Protocol Title: Task-dependent effects of TMS on the neural biomarkers of episodic memory
NCT#: NCT04694131
Document Date: 12/06/2022

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STUDY TITLE: Task-dependent effects of TMS on the neural biomarkers of episodic memory

STUDY SITE: National Institute of Neurological Disorders and Stroke, NIH

Cohort: Healthy Volunteer

Consent Version: 12/06/2022

WHO DO YOU CONTACT ABOUT THIS STUDY?

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KEY INFORMATION ABOUT THIS RESEARCH

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). This section provides the information we believe is most helpful and important to you in making your decision about participating in this study. Additional information that may help you decide can be found in other sections of the document. Taking part in research at the NIH is your choice.

This research study examines how different memory systems communicate. We will use transcranial magnetic stimulation (TMS) to temporarily change brain connections and see how this changes memory and patterns of activity on electroencephalogram scans.

You will come to NIH for 3 outpatient visits. Each visit will last between 2 and 3 hrs.

During the first visit, you will have a magnetic resonance imaging MRI scan. The session will last up to 1 hour. During the second visit, which will occur 1-7 days later, you will have EEG, TMS, and memory testing. The session will last for three hours. Four to fourteen days later you will have a third visit, which will also have EEG, TMS, and memory testing and last for three hours. Your involvement will last about 2-3 weeks.

There is no direct benefit to you, but it may help us discover how different memory systems communicate.

You may not participate if you are pregnant.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. 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). Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

This is a research study. The purpose of this research study is to help us learn how brain stimulation can be used to improve memory.

Transcranial magnetic stimulation (TMS) of the brain has been used to change the activity and connections in the brain to improve memory. We are interested in how these brain changes cause memory improvements and how activity at the time of stimulation may change the effects of TMS. The goal of this project is to deliver TMS during different tasks and see if it has different effects on brain activity and memory.

This could lead to ways of improving learning and memory in people with memory disorders and, perhaps, healthy people. However, it is important to know that we do not expect you to experience any noticeable changes in your memory.

We are asking you to join this research study because you are a healthy adult.

WHAT WILL HAPPEN DURING THE STUDY?

If you decide to take part in this study, you will be asked to undergo TMS which may temporarily change brain connections. We will measure those changes using EEG recording and memory tests. If you agree to participate, you will have 3 outpatient visits to the NIH. During the first visit, you will have an MRI, a clinical interview, and a physical exam. During the second visit, which will occur 1-31 days later, you will have EEG, TMS, and memory testing. 4-31 days later you will have a third visit, which will also have EEG, TMS, and memory testing and last for three hours. Your involvement will last about 2-3 weeks.

First visit: During the first visit you will have a clinical interview, physical exam and MRI.

Clinical Interview and Physical exam

One or more of the research doctors will talk to you about your health and examine you. You will be given a physical exam if you have not already had one by a NINDS physician or nurse practitioner in the last two years. This will be done for research purposes only. It does not replace any examination from your regular doctors. We will also measure your vital signs, such as blood pressure, heart rate, etc. Your medical history will also include review of your medical records and clinical tests you may have had prior to coming to the NIH. You will need to (or may have already) signed a release of records form to allow us to have access to records you want us to see.

MRI

You will also have a MRI), which may be on the same day as the exam. During the MRI, we will ask you to lie still and rest, but stay awake. If you have not had a routine, diagnostic, MRI of your brain within the last year at the NIH, you will have one (up to 20 minutes long) added to this first MRI session. If you are able to become pregnant, you will have a urine pregnancy test done on the morning before the MRI. If you are pregnant, you will not be able to continue in the study.

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 active and how they connect to each other. The MRI scanner is a metal 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. A device called a "coil" will be placed over your head.

For your fMRI scan you will be asked to keep your eyes focused on a small cross and let your mind wander. There is a computer screen that you can see when you are inside the scanner. The screen will show you the fixation cross.

You will be in the scanner about one hour, during which, you will be asked to lie still on your back. While in the scanner you will hear loud knocking noises and you will be fitted with earplugs 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 any time.

Visits two and three: You will have two experiment sessions, separated by 4-31 days. During these sessions, you will have EEG recorded while you receive TMS and complete two behavioral tasks (see below). The total time will be about 3 hours for each session. The first session will be longer because we will deliver some TMS pulses to measure your sensitivity to the stimulation. You may be asked to attend make-up sessions if there are technical problems during any of the sessions.

Behavioral Tasks

We will ask you to perform two tasks. The first is a memory task where we will show you pictures of objects in one of four different sections of the screen. You will be asked to remember those objects and their location. The second task is a spatial processing task. We will show you a series of arrows in one of four different sections of the screen. You will be asked to respond with information about the direction of the arrow.

We will also ask you to complete some surveys about your mental state. Each session of tasks will last about three hours, with three scheduled breaks.

EEG

EEG measures the electrical activity of your brain. A cloth cap with electrodes will be fitted on your head. Each electrode will be filled with a gel contacting your scalp to help the electrical signal from your brain reach the electrode. This will involve light scratching on your scalp with a sterile wooden stick to move hair aside and reduce the electrical resistance of the skin. You may have electrodes taped to your face. The cap will be in place for the full session.

TMS

For TMS, a wire coil encased in plastic is held on the scalp. When the coil is triggered a brief electrical current passes through the coil and creates a magnetic pulse that stimulates the brain. There may be a twitch in muscles of the face, arm or leg. During the behavioral tasks, we will deliver brief (2 sec) trains of stimulation right before or during task trials. We will additionally deliver single pulses of TMS independent of the behavioral task to measure your sensitivity to stimulation.

