DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study: Effects of rTMS on human brain activity measured with EEG and fMRI
Pro00082433

CONCISE SUMMARY

This study aims to determine the neural basis of effects caused by TMS when applied in a sequence of pulses, known as repetitive TMS (rTMS). This technique is approved by the FDA for depression, as TMS has demonstrated the ability to stimulate the brain and affect behavior. However, we do not yet understand how TMS is able to do this. As such, this study uses multiple methods of measuring neural activity, specifically fMRI and EEG recording, simultaneous with TMS in order to capture neural activity in the moment.

Participants in this study will be asked to perform a visual motion task that allows systematic manipulation of brain activity and cognitive state. Depending on the cohort involved, participation may involve TMS, EEG, and fMRI over up to seven visits.

You are being asked to take part in this research study because you are a healthy adult. Research studies are voluntary and include only 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 study staff if you are taking part in another research study.

A grant from the National Institutes of Health (NIH) will sponsor this study. Portions of Dr. Peterchev's salary and their research team's salaries will be paid by this grant.

WHO WILL BE MY DOCTOR ON THIS STUDY?
Angel Peterchev, Ph.D. is conducting the study. R. Alison Adcock, MD will be your study doctor.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to explore how connections in the human brain interact to process information, and how this processing can be changed by the use of repetitive transcranial magnetic stimulation (rTMS). Specifically, we are pairing TMS with two other methods of collecting data on the brain (fMRI and EEG) in order to maximize our understanding of how rTMS impacts the brain's networks.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Approximately 264 people will take part in this study at Duke.

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WHAT IS INVOLVED IN THE STUDY?
If you agree to be in this study, you will be asked to sign and date this consent form. You will have the following tests and procedures to make sure that you are eligible:

- Psychiatric screening and medical history
- TMS and MRI safety screening
- Urine screening

The purpose of the urine test is to make sure you are not using any substance which could increase the risks of TMS and, for women, to make sure you are not pregnant.

If you pass the screening procedure, you will be introduced to the motion task and transcranial magnetic stimulation (TMS) in order to allow you to find out what it is like. During this time, the study team will determine the proper strength of TMS to use on you in later visits. In this study, TMS will be used in a manner which is an investigational procedure, aimed at temporarily changing the way that a part of your brain works. TMS has been approved by the Food and Drug Administration (FDA) as a treatment for depression, but in this study TMS is being used to investigate the impact it has on connectivity between certain regions of your brain, so therefore is considered "investigational." The word "investigational" means TMS is still being tested in research studies and is not approved by the FDA for these purposes. 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, and it generates a magnetic pulse, the pulse can induce 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.

Before applying TMS, the study team will determine what strength of stimulation to use for you by establishing your personal "moving phosphene and motion disruption threshold" – a measure of the excitability of the area of the human brain called the visual cortex. To establish this threshold, the study doctor or a member of the study staff will first place the stimulator over the part of your brain that controls the visual activity in your visual cortex. You will hear a clicking sound and feel a tapping sensation at your scalp. The stimulator will be adjusted to give just enough energy so that the visual region of the brain sends signals to your visual cortex, to elicit spots of light, or phosphenes, in your visual field. The smallest amount of energy required to elicit moving phosphenes, when the spots of light start to move, is called your individual "moving phosphene threshold." We will ask you to report to us when you experience these sensations, and to roughly approximate where in your visual field you see them. Additionally, we will ask you to report any disruption in motion perception while viewing moving dots on the computer screen. Alternatively, the study team will determine what strength of stimulation to use for you by establishing your personal "motor threshold" – a measure of the excitability of the area of the human brain called the motor cortex. To establish this threshold, the study doctor or a member of the

study staff will first place the stimulator over the part of your brain that controls the motor activity in your right hand. Again, you will hear a clicking sound and feel a tapping sensation at your scalp. The stimulator will be adjusted to give just enough energy so that the motor region of the brain sends signals to your hand muscles, to make your hand twitch. The smallest amount of energy required to make your hand twitch is called your individual "motor threshold."

Your second visit will be an imaging visit, when you will have pictures of your brain taken using magnetic resonance imaging (MRI). MRI uses strong magnetic fields and radio waves to make pictures. Special pictures will be taken that provide information about the areas of the brain that become active when you perform the simple motion tasks you learned in the first visit. During this part of the study, 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 pictures. You will be able to communicate with the technician during the study using a microphone and speaker in the MRI machine. You may take a break at any time. You may stop your participation in this study at any time.

You will then take part in up to two sessions pairing TMS with another data collection procedure, either fMRI or EEG. These visits will take the same amount of time (<3 hours) regardless of procedure.

For TMS-fMRI, the session will proceed in the same manner as your previous imaging visit. You will have pictures taken of your brain in the same MRI machine previously used, however you will have TMS delivered during the session.
For TMS-EEG, you will wear an EEG cap containing 64 electrodes during the session. These electrodes will record your brain activity while you receive TMS and complete the motion task you previously practiced.

