Effects of Connectivity-based rTMS and State-Dependency on Amygdala Activation

NCT03746405

Informed Consent

Date of Approval: February 10th, 2020

DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study
(Effects of connectivity-based rTMS and
State-Dependency on amygdala activation)

Concise Summary:

The purpose of this study is to investigate whether applying repetitive transcranial magnetic stimulation (rTMS) over superficial cortical structures, the prefrontal cortex, is able to modulate deeper brain structure, the amygdala. Participants will undergo 2 different visits with approximately one week between each, and lasting about 2 hours each. During the first visit, participants will undergo a screening that includes medical, psychiatric screening, and urine sample. Once screening is complete, participants will receive TMS and undergo a magnetic resonance imaging (MRI) session. During the other visit, MRI acquisition will be obtained right after rTMS. Total study duration is no more than a month.

There are no known long-term health risks to the use of MRI and rTMS per se, but there are potential risks that are described in this document. Some risks include: seizure, muscle-tension headache, hearing impairment, dizziness, memory impairment, trouble concentrating, and acute mood changes from rTMS. There is no direct benefits to the participants.

If you are interested in learning more about this study, please continue to read below.

You are being asked to take part in this research study because you are a healthy adult. This is a research study in the Brain Stimulation Service Center (BSRC) and the Brain Imaging Analysis Center at Duke University (BIAC). This research study conducted by Dr. Lawrence G. Appelbaum and which is funded by Duke Institute for Brain Sciences (DIBS) involves transcranial magnetic stimulation (TMS) and magnetic resonance imaging (MRI). A description of this clinical trial is available on http://www.ClinicalTrials.gov. 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.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name or other personal information will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

Research studies are voluntary and only include people who choose to take part. 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. We encourage you to talk with your family and friends before you decide to take part

in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. Please tell the study doctor or his study staff if you are taking part in another research study.

Once you read the consent form, you will be asked if you wish to participate; if so, you will be asked to sign and date this form and initial at the bottom of each page. You can choose not to participate, and you can choose to end your participation at any time during the study.

Who will be my study doctor?
If you decide to participate, Dr. Noreen Bukhari-Parlakturk will be your study doctor.

Why is this study being done?
Repetitive transcranial magnetic stimulation (rTMS) is often used as a treatment for psychiatric disease such as posttraumatic stress disorders (PTSD), however the efficacy of this approach is limited. One factor that could explain this lack of efficacy is that the shallow penetration of rTMS is insufficient to directly affect deep brain structures such as the amygdala, the brain area affected in PTSD. The goal of this study is to investigate whether applying rTMS over a superficial cortical structure (medial prefrontal cortex) showing strong connections with deeper brain structure (amygdala), can indirectly modulate the activity of the deeper structure. If successful, this approach will be applied in patient with PTSD to improve the efficacy of rTMS to treat this disease.

How many people will take part in this study?
Approximately 25 people will take part in this study at Duke.

What is involved in this study?
This study consists of 2 different visits separated by about a week (according to your schedule).

During the first visit, you will be asked to sign and date this consent form prior to any procedures. You will then be screened for eligibility: you will be asked to undergo a medical and psychiatric screening, including a questionnaire concerning psychological disorders. You will be asked to give a urine sample before participating in this study. The purpose of the urine test is to make sure you are not using any substances that could increase the risks of TMS, and for women, to make sure you are not pregnant. If you choose to take part in this study, and if you pass the screening procedure, you will then receive TMS and undergo an MRI session.

TMS: The TMS equipment consists of an electric stimulator and a wire coil. Turning the stimulator on and off produces brief electrical currents in the coil, and these currents create a short-lived magnetic field around that coil (also called a 'magnetic pulse'). The wire coil is coated in plastic in order insulate the stimulator current, it is shaped like an '8', and it is a little larger than a letter-size piece of paper. When the coil is held close to the head, the magnetic pulse induces very small electric currents in the

part of the brain that is closest to the coil. These currents are similar to the currents that the neurons in the brain produce when communicating with each other. By inducing these currents with the TMS coil, we can temporarily change the way that brain region functions, either making the region work harder or less hard. The goal of this first TMS session is to establish the lowest intensity of stimulation that will cause your neurons to depolarize. This intensity is called resting motor threshold (rMT). To establish your rMT, the TMS coil will be placed over the part of your motor cortex that controls a muscle in your hand, the first dorsal interosseous. The activity from this muscle will be recorded by placing electrodes on your hand. For each TMS pulse you will hear a clicking sound, and feel a tapping sensation on your scalp. We will first look for the exact location on your scalp that makes your finger twitch, and we will then adjust the TMS intensity to find your rMT. This procedure will take about 20 minutes.

