Protocol Title: The effect of transcranial magnetic stimulation to the frontoparietal attention network on anxiety potentiated startle.

Date: 7/23/2021

NCT03027414

INSTITUTE: National Institute of Mental Health

STUDY NUMBER: 17-M-0042 PRINCIPAL INVESTIGATOR: Christian Grillon, PhD

STUDY TITLE: The Effect of Transcranial Magnetic Stimulation to the Frontoparietal Attention Nework on Anxiety Potentiated Startle

Continuing Review Approved by the IRB on 09/13/18
Amendment Approved by the IRB on 12/04/18 (G) Date Posted to Web: 12/21/18
TMS & Anxiety Healthy Volunteer Consent

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Purpose of This Study

The purpose of this study is to see how brain stimulation [transcranial magnetic stimulation (TMS)] affects fear and anxiety through memory and attention tasks. We hope to better understand brain processes related to fear and anxiety.

Background

Understanding the brain processes related to threat is very important for understanding fear and anxiety. Previous research has shown that the brain and body respond differently when something unpleasant is expected compared to when it is unexpected. Responses to fear and anxiety may differ in tasks that require more memory and attention. Performing a task can sometimes lessen anxiety by distracting people from the stress. TMS will better help identify these brain processes when people perform one of two possible tasks (i.e. a memory or passive task) in two situations. One

situation is when people feel safe. The other situation is when people are threatened by the possibility of receiving an electric shock.

Study Population
184 healthy individuals will be in this study.

Who Can Be In This Study
You may be eligible for this research study if:
- You have been screened through protocol #01-M-0254 and have been found eligible to participate in this study.
- You are between 18-50 years of age.
- You have the capacity to give your own consent.
- You are right-handed.

Who May Not Be In This Study
You may not be eligible for this research study if you:
- Do not speak English.
- Have a medical condition that might make your participation unsafe or would interfere with the study results. For example, you cannot participate if you have heart disease, a history of chest pain, respiratory illness, or seizures.
- Have a current or past psychiatric disorder like depression, anorexia, bulimia or anxiety.
- Are currently suicidal or have been in the past.
- You have a parent, brother, sister or child who has or has had psychosis or bipolar disorder
- Have abused alcohol or drugs in the past year or have ever had alcohol or drug dependence.
- Take certain medications that act on the central nervous system.
- Have had a seizure or history of epilepsy, stroke, brain surgery, head injury, cranial metal implants, or known structural brain lesion.
- A first-degree relative has had a seizure or history of epilepsy
- Are at an increased risk of seizure.
- Are pregnant.
- Have had problems with your wrists or arms, such as carpal tunnel syndrome.
- Test positive on a urine drug test during screening.
- Have an IQ lower than 80.
- You are an employee or staff of NIMH or an immediate family member of a NIMH employee or staff.
- Any medical condition that increases risk for fMRI or TMS:
    - You have metal in your body which would make having an MRI scan unsafe, such as pacemakers, stimulators, pumps, aneurysm clips, metallic prostheses, artificial heart valves, cochlear implants or shrapnel fragments, or if you were a welder or metal worker, since you may small metal fragments in the eye.
    - You are uncomfortable in small closed spaces (have claustrophobia) and would feel uncomfortable in the MRI machine
    - You are not able to lie comfortably on your back for up to 60 minutes.
    - You have a history of hearing loss.

Procedures
You will have screening examinations to see if you are eligible for this study under another of our protocols, protocol #01-M-0254, for which you will sign a separate consent. By signing this consent form, you are giving us permission to

use information obtained under protocol #01-M-0254 in this study. No procedures will be done until the consent is signed.

The study requires two outpatient visits (1 MRI visit and 1 TMS visit). All visits will take place at the NIH Clinical Center in Bethesda, MD. The first visit will take place at the NMR center. The second will take place on the 7th floor of the Clinical Center. Visits will be separated by ~1 week (no more than 2 weeks), according to your availability and may last up to 3 hours.

We do not know if fMRI or TMS can harm pregnancy or fetal development. Women who are able to become pregnant will have a pregnancy test before fMRI or TMS. You will not be able to participate if the pregnancy test is positive. During each visit, you will complete questionnaires about your mood and thinking. The questionnaires may be completed on paper or on a computer. The questionnaires will take *approximately 15 minutes* to complete.

