INFORMATION AND CONSENT FORM
For Adult Participants

Sponsor / Study Title:	**University of Minnesota / "Repetitive Transcranial Magnetic Stimulation for Adolescent Depression: Efficacy, Predictive Biomarkers, and Mechanisms"**
Protocol Number:	**rTMS**
Principal Investigator: (Study Doctor)	**Kathryn Cullen, MD**
Telephone:	**(612) 273-9762** **(612) 899-9475 (24 Hours)**
Address:	**Ambulatory Research Center (ARC)** **F212/2C West** **2450 Riverside Ave.** **Minneapolis, MN 55454** **Center for Magnetic Resonance Research (CMRR)** **2021 6th St. SE** **Minneapolis, MN 55455** **MINCEP Epilepsy Care - St. Louis Park** **5775 Wayzata Blvd.** **Ste. 255** **St. Louis Park, MN 55416**

You are invited to participate in a research study examining the effect of brain stimulation using a device called a transcranial magnetic stimulator for adolescents with treatment resistant depression. You were selected as a possible participant because you've undergone at least one failed intervention for depression. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

This study is being conducted by Kathryn Cullen, MD in the Department of Psychiatry at the University of Minnesota. It is funded by a MnDrive Brain Conditions Neuromodulation Innovations Grant through the University of Minnesota Department of Neuroscience.

Because you are now an adult, you have been asked to read this consent form. After you have read the form, you will be asked to sign it if you still want to be in the study.

Study Purpose

This study is exploring an experimental procedure for treatment resistant depression in adolescents called repeated deep transcranial magnetic brain stimulation (rTMS).

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"Experimental" means that rTMS is not approved in the United States by the U.S. Food and Drug Administration (FDA) for use in adolescents with depression.

rTMS uses a mechanism in which changes in magnetic fields in the brain induce electrical currents which can be used to activate specific parts of the brain. rTMS has been FDA approved as a treatment for depression in adults as young as age 22, but not much is known about its effects on adolescents with depression.

The purpose of this study is to test the feasibility, tolerability and efficacy of rTMS for reducing depression in adolescents with treatment resistant depression. Additionally, we will be using brain imaging techniques to look at the neural mechanisms of rTMS and to try to identify biomarkers (biologic indicators of body processes) to predict response to rTMS.

Be aware that this form refers to TMS as "study procedure."

It is planned that about 60 adolescents aged 12-18 will be in this study.

Study Procedures

If you decide to be in this study, you might have to stop taking your regular medication during the entire study.

If you agree to participate in this study and sign this form, we would ask you to come in for a number of visits over about 2 months. The procedures done at these visits could include:

- a diagnostic interview with cognitive assessments and questionnaires
- 2 brain MRIs
- 30 - 40 study procedure sessions
- a post-procedure assessment
- 6 monthly follow-up visits

In the first visit, you will be interviewed by research staff members from the University of Minnesota and asked questions about your health history and clinical symptoms. These research staff members will review your medical and clinical history to determine if you qualify for the study and if it is safe for you to participate. You will be asked to fill out some questionnaires about your depression and how it affects your life (including thoughts of hurting yourself or others), and complete some tests of cognitive functioning which include activities designed to look at your level of attention, memory, problem solving skills, vocabulary, and pattern recognition skills. You will be asked to repeat some of these tests at week 6. The study doctor will also ask you about your current stage of physical development. This session will take 2-3 hours and will take place at the Ambulatory Research Center (ARC) on the second floor of the Fairview Riverside West Building. Some of these study activities may also take place remotely depending on COVID-19 Guidelines at the time of the study procedures.

If you qualify to continue the study, we will proceed to the second session. You will be asked to visit the Center for Magnetic Resonance Research (CMRR) for a brain MRI. An MRI uses powerful magnets and radio waves to make pictures of body tissues and structure. The MRI scan is non-invasive and takes about 2 hours. You will also be asked to provide a urine sample to complete a urine drug test and pregnancy test (if female) prior to the MRI scan. You cannot continue in the study if the drug or pregnancy testing is positive. The results of these tests will be provided to you. If you are sexually active, you must agree to use an approved method of

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birth control during the study. Your study doctor or study staff can discuss acceptable methods of birth control with you.

