**Medical University of South Carolina**
**CONSENT TO BE A RESEARCH SUBJECT**

**TITLE OF RESEARCH:** Accelerated Repetitive TMS for Affective Dysfunction: Establishing the Dose-Response Curve: **Study 2 Targeting Variations**
**NCT04657432**
Version Date: 8/25/2020
Principal Investigator: Dr. Lisa McTeague

**Concise Summary:**

You are being asked to volunteer for a research study. Research studies are voluntary and include only people who choose to take part. The purpose of this study is to determine the most effective target on the head for brief, repetitive transcranial magnetic stimulation (rTMS) for improving daily difficulties related to emotional disorders.

You have already completed an eligibility screening on the telephone.

If you decide to participate, you would be asked to complete an interview and computerized forms that assess physical and mental health, medical, cognition, anxiety and depression history along with a MRI scan (1-2 hours). In the event that you are not able to physically come to the MUSC campus such as due to COVID19 precautions, a portion of the interview can be completed remotely over the phone and video conferencing.

These tasks can be scheduled for different days. After completing the forms and MRI scan, participants will be able to begin their Repetitive Transcranial Magnetic Stimulation (rTMS) treatment visits. Repetitive transcranial magnetic stimulation (rTMS) works by rapidly and repeatedly turning a focused magnetic field on-and-off over your head, which passes directly through your hair, scalp, and skull and onto your brain, and can temporarily increase brain activity under the magnetic field

All participants would then receive treatment on five different days. To allow some flexibility in scheduling, the five days of treatment can be completed within eight days. On each treatment day, you would receive repetitive TMS (rTMS) in 10 three-minute sessions, each separated by approximately 10 minutes (or more if that works better for your schedule).

After the final treatment session you will meet for an in-person appointment to repeat the initial assessment (computerized test and forms). You will receive a phone call each week after the final TMS treatment visit to complete brief forms

about difficulties related to depression, anxiety, and the treatment. You will additionally meet in person 1-month after completing your treatment to repeat the initial assessments. Total study duration is about one and a half months.

There are risks to the study treatment that are described in this document. Some of the risks include potential risk of seizure, worsening of neuropsychiatric symptoms, effects on brain tissue, changes in cognitive function, hearing loss, facial twitching or skin irritation, risk of a first-degree burn, delay of other psychotropic treatments, and MRI risks. Participation in this study may improve your physical and mental wellbeing, but that cannot be guaranteed. You do not have to participate in this study. If you are interested in learning more about this study, please continue to read below.

## A. PURPOSE OF THE RESEARCH

The purpose of this study is to determine if an accelerated treatment course of a kind of transcranial magnetic stimulation (rTMS), can be improved by assessing different stimulation regions as a treatment for moderate to severe depression and related emotional difficulties. The entire treatment will be given over five days. If you are interested in learning more about this study, please read this consent form closely and ask any questions you may have.

Repetitive transcranial magnetic stimulation (rTMS) is an FDA approved treatment for depression, and is used commonly to treat people for their depression. Repetitive transcranial magnetic stimulation (rTMS) works by rapidly turning a focused magnetic field on-and-off repeatedly over your head, which passes directly through your hair, scalp, and skull and onto your brain, and can temporarily increase brain activity under the magnetic field. Previous studies using rTMS have shown that it is helpful in treating depression.

The treatment used in this study is different from the FDA approved treatment because you will receive 10 treatments per day over five days instead of 25 treatments over 25 days. This sort of accelerated or high dose protocol has been shown to be safe and effective in reducing depressive symptoms in psychiatric patients. We are hoping to find out if this accelerated treatment can improve the difficulties related to depression.

In addition to the differences in treatment schedule, the number of total TMS pulses are different. The FDA-approved treatment is 12,000-18,000 pulses. In this study you will receive 30,000 pulses. This does has been shown to be safe and effective in prior studies,

You are being asked to participate in this study because you are experiencing moderate to severe depression. Your total participation would include an initial assessment and MRI scan. Treatment would then consist of 5 half-day sessions followed by another assessment. You would then come to one more post

treatment visit to repeat the initial assessments 1 month after completing your treatment.

Participation is entirely voluntary. Your participation may help develop an accelerated treatment for moderate to severe depression. If you consent and then change your mind at any time you are free to discontinue. Some participants receiving rTMS experience headaches and thus choose to stop. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand.

