Medical University of South Carolina
CONSENT TO BE A RESEARCH SUBJECT

TITLE OF RESEARCH: Safety, Parameterization, and Mechanism of Transcranial Focused Ultrasound Stimulation

NCT05792020

You are being asked to volunteer to participate in a research study. Your participation is voluntary, and you can withdraw at any time.

The purpose of this research is to test the safety and parameters of using transcranial focused ultrasound (tFUS), a form of noninvasive brain stimulation using sound waves, to the motor cortex and study how the brain changes in response to this. We will assess how the brain changes using Transcranial Magnetic Stimulation (TMS), another form of noninvasive brain stimulation using magnetic pulses, to study the excitability of the motor cortex and how it may changes as a result of the tFUS stimulation. If you agree to participate in the research study, your participation will last approximately 8 hours over five (5) days and will consist of Magnetic Resonance Imaging (MRI) scans, tFUS administration, and TMS administration.

Potential discomforts you may experience include feelings of claustrophobia in the MRI scanner, stimulation of nerves in your body which feels like a gentle tap or sensation of mild electric shock, coldness from cleaning and placement of focused ultrasound loudspeaker, emotional discomfort answering assessment questions, loss of confidentiality and other unknown risks.

If you choose to participate, there will be no direct benefit to you from taking part in this study. We hope this study will help the researchers learn more about the deep brain structures and their interaction with other brain regions as well as mechanisms and potential of ultrasound stimulation as a technique to understand how the human brain functions. Hopefully, this information will help the promote more personalized care in the field of noninvasive brain stimulation and aid in developing improved studies for the use of tFUS in clinical settings.

The alternative is to not participate in this research study. Research studies are voluntary and include only people who agree to take part. If you are interested in learning more about this study, please continue reading below.

A. PURPOSE OF THE RESEARCH

Recently, scientists have discovered that Transcranial Focused Ultrasound (tFUS) can stimulate the human brain. TFUS is like general ultrasound used in imaging, except that it is pulsed rather than continuous. In general, bone stops ultrasound signals, but scientists have found that if you have several ultrasound sources (transducers) or a broad transducer, you can focus the sound to converge on a single spot. Thus, tFUS is a new medical technology platform performed both inside and outside of the Magnetic Resonance Imaging (MRI) scanner that can modulate the brain. We want to see if we can individually target each participant's motor cortex, the area of the brain that controls your motor movements, and use tFUS to induce changes motor cortex excitability. This entire study is investigational.

You are being asked to participate in this research because you are a healthy individual who is interested in neuroscience research. The purposes of this research study are (1) to investigate personalized focused ultrasound (a method of noninvasively stimulating the brain using sound waves) as a technique to study how the brain works and (2) to evaluate the parameters of the NeuroFUS ultrasound device. This device is not an FDA-evaluated medical device, is intended for research purposes only, and is only available to recognized research institutions under the scope of ethics and safety approval. The system is not intended for the treatment of any medical disorder or condition. The researchers hope this study will potentially develop stronger research foundations for using tFUS.

Please read this consent form carefully and take your time making your decision. As the 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 study is sponsored by both the BrainBox and the Neuromodulation For Rehabilitation Initiatives. The investigator in charge of this study at MUSC is Kevin A. Caulfield. The study is being conducted at the Medical University of South Carolina and around 25 participants will take part in this study.

B. PROCEDURES

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

Visit #1: Structural MRI and Motor Hotspot Determination (Approx. 1 hour)

- Urine Pregnancy and Drug Test: Before continuing in the study, we will ask all woman of childbearing potential to take a pregnancy test. If you are a woman of childbearing potential and/or a man capable of fathering a child before, during, and/or after participation, precautions should be taken. Additionally, all participants will submit to a drug screening. You will be given a cup and instructed to fill the cup to the line described by the research assistant. The research assistant will then use a stick to determine pregnancy. In addition, urine will be used to determine if there are any drugs in your system within 5 half-lives of the procedure time.
- MRI Scanning: Participants will then enter the MRI scanner in order to obtain baseline structural and connectivity imaging in order to assess the status of the brain prior to treatment

and determine an accurate distance for targeting. Magnetic Resonance Imaging (MRI) uses a magnet and radio waves to make diagnostic medical images of the body. You will be placed on a narrow bed and then slid into a small tunnel approximately 6 feet in length and 25 inches in diameter. You will hear a loud machine-like noise.

