UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
INFORMED CONSENT FORM AND HIPAA AUTHORIZATION FORM

Protocol Title:	Task Augmentation of Transcranial Magnetic Stimulation (TMS)
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Emergency Contact:	If you have a study related medical emergency, please present to your nearest emergency room or call 911 and contact CNDS at the number listed above

Summary

You are being invited to participate in a research study. Your participation is voluntary and you should only participate if you completely understand what the study requires and what the risks of participation are. You should ask the study team any questions you have related to participating before agreeing to join the study. If you have any questions about your rights as a human research participant at any time before, during or after participation, please contact the Institutional Review Board (IRB) at (215) 898-2614 for assistance.

The research study is being conducted to The purpose of this study is to determine whether targeted stimulation using transcranial magnetic stimulation

(TMS) alone, or in combination with tasks, results in enhanced brain responsiveness. TMS is an FDA-approved non-invasive brain stimulation technique commonly used to treat a variety of disorders. You are being asked to voluntarily participate in a pilot research study because you are over the age of 18 without any current, or history of, negative mood symptoms such as depression, anxiety, or post-traumatic stress.

If you agree to join the study, you will be asked to complete the following research procedures: clinical assessments, self-report questionnaires, magnetic resonance imaging (MRI) scans, behavioral tasks, and TMS.

Your participation will last for approximately 5 – 7 weeks. This study does not require follow-up visits or biospecimen collection. This study will not provide direct benefit to individual participants, but a potential benefit of participation would be the advancement of science. The most common risks of participation are discomfort during the clinical interviews, assessments, Magnetic Resonance Imaging (MRI) scan, and Transcranial Magnetic Stimulation (TMS) treatment. You may discontinue participation in this study at any time with no loss of benefits you're otherwise entitled to. The alternative to participation is simply not to participate.

Please note that there are other factors to consider before agreeing to participate such as additional procedures, use of your personal information, costs, and other possible risks not discussed here. If you are interested in participating, a member of the study team will review the full information with you. You are free to decline or stop participation at any time during or after the initial consenting process.

Why am I being asked to volunteer?

You are being asked to voluntarily participate in a pilot research study because you are over the age of 18 without any current, or history of, negative mood symptoms such as depression, anxiety, or post-traumatic stress. Your participation is voluntary, which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled.

This consent form describes what this study is about, the possible risks and benefits of being in this study, and what we will ask you to do. The research team will explain the study and answer any questions you may have. You may also discuss it with your family, friends, or doctor. You may find some of the medical language difficult to understand, so please ask the research team about anything you would like to know. If you decide to participate, you will be asked to sign this form.

What is the purpose of this research study?

The purpose of this study is to determine whether targeted stimulation using transcranial magnetic stimulation (TMS) alone, or in combination with tasks, results in enhanced brain responsiveness. TMS is an FDA-approved non-invasive brain stimulation technique commonly used to treat a variety of disorders.

Standard methods of TMS treatment identify sites of stimulation by administering treatment to each patient in approximately the same area of the scalp. Due to this inexact targeting, standard TMS regimens are time consuming. However, recent studies suggest that identifying exact sites of stimulation for each patient we can increase the benefit and longevity of TMS as well as reduce the time required to administer.

In order to test whether tailored stimulation targets increase the benefits of TMS, each participant will undergo an MRI scan. The images collected from the scan will be used to pinpoint a specific area of the brain for stimulation called the 'Fitzgerald Target'. The Fitzgerald Target is located in the "dorsolateral prefrontal cortex" or DLPFC. Just like each person's face is unique, each person's brain is also unique. Therefore, as one person's nose may be a slightly different size or distance from their mouth than another person's the exact location of the 'Fitzgerald Target' in your DLPFC may be a slightly different size or distance from others.

We are asking 25 adults without any history of, or current negative mood disorders (such as depression, anxiety, & post-traumatic stress) to participate in this study.

How long will I be in the study?

Overall, this study is expected to go on for 6 months. If you agree to take part in this study, your participation will last approximately 5 - 7 weeks.