After having assessed your rMT, you will have images of your brain taken using magnetic resonance imaging (MRI).

(f)MRI: MRI uses strong magnetic fields and radio waves to create detailed images of your brain. These images can be obtained when you are at rest to get anatomical information (structural MRI); or when you are performing a task to find the areas that become active during this task (functional MRI, fMRI). The goal of this first (f)MRI session is to localize the specific region in your prefrontal cortex which is highly connected to the amygdala. During the acquisition, you will lie on your back on a narrow bed that will be pushed into the MRI machine. The MRI technician will provide padding for your head and knees to make you more comfortable. If you are uncomfortable or feel pain because of lying down, tell the technician immediately. The technician will position your head inside a head tube, and the platform will be pushed into the MRI machine. You will hear a loud noise while the machine is collecting images, and you will wear earplugs to protect your hearing. You will be able to communicate with the technician during the study using a microphone and speaker in the MRI machine. We will first obtain structural images of your brain, and then functional images. Emotional faces will be presented to you during the acquisition, you will be asked to simply passively look at these faces. It is expected that the MRI portion of this study will take about 30 minutes. You may take a break at any time. You may stop your participation in this study at any time.

During the second visit, rTMS will be applied on your prefrontal cortex in order to investigate whether rTMS over this superficial cortical surface can indirectly modulate the activation of the amygdala. To evaluate rTMS-induced changes in your brain, MRI acquisition will be obtained right before and right after rTMS. While rTMS has been approved by the Food and Drug Administration (FDA) as a treatment for depression, in this study, rTMS will be used in a manner which is an investigational procedure, meaning that rTMS is still being tested and is not approved by the FDA.

rTMS: During this procedure you will be seated comfortably in a chair, facing a computer screen placed about 5 feet away. Earplugs will be worn to protect your hearing. Your head will be held steady by a frame with a chin rest and the rTMS coil holder, and study staff will ensure your comfort during the

entire procedure. The TMS coil will be held against your head so that the magnetic pulses can be focused on the area of your prefrontal cortex which is the most connected to the amygdala. It is assumed that rTMS is more effective when stimulations are applied while the targeted brain regions are activated, therefore to activate your amygdala, rTMS will be applied while you will be viewing emotional video-clips. To ensure your involvement in the task, electrophysiological measurements (heart rate variability and skin galvanic response) will be acquired during the stimulation, using electrodes placed over your wrist and your fingers. We will administer rTMS at a rate of 5 Hz (5 TMS pulses per second), intermittently in brief bursts of 4 seconds, separated by a break of 12 seconds, at 120% rMT. If these parameters are still investigational, they are well below the safety guidelines. You will be required to sit still while you receive the stimulation. Overall, the rTMS stimulation will take approximately 40 minutes.

(f)MRI: To evaluate the rTMS-induced changes in your brain, structural and functional images of your brain will be taken for about an hour right after rTMS, and compared to the images obtained during your first visit.
These 2 visits will last 2 hours maximum each.

How long will I be in the study?
Your participation in the study will include two visits with approximately one week between each, depending on your schedule. Therefore, your participation would last one month. You may choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to the study staff or study doctor.