Your urine samples will be kept and used only until the tests described in this form are completed. The urine samples will not be stored.

Before the actual MRI scan, there is the option of being trained with the Mock Scanner. The Mock Scanner is similar to the real MRI scanner, but does not use a magnetic field. It is a "practice scanner", allowing for the practice of getting comfortable on the scanner bed, using the head coil, and going into the scanner. The MRI involves taking pictures of the brain, which measure the integrity of certain brain tissues. For the scan, you will be asked to lie down quietly on the scanner bed, which is then moved into the machine. Once you're inside the scanner, it will start to take pictures. While the scanner is working, you will hear noises, like knocking or beeping sounds. We will give you headphones to reduce the noise to a more comfortable level. While you're in the scanner, you will be doing things like resting, listening to music, and playing games using a button box.

You will also be asked to complete a task during the MRI in which you are presented with a series of visual images (human faces of varying emotion expressions with words printed over the faces). During the task, you will be asked to decide whether the words printed over the faces are positive or negative.

On rare occasions, the MRI data that we collect does not have the high quality that we need for the data analyses. If this were to happen, we would ask you to return to the CMRR to repeat all or a portion of the MRI visit.

The MRI images will be used to try and identify biomarkers, which are biologic indicators of body processes that may predict response to rTMS.

This study will be using the study procedure over the course of six to eight weeks (30-40 sessions). You will be asked to come to the MINCEP Epilepsy Care University of Minnesota Physicians clinic in St. Louis Park 5 days a week for 30 minute sessions of the study procedure administered by the research staff.

Before the actual study procedure we will determine your motor threshold, which is the lowest intensity of stimulation that produces a measurable response in the muscle. The motor threshold determination will be done before your first study procedure and once a week thereafter.

The intensity of the TMS may be adjusted if you have any bothersome symptoms. Be sure to tell your study doctor or study staff if you have a headache, or unpleasant sensations in other parts of your body.

For this test, you will be seated in a reclining chair and small surface electrodes will be attached to the skin of your hands and arm and connected to an electromyography (EMG) machine that shows the electrical response in your muscle as it is stimulated. Next, a cap will be applied to your head so that we can make measurements and mark spots for the brain stimulation. A helmet will be positioned over your scalp over a site that corresponds to the target area of your brain. A very brief pulse of electrical current will pass through the helmet coil once every 10 seconds and this will create a magnetic stimulus that will pass through your skull and activate the brain. For this you may feel a small tapping sensation on the scalp. After each pulse of stimulation we will check for a response from your muscle and lower the stimulation intensity for subsequent pulses until no response is seen. We will then move to another nearby site and do the same procedure. We will do this a number of times. At the end of this, we will mark the best

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location for producing a response in your muscle with the lowest intensity of stimulation. We will then present stimulus pulses at an intensity that will allow us to measure the level of excitability in that part of the brain.

During the course of the study, a member of the research staff will meet with you every week to complete some depression measures, monitor any side effects of the study procedure, and measure changes to the electrical response of your brain. During the sixth week of the study procedure, a member of the research staff will meet with you to complete some of the cognitive tests from the intake appointment. Some of these study activities may also take place remotely depending on COVID-19 Guidelines at the time of the study procedures.

After the completion of the 30-40 study procedures, you will be asked to complete another brain MRI, as well as a urine pregnancy test (if female) and urine drug screen. After this, you will come back to the Ambulatory Research Center for a post-procedure assessment to determine if you responded to the study procedure.

After you have completed the study procedures, you will be asked to complete 30-minute monthly follow-up assessments for the next 6 months, either in person or by video conference. At these appointments, you will meet with members of the research staff to discuss how your depression has progressed since the last visit, which will include completing questionnaires about your depression.

While you are in the study, you must:

- Follow the instructions you are given.
- Come to the study center for all visits with the study doctor or study staff.
- Tell the study doctor or study staff about any changes in your health or the way you feel.
- Tell the study doctor or study staff if you want to stop being in the study at any time.

