Institutional Review Board
Office of Research and Sponsored Programs
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940-898-3378
email: IRB@twu.edu
https://www.twu.edu/institutional-review-board-irb/

DATE: January 4, 2021

TO: Dr. Hui-Ting Goh
Physical Therapy - Dallas

FROM: Institutional Review Board (IRB) - Dallas

Re: Extension for High Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) Combined with Body Weight Supported Treadmill Training (BWSTT) After Stroke: a Pilot Study (Protocol #: 19883)

The request for an extension of the IRB approval for the above referenced study has been reviewed by the TWU IRB (operating under FWA00000178). This study was originally approved on January 18, 2018 and has been renewed. Approval for this study expires on January 17, 2022.

If applicable, agency approval letters must be submitted to the IRB upon receipt prior to any data collection at that agency. If subject recruitment is on-going, a copy of the approved consent form with the IRB approval stamp is enclosed. Please use the consent form with the most recent approval date stamp when obtaining consent from your participants. A copy of the signed consent forms must be submitted with the request to close the study file at the completion of the study.

Any modifications to this study must be submitted for review to the IRB using the Modification Request Form. Additionally, the IRB must be notified immediately of any unanticipated incidents. All forms are located on the IRB website. If you have any questions, please contact the TWU IRB.

cc. Dr. Mark Weber, Physical Therapy - Dallas

Texas Woman's University Institutional Review Board

Application for Expedited and Full Review

For office use only:

Protocol #:_____

Name of Principal Investigator (PI): Hui-Ting Goh Phone: (214)6897723

Status: ☒ faculty ☐ student ☐ staff ☐ other : _____ E-mail: hgoh1@twu.edu

Department: Physical Therapy

Colleague ID# (this is the 7-digit # on your ID): 0598520

Title of Study: High frequency repetitive transcranial magnetic stimulation (rTMS) combined with body weight supported treadmill training (BWSTT) after stroke: a pilot study

If the PI is a student, provide the following information for the faculty advisor:

Name of advisor: _____ E-mail: ___

TWU Department: _____

Estimated beginning date of study: 1/1/2018 Estimated duration of study December 2020

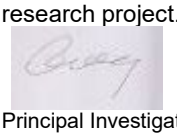
Campus (Denton, Dallas, or Houston) Dallas Level of review: ☒ expedited ☐ full

Type of Project : (check all that apply) ☐ thesis ☐ professional paper ☐ dissertation ☐ class project ☒ faculty research ☐ pilot ☐ other _____

Has project has been submitted for funding (internal or external)? ☒ yes ☐ no
If yes, funding source: American Society of NeuroRehabilitation Seed Grant

Signatures:

Principal Investigator (PI): Signature certifies that the investigator has primary responsibility for all aspects of the research project.



Principal Investigator — Date: Nov 13 2017

Faculty Research Advisor (for student research only): Signature certifies that the faculty member has read, reviewed, and approved the content of the application and is responsible for the supervision of this research study.

Faculty Research Advisor — Date

Academic Administrator: Signature certifies that the administrator has read, reviewed, and approved the content of the application.

Academic Administrator (Department Chair, Program Director, or Associate Dean) — Date: 11/15/2017

METHODOLOGY

Please refer to instructions when completing this form. The application must be typed using a font no smaller than 11-point.

1. Describe the purpose of study, including research questions and/or hypotheses.

The purpose of this pilot study is to examine the feasibility and efficacy of 5Hz repetitive transcranial magnetic stimulation (rTMS) applied to bilateral motor area as an adjuvant intervention to task-specific body weight supported treadmill training (BWSTT) in individuals with subacute stroke. The study has two specific aims:

Aim 1: To examine the feasibility and efficacy of 5Hz rTMS applied to bilateral leg motor cortices combined with BWSTT in individuals with subacute stroke

This aim will address the following two research questions:
1. Is a 5Hz rTMS protocol a feasible adjuvant intervention to BWSTT for individuals with subacute stroke?
2. Is a 5Hz rTMS protocol an effective adjuvant intervention to BWSTT for individuals with subacture stroke?