What are the Risks and Inconveniences of the study?
The particular treatment or procedure may involve risks to the participant, which are currently unforeseeable. Below is a list of all the known possible risks:

MRI Scanning: There are no known long-term health risks from exposure to the magnetic fields and radio waves used to make MRI brain pictures. However, it is not assured that harmful effects will not be recognized in the future. Strong magnetic fields pose safety risks because they attract metals such as iron, and radio waves can interfere with medical devices such as pacemakers. It can be dangerous for people that have medical devices, metal objects, or metal debris in their bodies to go into a MRI machine. This includes certain dyes found in some tattoos. It is also dangerous to bring loose metal objects into the room containing the MRI machine, because those objects may be pulled towards the magnet and could injure somebody in their way. For these reasons, you will be given an interview and questionnaire prior to this study to make sure that you can be safely scanned. You will be asked to leave all metal objects in lockers provided in the waiting room of the MRI center. You will also be asked to remove any jewelry and articles of clothing with metal inserts or clasps before entering the magnet room. In addition, the MRI scanner makes a loud buzzing noise that could affect your hearing. You will

be provided with earplugs and/or headphones in order to protect your hearing. Please ask the study staff or MRI technician if you are unsure about these instructions.

The study involves entering a large room in which a magnet is present. 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 be asked to lie still for about one hour on this bed. You will hear a loud machine-like noise. You may be asked to have a harmless monitoring device applied during the study. During the study, you can have voice contact and physical contact with someone in attendance if you desire.

Some people feel anxious when confined by the small space of the MRI machine. If you feel anxious or uncomfortable inside the MRI machine, you can tell the study staff over the intercom and you will be removed immediately from the MRI machine.

TMS:
The most serious known risk of TMS is convulsions (seizure), though TMS-induced seizures are very rare. In early safety guidelines (Rossi, 2008), 0.2% of reported procedures resulted in a convulsive event, while in recent consensus reviews (McClintock, 2018) such incidences dropped to 0.03% of reported procedures. TMS can produce a seizure when a series of pulses is given at high power and when repeated series of pulses are given extremely close together. This study will use only levels of TMS that are within safety guidelines. Levels of TMS that fall within the safety guidelines have not been associated with seizure in appropriately screened individuals. No seizures have occurred in normal volunteers with the dosage of TMS used in this study. To minimize this risk, we will medically screen you for any of the known characteristics that could lead to seizure. For example, persons with epilepsy cannot participate in this study. You will be visually monitored during the TMS for any signs of seizure or muscle twitching. In spite of these precautions, there is a chance that you will experience a seizure. Should this occur, all study staff is trained to respond to seizure and emergency facilities are available. If you have a seizure, you may require hospital admission and follow-up neurological evaluation. Having had a convulsion may make it difficult for you to obtain medical insurance, future employment, and to drive. It is not known whether having had one convulsion will make a person more prone to have future seizures. Should you have a seizure caused by TMS in this protocol, we will provide you with a letter documenting that the seizure was experimentally induced.

The most commonly reported side effect of TMS is a "muscle-tension" type headache. We expect that about three out of ten people may experience a headache with the types of TMS used in this study. We will make every effort to reduce any discomfort. If a headache occurs, it usually starts during or immediately after the TMS and lasts from minutes to hours after TMS. The headache usually goes away with standard over-the-counter pain medications. Neck pain may also occur. You may also experience some discomfort on your head where the coil is held. This is due to contraction of scalp muscles. If this occurs, topical lidocaine cream may be applied to the area of the scalp where stimulation will occur. Topical lidocaine is a local anesthetic which work by blocking nerves from sending pain signals to the brain. It has been shown to relieve discomfort resulting from rTMS for some people. When used

sparingly and as directed, topical lidocaine is generally safe. However, it should not be used on large areas or irritated skin. Twenty minutes must be allowed for the lidocaine cream to take effect, at which point TMS can be resumed should you still choose to participate.

Numbness of the face lasting for a short time has also been reported in rare instances that may last for several weeks after receiving the procedure. Syncope (fainting) is considered a rare side effect of TMS and has been reported in individuals who faint during blood draws. If you should experience syncope, you will be withdrawn from the study and have your blood pressure monitored until it returns to a healthy level.

The clicking noises produced by the TMS procedure are loud enough to be damaging to your ears. You will therefore be required to wear earplugs, provided by the experimenter.
Additional side effects considered to be rare in TMS are dizziness, memory impairment, trouble concentrating, and acute mood changes. If these occur, these effects do not last long and will resolve without need for treatment. There may be other risks that are currently unknown. The long-term effects of rTMS are not known.