Each visit will take the following approximate amount of time:

- Screening Visit: 2 hours
- Visit 1 - Baseline MRI Scan: 1 hour
- Visit 2 – Initial Task MRI: 2 hours
- Study Visits 3 – 5: 2 hours each
    - Includes 1 hour MRI scan after Visit 4
- 7 – 14 day break pending participant availabilityStudy Visits 6 – 8: 2 hours each
    - Includes 1 hour MRI scans before Visit 6 and after Visit 8

Please note that these times are approximates, some participants may take more time and some may take less time to complete these visits.

Where will the study take place?

You will be asked to come to the offices of the Center for Neuromodulation in Depression located in the Richards Building on the campus of the University of Pennsylvania. The times of study visits will depend on MRI scanner availability, your schedule, and study staff schedule, but will occur on weekdays typically during business hours.

What am I being asked to do?

If you agree to take part in this research, you will be asked to complete the following:

- **Clinical assessments with Study Staff**: regarding your thoughts, feelings, and behaviors, and thoughts of death, dying, or suicide.
- **Self-report Questionnaires**: regarding your thoughts, feelings, and behaviors.
- **Behavioral Tasks**: you will be asked to learn 3 different computer-based tasks. These tasks will ask you to view various images or letters and respond to questions based on the images you saw. All instructions will be provided beforehand.
- **Randomization**: like a coin-flip, randomization allows researchers to assign participants to groups without bias. Participants in this study will be randomized after Visits 1& 2
    - Visit 1 Randomization: assigns the order in which you complete 3 different behavioral tasks
    - Visit 2 Randomization: determines which of the 3 behavioral tasks you'll complete for the remainder of your study participation (Visits 3 - 8). This randomization will also assign you to receive 'Active TMS' or 'Sham TMS' for visits 3 - 5. You will then receive the opposite for visits 6 – 8. Study staff will not inform you which group (active TMS or sham TMS) you are randomized to receive first.
- **TMS with MRI:** your brain will be non-invasively (i.e. from the scalp) stimulated by magnetic pulses. For this procedure, you lie down in the MRI machine and will be asked to wear ear plugs as well as a swim cap to ensure the stimulation site remains consistent. A plastic-coated magnetic coil will be held against your scalp. You will hear a clicking noise as magnetic pulses are produced in the TMS coil. These magnetic pulses induce brief activity in brain areas underlying the TMS coil. Stimulation intensity will be calibrated according to the amount of energy needed in the coil to induce activity specifically for your brain. To determine the stimulation level, the researchers will move the intensity of the stimulation until it causes either your thumb or finger to twitch (when the coil is place over the part of the brain controlling movement on the other side of the body) or causes you to see a blob of light (when the coil is placed on the

back of your head). This calibration is done to ensure that sufficient stimulation intensity is used for each individual without excessive stimulation.

- **Magnetic Resonance Imaging (MRI) Scan**: an MRI uses electromagnetic radiation (radio waves) in a strong magnetic field to take clear pictures of your brain. These pictures will help us identify the precise location of your Fitzgerald target. In other words, exactly where the TMS should be administered on your head. You will be asked to lie still on a table in the MRI machine for 1, 2-hour scan & 5, 1-hour scans.

Procedure	Screening Visit	Visit 1 Baseline MRI	Visit 2 Initial Task MRI	Visit 3 & 4	Visit 5	Visit 6 & 7	Visit 8
Clinical Assessments	X						
Self-Report Questionnaires	X			X		X	
MRI Scan		X	X		X		X
Behavioral Tasks		X	X	X	X	X	X
TMS *(test pulse at Screening)*	X		X	X	X	X	X

What are the possible risks or discomforts?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

Clinical interviews and assessments: Some discomfort may be associated with the clinical assessments conducted in this study. You may experience emotional discomfort when answering some questions in the questionnaires or when talking about personal information. You may choose not to answer any of the questions and to terminate your participation.

MRI scan:

- **Claustrophobia**: You may experience claustrophobia (fear of enclosed spaces and/or anxious feelings accompanied by fast heart rate or shortness of breath) within the MRI scanner. A MRI scan requires you to be in a partially enclosed space inside the scanner. Some people may find this to be uncomfortable and claustrophobic. You need to inform the doctor ordering the scan, or the study staff, if you suffer from claustrophobia.