  - MRI is a widely used method used to access body tissues, including the brain, in a non-invasive manner. In the context of this study, MRI will be used to take pictures of your brain structure and function while you rest and during stimulation. All these procedures are non-invasive. Prior to the imaging exam, you will be asked to remove any magnetic materials from your pockets, clothing or your body (e.g., jewelry). During the procedure, you will be asked to lie down and will be placed in the center of the MRI scanner. Your head will be placed inside a special radio antenna called a head coil. Since the scanner is a noisy environment, you will be given special earplugs and earphones, and you will be given a mirror and goggles to allow you to see a computer screen. During this test you do not have to do anything, just relax and try to stay as still as possible.
  - For the case of incidental findings, we are performing imaging solely for the research purposes described above. It is not a clinical scan intended for diagnostic or therapeutic purposes. If participants want their scan to be reviewed by a physician or neuroradiologist so that they can look for medical issues, they can request a copy of their scan. We will provide an electronic copy at no charge.
  - The MRI scanner is located at 30 Bee St., Charleston SC 29403. Parking at this location is free.

- Motor Hotspot Determination: Through the use of Transcranial Magnetic Stimulation (TMS), a well-documented method of safely and reliably stimulating the motor cortex, we will obtain an exact cortical location that activates the muscles in the hand and thumb with the least amount of stimulation as possible. This “thumb twitch” assessment will establish a baseline level of excitability that will be tested throughout the study to understand how motor excitability may be altered by focused ultrasound stimulation. This will require around 30 TMS pulses to find an accurate location.

Visits #2-4: MRI Scanning, MEP Recording, and tFUS Stimulation (Approx. 2 hours/visit)

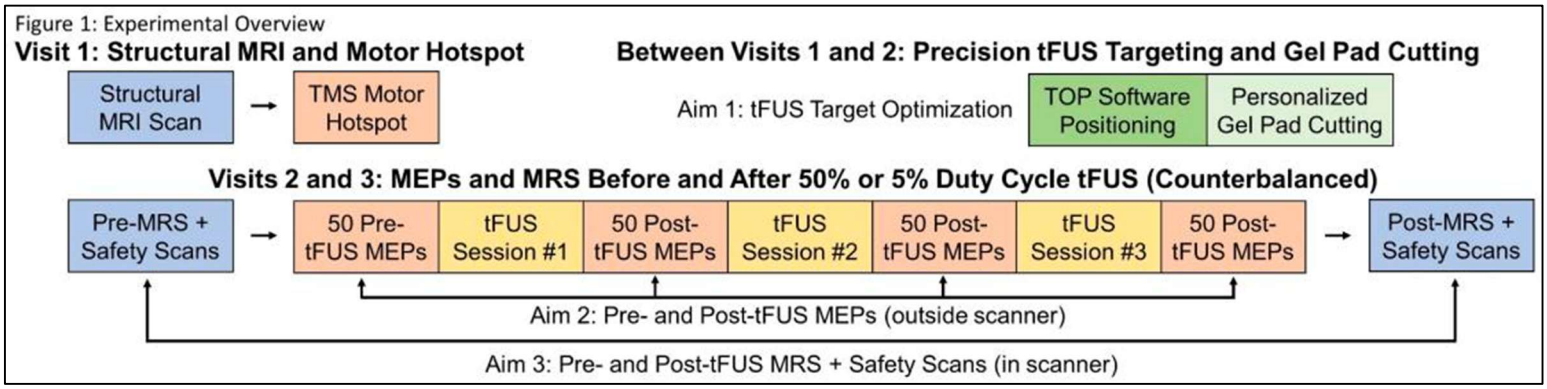
- Pre-Stimulation MRI Scanning: At the beginning of visits 2-4, you will enter the MRI scanner to obtain baseline levels of brain excitability through the use of MR Spectroscopy. This is a method of imaging that analyzes chemical levels in your brain. We are collecting this measure to fully understand how the excitability of the brain changes on a deeper level than motor evoked potentials in the hand and thumb. This process will take around 15 minutes.
- Motor Evoked Potential (MEP) Recording and Focused Ultrasound Administration: After the MRI scanning, we will obtain muscle recordings in the hand while stimulating at the determined motor hotspot from visit 1. This will require 50 TMS pulses. Then, you will be randomized into 3 groups to determine the order in which you receive the types of stimulation. Neither the researchers nor you will make the choice of which order you are assigned. There are three possible stimulation parameters. You will receive transcranial focused ultrasound stimulation in 3 sessions. Stimulation sessions will be administered in 3 blocks, each 20 minutes in length.

Each block will consist of 10 minutes of ultrasound stimulation, 5 minutes of MEP recording, and 5 minutes of rest.

- Post-Stimulation MRI Scanning: After completing the stimulation blocks, you will return to the MRI scanner to obtain post-stimulation chemical levels using MR Spectroscopy, which will take around 15 minutes.

Visit #5: Post-Stimulation MRI Scanning (Approx. 1 hour)

- This visit will be like the second half of visit 1. You will complete the same MRI scans. These visits will take place entirely at 30 Bee St., Charleston SC 29403. Parking at this location is free.