Risks of Study Participation

The study has the following risks. Ask the study doctor if you have questions about the signs or symptoms of any side effects that you read about in this consent form.

Repetitive Deep Transcranial Magnetic Stimulation (rTMS). There have been reports of a seizure from rTMS. We will exclude all individuals with a history of seizures. In the event you do have a seizure, the research team will provide initial supportive care. If emergency care is needed, we will call 888 which will prompt hospital staff to come to the rTMS administration location to provide further care and transportation to the ER if necessary.

A seizure can affect future employability, insurability, or eligibility to drive. To minimize potential problems, we will provide to any subject who experiences a seizure a letter documenting that the seizure was experimentally produced. There have been no reported cases of an individual developing repeated seizures if they experienced a rTMS induced seizure.

One of the risks associated with rTMS is treatment-induced mania. Mania refers to an altered state of being characterized by periods of great excitement, euphoria, delusions, and over activity. Mania may lead to impulsiveness and bad decision making. The research team will monitor you to make sure they are not experiencing a treatment-induced manic episode.

The possibility exists for a temporary headache due to the rTMS or the tight cap surrounding the head. There is also a risk for dental pain. If either of these pains occurs, we will manage them

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by administering acetaminophen (Tylenol). While the study procedure is occurring, you will hear noises, like knocking or beeping sounds, which should be significantly reduced by the earplugs we will provide.

rTMS may interfere with implanted devices. rTMS is not appropriate for persons with medical devices such as deep brain stimulators, pace-makers, or medication pumps. Participants will be screened prior to the study procedure to determine if it is safe to proceed. The effects of rTMS on thinking, memory, and mood in subjects with stroke are not known.

The effects of rTMS on the unborn fetus are not known and participating women should not be pregnant. If you think you are pregnant during the study, you must tell the study doctor or study staff immediately.

We may discontinue the study procedure without your consent if we recognize any abnormal signals in muscle recordings or any abnormal behavioral responses.

Please tell the study doctor or study staff right away if you have any side effects. Please tell them if you have any other problems with your health or the way you feel during the study, whether or not you think these problems are related to the study procedure.

Interviews/Questionnaires. Some of the questions that will be asked in the interviews or study questionnaires may make you feel uncomfortable or upset. Please tell the study doctor or study staff if you feel uncomfortable or upset while filling out a questionnaire or answering questions. You do not have to answer any question that makes you feel uncomfortable or upset.

MRI. For most people, there is no danger associated with having an MRI scan. However, an MRI could be very dangerous if you have certain objects or devices implanted in your body. The magnet in the scanner can cause electronic devices like watches to malfunction, and some metal objects can be pulled into the magnet. If you have an electronic device on your body, there is a risk that it may stop working. If you have iron or steel on or in your body (except teeth fillings), there is a risk that the metal may move or be dislodged. We will ask you a series of questions before the scan to make sure you do not have any metal on or in your body, and we will ask you to take off any metallic objects that you may be wearing (such as a watch or jewelry). If you have certain iron or steel implants in your body that cannot be removed, you may not have the scan.

It may be uncomfortable lying still in the magnet for the time required; you may experience some mild stiffness and soreness in the muscles from being still. To make you as comfortable as possible, we will provide soft pads to support the neck, back, and legs. While the scanner is working, you will hear noises, like knocking or beeping sounds, which will be significantly reduced by the headphones we will provide. Some people feel uncomfortable while in the magnet because they do not like to be in closed places. While in the scanner, you can talk to the person who is running the scanner. If you continue to feel discomfort while enclosed in the scanner and would like to be removed, we will stop the scan immediately.

The images or pictures created during this study are for research purposes only and are not intended to provide health care to you. However, if the results from the magnetic resonance imaging show something unusual in the pictures, a Radiologist trained in reading the pictures will look at them. The Radiologist would not receive any personal information except your age and pertinent medical history collected as part of the research. There will be no charge to you

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for having the Radiologist look at your pictures. While the pictures are normally viewed shortly after the scan, results might not be seen before you complete participation in the study. The investigator for this study will contact you if the recommendation is to further investigate the unusual results of the pictures with your personal doctor. However, further medical follow up is not a part of this study and the study does not have funds set aside. Therefore, if the results do show something unusual, any medical follow up cost will be your responsibility and/or the responsibility of your health insurance carrier.