First visit: The first visit will consist of tasks within a magnetic resonance imaging (MRI) machine. You will not receive any shocks or loud, sudden noises during this visit.

MRI:
Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves to take pictures of your brain. Functional MRI (fMRI) allows us to see what parts of the brain are used when you do a task. The MRI scanner is a cylinder surrounded by a strong magnetic field. During the MRI, you will lie on a table that can slide in and out of the cylinder. You will do a task during the scan. You will be told about the task before the scan and you may have the opportunity to practice.

You will be in the scanner about one hour. During the scan, you may be asked to do the study task or you may be asked to lie still for up to 60 minutes at a time. While in the scanner you will hear loud knocking noises and you will be fitted with earplugs or earmuffs to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan and you may ask to be moved out of the machine at anytime.

Study tasks:
For part of the scan, you will be asked to lie still with your eyes open and stare at a point on the computer screen for 10 minutes. You will be asked to remain as still as possible and to not fall asleep. You will also do a brief memory task during the scan. You will be told about the task before the scan and you may have the opportunity to practice. There is a computer screen that you can see when you are inside the scanner. The screen will show you task information.

Second visit: The second study visit you will receive transcranial magnetic stimulation (TMS) while completing one of two tasks. Both tasks will include stressful and non-stressful conditions. You may receive electric shocks or hear loud, sudden noises during certain conditions.

Shock and startle workup:
At the start of the visit, small metal disk or sticky pad electrodes will be taped to one of your wrists or to your fingers. The shocks feel like a rubber band snapping against the skin. You will have a small sample shock to see how it feels. We will slowly increase the level of the shock based on your report. We will try to find a level of shock that is uncomfortable but tolerable. We will use that level of shock during the study. You may also hear loud, sudden noises through headphones. We will give you sample noises before the start of the task. The noises may be unpleasant. If you cannot or do not want to tolerate the shock or noises, your participation will be complete. You will not continue the study. Once we have determined the level of shock that will be used, we will start the experiment.

TMS:
For transcranial magnetic stimulation (TMS), a wire coil is held on the scalp. A brief electrical current passes through the coil and creates a magnetic pulse that stimulates the brain. You will hear a click and may feel a pulling sensation on the skin under the coil. There may be a twitch in muscles of the face, arm or leg. We may ask you to tense certain muscles or perform simple actions or tasks during TMS. At some points in the experiment you will have real TMS. At other points you will have fake (sham) TMS. The fake TMS will sound and feel much like the real TMS, and you will likely not be able to tell which type of TMS you are receiving. The points where you will receive real vs. fake TMS will be chosen randomly (like flipping a coin).

Study Tasks:
You will be randomly assigned to one of two tasks while receiving TMS. The memory and attention tasks will ask you look at words, shapes and letters on a computer monitor. You will be asked to pay attention to them or remember them. You will answer questions about what you remember. The sub-study task you have been assigned is checked below.

____ You will look at a series of letters. You will be asked to remember the letter and the number of when it was shown in the series. This is called the Sternberg task.

____ You will see colored shapes. These shapes will tell you if you may or may not receive shocks or hear loud noises. This is called the NPU task.

Both thinking and memory tasks will be done during times when you may receive a shock or hear loud noises, and other times when you will not receive a shock.

Storage and Sharing of Data
Your data will be stored securely on the NIH campus. Your name and identifying information will not be on the data. The data will either have a code that links to your identifying information or will be stored without a code linking them to you. If they are coded, the key to the code will be kept at NIH in a separate, secure area and will not be shared.

Your data may be shared with others, including those not at NIH. Your data may be sent to a repository for storage and may be released for research purposes. Some repositories restrict access to the data they contain to researchers and projects they approve. Some repositories permit unrestricted access. The data may be used for other research projects, including those not related to anxiety. If you do not want your data used for other projects, you should not participate in this study.

Research using data from this study may lead to new tests, drugs, or devices with commercial value. You will not receive any payment for any product developed from research using your data.

