MINI THETA BURST TMS IN MDD PATIENTS (NARSAD)

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Investigational Product: MagPro X100* magnetic stimulator
Cool-B65 Butterfly Coil

IRB Number: 825761

ClinicalTrials.gov Number NCT04014959

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

Protocol Title:	Mini Theta Burst TMS to Promote Brain Plasticity Indexed by fMRI
Study Sponsor:	Brain and Behavior Research Foundation
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Emergency Contact:	If you have a study-related medical emergency, please contact the study staff or call 911.

Why am I being asked to volunteer?

You are being asked to voluntarily participate in a research study because you are between the ages of 18-60, you are experiencing depression, and you expressed an interest in participating. 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. We will be recruiting 45 subjects to participate.

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?

Participating in this study is not expected to treat your depression, but we hope that the information gained from this study will help guide treatment for future patients. The purpose of this research study is to implement and develop brain imaging methods for characterizing and treating psychological disorders. Results of the study will provide brain and behavior measures for future work, which may be critical to developing effective disease markers and novel treatments for psychiatric conditions.

We will ask you to complete three imaging sessions using a magnetic resonance imaging (MRI) scanner. MRI scans are commonly used by doctors to take pictures of your brain and to look at structures in the body. During three of the imaging sessions, we will also ask you to undergo non-invasive brain stimulation, called transcranial magnetic stimulation (TMS).

How long will I be in the study?

If you agree to take part in this study, your involvement will include seven closely-spaced study visits, one of which is an initial screening session.

Your participation will involve:

- **Visit 1**: **Initial Screening Session**. This will include a medical history, psychiatric interview, and a demonstration of the TMS procedures. The visit will be used to determine your eligibility for the current study, and will last approximately 3 hours.
- **Visit 2**: **Initial MRI Scan.** There will be one MRI scan, which will take place over a single 1-hour session.
- **Visit 3: TMS/ MRI Scan #1.** A second MRI scan will be done with TMS. We will spend 30 minutes marking sites on a swim cap to target areas of your brain for stimulation, and then you will spend 2 hours in the MRI scanner, where TMS will also be administered. You will also be asked to complete some baseline clinical and neuropsychological assessments, which will take approximately 1 hour to complete.
- **Visits 4-6**: **Three TMS visits**. At each visit, we will spend 20 minutes marking sites on a swim cap to target areas of your brain for stimulation; then we will administer TMS over the course of approximately 1 hour. We will also conduct a few short clinical assessments at these visits.
- **Visit 7**: **TMS/ MRI Scan #2.** A third MRI scan, also including TMS, will be administered. We will spend 30 minutes marking your target brain areas on a swim cap, and then you will spend 2 hours in the MRI scanner, where TMS will also be administered. The same clinical assessments as Visit #3will be re-administered.

In some instances, if you are also participating in one of our other studies at the CNDS, then some of the same procedures (i.e., baseline scan if done within ~1 month of Visit 3) may be used for both studies; in this case, the repeated procedures would not need to be repeated.

See below chart for an outline of all study visits.

Procedure	Visit 1: Screening (3 hrs)	Visit 2: Initial MRI (1 hr)	Visit 33: TMS+ MRI Scan 1 (3 hrs)	Visits4-6: Mini-TMS (1 hr each)	Visit 7: TMS+MRI Scan 2 (3 hrs)
Informed Consent	X				
Medical History	X				
MRI		X	X		X
TMS	X (demo)		X	X	X
Clinical Assessments			X	X	X

What am I being asked to do?

Medical History

We will ask you questions about your medical history. Because we require participants to abstain from drug use for the duration of the study, we may ask you to complete a urine drug screen to confirm adherence to this policy. This is to ensure patient safety and data quality. For this drug screen, we will use a secure urine analysis; the test will be collected by study staff. Results are available within approximately five minutes of collection. We will record the test results in our secure online database, which only team members have access to. We will then destroy the test immediately after.

Clinical Assessments

We will ask you questions about your psychological history. This may include descriptions of how you are feeling and other various symptoms.

Neuropsychological testing

We will conduct neuropsychological tests to assess your attention, concentration and memory. These tests will involve a combination of oral and written procedures.

MRI scans

We will ask you to undergo multiple MRI scans of your brain. For an MRI, you will be asked to lie still on a padded table in the scanner while images of your brain are obtained. The scanner produces loud repetitive knocking

noises during the study that some people find bothersome. Earplugs will be provided to lessen the noise.

TMS with MRI
TMS involves a procedure during which your brain will be non-invasively (i.e. from the scalp) stimulated by magnetic pulses. For this procedure, you will lie down in the MRI machine and will wear earplugs to protect your hearing. You may be asked to wear a swim cap for making measurements of your head. 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 in your brain. To determine the stimulation level, the researchers will change the intensity of the stimulation until it causes 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. This calibration is done to ensure that stimulation intensity is sufficient, but not excessive, for each individual.

TMS without MRI
Visits 4-6 will use TMS without MRI. We will ask you to sit still for approximately five minutes at a time when TMS is administered. TMS will be administered twice per session, with a 30 minute break between each round of TMS.

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 interview and assessment: 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: An MRI scan requires you to be in a partially enclosed space inside the scanner. Some people find this uncomfortable and

claustrophobic. You need to inform the doctor ordering the scan, or the study staff, if you suffer from claustrophobia (fear of enclosed spaces or anxious feelings accompanied by rapid heart rate or shortness of breath). The MRI scanner produces different types of noises during a scan. Since the noises can be loud, you will be given earplugs. The MRI scanner has an intercom which allows the technologist to talk to you and to hear you during the scan. You will be able to hear the technologist talking to you during the scan even if you wear earplugs.