Aim 2: To examine the neurophysiological changes associated with rTMS and BWSTT in individuals with subacute stroke

This aim will address the below research question:
1. Will 24 sessions of rTMS combined with BWSTT induce neurophysiological changes in individuals with subacute stroke?

Background:

Each year, cerebral vascular accidents strike millions of Americans and leave many with long-term disabilities.[1] Recovering the ability to walk is often listed as the primary goal of rehabilitation and has substantial impact on community reintegration.[2,3] Extensive resources are directed toward gait rehabilitation and various training strategies have been proposed, including task-oriented training, robotic assisted gait training, virtual reality, and body weight supported treadmill training (BWSTT).[4-9] Among these, BWSTT has been studied extensively. A recent systematic review concluded that BWSTT improves walking speed and walking endurance.[9] Several studies have suggested that BWSTT improves gait kinematics, such as gait symmetry,[10] hip extension angle,[11] and greater muscle activation.[11] Improvement in gait kinematics suggests that cortical circuitry involvement might be an important mechanism underlying the clinical effect of BWSTT.[12]

Mechanistic investigations on the benefits of BWSTT revealed significant cortical reorganization after training.[13-15] In general, increased excitability in the ipsilesional motor cortex,[13] increased excitability in bilateral motor cortices,[14] and increased activation in bilateral sensorimotor cortices and cingulate motor areas[15] were found to be associated with gait improvement after training. Cortical reorganization, a form of neuroplasticity, occurs spontaneously after injury and can be augmented by extrinsic factors, such as behavioral intervention and brain stimulation. Combining brain stimulation, for example repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS), and motor training has been shown to promote neuroplasticity and enhance motor recovery in the

affected upper extremity.[16-18] ***However, the application of brain stimulation for the promotion of gait recovery is relatively unexplored***. [3,19,20] Unlike upper extremity motor function, gait control involves complex interaction between the two lower limbs and bilateral associated cortices.[21] Application of non-invasive brain stimulation (NIBS) for upper extremity motor recovery is based on the interhemispheric competition model. In this approach, brain stimulation is often structured with the goal to either increase the excitability of the ipsilesional hemisphere or decrease the excitability of the contralesional hemisphere. Whether the model is suitable for gait recovery remains controversial providing that bilateral control of foot movements has been demonstrated in healthy individuals.[22] Stimulation models that are optimized for the lower extremities and gait are needed.

Preliminary evidence suggests that NIBS, either rTMS or tDCS, might hold promise for post-stroke gait rehabilitation.[19,20] Most tDCS studies adopted ipsilesional facilitation protocols by applying the anode to the ipsilesional motor area with the goal to increase cortical excitability. However, the results thus far are conflicting. For example, Danzl et al. and Tahtis et al. reported that anodal tDCS applied to the ipsilesional primary motor cortex (M1) increased walking speed.[23,24] In contrast, other investigations failed to demonstrate such gain in gait outcomes.[25,26] To date, there are only 5 published studies examining efficacy of rTMS on gait recovery after stroke. [14,27-30] Wang et al. employed a 1Hz rTMS protocol to the contralesional M1 in chronic stroke (> 1 year post onset) and reported that the 1Hz rTMS combined with task-oriented training significantly improved gait symmetry, walking speed, and motor function compared with sham stimulation. Similarly, Lin et al. applied 1Hz rTMS to contralesional M1 in 31 patients with subacute stroke for 15 sessions. They reported a positive effect on balance and activities of dail y life (ADL) independence. Other rTMS investigations utilized high frequency rTMS applied to bilateral motor cortices in individuals with chronic stroke; all showed a significant improvement in walking speed and motor function.[27,28,30] The somatotopical location of the legs is adjacent to midline and deep in the cerebral sulcus. Application of rTMS to either hemispheric leg area is very likely to spread over to the contralateral leg area. In an ongoing project using a figure-of-8 coil to deliver 5Hz rTMS to ipsilesional M1 over tibialis anterior hot-spot, we observed that this method of application increased motor evoked potential (MEP) amplitudes bilaterally. Taken together, bilateral stimulation (at vertex) with a facilitatory effect seems to be a more reasonable approach given the anatomical location of the leg representation in motor cortex and bilateral involvement of motor areas in lower limb control and gait recovery.[15,21] Previous bilateral high frequency rTMS studies were conducted in individuals with chronic stroke. ***It is unclear whether such benefits would be observed in patients in the acute or subacute phase in which neuroplasticity is believed to be more viable compared to the chronic phase.***