C. DURATION

Participation in the study will take 5 visits over a period of 1-2 weeks, for 8 hours. All research visits will be conducted in person at MUSC.

D. RISKS AND DISCOMFORTS

Known risks and discomforts:

The possible risks and/or discomforts associated with the procedures described in this consent form include:

1. MRI Procedure
    - There have been no ill effects reported from exposure to the magnetism or radio waves used in this test. A known risk is that the magnet could attract certain kinds of metal. Therefore, we will carefully ask you about metal within your body (this includes certain dyes found in tattoos). If there is any question about potentially hazardous metal within your body, you will be excluded from participation in this research study. We will also keep the examining room locked so that no one carrying metal objects can enter while you are in the scanner. Please inform the study staff if you have a history of claustrophobia (extreme anxiety in close spaces).

This may also be a contraindication to participation in the study.

- The MRI procedure uses a powerful magnetic field to generate detailed images of the body. It is therefore important that you do not have any metal in or on your body (dental fillings are ok) such as implants, clips, and pacemakers.
    - We will complete an MRI safety questionnaire prior to each visit at the MRI.
- MRI scanning is painless, but you might experience discomfort in the machine. In particular, loud beeping noises occur during the study when the scanner is collecting measurements. You will be given special earplugs to minimize the noise.
- You also may be bothered by feelings of claustrophobia (extreme anxiety in close spaces) when placed inside the MRI machine, or by lying in one position for a long time.
    - In the MRI scanner, you will be given headphones so that you are able to hear MRI technicians and research staff. You are also able to communicate with research staff and MRI technicians during the scan via a microphone in the scanner. You will be given a squeeze ball that when squeezed sends a signal to MRI technicians that you would like to be taken out of the scanner immediately.
- You might also experience stimulation of the nerves in your body, which feels like a gentle tap or sensation of mild electric shock.
- Since the risks to a fetus from MRI are unknown, pregnant women may not participate in studies involving MRI procedures.
- For the case of incidental findings, we are performing imaging solely for the research purposes described above. It is not a clinical scan intended for diagnostic or therapeutic purposes. If you want your scan to be reviewed by a physician so that the physician can look for medical issues, you can request a copy of your scan. We will provide an electronic copy at no charge

2. TMS Procedure

- TMS and seizure: TMS stimulates neurons at a level below what triggers seizures. Although single pulses of TMS are generally safe and well tolerated without enduring side effects, a total of 8 cases of seizure have been induced out of likely millions of stimulation sessions from similar TMS protocols. The risk is estimated to be less than 0.5% across individuals. 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.

- TMS and hearing loss: The TMS pulses can generates a high-energy click that may cause damage to your hearing. Humans exposed to TMS have shown temporary increases in the lowest audible intensity of sound (especially at high frequencies) lasting at least 5 minutes and less than 4 hours. However, this research study will use low frequency TMS (<1 pulse per second). In addition, foam earplugs can protect against

these effects and will be worn during TMS sessions.

- TMS and headaches: Some people report some mild discomfort when the magnetic pulses are applied over the scalp, and a small number of people (~5%) report headache following rTMS. However, the headaches are temporary and manageable with common over-the-counter pain remedies. In addition, we will stimulate over the motor cortex which further reduces the likelihood of headaches compared to other stimulation targets.

3. FUS Procedure
    - You might experience some minor cold or discomfort if the gel is applied to your skin in the location where the ultrasound loudspeaker is placed.
    - You might feel minor discomfort as your skin is cleaned from the gel.
4. Psychometric Testing
    - Psychometric testing is designed to measure your brain's performance. You may feel discomfort when hearing some questions, and you may choose to skip these questions if you wish.
5. Pregnancy & Illegal Drug Testing
    - If you are pregnant or become pregnant, there may be risks to the embryo or fetus that are unknown at this time. Therefore, breastfeeding and pregnant women are not allowed to take part in the study. Women who can become pregnant must take a pregnancy test before the start of the study. Additionally, if you are or become pregnant and test positive for illegal drugs, it is a law that the South Carolina Department of Social Services (DSS) must be notified. You and your family will be evaluated by the agency. You could be ordered to mandatory drug treatment, lose custody of your children, or be jailed.
6. Loss of Confidentiality
    - As this study involves the use of your identifiable, personal information, there is a chance that a loss of confidentiality will occur. The researchers have procedures in place to lessen the possibility of this happening.
7. Unknown Risks and/or Discomforts
    - The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about taking part in the study. No long-term negative effects are currently known to be associated with any of the procedures described above. The probability of unknown or unforeseen risks is unknown.