- **Magnetic Fields**: There is no known health risk associated with exposure to magnetic fields during an MRI. There are minimal risks from the loud noise associated with the MRI scanner and from the discomfort of lying on a hard surface. We shall provide you with protective earplugs as necessary and make every attempt to ensure your comfort with blankets, etc. during your time in the scanner.
- **Medical Implants & Foreign Bodies**: There is also a potential risk of MRI for subjects with medical implants or other metallic objects in their body. All subjects undergoing MRI scanning must complete a screening evaluation risk in advance of the study for the presence of medical implants or other foreign bodies that could pose an injury. Every effort will be made to insure that disclosed implants or foreign bodies do not pose a risk to subjects. In cases where there is insufficient information to evaluate the risks associated with an implant or foreign body, the MRI study will not be allowed to proceed.
- **Flying Objects**: The greatest risk of MRI is a magnetic object flying through the air toward the magnet and hitting you. To reduce this risk we require that all people involved with the study remove all magnetic metal from their clothing and all magnetic metal objects from their pockets. No magnetic metal objects are allowed to be brought into the magnet room at any time except by approved personnel. In addition, once you are in the magnet, the door to the room will be closed so that no one inadvertently walks into the room.
- **Research**: Some of the MRI pulse sequences and equipment components are not FDA-approved but are considered to pose no more than minimal risk.
- **Incidental Findings**: This MRI is not a clinical scan. It is possible that during the course of the research study, the research staff may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will inform you if necessary. These possible finding(s) may or may not be significant and may lead to anxiety about your condition and to further work-up by your physician.
- **Pregnancy**: Although there are no known risks related to MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no possible benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women.

TMS: this study utilizes two forms of Transcranial Magnetic Stimulation (TMS): intermittent Theta Burst Stimulation (iTBS) & single pulse TMS. TMS is a FDA-approved non-invasive brain stimulation technique for a variety of diagnoses. As with any technique, there may be long-term risks due to TMS that are currently unknown. The most common side effect of TMS (approximately 25% of patients) is a mild headache. There are no known long-term adverse effects reported with the use of this device. Rarely, device malfunction could result in a scalp burn (less than 1% of patients). There may be long-term risks that are currently unknown.

- **Magnetic Fields**: produced during TMS treatment the stimulation intensity used are thought to be without harm. The exception is if you have a cardiac pacemaker, or a certain type of metallic clip in your body (i.e., an aneurysm clip in your brain). Participants with these devices will be excluded from this study, as TMS could cause these object to heat up, move, or malfunction. Objects such as watches and credit cards should also be removed as these could be damaged.
- **Certain Medical Diagnoses**: for patients with epilepsy, activation of the brain by TMS could also activate a seizure. Patients with stroke may be at increased risk for a seizure due to the brain scar. Therefore those with history of epilepsy or stroke will be excluded from the study. For a typical physically healthy person, a TMS-induced seizure in this experiment is very unlikely.
- **Noise**: the TMS device produces a clicking sound. To minimize this possibility, you will be given protective earplugs or headphones.
- **Nausea**: although it is uncommon, approximately 5% of subjects have experienced nausea during the experiment. You can discontinue the experiment if you experience any discomfort during the study.
- **Mild Swelling or Bruising**: You may also experience temporary and local bruising, swelling, or pain from the swim cap and/or muscle activation by TMS.

Risk to confidentiality: There is a rare risk that confidentiality could be breached in this study. Breaches in confidentiality could impact your future insurability and/or employability.

Will I receive the results of research testing?

Most tests done in research studies are only for research and have no clear meaning for health care. Research results will not be returned to you because they would not be relevant to your health care. However, as discussed in the MRI scan risks section above, it is possible that during the course of the research study, the research staff may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will inform you if necessary. These possible finding(s) may or may not be significant and may lead to anxiety about your condition and to further work-up by your physician.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?
There are no direct benefits to you for your participation in this study. One potential benefit of participation includes the advancement of science.

What other choices do I have if I do not participate?
This is a voluntary study. If you choose not to participate, there will be no loss of benefit to you.

Will I be paid for being in this study?
You will receive compensation for your time and participation, up to $200.00 if you complete the entire study.

Your payments will be given to you in the form of a Greenphire ClinCard. This is a reloadable prepaid card (similar to a debit/credit card) that allows funds to be available immediately. Please note that payments of $100.00 or more may take up to 1 full business day to appear available on your ClinCard. You can use it for in-store or online purchases by selecting the “Credit” option at check-out, or it can be cashed out by presenting to a teller at any MasterCard member bank (look for a MC logo on the bank window). Study staff will provide you with a “ClinCard Cardholder FAQ: US” document to help answer any questions you may have.