The **primary objective** of the proposed study is to examine the feasibility and clinical efficacy of using high frequency rTMS applied to bilateral motor area as an adjuvant intervention to task-specific BWSTT in a group of patients with subacute stroke. We have previously demonstrated the feasibility and efficacy of a gait training protocol incorporated BWSTT in individuals with acute stroke (< 6 weeks post-stroke) in an inpatient rehabilitation setting.[31] However, there is a growing trend towards reduced lengths of stay (LOS) in rehabilitation for persons with stroke.[32,33] For example, from 2000 to 2007 the LOS decreased from a mean of 19.6 days to 16.5 days.[32] The trend towards shorter LOS is particularly concerning given the well-established fact the most functional motor recovery happens early after stroke.[34,35] There is evidence to suggest the period immediately following the stroke up to about 2 months post is critical for gait recovery.[34,36,37] Baer and Smith, for example, found in a heterogeneous population of persons with stroke that 75% of the cohort regained gait function within 25 days of stroke onset.[36] These studies highlight the reality that walking recovery happens early after stroke. Therefore, gait recovery efforts must be focused on this critical period. Given the trend

towards shorter LOS in the inpatient rehab setting and less available time to focus on the important task of gait recovery, gait training during this critical period will likely occur in the outpatient rehabilitation setting.

BWSTT is beneficial in the way that it allows for maximum stepping repetitions and focuses on optimum gait kinematics. BWSTT delivered during early recovery period (subacute) provides opportunity to promote an optimal gait pattern or to limit abnormal gait patterns developed right after stroke. Abnormal compensatory movement patterns are associated with maladaptive neuroplasticity that further interfere with recovery.[38] Our previous work has shown that a BWSTT protocol can be easily implemented in a clinical setting and resulted in favorable outcomes.[31] Our studies found that persons trained with this approach utilized fewer assistive devices, experienced fewer falls, walked faster and further with improved temporal and spatial symmetry and experienced less fatigue when compared to published data of patients that received traditional rehabilitation.[10,31,39-42]***However, it is unknown whether this body weight supported gait training protocol could be augmented with non-invasive brain stimulation.*** Further, our previous investigations did not include neurophysiological measures to demonstrate a training-induced neuroplasticity. Thus, the **secondary objective** of the proposed study is to determine the extent to which neuroplasticity could be induced by non-invasive brain stimulation and BWSTT.

This pilot study has been awarded by the American Society of NeuroRehabilitation with a seed grant of $4,900. The deposit of the fund is pending upon the IRB approval. The fund is provided to collect preliminary data for preparation for extramural fund applications. A larger scale randomized controlled trial will be conducted upon securing funding.

2. Participant Information:

a. Description of participants in study:

2. 5 individuals (men or women) with a diagnosis of subacute stroke will be recruited.

b. Approximate number of participants: 5

c. Vulnerable populations as participants (check all that apply):

Prisoners .....☐
Pregnant women .....☐
Fetuses / neonates .....☐
Minors..... ☐

NOTE: Researchers must comply with the federal mandate to report child abuse. See instructions for details.

d. Age (or age range) of participants: 18 to 80 years

Provide the rationale for inclusion/exclusion on the basis of age:

Stroke is relatively uncommon in persons younger than 18 years. Further, TMS safety data in children and adolescents are less well-established. We exclude individuals younger than 18 years for both scientific merit and safety concern. Individuals older than 80 years often have multiple comorbidities (e.g. cardiac problem, joint pathology) that will interfere with their ability to participate in physical exercise.