The investigator in charge of this study is Lisa McTeague, Ph.D. This study is being done at one site and will involve approximately 60 volunteers.

This study is sponsored by a grant from the Brain and Behavior Research Foundation. Portions of Dr. McTeague' and her research team's salaries will be paid by this grant.

## B. PROCEDURES

If you agree to be in this study, the following will happen:

You will meet with research staff once to sign up for the study and learn about your depression and your depression related difficulties. If you are female, you will receive a urine pregnancy test. You cannot participate in this study if you are pregnant. You will then complete an MRI scan of your brain. With study personnel you will choose a 5-day treatment schedule that best suits your other demands such as your work, family, and healthcare. On each of five days, you will receive 10 three-minute treatments of rTMS. These will be separated by about 10 minutes or more if you prefer. Twice for follow up visits (1 month) after treatment you will complete the same forms to see if the TMS helped your depression and its related difficulties. You will receive a phone call each week for 4 weeks after treatment to discuss your depression and anxiety.

**On your first visit:**

1) You will complete several computerized forms and tasks and a staff member will ask you several questions (3-4 hours). These questions will ask about your physical and mental health. Please note that while we expect that this rTMS treatment may help reduce depression symptoms, rTMS has been shown to improve a wide range of difficulties. As such, we will ask you to complete questionnaires that cover your physical health as well as you depression history. However, we will also ask about substance use, and trauma and stress history and anxiety. Anxiety symptoms we will ask about will include worry, posttraumatic stress and physiological symptoms.

2) If you are female, you will receive a urine pregnancy test. You cannot participate in this study if you are pregnant.

***COVID-19 / Remote 1st visit***

3) You will be asked to complete several questionnaires and assessments of your physical and mental health (1st diagnostic interview). Please note that while we expect that this rTMS treatment may help reduce depression symptoms, rTMS has been shown to improve a wide range of difficulties. As such, we will ask you to complete questionnaires that cover your physical and mental health, medical, anxiety, and depression history. Some of these assessments and questionnaires can be completed remotely, due to participation restrictions and COVID19 precautions.

**On your second visit:**

1) You will complete an MRI scan (approximately 1-2 hours). MRI machines use a strong magnet and radiofrequency magnetic fields to make images your body. You will be asked to lie on a long narrow couch while the machine gathers data. During this time, you will not be exposed to x-rays, but rather a strong magnetic field and radiofrequency magnetic fields, which you will not feel. You will, however, hear repetitive tapping noises that arise from the Magnetic Resonance scanner. We will provide earplugs or headphones that you will be required to wear. There will be a device that looks like a birdcage around your head, which helps to make the images of your brain. The space within the large magnet in which you lie is somewhat small, although we have taken steps to relieve the "claustrophobic" feeling. If you feel uncomfortable in the scanner, you are free to discontinue at any time. During this we will collect a picture of the structure or your brain (structural MRI) as well as a scan of how different brain areas communicate (functional MRI) while you are at rest.
2) You will complete several computerized forms (approximately 1 hour). You have the option to complete these on paper.

**How your amount of TMS will be determined.**

All participants will receive active rTMS shown to be effective in treating depression. You will be receive 10 doses of rTMS for each of the 5 treatment days

**On your treatment visits:**

Again, repetitive transcranial magnetic stimulation (rTMS) works by rapidly and repeatedly turning a focused magnetic field on-and-off over your head, which passes directly through your hair, scalp, and skull and onto your brain, and can temporarily increase brain activity under the magnetic field.

1) You will join us for a total of 5 treatment days. During these days, you will receive ten 3- minute treatments separated by about 10 minutes. The total time for a treatment visit will be about 3 hours.
2) Prior to your first treatment, we will determine the intensity of TMS for you. In order to do that we will put the TMS coil over the part of your brain that moves your hand, and find the lowest amount of magnetic stimulation needed to move your hand.
3) You will then receive 10 treatments each day. Each treatment takes about 3-minutes. You will wait about 10 minutes between treatments. You can wait longer between same-day sessions if you prefer. Just let us know.
4) You will complete a short-computerized form each day.