Please note: In order to be compensated for your participation in this study, you must provide your Social Security Number. Additionally, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year

Will I have to pay for anything?
You will not have any costs for participating in this research study. The administration of all procedures will be covered by the study.

What happens if I am injured from being in the study?
We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them. If you are injured, you should inform the physician who treats you that you are participating in this study.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

This research may involve risks that are currently unforeseeable. University of Pennsylvania investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study,

please contact the investigator, Dr. Yvette Sheline at:
sheline@pennmedicine.upenn.edu

When is the study over? Can I leave the study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. Your personal participation in the study will last approximately 6 weeks. This study may be stopped by you at any time. It may also be stopped by the Principal Investigator, the study Sponsor, or the Food and Drug Administration (FDA) without your consent if:

- The Principal Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor or the study Principal Investigator has decided to stop the study.
- Other administrative reasons
- Unanticipated circumstances

If you decide to participate, you are free to leave the study at any time. There are no medical risks involved in the early termination of this study.

Who, outside of the School of Medicine, might receive my information?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy.

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- Government representatives, (including the Office for Human Research Protections) to complete federal or state responsibilities
- The U.S. Food and Drug Administration
- Hospital or University representatives, to complete Hospital or University responsibilities
- University Pennsylvania's Institutional Review Board (a committee that oversees the conduct of research involving human participants).

Once all hard copy records are collected, they will be kept in a double-locked environment. Data collected during the study will be entered and stored in a password-protected database, accessible only to engaged study members. All electronic data will be coded and assigned a randomly generated research identification number. If we write a report or article about this study or share the

study data set with others, we will do so in such a way that you cannot be directly identified.

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form.

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form. When possible, the research team will make sure information cannot be linked to you; that is, the information will be de-identified. Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form.

Future Use of Data

Your information will be de-identified. De-identified means that all identifiers have been removed. The information could be stored and shared for future research in this de-identified fashion. It would not be possible for future researchers to identify you as we would not share any identifiable information about you with future researchers. This can be done without again seeking your consent in the future, as permitted by law. The future use of your information only applies to the information collected on this study.

Who may use and share information about me? During your participation, you will be asked to provide your name, address, telephone number, email address, date of birth, and your social security number (so that we may compensate you for participation). This identifiable information will be held in strict confidence and will be kept in password protected files behind locked doors. Your personally identifying information will not be linked to any of the data that is analyzed and reported. All data will be de-identified when reported.

You will also be asked to answer questions about your medical history including questions about your physical and mental health. All research data will be de-identified and assigned a randomly generated research identification number. All information obtained will be kept completely confidential and will be in locked files behind locked doors. Electronic data will be encrypted and password protected.

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures also are used to:

- Do the research

- Oversee the research
- To see if the research was done correctly.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

You will be given a copy of this Research Subject Informed Consent Form and HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document you are permitting the School of Medicine to use and disclose personal health information collected about you for research purposes as described above. If you do not sign this form, you will not be able to participate in the study.

If you decide not to participate, it will not affect

- Your treatment or the care given by your health provider.
- Your insurance payment or enrollment in any health plans.
- Any benefits to which you are entitled.

If you sign this form:

- You authorize the use of your PHI for this research

- Your signature and this form will not expire as long as you wish to participate.
- You may later change your mind and not let the research team use or share your information

If you revoke your authorization:

- The research team may only use and share information already collected for the study.
- Your information may still be used and shared if necessary for safety reasons.
- You will not be allowed to continue to participate in the study.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

For general questions or for scheduling, please call the Center for Neuroscience of Depression and Stress at 215-746-2637. If you have concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, please call the study supervisor at 215-746-2637. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

How will I be contacted?

We would like to contact you by phone, email, or mail in order to arrange your appointments. Some of these messages may contain information that identifies you. We will also be contacting you in the future, after the conclusion of the study, in order to follow up on your status. We will ask you to provide contact information for an additional individual who knows where to find you in the event that we cannot reach you.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

_____
Name of Subject (Please Print)

_____
Signature of Subject Date

_____
Name of Person Obtaining Consent (Please Print)

_____
Signature Date