In obtaining a urine pregnancy test (for females only), it is possible that we may discover you are pregnant. If this is the case, we will inform you of the results. Although there are no known risks associated with scanning pregnant women, we will not scan someone who is pregnant. Additionally, we may obtain a false positive with the pregnancy test. If we obtain a positive pregnancy test, we will recommend you follow up with your primary care physician.

Washout. If you stop your regular medication to be in the study, your depression symptoms might come back or get worse. Please tell the study doctor or study staff right away if you have any problems when you stop or change your regular medication.

Loss of Confidentiality. There is a risk of loss of confidentiality of your information. You will read more about the protection of your information later in this form. Please ask the study doctor or study staff if you would like to know more about how your information will be protected while you are in this study.

Unknown Risks. It is possible that you could have problems and side effects of the rTMS procedure that nobody knows about yet, which include your depression getting worse.

New Information

If the study doctor or study staff learns any new information that might change your mind about continuing in the study, the study doctor or study staff will tell you about it.

Benefits of Study Participation

It is possible that you may experience a reduction in depressive symptoms and improvement in social and family functioning due to your participation in the study. However, this is not guaranteed and there may be no direct benefit to you from being in the study. The knowledge gained from this study may benefit others in the future.

Alternatives to Study Participation

You can choose to not to participate in this study. You can continue to work with your current provider to manage depression.

You should discuss your alternatives to participating in this research with the study doctor or study staff. In addition, you may discuss your options with your regular health care provider.

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Study Costs/Compensation

Participation in this study will be at no cost to you. The principal investigator of this study is paid to cover the costs of conducting the research.

You will be compensated up to $220 for your participation at different time points: $40 for the initial clinical assessments, $20 for the final assessment, $50 for each MRI (2 total), and $10 for each follow-up visits (6 total). There will be no reimbursement for the study procedure visits. If you start, but do not finish the study, compensation will be pro-rated according to each completed visit. If you agree to repeat the MRI scan, you would be compensated again.

In addition to study payment, you may be given up to 8 parking vouchers ($10 each) for parking at the study center. These vouchers have no cash surrender value.

Payment will be made using a pre-paid debit card called Greenphire ClinCard. It works like a bank debit card. We will give you a debit card and each time you receive a payment for participation in this study, the money will be added to the card after each completed visit.

You may use this card at any store that accepts MasterCard or you can use a bank machine to remove cash. However, there may be fees drawn against the balance of the card for cash withdrawals (ATM use) and inactivity (no use for 3 months). We will give you the ClinCard Frequently Asked Questions information sheet that answers common questions about the debit card. You will also receive letters with additional information on how you can use this card and who to call if you have any questions. Be sure to read these letters, including the cardholder agreement, for details about fees.

The debit card system is administered by an outside company. The company, Greenphire, will be given your name. They will use this information only as part of the payment system. Your information will not be used for any other purposes and will not be given or sold to any other company. Greenphire will not receive any information about your health status or the study in which you are participating.

Any demographic information collected and provided to Greenphire is stored in a secure fashion and will be kept confidential, except as required by law.

Payment you receive as compensation for participation in research is considered taxable income. If payment to an individual exceeds $600 in any one calendar year, the University of Minnesota is required to report this information to the Internal Revenue Service (IRS). Research payments to study participants exceeding $600.00 during any calendar year will result in a FORM 1099 (Miscellaneous Income) being issued to you and a copy sent to the IRS.

Research Related Injury

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury let the study doctor or study staff know right away.

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You do not give up any of your legal rights by signing this form.

Be aware that your health-care payer/insurer might not cover the costs of study-related injuries or illnesses.

Confidentiality

The records of this study will be kept private. In any publications or presentations, you will not be identified by name or other recognizable way on any records, results or publications relating to the study. Your medical records, as they relate to the research study, may be reviewed by the U.S. Food and Drug Administration, CMRR personnel, other regulatory authorities, and Advarra Review (a group of people who review research studies to protect the rights and welfare of research participants) to check trial data and procedures and ensure that the information is accurate.

