Feasibility of Combination Exercise and Neuromodulation Rehabilitation to Improve Post-stroke Chronic Pain

NCT04672044

March 13, 2024

Participant Name: _____ Date:_____

Title of Study: **Feasibility of combination exercise and neuromodulation rehabilitation to improve post-stroke chronic pain**

Principal Investigator: __Chen Lin_____ VA Facility: __Birmingham (521)_

KEY SUMMARY INFORMATION ABOUT THIS STUDY

This research is being sponsored by the VA Office of Rehabilitation Research and Development. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive. Taking part in this study is completely voluntary.

WHAT IS THE STUDY ABOUT AND WHY ARE WE DOING IT?

This study is about treating post-stroke pain. It is being funded by the Department of Veterans Affairs. Chronic pain after stroke can occur between 10-50% of stroke survivors. Post-stroke pain (PSP) can lead to further complications in a stroke survivor's recovery. Exercise has improved PSP. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive technique using electromagnetic induction for brain stimulation. The use of rTMS has been shown to be effective in treating chronic PSP but is limited in duration. The purpose of this research is to gather information on the safety and effectiveness of rTMS, an FDA-approved device, in combination with exercise as a treatment for chronic PSP. By doing this study, we hope to learn if rTMS is feasible and safe to be paired with exercise. Additionally, we believe a complementary effect can develop to enhance the treatment duration of rTMS.

WHAT DOES THE STUDY INVOLVE AND HOW LONG WILL IT LAST?

Your participation in this research will last about 3 months. The purpose of this research is to gather information on the safety and effectiveness of rTMS, an FDA-approved device, as a treatment for chronic post-stroke pain. You will receive either active or sham rTMS for 10 sessions. All participants will have monitored exercise sessions after their rTMS session.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

If you agree to take part in this research study, there may not be a direct benefit to you. Potential benefits to you may include a reduction in post-stroke pain symptoms. The investigators hope the information learned from this research study will benefit other patients with post-stroke pain in the future. All participants will receive exercise, so you have the potential to be more fit.

For a complete description of benefits, refer to the Detailed Consent.

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WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

Each of the interventions (rTMS and exercise) independently have been studied and used to help treat pain symptoms and psychiatric issues. However, the combination of the two interventions have not been studied specifically for post-stroke pain. All interventions have risks.

rTMS: Although extremely rare, seizures have been described with rTMS, mainly in patients who have a history of seizure. In some case reports, it was difficult to differentiate seizures from fainting or passing out. The TMS coil makes noise, much like a loud pop when it produces its magnetic energy. You may or may not feel thumb twitch depending on the strength of the TMS pulse, but you might also feel your facial muscles twitch slightly just around the eye. It is not painful. TMS can cause heating or movement of metallic objects in or near the head. In addition, the inactivation of pacemakers, medication pumps, cochlear prostheses and other implantable hardware may occur.

Exercise Training: There are no significant risks to you in the proposed exercise methods. The risks to participating in this portion of the study are no greater than the risks when providing conventional physical therapy services to you after stroke. The exercise program and the clinical testing should not present a risk for you but could result in muscle soreness and/or joint stiffness. These symptoms should not persist more than a few days. There is a minimal risk for muscle strains during the testing and training.

For a complete description of risks, refer to the Detailed Consent.

WHAT IS THE PURPOSE OF THIS STUDY?

There are over 7 million stroke survivors in the United States. In the Veteran population, stroke is the leading cause of neurological disability, and one of leading causes of hospitalization. Chronic pain after stroke can occur between 10-50% of stroke survivors. Post-stroke pain (PSP) can lead to further complications in a stroke survivor's recovery. Exercise has been shown to improve pain symptoms of patients with PSP. the American Heart/Stroke Association recommended that exercise should be incorporated into the management of stroke survivors. Repetitive transcranial magnetic stimulation (rTMS) uses noninvasive brain stimulation to improve neuropathic pain. A European commission to establish guidelines on therapeutic use

of rTMS stated the evidence of rTMS on the motor area of the brain as definite analgesic effect with few safety issues (Level A recommendation). However, the effects of the treatment are transient, usually lasting a few hours to days. While non-invasive, as a practical therapy for chronic PSP, more sustained efficacy of rTMS would be needed to be demonstrated. We hypothesize that pairing rTMS with exercise may develop a complementary effect to enhance the duration of symptomatic relief.

