Official Title: H-coil TMS to Reduce Pain: A Pilot Study Evaluating Relative Efficacy of the H1 vs H7 Coil
NCT04203199
IRB-Approved Date: 12/20/2021

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School of Medicine

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Department of Cancer Biology

H-COIL TMS TO REDUCE PAIN: A PILOT STUDY EVALUATING RELATIVE EFFICACY OF THE H1 VS H7 COIL

Informed Consent Form to Participate in Research
Colleen Hanlon, PhD, Principal Investigator

SUMMARY

You are invited to participate in a research study. The purpose of this research is to examine the use of repetitive transcranial magnetic stimulation (rTMS), and its effect on pain sensitivity. rTMS is a technique that uses magnetic pulses to temporarily stimulate specific brain areas in awake people (without the need for surgery, anesthetic, or other invasive procedures). You are being asked to volunteer for a research study because you have acknowledged that you are between 18-75 years of age. Your participation in this research will involve three visits and last about 5 hours total.

Participation in this study will involve a screening visit and 2 rTMS visits. All research studies involve some risks. There are rTMS risks to this study that you should be aware. While there are risks associated with rTMS, the procedure is very safe. The most common side-effects you may experience are discomfort in your scalp during the rTMS session or a headache after the rTMS session. There are no direct benefits from participation in this study.

Your participation in this study is voluntary. You do not have to participate in this study if you do not want to. You can decide not to participate in this study at any time. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions if you need help deciding whether to join the study. The person in charge of this study is Dr. Colleen Hanlon. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his/her contact information is: chanlon@wakehealth.edu.

If you have any questions, suggestions or concerns about your rights as a volunteer in this research, contact the Institutional Review Board at [redacted] or the Research Subject Advocate at Wake Forest at [redacted].

Version Date: 09/16/2021

WFU School of Medicine
Institutional Review Board
IRB Number:IRB00062742
Meeting Date Approved 12/20/2021
Version Valid Until: 12/19/2022

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you are between 18-75 years of age. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this project is to study how a non-invasive form of brain stimulation called transcranial magnetic stimulation (TMS) affects the brain and changes the brain's response to pain. TMS is a technique that uses magnetic pulses to temporarily stimulate specific brain areas in awake people (without the need for surgery, anesthetic, or other invasive procedures). TMS has not been proven to help with pain, but this study is intended to determine whether it might be an effective treatment in the future. TMS has been approved by the FDA as an investigational tool, as well a therapy for depression. The study will examine the use of two novel coil designs that administer rTMS.

The two devices being examined are the H1 coil, which uses an FDA-approved protocol to treat depression, and the H7 coil, which uses an FDA-approved protocol to treat obsessive-compulsive disorder (OCD). The relative efficacy of these two treatment strategies will be useful for establishing rTMS as an effective strategy for chronic pain management and determining the direction for future rTMS research.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

60 people will be enrolled at this research site (Wake Forest Health Sciences). In order to identify the 60 subjects needed, we may need to screen as many as 82 because some people will not qualify to be included in the study.

WHAT IS INVOLVED IN THE STUDY?

If you take part in this study, you will have the following tests and procedures:

1. (Screening visit): You will need to have the following exams, tests, or procedures to find out if you can be in the study. This will last approximately 60 minutes. Following the informed consent procedure, if you are female you will be asked to provide a urine sample for a pregnancy test. If you are pregnant, you will not be eligible to participate in the study. Both males and females will then be asked to provide urine to assess for drugs of abuse. You will be asked about your medical history that is pertinent to the safety of TMS, and you will be asked about recent drug use. If you are unwilling or unable to provide these samples you will be excused from the study. If you do not report current drug use during your screening visit, but your urine tests positive for illicit substances you will be excused from the study. You will be evaluated first to see if you meet the study requirements. You will be asked to fill out several questionnaires about your mood,

pain and health today.