- An MRI scanner has a strong magnet which attracts certain metals. If anyone has these types of metal in their body, the MRI's strong magnetic field can cause metal to move, resulting in injury. To prevent an injury, you will be asked questions or given a form requesting information about any metal in your body, including implanted medical devices, and asking if you work with metals. If you have metallic devices or fragments in your body, you will not be able to participate in this study.
- Some dyes in tattoos and permanent eyeliner contain metals which may heat up during the MRI scan, causing the area with the tattoo to become irritated and swollen.
- No metal objects can be brought into the MRI scan room at any time, because the MRI magnet will quickly and strongly pull those items into the scanner. To prevent any injury to patients and staff and any damage to the MRI scanner, you will be asked to remove all jewelry and clothing containing metal before you enter the MRI scan room. Also, since the MRI magnet will erase credit cards, they must not be taken into the scan room. Once you are positioned in the scanner, the door to the room will be closed to prevent anyone with any metal object entering the scan room.
- It is possible that during the course of the research study, the research staff may notice unexpected findings on an MRI scan. Should this occur, the findings will be considered by the appropriate personnel and the study doctor will inform you. This information may or may not be significant and may lead to anxiety about your condition and to further evaluation by your physician.
- Although there are no known risks related to MRI in pregnancy, there is a possibility of undiscovered risks. Since there is no possible benefit from participating in this study for a pregnant woman, we will exclude pregnant women. Likewise, women of childbearing potential should use an acceptable method of contraception for the duration of

the study (condoms with spermicide, intrauterine device, oral contraceptive pills, sterilization, or abstinence). Implantable contraceptives are generally very safe for MRI, but the MRI technician may ask you additional questions before entering the MRI suite to ensure your safety.

TMS: 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. The specific form of TMS used in this study is called Theta Burst Stimulation (TBS). While this newer stimulation protocol is used widely, there is less research using TBS compared with other TMS procedures. TBS is not approved by the FDA for treatment of depression. There may be long-term risks due to TBS that are currently unknown.

- Risk with TMS is considered low because the magnetic fields produced at 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.
- In 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.
- The TMS device produces a clicking sound. Although studies have found no hearing impairments as a result of this sound, some subjects experience a mild temporary effect on their hearing. To minimize this possibility, you will be given protective earplugs or headphones.
- Although it is uncommon, some subjects have experienced nausea during the experiment. If this occurs you can discontinue the experiment.
- Objects such as watches and credit cards should also be removed as these could be damaged.
- Some subjects experience a minor headache or local pain or swelling as a result of the TMS procedure; you may discontinue the experiment at any time.

- 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.

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. However, the knowledge gained may advance the field of psychiatry.

What other choices do I have if I do not participate?

This is a voluntary study. If you choose not to participate, you may seek information about other alternatives and treatments available by discussing options with your personal physician.

Will I be paid for being in this study?

Your study compensation is based on the following schedule:

- Visit 1: Screening Assessment = $20.00 (~3 hours)
- Visit 2: Initial MRI Scan = $40.00 (1 hour + preparation time)
- Visit 3: TMS + MRI Scan #1 = $60.00 (~3 hours)
- Visits 4-6: TMS sessions = $70.00 each (1hr each + preparation time)
- Visit 7: TMS + MRI Scan #2 = $120.00 (~3 hours)

Following the screening visit, subject participation is expected to take approximately 12 hours total over 7 study sessions. Your final compensation will be based on the length of your participation as outlined above. You may receive up to $450 for your participation.

For any visits completed through another study, you will not be compensated again.

Your payments will be given to you in the form of a Greenphire ClinCard at the end of study participation. This is a reloadable prepaid card (similar to a debit/credit card) which allows funds to be available immediately. 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. 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 costs 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. Desmond Oathes at (215)-573-9390.

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 about t3 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 can see or use my information? How will my personal information be protected?

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. An exception to confidentiality is if you report child abuse or neglect or if you report **current** suicidal or homicidal ideation **of concern** to the research team. Any information about child abuse or **imminent** intent to harm yourself or others will be reported to authorities, as required by law.

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).
- Representatives from collaborating institutions

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.

What information about me may be collected, used or shared with others?

During your participation, you will be asked to provide your name, address, telephone number, email address, date of birth, health plan ID numbers,

and your social security number (so that we may issue you a check to compensate you for participation). We will also obtain or create a medical record number (in the event that we need to order procedures and to access your medical records to collect information about your medical history). 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. Results from physical exams and cognitive assessments will be part of the research record. 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.

Will information about this study be available to the public?

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 than can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an

EMR will be created for you for the purpose of maintaining any results of procedures performed as part of this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have).

Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

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 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. In addition, we would like your permission to contact you about future studies to see if you are interested in participating in them.

May we contact you to invite you to participate in future studies if we determine that you may be eligible for them?

☐ *Yes* ☐ *No*

If you choose to participate in future studies at the Center for Neuromodulation in Depression and Stress, may research staff have access to and use your data that is collected as a part of this study?

☐ *Yes* ☐ *No*

If you have previously participated in a study at the Center for Neuromodulation in Depression and Stress, may research staff have access to and use your data as collected as a part of that study for the current study?

☐ *Yes* ☐ *No*

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