This proposal is a single-site, randomized sham-controlled trial of rTMS and exercise in the treatment of Veterans with a diagnosis of chronic PSP who are at least 3-months from their cerebral stroke. The purpose of the pilot study is to evaluate the feasibility and safety of rTMS+exercise in Veterans diagnosed with chronic PSP. We will gather data to plan for a larger efficacy trial to assess sustained rTMS effects with exercise on pain outcomes. The long-term goal of the proposed work is to develop a non-pharmacologic intervention that also increases physical activity for patients suffering from chronic PSP.

HOW LONG WILL I BE IN THE STUDY?

This research study is expected to take approximately 2 years. Your individual participation in the project will take approximately 3 months.

WHAT WILL HAPPEN AND WHAT CAN I EXPECT IF I TAKE PART IN THIS STUDY?

Following screening, a cardiologist will review your records including 12-lead ECG to confirm your cardiac ability to tolerate exercise before randomization. After completing the eligibility screening, you will be randomized to either active rTMS or sham rTMS. You will receive the assigned rTMS arm followed by supervised exercise for 10 sessions, each session up to 72 hours apart, with outcomes assessed at the end of each week and at final assessment and at 1-month post-intervention (Table 1).

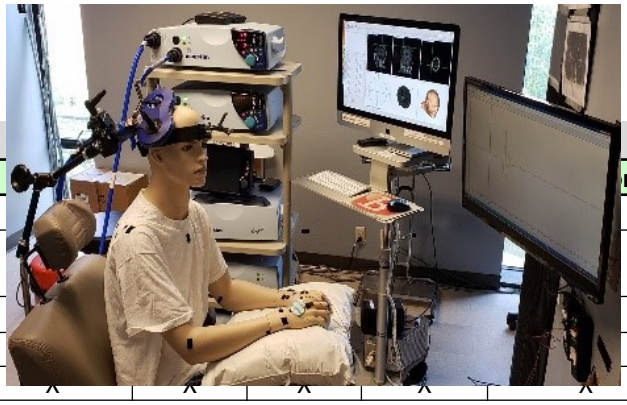

Table 1: Schedule of Events

Assessments	Screen						nth
Informed Consent and HIPAA	X						
Demographics, Medical History, Physical, Height, ECG, Exercise Tolerance Test	X						
Vital Signs and Weight	X						
Visual Analogue Scale (VAS) for Pain							
Brief Pain Inventory (BPI), Migraine Disability		X	X	X	X	X	

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Assessment (MIDAS), Pain, Journal, and Borg Rating of perceived exertion						
PTSD Checklist for DSM-5		X				X
Columbia-Suicide Severity/PHQ-9	X	X				X
modified Rankin Score and Stroke Scale		X				X
Montreal Cognitive Assessment		X				X
Stroke Impact Scale		X				X
Adverse Events and medications			X	X	X	X
Neuroimaging		X				x

rTMS protocol: Both rTMS groups, active and sham, will be conducted identically. Sham rTMS involves using an inactive rTMS machine coil that makes identical noises as the active rTMS machine coil but does not induce any brain stimulation. During the 10 intervention sessions of rTMS+ exercise protocol, you will receive assigned rTMS treatment (rTMS vs sham rTMS) on the same day prior to each session of exercise. Each intervention session of both rTMS+exercise will occur around 72 hours apart. Stimulation will be delivered using the Magstim magnetic stimulator (The Magstim Co., Whitland, UK) with a figure-of-eight shaped coil (70-mm Double Coil, #9925-00, Magstim). rTMS will be performed using the Super-Rapid Magstim magnetic stimulator with a figure-of-eight shaped coil centered over the RMT target. Each rTMS session will likely take 30-60 minutes.