e. Sex of participants ..... ☐ Male ☐ Female ☒ Both

Provide the rationale for inclusion/exclusion on the basis of sex:

f. Participants will be excluded based on ethnicity: ..... ☐ Yes ☒ No

If yes, provide a description of the exclusion criteria and the rationale for using these criteria:

g. List and provide rationale for any other inclusion/exclusion criteria:

The inclusion criteria are:
1) 18-80 years old: This study will not include individuals age below 18 years for a few reasons. Stroke is relatively uncommon in persons younger than 18 years. Further, TMS safety data in children and adolescents are less well-established. We exclude individuals younger than 18 years for both scientific merit and safety concern. Individuals older than 80 years often have multiple comorbidities (e.g. cardiac problem, joint pathology) that will interfere with their ability to participate in physical exercise.

2) < 2 months post stroke at the time of enrollment: the purpose of this study is to determine the feasibility and efficacy of high frequency rTMS in gait recovery among individuals with subacute stroke. Our rationale to recruit individuals with a recent stroke is that neuroplasticity is most evident during early phase of recovery.

3) first time stroke: individuals with a previous history of stroke leaving them with significant gait dysfunction are anticipated to respond differently to the training. In order to ensure we have a homogenous sample in this pilot study, we will only recruit those with a first time stroke.

4) able to walk > 25 feet with or without assistive device and with no more than moderate assistance: The training is structured for 2-3 times per week for sessions of 45 minutes in duration. To ensure that the participants will be able to tolerate the training in a safe manner, we will recruit individuals with the ability to walk at least 25 feet.

5) able to follow 1-step commands: Stroke can lead to significant cognitive impairment interfering with training and testing. To ensure participant's safety and compliance, we will only recruit individuals with the ability to follow at least one-step commands.

3. 6) able to communicate verbally

The exclusion criteria are:
1) severe medical problems (e.g. recent cardiac infarct, heart failure, cancer): Severe cardiac problems will forbid participants from any physical exercises.

2) presence of conditions that could affect gait training (e.g. amputation, severe arthritis): Individuals with gait dysfunction resulted from other diagnoses will be excluded as they will not represent a typical individual post stroke.

3) bilateral stroke: Individuals with bilateral stroke often exhibit different clinical presentations and recovery pathways than unilateral stroke. Excluding persons with bilateral stroke is to make sure that we will have a homogenous sample.

4) non-ambulatory prior to stroke: Individuals who are non-ambulatory before stroke are unlikely to become ambulatory and they will not be able to participate in the training

5) BMI > 40: The standardized gait training includes using a harness system to support body weight. There is a safety concern of using the harness system in overweight persons.

6) any contraindications to TMS (e.g. history of seizure, cardiac pacemaker, metal or magnetic implants): The study involves using TMS to facilitate cortical excitability. Individuals with contraindications to TMS will not be included.

7) pregnant or potentially to be pregnant: pregnancy is a contraindication to TMS.

3. Describe the participant recruitment process in detail. Make sure that you attach any recruitment materials or scripts in the attachment section.

The team will recruit potential participants from hospitals in the community. Facilities will be provided with information regarding the study by members of the team at the facilities. The information will direct participants and/or caregivers to contact the PI or co-I for telephone screening before scheduling for consent and testing. Those who are deemed to meet the inclusion and exclusion criteria may be scheduled for initial testing.

4. Research Procedures:

a. In the space below, describe in detail the research procedures (do not use an attachment):

Assessment procedure: Once study eligibility is confirmed, participants will be scheduled for two pre-training assessments. The first assessment session will consist of several clinical and behavioral outcomes, including the Functional Independent Measure (FIM) locomotion subscale, temporal-spatial gait analysis using a GaitRite system, 6 Minute Walk Test, Stroke Rehabilitation Assessment of Movement (STREAM), modified Ashworth scale, Stroke Impact Scale and Fatigue Severity Scale. The second assessment session will include measures of cortical excitability using single pulse MagstimTMS stimulator. Motor threshold (MT) and motor evoked potential (MEP) amplitudes will be acquired from bilateral M1 corresponding to the respective Tibialis Anterior (TA) muscle. All assessments will take place at The Stroke Center-Dallas, Texas Woman's University. A blinded tester will administer all assessments and will not be involved in the rTMS or gait training sessions.