2. (Screening visit – Randomization): If the pregnancy and drug use test results come back negative, you will be randomly assigned to receive either Order A or Order B. The two orders are Order A (H1 coil at TMS visit 1, H7 coil at TMS visit 2), Order B (H7 coil at TMS visit 1, H1 coil at TMS visit 2)
3. (TMS Visit 1, 2 – Quantitative Sensory Testing): You will receive Quantitative Sensory Testing (QST) before and after the TMS session. QST is delivered by a device called an Algometer. The Algometer has a rubber tip which will be pressed into your right forearm. You will be asked to indicate when you first detect a pressure change (sensory threshold), when the stimulus becomes painful (pain threshold), and when you want the threshold testing to end (tolerance threshold). At this time, the Algometer will immediately be released.
4. (TMS Visit 1, 2 – Pre/Post Delayed discounting assessment): Before and after the rTMS session, you will complete the same set of computer based visual analog tasks in which you will be asked to choose between two conditions in which varying amounts and delays to behavioral outcomes (e.g., $50 now or $100 later) are presented. Across consecutive choices, the delay to the larger outcome will be titrated until reaching the participant's indifference delay (i.e., the delay at which s/he equally values both options). You will be asked these questions after each QST round (before and after the rTMS session).
5. (TMS Visit 1, 2 – TMS dose): Before receiving rTMS, a researcher will first determine how much TMS it takes to make your thumb (H1) or foot (H7) muscles twitch. This process, called "finding your resting motor threshold," is done to help the researcher choose the right "dose" of TMS for you. The researcher will ask you to hold out your hand or rest your foot. Next, the researcher will slowly move a TMS coil over your head. The coil will send a single electromagnetic pulse every few seconds. The researcher will continue until, he/she finds the specific brain area, that when stimulated, causes a slight movement of your thumb or in your foot.
6. (TMS Visit 1, 2 – Treatment): Order A will receive one session of stimulation from the H1 TMS coil at visit 1, from the H7 coil at visit 2. Order B will receive one session of stimulation from the H7 TMS coil at visit 1, from the H1 coil at visit 2. Each TMS sessions for each order will last approximately 20 minutes.

Study Schedule

Consent/Screening Visit	- Consent process - Urine screen - Questionnaires that assess pain and mood	$10
TMS Visit 1	- Urine screen if not done the same day as consent/screening visit - TMS Safety Update - Health and Medication Changes -Questionnaires	$20

	- QST Pre-Treatment - Delayed Discounting Pre-Treatment - Motor threshold - Treatment (about 20 min.) - QST Post-Treatment - Delayed Discounting Post-Treatment	
TMS Visit 2	- Urine screen - TMS Safety Update Health and Medication Changes - Questionnaires - QST Pre-Treatment - Delayed Discounting Pre-Treatment - Motor threshold - Treatment (about 20 min.) - QST Post-Treatment - Delayed Discounting Post-Treatment	$20
Study Completion		$20

You may be withdrawn from this study without your consent if the researchers believe it is in your best interest or if you fail to follow study procedures. For example, you may not be permitted to proceed with the experiment if you have a history of seizures in your medical history.

How Long Will I Be in the Study?

You will be in the study for 3 visits. The screening visit will take approximately 60 minutes of your time. Each TMS visit will take about 60-90 minutes of your time. If eligible, you may complete the screening visit and TMS visit 1 in the same day.

You can stop participating at any time. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. If you choose not to participate, it 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.

What Are the Risks of the Study?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. Risks and side effects related to the device we are studying include the

following:

Potential risks of quantitative sensory testing (QST):

1. Quantitative sensory testing will be delivered with the Medoc Pathway system which is specifically designed for safe pain assessments. It has built-in safety mechanisms (e.g., real-time visual and auditory feedback, threshold selection, and an easy to reach shut-off button). Participants may experience redness or irritation of the skin in the area stimulated, and vitamin E cream will be provided after the trial to reduce this potential. If redness occurs, it tends to go away on its own within about 60 minutes. The application of vitamin E cream may speed this up (i.e., redness goes away within about 20 minutes). Participants may also experience bruising in the area stimulated; bruising typically resolves itself within a few days.