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your involvement is expected to last for approximately eight hours in three sessions over two to three weeks.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have up to 50 subjects participate in this study.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

History, Physical Examination and measurement of vital signs

There are no known risks associated with this part of the study but some of the questions may make you feel uncomfortable. We will also collect some information from your medical record. This will include information such as your age, sex, and race

Magnetic Resonance Imaging (MRI)

We will be using the MRI for investigational research. This means that the way the MRI is generating the images may be different than what is normally done in a routine clinical scan. However, the imaging done under this protocol will be performed within FDA safety guidelines. This use of these research tools in the MRI has not been approved by the FDA and is considered investigational.

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips

on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

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.

There are no known long-term risks of MRI scans.

Behavioral Tasks

The behavioral tasks are not harmful but may be frustrating or stressful. We only ask that you try your best. No one performs perfectly on these tasks.

EEG

EEG recording is not harmful, but there may be some discomfort from the cap, scratching the scalp, or the application of electrodes and gel. We will use care in securing the cap and moving hair aside to make the process as comfortable as possible. Additionally, there may be electrode gel remaining in your hair after the cap is removed. We will provide you with shampoo and sink space to clean gel from your hair if you choose.

The study will use the BrainVision actiCHamp plus EEG system for investigational research. This means that it will be used to study brain function rather than to treat patients. However, all studies done under this protocol will be performed within established safety guidelines. The use of the EEG system for research has not been approved by the FDA and is considered investigational.

TMS

We will be using the TMS System and the coil for investigational research. This means that we are using it to study brain function rather than to treat patients. However, all studies done under this protocol will be performed within established safety guidelines. The use of the TMS system and coil for research has not been approved by the FDA and is considered investigational.

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 earplugs 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 that TMS will cause an epileptic seizure, especially if it 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. The effects of TMS on fetal development are unknown.

What are the risks related to pregnancy?

If you are able to become pregnant, we will ask you to have a pregnancy test before your MRI. You must use effective birth control methods and try not to become pregnant while participating in this study. If you become pregnant, there may be unknown risks to the fetus or unborn child, or risks that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to a fetus. You must tell the study doctor if your birth control method fails while you are in the study. If you think or know you have become pregnant while participating in this research study, please contact the study team as soon as possible. If you plan to become pregnant in the future, please discuss with the study team how long you need to wait before becoming pregnant after completing the study.

What are the benefits of being in the study?

Are there any potential benefits to others that might result from the study?

You will not benefit from being in this study.

In the future, other people might benefit from this study because we hope to learn more about how brain stimulation can be used to improve memory.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Instead of being in this study, you could decide not to participate.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

All participants will have an MRI scan read by a neuroradiologist. Sometimes, there are unexpected findings on an MRI scan. Some findings are of unknown significance or importance to your health, which may make you anxious. We will inform you about any finding that may require further evaluation or care. We are not able to provide evaluation or treatment for these conditions at NIH. If needed, we will refer you to a health care provider.

EARLY WITHDRAWAL FROM THE STUDY

You may withdraw from this study at any time for any reason without loss of benefits to which you are otherwise entitled. We may end your participation in this study 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.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved for use in other research studies?

There are no specimens collected in this study.

As part of this study, we are obtaining data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use the data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding how brain stimulation can be used to improve memory, or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my coded specimens and data to be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

Will your specimens or data be shared for use in other research studies?

We may share your coded data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas that are similar to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

I give permission for my coded data to be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

If you change your mind and do not want us to store and use your data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your data. For example, if some research with your data has already been completed, the information from that research may still be used. Also, for example, if the data have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your data.

NIH policies require that your clinical and other study data be placed in an internal NIH database that is accessible to other NIH researchers for future research. Usually, these researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether your data to be placed in this database or not. If you do not wish to have your data placed in this database, you should not enroll in this study.

How long will your specimens and data be stored by the NIH?

Your data may be stored by the NIH indefinitely.

Risks of storage and sharing of specimens and data

When we store your data, we take precautions to protect your information from others that should not have access to it. When we share your data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your data.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

Some NIH Clinical Center studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines.

Participant will be compensated for time and research-related inconveniences as follows: $20 for the first hour

$10/ each additional hour

$40/ MRI scan

$40/ TMS

$20/ EEG

$20/ Behavioral test

$10/ Pregnancy test

- Payment will be provided via check or direct deposit through the NIH ATV system.

If you are unable to finish the study, you will receive compensation for inconveniences and time for the parts you completed. The maximum compensation you will receive as a subject is $600.00.

With few exceptions, study compensation is considered taxable income that is reportable to the Internal Revenue Service (IRS). A "Form 1099-Other Income" will be sent to you if your total payments for research participation are $600 or more in a calendar year. If you have unpaid debt to the federal government, please be aware that some or all of your compensation may be automatically reduced to repay that debt on your behalf.

Will you receive reimbursement or direct payment by NIH as part of your participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

This study does not offer reimbursement for, or payment of, travel, lodging or meals.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

CONFLICT OF INTEREST (COI) (INSERT THIS SECTION FOR COVERED PROTOCOLS ONLY)

The NIH reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

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.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens or data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical information that we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH 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 NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

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 the Principal Investigator, Eric Wassermann, MD, wassermanne@ninds.nih.gov, 301-496-0151. Other researchers you may call are: Kristen Warren, at 708-203-2903. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

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

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only:

Signature of Witness*	Print Name of Witness	Date