Any information obtained from you in connection with this study that can be identified will remain as confidential as possible and will be disclosed only with your permission. However, mental health professionals are mandated reporters, which means that we are obliged to report alleged or probable abuse, as well as known abuse. If there are any concerns about maltreatment, they will be reported in accordance to the law. If you tell us that someone (including yourself) is in danger of serious harm, we may need to obtain outside assistance.

Only researchers associated with this study and other authorized personnel will have access to the records; research records will be kept in a locked file. In any sort of report we might publish, we will not include any information that will make it possible to identify you.

Your protected health information created or received for the purposes of this study is protected under the federal law known as HIPAA. This means that we must keep your medical information private and confidential to the greatest extent possible. Your protected health information includes contact information or any identifying information. You will be asked to review and sign a separate HIPAA authorization form concerning the use of this information.

To these extents, confidentiality is not absolute.

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.

Voluntary Nature of the Study

Participation in this study is voluntary. You can decide not to be in the study, and you can change your mind about being in the study at any time. There will be no penalty to you, and you won't lose any benefits (except for benefits having to do with the study). Your decision whether or not to participate in this study will not affect your current or future relations with the University, the University of Minnesota Medical Center, or Fairview. If you decide to participate, you are free to withdraw at any time without affecting those relationships. If you want to stop being in the study, tell the study doctor or study staff.

The study doctor or study staff or sponsor can remove you from the study at any time, even if you want to stay in the study. This could happen if:

- The study doctor or study staff believes it is best for you to stop being in the study.

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- You do not follow directions about the study.
- The sponsor stops the study for any reason.

If you stop being in the study early, the study doctor or study staff may ask you some questions about being in the study. The study doctor or study staff may ask you to participate in some procedures or tests to help you leave the study safely and/or to collect more information for the study. If you leave the study, the study doctor and study staff will still be able to use your information that they have already collected.

Whom to Contact About This Study

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact**:**

- By mail:
  Study Subject Adviser
  Advarra IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00038435.

Permission to Share Data Outside the Study

The data that you provide in this study is valuable and could be useful for other studies of adolescent health problems. When individuals provide consent to be in a research study, they are consenting for their information to be used only for the purpose of that study. The data cannot be combined with data from other studies. Investigators who focus on clinical samples do not always have easy access to comparison groups. Therefore, we request your consent to use your data in the context of other studies where Dr. Cullen is a co-investigator. We need to know if this is okay with you. If you agree to have your data shared across studies, your data will be grouped with that of other study participants for comparison with groups from other studies (for example, other groups of people with depression or other conditions, other healthy groups, groups of different ages.) Data to be shared may include results from any of the tests that are described above in the study procedures. We will not share your name, address, or other contact information.

You will indicate your choice regarding data sharing at the end of this form.

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Permission for Future Re-Contact

The study team wants to know if you will allow the members of the study team to contact you in the future to request information about your progress, and possibly to request further participation in an expanded portion of this study. Allowing the study team to contact you again does not obligate you to join any study or take part in any activities. If you do not want to allow this contact, you can still be in the study. If you agree now, you can change your mind at any time.

You will indicate your choice regarding future re-contact at the end of this form.

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Statement of Consent

I have read the above information. The study doctor or study staff has talked with me about this study. I have asked questions and have received answers. I voluntarily consent to participate in the study.

By signing this form, I do not give up any of my legal rights. I will get a signed copy of this consent form.

Permission for Data-Sharing: Please initial one line regarding data-sharing as described above.

_____ I agree to have my data shared with other studies where Dr. Cullen is a co-investigator. I may withdraw this consent to share data at any time in the future by contacting Dr. Cullen at (612)-273-9711.

_____ I do not agree to have my data shared with other studies. I can still be in the study.

Permission for Future Re-Contact: Please initial one line regarding your choice to be contacted in the future as described above.

_____ I agree to be re-contacted.

_____ I do not agree to be re-contacted. I can still be in the study.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

I attest that the individual providing consent had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to participation in this study.

_____
Printed Name of Person Explaining Consent

_____ _____
Signature of Person Explaining Consent Date

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