rTMS procedure: After the pre-training assessments, participants will be assigned to either the real-rTMS or sham-rTMS group. The real-rTMS group will receive a 5Hz rTMS protocol applied to the vertex via a figure-of-8 air-filmed coil that is coupled with a Magstim Rapid^2 stimulator. Stimulation will be delivered at the intensity of 90% of resting MT of the lesion M1. We have previously shown that this stimulation protocol effectively increased cortical excitability in persons with stroke.[43] For the sham-rTMS group, a figure-of-8 sham coil will be placed at the same location on the scalp. The sham stimulation will induce a similar acoustic artifact and

some scalp sensation without an effective electrical field. Each rTMS session will last about 30 minutes. During stimulation, participants will sit in a reclining chair with their arms and legs supported. Vital signs (heart rate and blood pressure) will be measured before and after each rTMS session. Participants will be asked to report any adverse effects, such as headaches or dizziness. All reported adverse effects or measured abnormal responses will be documented. The rTMS sessions will be delivered at The Stroke Center-Dallas. The persons administering the rTMS sessions will not participate in any other assessment or gait training sessions.

Gait training procedure: After the rTMS session, participants will go to the Gait Disorders Clinic at UT Southwestern Medical Center to receive a 45-minute gait training session. The Gait Disorders Clinic is approximately 10 minutes (0.5 mile) away from The Stroke Center-Dallas. Our previous investigation showed that the effect of the rTMS lasted up to 90 minutes post-stimulation.[43] We are confident that the distance between the two study sites will not present a problem. Gait training will start on a treadmill equipped with an unweighting mechanism. Initially, the body weight support will be set between 30-50% of body weight and the starting velocity set at 0.7 mph or 1.5 times the velocity of the initial walking speed (whichever is greater). A trained therapist will assist participants with weight shift and hemiparetic limb advancement with the goal to duplicate typical gait mechanics and optimum kinematics. Upper extremity support will not be allowed throughout the training. Participants will walk on the treadmill for 30 minutes with a goal of 3-minute minimum bouts. Body weight support will be progressively reduced as treadmill speed is increased until participants are able to walk at a speed of 1.8 mph with no body weight support, good kinematics and no assistance from the therapist. The remaining 15 minutes of each session will be spent on over ground walking and/or standing activities. Each participant will engage in a home exercise program comprised of home walking and standardized exercise. Participants will be prescribed an appropriate walking orthosis or aid when the therapist deems it is necessary. The therapist involved in gait training will have no knowledge of group assignment or the assessment results with the exception of participant's initial walking speed.

After participants finish the 24 sessions of training, both assessment sessions (clinical/behavioral and neurophysiological) will be repeated. These sessions will be completed by the same tester as before training.

The table below presents the timeline of the study procedure.

Week 1	Visit 1: obtain consent, clinical and behavioral outcomes Visit 2: TMS assessment
Week 2 to Week 11	Treatment session 1 to 24 will be scheduled over a 10-week period (2-3 sessions per week) Each session starts at TWU-Dallas campus with a 30 minute brain stimulation followed by a 45 minute gait training at the UTSW -Gait Disorder Clinic.
Week 12	Visit 1: obtain consent, clinical and behavioral outcomes Visit 2: TMS assessment

Data analysis:

Outcomes used to examine the feasibility include recruitment rate, reasons for declining participation, retention rate, compliance to study protocol, time required to conduct the intervention (visit duration and actual treatment duration), and number of adverse events. This pilot study is a collaboration between two institutes and the participants will travel between the two sites to receive the treatments in a timely manner. It is critical for the research team to establish the feasibility and a logistic plan before planning for a bigger trial.

Outcomes used to determine clinical efficacy include walking speed, FIM locomotion score, 6 Minute Walk Test score, STREAM, modified Ashworth scale, Stroke Impact Scale and Fatigue

Severity Scale. The walking speed (in m/s) will be the primary outcome to examine efficacy and walking speed will be used to calculate effect size for sample size estimation in grant preparation.

