteer will take part in two experimental sessions: First, for assessment of stroke characteristics and second the main TMS experiment.

The first session will assess the severity of stroke symptoms as well as localization of brain lesions in stroke volunteers. Therefore, during the first session a trained physical therapist will perform a motor exam on the upper extremities to assess severity of motor impairments and ensure that the presentation is consistent with a unilateral stroke, such that the participant is eligible for participation. The therapist will assess upper extremity range of motion and strength. Spasticity will be assessed with the Modified Ashworth Scale by passively moving the elbow and wrist joints (Ashworth, 1964). The Fugl-Meyer Assessment will be performed, which consists of having the participant perform different movements with their upper extremities as well as grasp different objects (Fugl-Meyer et al., 1975). In addition, participants will be asked to rate their symptoms subjectively in a short questionnaire (to be filled out by the investigator). Following motor assessment a 3T MRI-scan of the brain will be taken to assess lesion location. For healthy volunteers the first session only includes the MRI-scan.

During the second session, we will collect MEPs using single-pulse TMS applied at different phases (0, 90, 180, 270 degrees – 4 stimulation conditions) of the

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ongoing mu-rhythm. In stroke volunteers TMS will be applied over the motor cortex on the affected and non-affected hemisphere at the intensity of up to 120% resting motor threshold (RMT). In healthy volunteers the procedure will be the same targeting both left and right hemisphere. Positioning of the TMS coil will be neuronavigated based on individual MRI scans. Stimulation will be applied in a closed-loop fashion while the participant is at rest and their EEG activity is recorded.

### 5.2 Study Procedures:

#### First Session:

- Motor assessment: A trained physical therapist will assess spasticity and stroke symptom severity using the Modified Ashworth Scale and Fugl-Meyer Assessment, respectively (Ashworth, 1964; Fugl-Meyer et al., 1975). Duration of assessment will be approximately 20 minutes.
- MRI-scan: 3T MRI scans will be performed at the Center for Magnetic Resonance Research (CMRR). During each scan participants are laid down in the scanner and will be asked to relax. T1- and T2-weighted and diffusion weighted images will be collected, which will be used to assess stroke lesion location. Further, resting state-fMRI scans will be collected. Also, the scans will be used for neuronavigation to place the TMS coil in the second session.

#### Second session:

- Pre-/post-task resting state recording: At the beginning and end of the session, eyes-open resting state EEG will be recorded for up to 10 minutes (see the description of the technique below). The volunteers will be asked to fixate the eyes on the cross at the center of the presentation screen. This pre-measurement will be used to optimize the closed-loop application of TMS, and the post-measurement – for quality control purposes.
- EEG recording: EEG will be recorded before, after, and during the whole experimental session using a 24-bit, battery-driven, active channel amplifiers actiCHamp or BrainAmp from BrainVision® (or equivalent) with 64 electrode cap actiCap from BrainVision® (or equivalent). US Federal Law classifies this equipment as investigational devices.
- TMS will be delivered with a Magstim Rapid Stimulator or Magventure X100. The TMS coil will be placed over the motor cortex of the affected and non-affected hemisphere and single TMS pulses will be delivered at the intensity of up to 120% RMT. RMT is determined as the intensity needed to elicit a motor evoked potential (MEP) with 50% chance. RMT will be determined at the beginning of each session. We may reduce the intensity on an individual basis in the case of volunteer discomfort during

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stimulation. The minimum intensity of TMS is 105% of RMT. If the participant does not tolerate this intensity, they will be excluded. Location of the TMS coil will be monitored with a neuronavigation system (BrainSight from Rogue Research Inc or equivalent).

The stimulation will be performed by the co-investigators / student investigators in the present protocol after the safety and application training by the principal investigator and under his oversight. The stimulation will follow the guidelines of the International Federation of Clinical Neurophysiology (TMS: Rossi et al., Clin. Neurophys., 2009).

- MEP recordings: We will record MEP from the right and left hand muscles, such as first dorsal interosseous muscle, using a 4-ch bipolar electromyogram pre-amplifier (Motion Lab Systems, Inc).
- After-session questionnaire: 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.