Exercise Protocol: You will participate in the exercise protocol for 10 sessions. The 10 sessions of exercise training will take about 45-minutes of in-person exercise (10 total sessions). You will receive rTMS prior to each exercise session on the same day. Exercise sessions: Each session begins with a 10-minute warm-up at 30% exercise target, followed by the 25-minute or moderate intensity and ends with a 10-minute cool-down at 30% exercise target. The exercise prescription will use a percentage of the exercise target during the exercise test and ensure appropriate heart rate zones.

Moderate Intensity Interval Training (MIIT) exercise: After the 10-minute warm-up, MIIT will consist of repeated 1-minute moderate intensity bursts (“on” interval) alternated with 1-minute interval recovery (“off” interval) for 25 minutes. The “on” interval will begin at 60% of peak watts (range: 55%-65%) followed by the “off” interval at 45% of peak watts (range: 40-50%). The average HR for the “on” intervals should not exceed 60% HR reserve. There will be 13 minutes of “on” and 12 minutes of “off” interval exercise. Cool-down will commence after the last interval. **Stopping rules:** Exercise will be stopped due to inappropriate HR or BP responses, or at your discretion. In cases where you report intolerance or undue fatigue,

workload adjustments (e.g., 10% reduction) may be made (and recorded) to encourage completion of the exercise session.

Neuroimaging: Before and after intervention, you will return for an MRI scanning session and a repeat of the questionnaires that were done at your first visit. This visit should take approximately 1-hour for MRI scanning. MRI takes advantage of the magnetic properties of water in your body to take pictures. The MRI machine consists of a very strong (3.0 Tesla) magnet. The MRI scanner is commonly used in clinical care and is not investigational. You will be asked to lie on a long narrow padded table for approximately 60 minutes while the MRI scanner gathers information. The space within the magnet that you lie in is somewhat confined. If you feel claustrophobic (an unpleasant feeling of being closed in) you can discontinue the scan at any time. During the scan, you will be exposed to a magnetic field and radiofrequency magnetic fields, but you will not feel either. You will hear repetitive noises; however, you will wear earplugs or headphones to reduce the noise. You will be given a squeeze ball that activates an alarm if you need to stop the scan at any time.

WHAT POSSIBLE RISKS OR DISCOMFORTS MIGHT I HAVE IF I TAKE PART IN THIS STUDY?

Any procedure has possible risks and discomforts. The procedures in this study may cause all, some, or none of the risks or side effects listed. Rare, unknown, or unexpected risks also may occur.

Physical Risks

rTMS: Although extremely rare, seizures have been described with rTMS, mainly in subjects who have a history of seizure. In some case reports, it was difficult to differentiate seizures from fainting or passing out. The TMS coil makes noise, much like a loud pop when it produces its magnetic energy. You may or may not feel thumb twitch depending on the strength of the TMS pulse, but you might also feel your facial muscles twitch slightly just around the eye. It is not painful. TMS can cause heating or movement of metallic objects in or near the head. In addition, the inactivation of pacemakers, medication pumps, cochlear prostheses and other implantable hardware may occur, but you would be excluded from the study with these metal implants.

Exercise

Aerobic Exercise Training (AET): There are no significant risks to the subjects in the proposed AET methods. The risks for participating in this portion of the study are no greater than the risks when providing conventional physical therapy services after stroke. The AET program and the clinical testing should not present a risk for the patient but could result in muscle soreness and/or joint stiffness, but these symptoms should not persist more than a few days. There is a minimal risk for muscle strains during the testing and training.

Clinical Testing: The functional assessments used in the proposed study are routine, clinical assessments of gait and stroke impairments used in stroke outpatient and therapy clinics. The experimental protocol to be used in this portion of the proposal involves minimal risk and is considered standard clinical practice.