Outcomes used to examine the effect on cortical excitability (Aim 2) include resting motor threshold, motor evoked potential amplitudes, intracortical facilitation and intracortical inhibition. Given the small sample, these outcome will be analyzed descriptively and be used to demonstrate technical feasibility for future grant submission.

b. Is video recording a part of the study? ☐Yes ☒ No

With sound ☐ Without sound ☐

c. Is audio recording a part of the study?..... ..... ☐Yes ☒ No

If you answered "yes" to question #4b or 4c, describe the purpose of the recording and who will have access to these recordings.

d. Is internet / email a part of the study? .... ☐Yes ☒ No

If you answered "yes" to question #4d, describe how the internet and/or email will be used.

5. What is the time commitment for the participants? Include the number of sessions, maximum time commitment per session, and the maximum cumulative time commitment.

The study involves 2 assessment sessions (pre- and post-training) and each session is estimated to be completed within 3 hours.

The training involves 24 sessions and each session is estimated to take 2 hours including the transportation time between two sites and waiting time.

The total time commitment for the participants is 54 hours (2 x 3 hours + 24 x 2 hours).

6. Site / location of the study.

a. Will participants be affiliated with a specific non-TWU agency, institution, or organization?..... ☐ **Yes** ☒ **No**

If yes:

Name of the site(s)?

*Affiliation of the **principal investigator** to this site(s)?*

*Affiliation of the **participants** to this site(s)?*

Agency approval letters are required by the IRB before data can be collected at a site. If you answered "yes" to 6a, attach the signed agency approval letter on letterhead from each agency. If agency approval cannot be obtained prior to submitting the IRB application, explain here.

b. Describe the setting of the study (i.e. physical location, surroundings, privacy aspects, etc.)

The study will take place at the TWU – Dallas Campus Neurophysiology Lab and the UTSW-Gait Disorder Clinic. The Neurophysiology lab is located on the first floor of the Stroke Center-Dallas. The center has an attached parking garage with easy access to the lab. The lab is in an independent suite with limited access. Participant interview and data collection will be conducted in private. The lab is equipped with all necessary equipment to carry out the study.

The gait training will take place at the UTSW-Gait Disorder Clinic. The gait clinic is located on the first floor of the School of Health Professions on the campus of the University of Texas Southwestern Medical Center campus. The clinic has an attached parking garage and easy access to the clinic. The clinic has all the equipment necessary to conduct the study including treadmill equipped with a body weigh support unit.

POTENTIAL RISKS AND PROTECTION OF PARTICIPANTS

7. Explain the potential risks to the human participants involved in this research. All risks must be identified and listed on the consent form (if applicable).

RISK	STEPS TO MINIMIZE RISK
Loss of confidentiality	The investigators will attempt to maintain confidentiality to the extent that is allowed by law. The study will take place at Texas Woman's University, School of Physical Therapy – Dallas Campus and the University of Southwestern Medical Center. Codes, rather than names, will be used in the data analysis and in the final report. The data will be stored in a locked file cabinet. The data recorded on papers will be stored for approximately 5 years and then will be shredded. The data recorded on disks will be stored for 5 years and then will be deleted. It is anticipated that data will be published in books and/or journals. However, names or other identifying information will not be included in any publication.
RISK	STEPS TO MINIMIZE RISK
Loss of balance /fall There is a minimal risk of falling while walking after stroke but this risk is small	Participants will always be closely guarded during any gait training and assessment. All members of the research team are professionally trained to manage individuals with balance deficits.
RISK	STEPS TO MINIMIZE RISK
Fatigue The participants may experience fatigue during the assessment or training sessions.	The estimated duration of each session includes scheduled breaks. Participants will be reminded to request breaks whenever they feel tired. The therapists and testers will also pause or stop the procedure when they deem necessary.
RISK	STEPS TO MINIMIZE RISK