5.3 Study Duration: Before the first session, volunteers will have to come for the introductory meeting. The first, motor assessment session, including 3T MRI scan, will last approximately 1,5 hours. The second, main TMS experimental session will last approximately 3 hours. Thus, we anticipate that the individual volunteer will stay in the study for 1-2 weeks. We anticipate completing the whole study, including data analysis, within three years from the first session, according to this plan:

| Year 1                                                                                                                                               | Year 2                            | Year 3                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------|
| Estimated N stroke = 6 completed                                                                                                                     | Estimated N stroke = 18 completed | Estimated N stroke = 30 completed          |
| Estimated N healthy control = 6                                                                                                                      | Estimated N healthy control = 18  | Estimated N healthy control = 30 completed |
|                                                                                                                                                      |                                   |                                            |
| Evaluation after 18 months: if N(stroke) < 12, add 1 year of recruitment<br>Evaluation after 18 months: if N(stroke) < 6, add 2 years of recruitment |                                   |                                            |

5.4 Individually Identifiable Health Information:

- Before the experiment: We will collect personal information from the volunteers (name, date of birth, biological sex, date of enrollment, phone number, and email). In addition, information regarding the conformity of the volunteers with the inclusion and exclusion criteria will be recorded.
- During the experiment: Biomedical data will be recorded (MRI, EEG, MEPs). 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 anatomical and functional 3T MRI scans will be recorded at the CMRR. Anatomical Images will be used for neuronavigation during the TMS application. Functional MRI will be used to identify brain circuits.

## **6.0 Data and Specimen Banking**

- 6.1 Storage and Access: Informed consents will be safely secured under lock and key. Experimental data (MRI, EEG, TMS) will be saved on Box (box.umn.edu) and used for data analysis. Access to Box is limited to researcher involved in this study. These data will be destroyed after 6 yrs. In line with recent requirements of scientific journals and National Institute of Health, preprocessed and anonymized data will be made available for the research community using a community supported public repository. Data will be put in open repositories Zenodo (zenodo.org) and National Institute of Mental Health Data Archive (NDA). Data will remain for 20 years.
- 6.2 Data: The MRI, EEG and MEP data will be preprocessed to comply with the HIPCO standards for a de-identified dataset. We will remove all information about the volunteers except for their age (in full years), handedness, and biological sex. MRI facial features will be deidentified.
- 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.

## **7.0 Sharing of Results with Participants**

- 7.1 The data that will be collected in this study (MRI, EEG and MEP) will not be shared with the participants. In case when there will be a concerning result, the volunteer will be advised to contact their physician.
- 7.2 Sharing of genetic testing:  
n/A

## **8.0 Study Population**

- 8.1 Inclusion Criteria:
1. Suffering from chronic stroke, resulting in self-reported motor deficits (stroke occurring more than 6 months before study enrollment). Motor deficits will be confirmed and assessed during a motor exam in the first session.
  2. Stated willingness to participate and comply with all study procedures.
  3. Stated availability for the duration of the study.
  4. Confident level of English language.

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### 8.2 Exclusion Criteria:

1. Metal or electric implant in the head, neck, or chest area.
2. No upper extremity botulinum toxin treatment in the last 6 months
3. Pregnancy or breast-feeding.
4. Prior occurrence of an unprovoked seizure.
5. Any legal reason why the candidate cannot participate.
6. No volunteers below the age of 18.

- 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.

## 9.0 Vulnerable Populations

### 9.1 Vulnerable Populations:

| Population / Group                                                                                                                                                                                                                                       | Identify whether any of the following populations will be targeted, included (not necessarily targeted) or excluded from participation in the study. |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Children                                                                                                                                                                                                                                                 | Excluded from Participation                                                                                                                          |
| Pregnant women/fetuses/neonates                                                                                                                                                                                                                          | Excluded from Participation                                                                                                                          |
| Prisoners                                                                                                                                                                                                                                                | Excluded from Participation                                                                                                                          |
| 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 from Participation                                                                                                                          |
| Non-English speakers                                                                                                                                                                                                                                     | Excluded from Participation                                                                                                                          |
| Those unable to read (illiterate)                                                                                                                                                                                                                        | Excluded from Participation                                                                                                                          |

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|                                                                                                                                                                               |                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Employees of the researcher                                                                                                                                                   | Excluded from Participation     |
| Students of the researcher                                                                                                                                                    | Excluded from Participation     |
| Undervalued or disenfranchised social group                                                                                                                                   | Included/Allowed to Participate |
| Active members of the military (service members), DoD personnel (including civilian employees)                                                                                | Included/Allowed to Participate |
| Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.                    | Excluded from Participation     |
| Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.                                            | Included/Allowed to Participate |
| Individual or group with a serious health condition for which there are no satisfactory standard treatments.                                                                  | Targeted Population             |
| Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior). | Excluded from Participation     |
| 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 from Participation     |

## 9.2 Additional Safeguards:

The present study aims to investigate motor cortex excitability in stroke volunteers in relation to phase of brain oscillations. Results will provide important insights into stroke-related motor cortex physiology. This information is needed to improve current therapeutic TMS paradigms to relieve motor deficits in stroke volunteers.