Potential Risks of TMS:

1. Potential risk of a seizure: TMS stimulates the neurons at a level below what is required to cause a seizure, although eight seizures have been noted in the literature in the past 20 years. Six of them have been in healthy volunteers (without any history of seizures, brain masses or traumatic brain injuries). The risk of seizure induction is related to the intensity, duration, frequency and rest interval of stimulation. Following the adoption and widespread use of the safety guidelines, 1 seizure has been reported since 1997 and it involved parameters of higher settings then the safe range. To our knowledge, stimulation with the parameters and settings we propose to use does not cause seizures. We will carefully adjust your stimulus intensity to your motor threshold, before beginning treatment.
2. Potential for scalp discomfort and headaches: You may report some mild discomfort when the magnetic pulses are applied over your scalp. Some people (~30%) report headache following TMS. These headaches are temporaryand are manageable with common over-the-counter pain remedies.
3. Potential hearing loss: The TMS coil generates a high energy click that may cause hearing damage. 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. Foam ear plugs can protect against these changes and will be provided to you during TMS sessions
4. Potential worsening of mood with TMS: Several studies have so far demonstrated the feasibility of TMS as a treatment for depression. However, there is a chance you may feel that your mood is worsened, though there is no evidence that this will occur.
5. Potential Worsening of Pain with TMS: To date, we have not seen any evidence that TMS is associated with increases in pain perception or worsening of pain conditions. Most of the available evidence of the effects of TMS on pain perception suggests that TMS provides temporary relief from pain, a temporary decrease in sensitivity to pain, or no effect at all.
6. Other potential effects of TMS on brain tissue: TMS is thought to be safe, with no brain damage, despite its large-scale use in humans and other animals. Within our laboratory,

multiple safety studies have found no changes in the structure of the brain following TMS.

7. Potential changes in cognitive function: There have been no reports of long-term changes (more than a minute) in cognitive function (memory, attention, etc.) in TMS studies.
8. Safety in case of pregnancy: If you are pregnant, you will be excluded from this study. The risks of using TMS with pregnant women are currently largely unknown. All female participants will be required to be using an acceptable form of birth control (including abstinence) during the TMS visits in order to continue participation. If there is a chance you may be pregnant, a urine pregnancy test will be done. Further, while the risks of using TMS with pregnant women are unknown, there is no available evidence to date suggesting that TMS is harmful during pregnancy. Of note, South Carolina state law requires that the South Carolina Department of Social Services (DSS) be notified if a pregnant woman tests positive for illegal drugs. You will be at risk of going to jail or losing custody of your children.
9. Potential for fainting event: Fainting or "passing out" is defined as a temporary loss of conscious. Although fainting episodes are very rare with TMS (less than 1 in 100 people), they typically occur before the TMS treatment, when the study members are finding your "dose" of TMS, known as the motor threshold. Individuals that are sleep deprived and have low or unstable blood pressure are at greater risk.
10. Interaction with electrical or metal implants: Electrically, magnetically or mechanically activated implants (such as pacemakers), as well as clips on blood vessels in the brain may be affected by rTMS and cause pain or abnormal signal propagation. Therefore individuals that have these implants and devices or suspect that they may have pieces of metal in their eyes, head, or body (e.g. bullets, shrapnel, fragments from metallurgy) will be excluded from the study.
11. Unknown Risks: TMS is an experimental procedure that has not been approved by the FDA as a treatment for pain and it 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.

Other Risks

1. Risks of Confidentiality: Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.
2. Potential Risk of Interviewing (minimal risk): As part of this study, you will be asked questions about sensitive personal information. You may feel anxiety about disclosing some aspects of your demographics. The Beck Depression Inventory (BDI) scale includes a question on suicidal ideation. In the event that you endorse suicidal ideation on the BDI, the staff present with you will be authorized to contact the PI or one of the Co-I's on the study who will then assess the situation to see whether further intervention is required. Based upon the answers to these questions the study personnel will provide the participant with means to help them receive treatment. This may include providing the

patient with information on contacting a physician or therapist to discuss their thoughts or to work with them on a plan to get them to the emergency room for safety if they indicate that they are in danger of harming themselves within the next 24-48 hours.