Skin irritation or shortness of breath There is also a very minimal risk of injury with the vest that is worn during the treadmill training (such as irritation from the straps that secure the harness, shortness of breath if the vest is secured too tightly, irritation to sensitive skin or tubes such as a feeding tube in the stomach.	Therapists involved in the training will be trained to put on the vest and harness properly. Participants will be instructed to report immediately to the therapist if they feel that the harness/vest is too tight. Therapists will also perform skin check after the gait training sessions to detect any skin irritations.
RISK	STEPS TO MINIMIZE RISK
Changes in auditory threshold There is a minimal risk of alteration in auditory threshold after TMS protocols as TMS produces loud click when it is charged. The changes in auditory threshold are transient (lasts about 1 day) and not different from going to a music concert.	To minimize the risk, we will provide earplugs during TMS testing.
RISK	STEPS TO MINIMIZE RISK
Headaches There is a minimal risk of developing headaches during or after rTMS procedure. The effect is transient and can be resolved with over-the-counter medications.	The intensity of the procedure is relatively low and should reduce the likelihood of developing headaches. If participants develop a severe headache during the testing, we will stop the testing and withdraw them from the study.
RISK	STEPS TO MINIMIZE RISK
Seizure There is an increased risk of triggering a seizure in persons with a history of seizures or in persons taking medications that are known to reduce seizure threshold while receiving TMS.	In the case of the low frequency and low intensity stimulation (as in this study), the risk of triggering a seizure is very small. All known cases of TMS-induced seizures in neurologically normally persons have happened at frequencies and intensities greater than what will be used in this study. The TMS frequencies and intensities will be kept within extremely safe limits. Since there are no known reports of seizures in individuals undergoing TMS without a history of seizures, the probability of a TMS-induced seizure is extremely rare.

(Use continuation pages if necessary)

8. Will participants be told about the intent of the study prior to participating? ..☒ Yes ☐ No

If "no," provide an explanation of why deception is necessary and the debriefing method to be used to fully inform the participants of the study's intent.

9. Explain when and how the participants will be given the opportunity to ask questions.

Participants will have the opportunity to ask questions anytime during the initial meeting with researchers or throughout the duration of the study.

10. Identifiable Data

Outline the steps to ensure the confidentiality of identifiable data. Identifiable data includes documents, audio and video recordings, electronic data, and blood or other human specimens.

a. Explain what identifiable data, if any, will be collected.

Name, date of birth, gender, self and family medical history

b. Where will identifiable data be stored? (Specify precise location, preferably in a locked file cabinet with limited access.)

Identifiable data will be stored in a locked file cabinet in the School of Physical Therapy, Dallas Campus research lab room 8811. Access will be limited to the researchers.

c. Give the date that identifiable data will be destroyed (mm/dd/yy). If identifiable data will be stored for an indefinite period of time, please explain.

The identifiable data will be destroyed by 12/31/2024 by shredding all paper documents. Electronic data will be destroyed by 12/31/2024 by deleting all files containing identifiable data from any and all electronic devices including computers and portable storage devices.

d. Identify specific ways that identifiable data will be destroyed at the end of this period of time.

The identifiable data will be destroyed by 12/31/2024 by shredding all paper documents. Electronic data will be destroyed by 12/31/2024 by deleting all files containing identifiable data from any and all electronic devices including computers and portable storage devices.

e. Because the academic component of TWU is classified as a non-covered HIPAA entity, identifiable health or health-related data cannot be transmitted electronically. You must be able to answer "no" to at least one of the following questions in order for your study to be approved.

Does this research involve health or health-related data? ..... ☒ Yes ☐ No
If yes, are the data identifiable? ..... ☒ Yes ☐ No
If yes, will data be transmitted electronically? ..... ☐ Yes ☒ No

BENEFITS/REMUNERATION

11. **What will the participant receive for taking part in the study (***i.e., financial remuneration, free services, access to information, and access to an intervention)***? I***f there are none, state below that there are no direct benefits to the participant.*

Each participant will receive $200 in cash upon completion of the last assessment session. Participants will receive standarized gait intervention at no cost. Participants will have access to their own data upon request.

12. What are the generalizable benefits of this study? *(e.g., contribution to knowledge in field).*

There is limited research investigating the effects of non-invasive brain stimulation in gait recovery. The findings of this pilot study will allow the research team to develop a larger trial to systematcially examine the effects.