MRI Neuroimaging: The MRI scanner contains a very strong magnet. Therefore, you will be excluded from the study if you have certain types of metal implanted in your body, for example, any pacing device (such as a heart pacer), any metal in their eyes, or certain types of heart valves or brain aneurysm clips. Although there is no indication that MRI is unsafe during pregnancy, if you are female, you will be asked to take a urine pregnancy test to verify that you are not pregnant. There is not much room inside the MRI scanner. You may be uncomfortable if you do not like to be in close spaces ("claustrophobia"). If you become uncomfortable at any time, you can request that the scan be stopped. All participants will pass an MRI screen to decrease risk of adverse events.

Psychological Risks

Those with chronic pain syndromes are at risk for also having comorbid psychological conditions such as PTSD and are also at risks of having suicidal thoughts or behaviors. You may experience prolongation or worsening of pain because of ineffectiveness of rTMS and/or exercise which could link to worsened psychological symptoms. You will continue to have access to your regular pain medications. Study staff will assess suicidality and adhere to the suicide prevention plan (see Suicide Prevention Plan described below). These are research risks but may also be partly attributed to the course of illness.

Economic, Legal, and Social Risks

You may have to miss work and lose income or spend money on transportation or childcare to attend the assessment visits. These are research risks, not therapeutic risks. An unlikely legal or social risk associated with participating with this study may be invasion of privacy or breach of confidentiality in the remote chance that there is a loss of data containing PHI or PII. These are research risks, not therapeutic risks.

There is always a chance that any procedure can harm you. The procedures in this study are no different. In addition to the risks described above, you may experience a previously unknown risk or side effect.

Risks of the usual care you receive are not risks of the research. Those risks are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

If you agree to take part in this research study, there may not be a direct benefit to you. Potential benefits to you may include a reduction in your symptoms. However, your post-stroke pain symptoms may get better, get worse, or may not change. Since you will receive exercise as part of the study, you have the potential to be more fit. The investigators hope the information learned from this research study will benefit other patients with chronic post-stroke pain in the future. The knowledge gained from this study will serve to inform future research and clinical care for veterans.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO JOIN THIS STUDY?

You may choose not to participate in this study. Instead of being in this research study, you may discuss with your doctor other treatment options such as lifestyle changes and different medication regimens.

HOW WILL MY PRIVATE INFORMATION BE PROTECTED?

Every effort will be made to maintain the confidentiality of your study records. Your identity will remain confidential unless disclosure is required by law. All data will be identified by code numbers. These data will be stored in locked file cabinets that will be accessible only to study staff. The key listing names and code numbers will be kept in a separate locked filing cabinet or separate secure computer drive. During the study, records will be released only with your written consent and HIPAA authorization to appropriate VA research team members including, if requested and warranted, people from the Food and Drug Administration, the General

Accountability Office, the Office of the Inspector General, the VA Office of Research Oversight, the VA Central Institutional Review Board (IRB), the VA Research and Development Committee. Destruction of all research records pertaining to this study will be in accordance with the Federal Policy of the Department of Veterans Affairs and will be retained for a minimum of 6 years after the end of the study.

Your imaging information will be released to University of Alabama-Birmingham, Department of Radiology at the Highlands Neuroimaging Laboratory. The information obtained in this study may be published, but your identity will not be revealed. The VA personnel VA Institutional Review Board (IRB), and other federal oversight agencies reserve the right to inspect both the research data and your medical records. The information from the research may be published for scientific purposes; however, your identity will not be given out.

We will put information about your participation in this study into your medical record. This electronic medical record will be kept in accordance with the VA-approved records retention schedule. Authorized users of electronic VA medical records can access your medical record.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHAT ARE THE COSTS TO ME IF I TAKE PART IN THIS STUDY?