**After your final TMS treatment visit:**

1) We will meet with you in person for an appointment immediately after finishing your five days of treatment to repeat the initial assessment (computerized test and forms)
2) You will also receive a phone call each week for 4 weeks after your final TMS treatment visit. During this time you will complete the brief forms about anxiety and depression. Each phone call will take about 15-20 minutes.
3) You will additionally meet with us in-person 1-month after completing your treatment. During these sessions you will repeat the computerized battery and forms you completed at your initial assessment.

**Birth control precautions.**

If you are a woman of childbearing potential and /or a man capable of fathering a child before, during, and/or after participation precaution should be taken. Examples of acceptable methods of birth control for participants involved in the study includes: birth control pills, patch, IUD, condom, sponge, diaphragm with spermicide, or avoiding sexual activity that could cause you to become pregnant.

If a participant (is or) becomes pregnant, the rTMS might involve risks to the embryo or fetus, which are currently unforeseeable.

**Early withdrawal from study.**

You have the right to withdraw from the clinical investigation at any time. The Investigator for any of the following reasons may discontinue your participation.

- You are found to have entered the study not according to the protocol.
- You withdraw consent to participate in the study.
- You are do not follow with procedures stated in the protocol.
- You experience an Adverse Event that warrants withdrawal from the study.
- It is the Investigator's opinion that it is not in your best interest to continue.

- You display abnormal laboratory, medical or clinical findings for which clinical intervention should be prioritized over study participation including:
- a) Development of mania/hypomania
- b) Generalized seizure
- c) Inpatient hospitalization

The Investigator reserves the right to discontinue study participation for any individual who is determined to be a threat to self, staff or other study participants or who is unable to complete the study assessments, sessions or provide informed consent.

## C. DURATION

Participation in the study will take about 7 visits over a period of 7 weeks.

## D. RISKS AND DISCOMFORTS

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with Dr. McTeague if you have any questions.

Common adverse events occurring in approximately 15% of subjects:

Risks of Emotional Distress. You will be asked at some of these appointments to think and talk about emotional experiences including difficulties related to anxiety and depression. This may cause you to become upset, especially if you have been trying to avoid these thoughts. If you want to discontinue at any time, let Dr. McTeague and her staff know. Dr. McTeague will immediately meet with you privately to discuss how you are feeling, how to manage your distress, and to plan follow-up care if necessary.

Common adverse events occurring in approximately 5% of subjects:

TMS & Pain. Some people report some mild discomfort when the magnetic pulses are applied over the scalp, and a small number of people (approximately 5%) report headache or toothache following TMS. However, these side effects are temporary and manageable with common over-the-counter pain remedies, such as Acetaminophen or Ibuprofen. You will be monitored closely for any potential side effects including any discomfort and headaches. We will discuss with you how to manage the side effects if they occur. As concerning TMS and more severe and chronic pain conditions, accumulating evidence suggests TMS provides temporary relief from pain, a temporary decrease in sensitivity to pain, or no effect at all.

MRI & Pain. Some people report some mild back and/or neck discomfort due to remaining still in the scanner for up to an hour at a time.

MRI & Claustrophobia. Having a MRI may mean you may be bothered by feelings of claustrophobia and by the loud banging noise during the study.

MRI & Metal. Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which could in the process possibly harm you. Precautions have been taken to prevent such an event from happening; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have a MRI. It is important that you consider whether you have ever been in a situation where metal fragments may have ended up in your body and you inform us of any such possibilities.

Less common adverse events occurring in 0.5% of subjects:

TMS & Seizure. TMS stimulates neurons at a level below what triggers seizures. Although TMS is generally safe and well tolerated without enduring side effects, with a sample size of several thousand patients and healthy volunteers a total 20 cases of accidental seizures induced with TMS were reported. The risk is estimated to be probably less than 0.5% across individuals. There has been one report of seizure in a patient recovering from chronic stroke. This individual was receiving rTMS over the motor cortex, a region more sensitive to the possibility of seizure. In this study you will receive rTMS to the frontal cortex. This part of your brain is involved in problem solving and attention and is less prone to seizure. Nonetheless, we will watch you closely for any signs of seizure throughout all procedures. This will include sensors that we will place on your hand. These will provide very early signs of seizure risk and we will immediately discontinue if warranted.