13. Explain when and how the participants will be provided with the results of the study.

Participants will be provided with the results of the study if they choose to receive one. A copy of result summary 3. with aggregate results of all participants will be mailed or e-mailed to them when the study is completed.

INFORMED CONSENT PROCEDURES

14. Written Informed Consent

a. Explain the PROCESS you will use to obtain informed consent.

Prospective participants will have the opportunity to read a written informed consent form describing this study and ask questions regarding this study with research study personnel. Each participant will sign the informed consent form in order to participate in this study after Institutional Review Board approval.

b. Unless there are unusual circumstances, investigators are required to document informed consent by obtaining the participant's signature (or the signature of their parent or guardian) on a written consent form. Explain when and how that signature will be obtained. Explain where the signed consent forms will be stored (specify precise location, preferably in a locked file cabinet with limited access), how long the signed consent forms will be kept, and identify specific ways that the signed consent forms will be destroyed at the end of this period of time. Note that a copy of the signed consent forms will need to be placed on file with the IRB when the study file is closed.

The signature will be obtained after the prospective participant has read the written informed consent and agreed to participate. The signed consent forms will be stored in a locked file cabinet in the School of Physical Therapy, Dallas Campus research lab room 8811 where only the researchers have access to it. The signed consent forms will be kept until 12/31/2024 and then be destroyed using a paper shredder. A copy of the signed consent form will be placed on file with the IRB when the study file is closed (estimated closing date December 2020)

c. If you will not use a written consent form, provide a detailed rationale and explain how informed consent will be obtained

N/A

RESEARCH TEAM MEMBERS

15. Provide a list of all research team members other than the investigator and faculty advisor.

A current **human subjects** training certificate (less than 3 years old) must be on file for the investigator, advisor, and all research team members before an approval letter will be sent. These training certificates may be sent directly to the IRB separately or attached to this application in the attachment section. If a current training certificate is already on file with the IRB, there is no need to attach another copy.

Name	Karen McCain
TWU 7-digit Colleague ID # (if applicable)	N/A
Email Address:	karen.mccain@utsouthwestern.edu
TWU Department or Name of Other Institution	The University of Southwestern Medical Center
Role on Project	co-Investigator

Name	Vyoma Parikh
TWU 7-digit Colleague ID # (if applicable)	0927661
Email Address:	vparikh@twu.edu
TWU Department or Name of Other Institution	School of Physical Therapy
Role on Project	Research Assistant

(Attach additional sheets if necessary)

ATTACHMENTS

16. **List and describe all attachments** (Include forms, scripts, flyers, consent forms, agency approval letters, human subjects training certificates, signed confidentiality agreement forms, referral lists, surveys, questionnaires, or any other instrument used in the study.) Attachments should be listed below in the same order in which they are attached.

1. Human subjects training certificates
2. Consent forms

SUBMISSION INSTRUCTIONS

The application should be submitted to the appropriate campus IRB.

Denton and Dallas

Mail the signed original to the address below. If electronic submission is preferred, combine all parts of application into single .pdf document and email to irb@twu.edu. If the application is submitted electronically as a fully signed .pdf, the original copy is not required.

TWU's Office of Research & Sponsored Programs
Institutional Review Board
PO Box 425619
Denton, TX 76204-5619

Applications may also be hand delivered to the Denton campus ACT 7th floor or the Dallas campus Office of Research IHSD 8th floor.

Houston

All parts of the application (including the signed cover page and appendices in order) should be combined into one single .pdf or Word document and emailed to irb-houston@twu.edu. The original copy is not required. If you have any difficulty with preparing a .pdf file, please contact the Houston Office of Research via email for assistance.

RESPONSE TIMES

Upon receipt of the application, the investigator will receive an email notifying them that the application has been received, the level of review that the application has been assigned, and the protocol number that has been assigned. Applicants can expect to receive a response from the IRB regarding the review within three weeks for an expedited application and within two weeks from the date of the meeting for a full review application. Note that these times are estimates and additional time may be required during certain times of the academic calendar such as summer, semester breaks, and Holidays.

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