If you withdraw from this research study before it is done, we will keep and continue to use data that have already been collected. Your privacy will be protected as much as possible.

Risks, Inconveniences and Discomforts

MRI: You may be at risk for injury from the MRI magnet if you have some kinds of metal in your body. It may be unsafe for you to have a MRI scan if you have a pacemaker or other implanted electrical device, brain stimulator, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for such metal before having any scan. If you have any, you will not receive an MRI scan. If you have a question about metal in your body, you should inform us. You will be asked to complete an MRI screening form before each MRI scan you have.

All magnetic objects must be removed before entering the MRI scan room. This includes items like watches, coins, jewelry, and credit cards.

It is not known if MRI is completely safe for a developing fetus. Therefore, all women who are able to get pregnant will have a pregnancy test done no more than 24 hours before each MRI scan. The scan will not be done if the pregnancy test is positive.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

TMS: Strong contractions of scalp muscles from TMS can cause discomfort or headache. If the procedure is too uncomfortable, you may stop it at any time. Headaches usually go away on their own or with over the counter medicine. The noise of the TMS magnet can damage hearing, so you will be fitted with ear protection which must be worn during TMS. TMS can interfere with implanted medical devices. You will not be able to have TMS if you have a pacemaker, implanted pump, a stimulator (such as a cochlear implant) or metal objects inside the eye or skull. Please let us know if you have any of these or hearing loss.

There is a very small risk of seizures if rTMS is done with very intense, high frequency stimulation or with trains of stimulation separated by a second or less. We will not use this type of stimulation in this study. Some people may feel faint when they receive TMS. This usually goes away if TMS is stopped. Please let us know if you begin to feel faint, and we will immediately stop the TMS. The effects of rTMS on fetal development are unknown. You will not be able to have rTMS if you are pregnant. Women who are able to get pregnant will have a pregnancy test before each rTMS session.

Scalp stimulation: The scalp stimulation is not dangerous. If you find the stimulation too uncomfortable, you can stop the experiment and withdraw from the study at any time.

Study tasks: The tests may be frustrating. You may refuse to answer any question or to stop a test at any time and for any reason.

Loud Noises: The loud noises are unpleasant but not harmful. They may make you jump at first or make you anxious.

Electric shocks: The electric shocks that you will receive are intended to make you anxious. They are not dangerous. We will try to find a level of intensity that is unpleasant, but tolerable. If you find the shocks too uncomfortable, you can stop the experiment and withdraw from the study at any time.

Monitoring: There are no medical risks from monitoring your heart, breathing or sweating. There may be slight skin irritation from the tape or paste used to place the electrodes or equipment on your skin.
Questionnaires: There is minimal medical risk in completing the questionnaires. Some of the questions may make you feel uncomfortable or anxious. You may refuse to answer any question or to stop a test at any time and for any reason.

Urine Collection for Pregnancy Testing: There is little medical risk or discomfort from giving a urine sample.

Risks of Storage and Sharing of Data:
Even though we will remove information that could identify you from data that are sent to repositories or shared, there is a very small chance that the data could be identified as yours.

Anticipated Benefits
There is no direct benefit to you from participating in this research study, however, we hope to learn more about TMS and anxiety disorders.

Right of Withdrawal and Conditions for Early Withdrawal
You may withdraw from the study at any time and for any reason without loss of benefits or privileges to which you are otherwise entitled. We can remove you from the study at any time if we believe that continuation is not in your best medical interest or if you are unable to comply with the requirements of the study.

Results From this Study
The information we obtain from this study will not provide information on your health. You will not receive any individual results.

Alternatives to Participation or Treatment
The alternative to participating in this study is not to participate.

Compensation and Travel costs
You will be compensated for research-related discomfort and inconveniences in accord with NIH guidelines. You will receive $170 per visit. If you are unable to finish the study, you will be paid for those parts completed. NIH employees and staff who participate during work hours must have permission from their supervisor. NIH employees must either participate outside of work hours or take leave in order to receive compensation.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact Dr. Christian Grillon, in Building 15k, Room 203, 301-594-2894.

You may also call the Clinical Center Patient Representative at (301) 496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM SEPTEMBER 13, 2018 THROUGH SEPTEMBER 03, 2019.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____