The research team has a plan for dealing with fainting and seizures, and every TMS researcher is familiar with it. If you have a seizure, you will be made to lie down with your legs elevated. An emergency response team will be called. Most seizures, including those caused by TMS, last less than 60 seconds and do not require any medication. Once you recover from the seizure, you will be seen by a neurologist. Any participant who has a seizure cannot continue with the study.

Hearing Sensitivity. The discharge of the TMS coil and the MRI scanner generate loud, sustained noises that may cause damage to the inner ear. Humans exposed to TMS have shown temporary increases in auditory threshold (especially at high frequencies) lasting at least 5 minutes and less than 4 hours. Although uncommon, tinnitus has been reported after TMS exposure. Foam earplugs can protect against these changes and you will be required to wear these during TMS sessions.

TMS & Cognitive function. There have been no reports of long-

term impairment (more than a minute) in cognitive function (memory, attention, etc.) in TMS studies. Rather, modestly improved cognitive function has been observed.

Confidentiality Risks. All study records will be placed in a locked, secure, limited access location. Your participation in the study and the information you provide will be treated as confidential. The information we collect will contain a code number and not your name to protect your confidentiality. Codes linking numbers and names will be kept in a locked secure location and will not be accessible to anyone outside the research team. Despite these efforts to maintain subjects' anonymity and confidentiality, there is always some minimal risk of people other than the study investigators gaining access to your health information. Every effort will be made to ensure that your health information will be collected and stored in a manner that ensures the highest level of protection of confidentiality.

You should also know that if you threaten to harm yourself or others or give information about child or elder abuse, this information will be reported to appropriate clinical staff and other persons outside the research program as necessary to protect yourself and others and as mandated by law.

If you test positive for both pregnancy and illicit substances, South Carolina state law requires that the South Carolina Department of Social Services (DSS) be notified and you will be at risk of legal action.

Incidental Findings & MRI. The scans performed in this study are for specific research purposes and are not optimized to find medical abnormalities. The investigators for this project may not be trained to perform medical diagnosis. The investigators and MUSC are not responsible for failure to find existing abnormalities with these MRI scans. However, on occasion the investigator may notice a finding on an MRI scan that seems abnormal. When this occurs, a physician will be consulted as to whether the findings merit further investigation, in which case the investigator will contact you and your primary care physician and inform you of the finding. The decision as to whether to proceed with further examination or treatment lies solely with you and your physician. The investigators, the consulting physician, and MUSC are not responsible for any examination or treatment that you undertake based on these findings. Because the images collected in this study may not comprise a proper clinical MRI scan, these images will not be made available for diagnostic purposes.

Other risks relate to finding out that you may have a medical abnormality that you had not been aware of before. This knowledge could cause psychological stress to you or your family and possibly affect your health insurance coverage in the future.

Unknown Risks. The experimental treatments may have unknown side effects. The researchers will let you know if they learn anything that might make you change your mind about participating in the study. There risks of TMS and MRI to a pregnant women/ fetus are unknown.

## E. MEDICAL RECORDS

Information about your study participation will not be in your medical record. This means that neither your research participation nor any of your research results will be included in any MUSC medical record.

## F. BENEFITS

Regardless of the amount of TMS you receive, you will receive a number of rTMS treatments that has been used to treat depression but over fewer days. You may experience improvement of depressive symptoms and related difficulties, in a shorter period of time than is typical. However, this cannot be guaranteed. It is hoped that the information gained from this study will help the investigators learn more about how to better offer accelerated rTMS protocols to civilians with emotional difficulties. There is the possibility of no direct benefits.

## G. COSTS

There will be no cost to you as a result of participation in this study. The costs of all tests associated with this study will be covered by the study.

## H. PAYMENT TO PARTICIPANTS

In return for your time, effort and travel expenses, you will be paid $400 for participation in this study. If you do not complete the study, you will receive the following for each completed procedure: Initial diagnostic assessment and scan $50; 5 days of rTMS sessions in week 1 $250; 1-month post-treatment follow-up assessment $100;

You will receive payments after completion of each screening session and after 5 days of rTMS

Payments that you receive from MUSC for participating in a research study are considered taxable income per IRS regulations. Payment types may include, but are not limited to: checks, cash, gift certificates/cards, personal property, and other items of value. If the total amount of payment you receive from MUSC reaches or exceeds $600.00 in a calendar year, you will be issued a Form 1099.