TMS is a non-invasive method, with relatively low levels of discomfort and small chance of mild adverse events. A detailed description of potential side effects is provided in section 13.1. Potential discomforts are similar to those in healthy volunteers. If volunteers report discomfort, stimulation intensity will be reduced. Furthermore, volunteers who report discomfort are allowed to withdraw from the study at any time.

## **10.0 Local Number of Participants**

*10.1* Local Number of Participants to be Consented: We estimate that a sample size of N=30 volunteers per group will allow us to reach the primary endpoints, corresponding to an medium effect size. To account for drop out due to screening failure or intolerance of TMS (approximately 15%), we recruit up to 36 stroke volunteers and 36 healthy control volunteers.

## **11.0 Local Recruitment Methods**

- 11.1* Recruitment Process: Both stroke and healthy volunteers will be recruited by open advertisement that will be placed around the Twin City Campus of the University of Minnesota. Additionally, health care professionals working with stroke volunteers at clinics and hospitals affiliated with the University of Minnesota will be asked to refer volunteers to this study, if they are interested.
- 11.2* Identification of Potential Participants: Identification of Potential Participants: The potential participant will contact the investigators in this study via the institutional e-mail in response to the poster advertisement.
- 11.3* Recruitment Materials: A printed flyer will be posted on the advertisement board. The flyer will include a brief description of the study, experimental procedures, monetary compensation, summary of inclusion and exclusion criteria, and contact email.
- 11.4* Payment: The participants will receive a monetary compensation at the end of every experimental session. The base rate of compensation is \$35 per hour. Therefore, the estimated compensation will be \$192.50 (2.5 + 3 hours), not exceeding a maximum of \$250. We will use the Greenphire ClinCard to execute and track the payment. Additionally, costs for transportation to the lab will be covered.

## **12.0 Withdrawal of Participants**

*12.1* Withdrawal Circumstances: Participants can withdraw from the study at any time. Participants will be removed from the study if any legal or medical reason indicates that they cannot continue with participation.

- 12.2* Withdrawal Procedures: Voluntary withdrawal by any participant for any reason will be honored. Participants will be asked if already collected data can be used in the data analysis. If a participant would like all data removed, then everything will be deleted. Following withdrawal, the participant will receive a payment for participant according to time spent in the study, if any (see section 11.4).
- 12.3* Termination Procedures: Following the final study procedures, the volunteer will receive payment (see point 11.4) and the data will enter the dataset for further analysis.

### **13.0 Risks to Participants**

- 13.1* Foreseeable Risks: TMS is FDA approved for the 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 the following:
- To avoid head and neck aches, measures to minimize TMS intensity to avoid sensitive areas of scalp muscles or nerves will be taken.
  - In order to prevent transient hearing threshold shifts due to TMS, subjects and investigators will be offered earplugs during TMS.
  - In order to minimize risk of inadvertent seizures, screening and enrollment procedures will exclude subjects for whom TMS is contraindicated or who are at increased risk of seizure or 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 every lab we have a plan of action in place in case of an epileptic seizure, which is based on NIH recommendations:

#### **Plan of actions due to seizure**

- 1) Roll the volunteer on his or her side to prevent choking on any fluids or vomit.
- 2) Cushion the person's head.
- 3) Loosen any tight clothing around the neck.
- 4) Do not restrict the person from moving or wandering unless he or she is in danger.

Important! Do not put anything into the person's mouth – it can cause choking or trauma.

- 5) Remove any dangerous objects the person might hit or walk into during the seizure.

6) Call 911.

7) Note how long the seizure lasts and what symptoms occurred so you can tell emergency personnel.

8) Stay with the person until the seizure ends and the emergency personnel arrive.

### **End of plan**

*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.