You will not be charged for any treatments or procedures that are part of this study. All study treatment is free of charge to study participants. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

You will be given $250 total in check or direct deposit for completing the entirety of the study including the final 1-month post-intervention follow-up. $50 each after completing the following: baseline visit, first 5 intervention sessions, second 5 intervention sessions. $100 for completing the final follow-up.

Payments will be made in the form of electronic funds transfer or by check. Payments involved for being a part of this research study will count as income and may affect your income taxes.

WHAT WILL HAPPEN IF I AM INJURED BECAUSE OF MY BEING IN THE STUDY?

If you are injured because of taking part in this study, the VA will provide necessary medical treatment at no cost to you unless the injury is due to non-compliance with study procedures. The Department of Veterans Affairs does not normally provide any other form of compensation for injury. By signing this form, you have not released this institution from liability for negligence.

If you should have a medical concern or get hurt or sick because of taking part in this study, call:

DURING THE DAY:

Dr. Chen Lin at **205-934-0634 or 205-975-8699**and

AFTER HOURS:

The VA Emergency Room at 205-558-4725 after hours for urgent medical issues.

Dr. Chen Lin at **205-934-0634 or 205-975-8699**

Emergency and ongoing medical treatment will be provided as needed.

DO I HAVE TO TAKE PART IN THE STUDY?

PARTICIPATION IS VOLUNTARY

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It is up to you to decide whether to take part in this study. If you decide to take part, you may still withdraw at any time. If you do not wish to be in this study or leave the study early, you will not lose any benefits to which you are entitled. If you are a VA employee, refusal to take part in this study will in no way influence your employment. If you do not take part, you can still receive all usual care that is available to you. Your decision not to take part will not affect the relationship you have with your doctor or other staff, and it will not affect the usual care that you receive as a patient. If you decide to stop taking study medication you will be asked to come to the remaining visits, but again, this is voluntary, and you will not be penalized for declining. If you withdraw completely from the study and discontinue study interventions and study follow-ups, data that has already been collected as part of the study can be utilized by the study team.

RIGHT OF INVESTIGATOR TO TERMINATE MY PARTICIPATION

The study staff may end your participation in the study if they believe it is in your best interest or if you are not following study requirements. If so, your study doctor will explain the reasons and arrange for your usual medical care to continue. Termination from the study will not affect the relationship you have with your doctor or other staff, and it will not affect the usual care that you receive as a patient.

WHO DO I CONTACT ABOUT THIS STUDY IF I HAVE QUESTIONS?

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may contact the Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. The IRB Administrator phone number is 205-558-4747. You may call the Principal Investigator, **Dr. Chen Lin, MD at 205-934-0634 or 205-975-8699**if you have questions, complaints or concerns about the study or if you would like to obtain information or offer input.

WILL I BE TOLD NEW INFORMATION ABOUT THIS STUDY?

Sometimes during a research study, new information becomes available about the treatments being studied that might change a person's decision to stay in the study. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your study doctor will arrange for your medical care to continue. If you decide to continue in the study, you might be asked to sign an updated informed consent form.

Individual research results from this study will not be available and/or disclosed to participants at any time. However, a summary of the overall results will be available at the end of the study in the following website: http://www.ClinicalTrials.gov. In addition, participants will be notified of their treatment assignment when the study ends.

FUTURE USE OF DATA

The information collected about you during the study will be stored in a research database maintained by the local investigators until destroyed according to VA regulations. The database will be shared per VA policy and applicable Federal requirements among the researchers involved in this project and others in the future who have a VA-approved agreement to use the study data. Information that discloses your personal identity will not be released without your permission unless required by law. Your personal information will always be kept separate from the research database.

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

Dr./Mr./Ms._____ has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

By signing this document below, you voluntarily consent to participate in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of

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this consent after you sign it. A copy of this signed consent may also be put in your medical record per local VA policy.

I agree to participate in this research study as has been explained in this document.		
_____ Participant's Name	_____ Participant's Signature	_____ Date