E. MEDICAL RECORDS AND/OR CERTIFICATE OF CONFIDENTIALITY

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

Although there may be no direct benefit to you from participating in this study, it is hoped that the information gained from the study will help in the creation of personalized treatments using focused ultrasound stimulation. This will also help the researcher learn more about deep brain structures and their interaction with cortical (surface) brain regions, as well as the mechanisms and potential of ultrasound stimulation as a technique to understand how the human brain functions. Hopefully, this information will help in the treatment of future patients with disorders affecting mood, including posttraumatic stress disorder.

G. COSTS

There will be no cost to you as a result of your participation in this study.

H. PAYMENT TO PARTICIPANTS

You will be paid $20 for completing Visit 1, $40 for completing Visit 2, $40 for completing Visit 3, $40 for completing Visit 4, and $60 for completing Visit 5. Therefore, you will be paid up to $200 for completion of all five visits which include the screening session and participation in all MRI sessions.

Payment for study visits will be made using a pre-paid debit card, called a ClinCard. It works like a bank debit card and you may use the card to purchase goods or services everywhere Debit MasterCard is accepted. You will be given a ClinCard at the beginning of the study. Each time you receive payment for participation in this study, the money will be added to the card, as outlined in the payment schedule above. Details of the debit card system are explained on an additional sheet. 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.

I. ALTERNATIVES

Your alternative is to not participate in this study.

J. DATA SHARING

Information about you (including your identifiable private information and/or any identifiable biospecimens) will have all of your identifiers removed and will not be used for future research studies or distributed to other researchers for future research without additional informed consent from you or your legally authorized consent.

K. DISCLOSURE OF RESULTS

The information collected as part of this study is being obtained for research purposes only. The data are not being collected for clinical purposes and will not be provided to you unless there are clinically relevant findings that may be reviewed by a study physician or provided to you to take to your primary care physician.

L. AUTHORIZATION TO USE AND DISCLOSE (RELEASE) MEDICAL INFORMATION

As part of this research study, your study doctor and his/her research team will keep records of your participation in this study.

The health information MUSC may use or disclose (release) for this research study includes information in your medical record, results of physical exams, medical history, lab tests or certain health information indicating or relating to your condition.

Your study doctor and his/her research team will use and disclose (release) your health information to conduct this study. The health information listed above may be used by and/or disclosed (released) to the following, as applicable:

- The sponsor of the study including its agents such as data repositories or contract research organizations monitoring the study;
- Other institutions and investigators participating in the study;
- Data Safety Monitoring Boards;
- Accrediting agencies;
- Clinical staff not involved in the study whom may become involved if it is relevant;
- Parents of minor children if less than 16 years old. Parents of children 16 years old or older require authorization from the child; or
- Health insurer or payer in order to secure payment for covered treatment;
- Federal and state agencies and MUSC committees having authority over the study such as:

    - The Institutional Review Board (IRB) overseeing this study; Committees with quality improvement responsibilities; Office of Human Research Protections; Food and Drug Administration; National Institutes of Health or Other governmental offices, such as a public health agency or as required by law.

Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them. You do not have to sign this consent form. If you choose not to sign, it will not affect your treatment, payment or enrollment in any health plan or affect your eligibility for benefits. However, you will not be allowed to be a participant in this research study.

You will be given a copy of this consent form. Your authorization will expire at the conclusion of this study or, if you are participating in a study designed for the development of a drug or device, your authorization will remain in effect until the drug or device is approved by the FDA or until the company's application to study the drug/device is withdrawn. You have the right to withdraw your agreement at any time. You can do this by giving written notice to your study doctor. If you withdraw your agreement, you will not be allowed to continue participation in this research study. However, the information that has already been collected will still be used and released as described above. You have the right to review your health information that is created during your participation in this study. After the study is completed, you may request this information.

Your health information will be used or disclosed when required by law. Your health information may be shared with a public health authority authorized by law to collect or receive such information to prevent or control disease, injury or disability and conduct public health surveillance, investigations or interventions. No publication or public presentation about the research study will reveal your identity without another signed authorization from you.

If you have questions or concerns about this Authorization or your privacy rights, please contact MUSC's Privacy Officer at (843) 792-8740.

Regulations require that you be given a copy of the MUSC Notice of Privacy Practices (NPP) describing the practices of MUSC regarding your health information. One can be found at the end of this form.

M. SIGNIFICANT NEW FINDINGS

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

N. STUDENT PARTICIPATION

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.

O. EMPLOYEE PARTICIPATION

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.

P. 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.

Q. FUTURE CONTACT

The researcher in charge of this study might like to contact you in the future about other research opportunities. Please initial by your choice below:

____Yes, I agree to be contacted

____No, I do not agree to be contacted

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 investigators associated with this study, the sponsor, 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 that you are injured as a result of participation in this study, 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. 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 Kevin Caulfield at 808-304-2460. 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.

_____

Signature of Person Obtaining Consent Date

_____

Signature of Participant Date