## **14.0 Potential Benefits to Participants**

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

## **15.0 Statistical Considerations**

*15.1* Data Analysis Plan: The primary outcome in the main TMS session is MEPs. We will collect MEPs at each of four phase angles of the ongoing motor cortical mu rhythm. In all four sessions, there will be four conditions: phase angles of 0 deg (peak), 90 deg, 180 deg (trough), and 270 deg. We will use a generalized linear mixed effect model to identify the statistical effects of stimulation conditions (factor of phase angle). Effects will be compared between affected and non-affected side (hemisphere) and between participant group (stroke and healthy). In addition, we will analyze the TMS-evoked potentials (TEPs) in EEG with respect to the phase angle of the stimulation.

*15.2* Power Analysis: We aim for a sample size of  $n = 30$  per group (stroke and healthy individuals each), which corresponds to a medium effect size (Cohen's  $d = 0.5$ ), based on previous studies (Shirinpour 2020; Zrenner et al., 2017).

*15.3* Statistical Analysis: MEPs will be analyzed using a general linear mixed effect model. The stimulation condition (phase angle) will be encoded as fixed effect factors, the subject's id will serve as random effect factor, and the outcomes of MEP will be the independent variable. Both fixed effect factors will be examined separately and in interaction with each other. The post-hoc comparisons between the groups will be done with a non-parametric bootstrap test.

For TEP analysis, we will first high-pass filter and detrend the EEG data, and then cut it into epochs around the TMS pulses. The epochs will be averaged according

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to the stimulation condition (phase angle) and compared using non-parametric cluster-based permutation test.

- 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 and MEP 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.

## 16.0 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.

Appropriate Use for Research:

- ☐ An external IRB (e.g. Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of M 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.

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- ☐ 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.

- 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.
- 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 anonymized. 3T MRI scans will be collected to obtain insight into the location of damaged tissue related to stroke. For example, subcortical and cortical damage can be distinguished, as well as the extent of a lesion. Screening questionnaires will be used during enrollment to assess eligibility of a volunteer. EEG and MEP data are collected during the main experiment 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

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☐ 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:

☐ Store      ☐ Analyze      ☐ Share

☐ Other. Describe:

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 REDCap or OnCore).

*16.9* Links to identifiable data: 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. Anonymous research data, that is MEP and EEG data will be stored on University's Box Secure Storage (box.umn.edu) and shared with relevant team members if necessary.

- 16.11* Storage and Disposal of Paper Documents: Anonymized discomfort questionnaires on will be stored electronically. Screening forms and informed consents will be stored under lock and key for 6 years in accordance with the HIPAA guidelines.

## **17.0 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 16.1), 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.

## **18.0 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 and HIPAA authorization forms, and standardized questionnaires to ensure that the all procedures are executed in 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 every 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.

## **19.0 Provisions to Protect the Privacy Interests of Participants**

- 19.1* Protecting Privacy: We will obtain personal information about the volunteer that is necessary for this study (day of enrollment, name, day of birth, biological sex,

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handedness, phone number, email, screening results regarding the study criteria) and store it in paper form and in the 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' enrolment 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 sessions by using their personal phone or email. During the study, the stroke volunteers will be asked about their physical and psychological state using the standardized questionnaires to monitor possible adverse effects of TMS. The volunteers will be informed about this and about the content of the questionnaires prior to their participation during the introductory meeting. The volunteers will also be informed prior to their participation that an application of MRI, EEG, MEP, and TMS (technologies in the study) will require an investigator to touch their head and hand in order to set-up the equipment.

- 19.2 Access to Participants: No personal health information will be collected from medical records. Stroke-related motor symptoms will be assessed during the first session, by means of a 3T MRI scan and movement performance tasks. That is, the information necessary for the study will be obtained by the investigators directly from the participants during the initial meeting and experimental sessions (see point 5.4).

### 20.0 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

### 21.0 Consent Process

- 21.1 Consent Process (when consent will be obtained): The consent process will take place at the research sites (see point 21.1) in the presence of the investigator who is involved in this study. The investigator will be responsible to ensure that the participant 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 the end of every session. At this point the volunteer will 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

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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: All research procedures will be conducted in (1) the laboratory of the Department of Biomedical Engineering at the University of Minnesota Twin Cities Campus; and/or (2) Non-invasive Neuromodulation Laboratory at the University of Minnesota Twin Cities Campus located at 717 Delaware. Only authorized personnel have access to the laboratories.

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: Motor assessment, 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. This facility is fully equipped for the TMS-EEG experiment. Co-investigators will primarily dedicate their work efforts in completing the study. Given this time dedication, as well as the broad network of stroke-related research at the UMN, recruitment of thirty stroke volunteers over 3 years is feasible. Similarly, recruitment of 30 healthy control volunteers is feasible.

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