If any study related injury occurs further information may be obtained from the Medical University of SC Hospital Medical Director (843) 792-9537 concerning medical treatment.

## I. ALTERNATIVES

This is a scientific investigation and not part of standard clinical care. This study is voluntary and you may choose to not participate in this study. Whether or not you choose to participate in this study will not affect your relationship with any current treatment provider you may have, or your right to health care or other services to which you are otherwise entitled now or in the future.

If you choose not to participate in this study, you could receive other treatments for your condition. The standard therapy for your condition is pharmacotherapy, conventional (i.e., 1 session daily for 4-6 weeks) rTMS, and psychotherapy. Each of these types of treatment are available here at MUSC and we can provide referrals and contact information.

## J. DATA SHARING

Information about you (including your identifiable private information and/or any identifiable biospecimens) may have all of your identifiers removed and used for future research studies or distributed to other researchers for future research without additional informed consent from you or your legally authorized representative.

## K. DISCLOSURE OF RESULTS

You will be provided an oral description and summary of your results over the course of the study. If you would like, we will also provide referrals for follow-up care. Additionally, if you would like your results forwarded to another healthcare professional, we will ask you to sign a release of your research related medical records.

## L. SIGNIFICANT NEW FINDINGS

If there are significant new findings during the course of the study, you will be notified.

## M. STUDENT AND EMPLOYEE PARTICIPATION

**If you are a student or trainee in the MUSC system,** *your participation or discontinuance will not constitute an element of your academic performance nor will it be a part of your academic record at this Institution. Similarly, if you are an employee* **in the MUSC system** *your participation or discontinuance will not constitute an element of your job performance or evaluation nor will it be a part of your personnel record at this Institution.*

## N. CLINICAL TRIALS.GOV

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At

most, the Web site will include a summary of the results. You can search this Web site at any time.

## O. FUTURE CONTACT

The researcher in charge of this study might like to contact you in the future about other research opportunities. If consenting on paper, please initial by your choice below and if consenting electronically scroll to the bottom of the screen and indicate your choice by selecting 'yes' or 'no' and then initial the statement confirming your choice in the space that follows.
____Yes, I agree to be contacted
____No, I do not agree to be contacted

*If you wish to participate, you should sign below if consenting on paper and if you are consenting electronically you should scroll to the bottom of the screen to sign.*

Results of this research will be used for the purposes described in this study. This information may be published, but you will not be identified. Information that is obtained concerning this research that can be identified with you will remain confidential to the extent possible within State and Federal law. The sponsor and the Food and Drug Administration (FDA) will receive copies of the research records. The investigators associated with this study, employees of the sponsor, the FDA, and the MUSC Institutional Review Board for Human Research will have access to identifying information. All records in South Carolina are subject to subpoena by a court of law.

In the event of a study related injury, you should immediately go to the emergency room of the Medical University Hospital, or in case of an emergency go to the nearest hospital, and tell the physician on call that you are in a research study. They will call your study doctor who will make arrangements for your treatment. If the study sponsor does not pay for your treatment, the Medical University Hospital and the physicians who render treatment to you will bill your insurance company. If your insurance company denies coverage or insurance is not available, you will be responsible for payment for all services rendered to you.

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should call the investigator in charge of this study if you decide to do this. The data collected on you to this point remains part of the study database and may not be removed. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled.

The investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in your best interest. They may also do this if you do not follow the investigator's instructions.

### Volunteers Statement

I have been given a chance to ask questions about this research

study. These questions have been answered to my satisfaction. If I have any more questions about my participation in this study or study related injury, I may contact Lisa McTeague, Ph.D. at (843) 792-8274. I may contact the Medical University of SC Patient and Family Care Liaison (843) 792-5555 concerning medical treatment.

If I have any questions, problems, or concerns, desire further information or wish to offer input, I may contact the Medical University of SC Institutional Review Board for Human Research IRB Manager or the Office of Research Integrity Director at (843) 792-4148. This includes any questions about my rights as a research subject in this study.

I agree to participate in this study. I have been given a copy of this form for my own records.

*If you wish to participate, you should sign below if consenting on paper and if you are consenting electronically you should scroll to the bottom of the screen to sign.*

_____

Signature of Person Obtaining Consent Date *Name of Participant

_____

Signature of Participant Date