There is also a risk of potential loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

If you experience any adverse events (a bad effect) after leaving the TMS laboratory, please contact Dr. Bukhari-Parlakturk at 919-970-2151. If outside regular business hours, please contact in emergency situations. Should your doctor need to contact Dr. Bukhari-Parlakturk, she can be reached at 919-970-2151.

For women of child-bearing potential:
The effects of the study tests on a developing pregnancy are unknown, and therefore women who are pregnant or planning a pregnancy are excluded from the study. If you are a woman who could possibly become pregnant (you have not completed menopause, or you have not had a hysterectomy and/or both tubes and/or both ovaries removed), a urine pregnancy test will be performed prior to each TMS/MRI study and it must be negative in order to continue. Although there are no study-associated risks to pregnancy in between the imaging sessions, if you become pregnant during the study you will not be able to continue. If you have a partner who is able to father children, you must use an effective method of birth control until your last study visit. Effective methods include (a) partner vasectomy, (b) bilateral tubal ligation, (c) intrauterine devices (IUDs), (d) hormonal methods (birth control pills, implants, injections, patchs, vaginal rings, or (e) barrier methods (condoms, diaphragms, cervical caps) with a spermicide.

What about research related injuries?
Immediate necessary medical care is available at Duke University Medical Center in the event that you

are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, please call Dr. Appelbaum at 919- 613-7664 or Dr. Bukhari-Parlakturk at 919-970-2151.

Are there any Benefits in taking part in the study?
This research study is not a diagnostic medical test and will be of no direct benefit to you. We hope that the information we collect in this study will improve our knowledge about the function of the human brain.

Incidental MRI Findings:
Medical specialists will not examine the research brain pictures. If you believe that you require a diagnostic MRI test, you should discuss your concerns with your doctor. The brain pictures obtained during this study are for research only and are not designed to search for any existing brain abnormalities. The study staff at Duke is not responsible for a failure to find any existing brain abnormalities. However, in the unlikely event that the technician or study staff collecting the scans notices something that appears abnormal, the technician will ask your permission to obtain an additional set of brain pictures that will be shown to a medically trained expert for clinical evaluation. The results of this evaluation will be provided to you at no charge. The decision to proceed with further examination or treatment based upon this evaluation lies solely with you. You will be responsible for any treatment that you undertake based upon this evaluation.

What are the Costs?
There will be no costs to you for the research procedure and your participation in this research study.

What about Compensation?
You will be paid $20 per hour for participating in this study. The total amount of time required for participating in this study will be about 4 hours. Therefore, total compensation for completion of the study is $80.If you withdraw from the study, your remuneration will be pro-rated according to the actual total number of hours you spent in this study. Payments will be issued in check form and mailed to your home. Payment will be processed and sent for your receipt within a few weeks of your completion of the study.

Will my information be kept confidential?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential. Your personal information may be viewed by individuals involved in analyzing, funding, and regulating the study. Your personal information may also be given out if required by law.

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As part of the study, results of your study-related activity may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, the Duke University Health System Institutional Review Board, and others as appropriate. While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name or other personal information will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

What about my Rights to Decline Participation or Withdraw from the Study?
You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. Nonparticipation or withdrawal from this study will not affect your job status if you are a Duke employee and will not affect your grades if you are a Duke student. If you do decide to withdraw, we ask that you contact Dr. Dr. Appelbaum in writing and let him know that you are withdrawing from the study. His email address is: greg@duke.edu

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Dr. Appelbaum may decide to take you off this study without regard to your consent according to anticipated circumstances such as: inability to comply with study instructions; resting motor threshold higher than 83% of the maximum stimulator output (as we won't be able to apply rTMS at the correct intensity), inability to make your scheduled session appointments. If this occurs you will be notified.

Whom Do I call If I Have Questions or Problems?
For questions about the study or research-related injury or if you have problems, please call Dr. Appelbaum at 919- 613-7664 or Dr. Bukhari-Parlakturk at 919-970-2151.

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For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668- 5111.

STATEMENT OF CONSENT

"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____	_____	_____
Signature of Subject	Date	Time
_____	_____	_____
Signature of Person Obtaining Consent	Date	Time