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. There also may be other risks that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

Reproductive Risks and other Issues to Participating in Research

Due to unknown risks and potential harm to the unborn fetus

pregnant women are excluded from participation in this study. This will be verified via urine screening on each TMS visits.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You are not expected to receive any direct benefit from taking part in this research study. We hope the information learned from this study will benefit other people in the future.

WHAT OTHER CHOICES ARE THERE?

This is not a treatment study. Your alternative is to not participate in this study.

WHAT ARE THE COSTS?

All study costs, including any study medications and procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

WILL YOU BE PAID FOR PARTICIPATING?

You will be paid $70.00 if you complete all the scheduled study visits. If you withdraw for any reason from the study before completion you will be paid for the portions you complete ($10.00 for completing the screening visit, $20.00 for completing each TMS visit, plus $20 completion bonus

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

The card may be used at any store that accepts MasterCard or cash can be removed at a bank machine. However, there may be fees drawn against the balance of the card for cash withdrawals (ATM use) and inactivity (no use for 6 months). Participants will be given the ClinCard Frequently Asked Questions information sheet that answers common questions about the debit card. Participants will also receive letters with additional information on how to use this card and who to call if there's any questions.

The debit card system is administered by an outside company in conjunction with the Wake Forest Office of Clinical Research (OCR) who will distribute the cards in sealed envelopes to study staff prior to a participant's screening visit. The company, Greenphire, will not be given the participant's name and social security number. The 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 the participant's health status or the study in which they are participating.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by Wake Forest University of Health Sciences. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at [redacted].

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Dr. Colleen Hanlon at [redacted].

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:** Names, all elements of date (except year) for dates directly related to an individual (DOB), telephone numbers, and electronic mail addresses.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), the Department of Health and Human Services (DHHS) and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

Monitors, auditors, IRB or other regulatory agencies will be granted direct access to the participant's original medical record for verification of clinical trial procedures or data, without violating confidentiality of the participant and to the extent permitted by other applicable laws.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for at least six years after the study is finished. At that time any research information not already in your medical record will either be destroyed or it will be de-

identified.

You can tell Dr. Colleen Hanlon that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Dr. Colleen Hanlon
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.
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 Web site at any time.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because it is in your best medical interest, your condition worsened, new information becomes available, you had an unexpected reaction, you failed to follow instructions, or because the entire study has been stopped. Information that identifies you may be removed from the data or specimens that are collected as part of this study and could be used for future research or shared with others without additional consent.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

This study may be enrolling students from the Wake Forest University and Wake Forest University Medical Center campus. In addition to your rights as a research participant noted in the previous section, as a student, you are under no obligation to participate in this study. You may refuse to participate or withdraw from the study at any time and for any reason without affecting your grades, performance evaluations, or assignments. You will not be pressured into participating in this research study by any statements or implied statements that your grades, performance evaluations or assignments will be affected by your willingness to enroll in the study. Your medical records/information will not be used by the faculty, administration or study staff to make decisions regarding the status of your medical benefits. If you have questions regarding your enrollment in the study and your status as a medical student, please contact the Office of Student Services for additional information.

FUTURE RESEARCH?

From time to time we have other research studies that you may be eligible to participate in. We are inviting you to allow us to contact you by phone, mail, or both to see if you would be interested in participating in any future studies. By initialing next to the "yes" box below, you are indicating that you would like to give us your phone number, any alternate phone numbers, and address so that we may contact you if another study becomes available that you might qualify for. **To maintain your confidentiality, we will <u>not</u> leave identifiable messages or any identifiable information on letters or envelopes that are mailed to you.** By initialing next to the "no" box below, you are indicating that you do not want study personnel to contact you for any future studies. You may still participate in the current study if you choose "no" and you will not suffer any adverse consequences in doing so.

☐ Yes. I would like to be re-contacted for future studies. I give permission for study personnel to contact me by phone or by mail to inform me of other available studies I may be eligible for. Please initial here_____.

☐ No. I do not wish to be re-contacted for any future studies. Please initial here_____.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Dr. Colleen Hanlon at [redacted].

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted] or the Research Subject Advocate at [redacted].

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent (Printed):_____

Person Obtaining Consent:_____ Date:_____ Time:_____ am pm