HOW LONG WILL I BE IN THIS STUDY?
Your participation in this study will include up to 7 visits: two pilot sessions, the screening visit, MRI visit, and either one or two sessions of TMS paired with another source of data collection (either MRI or EEG) over the following weeks, allowing up to 3 months for participation.

You can 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 your doctor first.

WHAT ARE THE RISKS OF THE STUDY?
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). TMS procedures are associated with a very low risk of seizures. Out of over 10,000 people given various forms of TMS to date, 16 people (less than 0.2%) have been reported to have had a seizure. 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, 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. 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.

EEG:
The sticky patches may pull on your skin or cause redness or itching. Additionally, you may feel some mild discomfort in the certain areas where the testing was done. This discomfort may last about 30 minutes.

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) or study-related emergencies after leaving the TMS laboratory, please contact Dr. Adcock at 919-681-7486 during regular business hours. If outside regular business hours, please contact Dr. Adcock at 919-699-7326 in emergency situations. Should your doctor need to contact Dr. Adcock, she can be reached at 919-699-7326. If you have any questions about research design, please contact Dr. Peterchev at 919-684-0383.

For women of child-bearing potential:
Being a part of this study while pregnant may expose the unborn child to significant risks, some of which may be currently unforeseeable. Therefore, pregnant women will be excluded from the study. If you are a woman of childbearing potential, a urine pregnancy test will be done, and it must be negative before you can continue in this study. If sexually active, you must agree to use appropriate contraceptive measures for the duration of the study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use.

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If you do become pregnant during this study or if you have unprotected sex, you must inform your study physician immediately.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
This 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.

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, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

As part of the study, results of your study-related laboratory tests, x-rays, and procedures may be reported to National Institute on Aging and its affiliates. In addition, your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, representatives of the National Institute on Aging, the Duke University Health System Institutional Review Board. If any of these groups review your research record, they may also need to review your entire medical record. For records disclosed outside of DUHS, you will be assigned a unique code number. The key to the code will be kept securely in a locked filing cabinet in Room 54236, Red Zone, which is locked and only accessible to members of the study team.

The study results will not be sent to your physician to include in your medical record. However, in case you experience a seizure, the study staff will urge you to notify your primary care physician about the incidence.

The study results will be retained in your research record for at least six years after the study is completed. At that time either the research information not already in your medical record will be

destroyed or information identifying you will be removed from such study results at DUHS. Any research information in your medical record will be kept indefinitely.

This information may be further disclosed by the sponsor of this study. If disclosed by the sponsor, the information is no longer covered by federal privacy regulations.
If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

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.

The Department of Health and Human Services (HHS) has issued a Certificate of Confidentiality to further protect your privacy. With this Certificate, the investigators may not disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, unless you have consented for this use. Research information protected by this Certificate cannot be disclosed to anyone else who is not connected with the research unless:

1) there is a law that requires disclosure (such as to report child abuse or communicable diseases but not for legal proceedings);
2) you have consented to the disclosure, including for your medical treatment; or
3) the research information is used for other scientific research, as allowed by federal regulations protecting research subjects.

Disclosure is required, however, for audit or program evaluation requested by the agency that is funding this project or for information that is required by the Food and Drug Administration (FDA).

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it. This means that you and your family must also actively protect your own privacy.
Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

WHAT ABOUT COMPENSATION?
You will be paid $20 per hour for participating in this study, up to $300. This is to compensate you for your expenses related to participation (parking, gas, and time). You will have the option to participate in

this study for up to 15 hours. Fifteen hours represents the maximum possible participation, including piloting (2 x 2 hour visits) and the full study (anticipating 4 x 2 hour visits, with the possibility of makeup visits. Payments will be issued either via direct deposit within the Duke Unique ID system or by check form mailed to your home. Payment will be processed and sent for your receipt within a few weeks of your completion of the study.

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 research-related injury or emergencies, contact Dr. Adcock at 919-699-7326. For questions about research design, please contact Dr. Peterchev at 919-684-0383 during regular business hours. If outside regular business hours, please contact Dr. Peterchev at 510-710-1922.

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 other than data needed to keep track of your withdrawal.

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. Peterchev in writing and let him know that you are withdrawing from the study. His mailing address is Department of Psychiatry and Behavioral Sciences, Box 3620, Duke University Medical Center, Durham, NC 27710.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. Dr. Peterchev may decide to take you off this study if you are unable to make your scheduled session appointments. If this occurs, you will be notified.

A description of this clinical trial will be available on https://www.clinicaltrials.gov/ct2/home 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.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about emergencies or a research-related injury, please contact Dr. Adcock at 919-681-7486. If you have problems, concerns, questions or suggestions about the research, contact Dr.

DUKE UNIVERSITY HEALTH SYSTEM

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Peterchev at 919-684-0383 during regular business hours and at 510-710-1922 after hours and on weekends and holidays.
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