

STANFORD UNIVERSITY Research Consent Form

Protocol Director: Sean Mackey, MD, PhD

*IRB Use Only*Approval Date: September 19, 2023Expiration Date: September 19, 2024

Protocol Title: TMS and Pain – Piloting Consent

Are you participating in any other research studies? yes ____ no ____

PURPOSE OF RESEARCH

You are invited to participate in a study of the processing of pain and Magnetic Stimulation. This research project aims to use Magnetic Stimulation to affect the processing of pain and learn more about how it works.

You have been asked to participate because you are either a person suffering from chronic pain or a healthy adult without acute or chronic pain.

Your participation in this study is entirely voluntary.

Your decision whether or not to participate will not prejudice you or your medical care. If you wish to participate in this study, you must sign this form. If you decide to participate, you are free to withdraw your consent, including your authorization regarding the use and disclosure of your health information, and to discontinue participation at any time without prejudice to you or effect on your medical care. If you decide to terminate your participation in this study, you should notify Dr. Sean Mackey at (650) 725-9636.

This research study is looking for 225 participants to be enrolled at Stanford University.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take 5 years, but you will only participate for up to 1 year. Each participant may have one to twelve behavioral sessions, one to three Magnetic Resonance Imaging (MRI) sessions, and/or one to fifteen Magnetic Stimulation sessions. Sessions will last about one to three hours in length. You will be told the details of each session, and how many you will participate in, before you begin. You may also have the opportunity to enroll in multiple cycles of TMS treatment to monitor the clinical effects of the treatment.

PROCEDURES

If you choose to participate, a member of the research team will walk you through the procedures, described below. When there are checkboxes present, you will only participate in the procedures checked off by a member of the research team and by which you initial. The procedures you undergo will depend on which part of the study is underway. This study is investigating a number of different questions about TMS and pain, and each part of the study uses a slightly different combination of tests. For example, we may want to know how TMS affects heat pain processing; another study may investigate how TMS affects the interaction between memory and cold pain processing.

Assessments:

- A. Medical History: A history of medical issues pertaining to the pain condition of interest may be obtained. This includes nature, cause and duration of the pain condition, existence and nature of other potentially contributing disorders, and presence of behaviors that could lead to increased pain symptoms (e.g. caffeine intake, sleep

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patterns). A brief physical exam may also be administered to characterize pain and other relevant symptoms.

- B. Psychophysical Testing: Psychophysical stimuli may be delivered to an area of the body that hurts (for chronic pain patients), and/or to non-painful area(s) of the body. The area(s) to be stimulated will be described to the participant before the experiment begins. The following tests may be part of the psychophysical testing:

☐ Tactile Stimulation: Area(s) of your body will be stimulated by touch with a plunger, weighted pin-prick, and/or Von Frey fibers. The pressure plunger has a rubber tipped end that will apply various pressures to your skin ranging from a light tapping sensation to painful pressures. The weighted pins feel similar to a pin prick but the weighted pins are less sharp and are designed not to break the skin. The Von Frey fibers are filaments that bend when applying pressure to the skin—these sensations are typically not painful for participants without chronic pain.

Before you begin this experiment, your pain response may be tested using tactile and/or thermal stimulation (listed above) in order to determine the appropriate stimulus levels. Each stimulus may be used to induce a sensation of pain, but not so much pain that you are in great discomfort or feel the need to remove the stimulus from your body.

If you feel that you will not be able to endure the painful stimulus throughout the behavioral testing, you may discontinue the session and withdraw from the study. Alternatively, you have the option to be retested with the tactile and/or thermal stimuli to determine a more appropriate and tolerable setting and continue with the study.

☐ Thermal Testing: Painful stimulation may be delivered by a thermode attached with a strap or held in place. Different sizes and types of thermodes may be used. The standard thermode is a black piece of metal and plastic roughly the size of two stacked matchboxes. It is connected to a long cord which attaches to a machine that generates heat or cold. You may feel a steady increase/decrease in temperature as the heat/cold is delivered to the thermode. Use of this heating device has not been FDA approved for use in an MRI. The temperatures and times used have been shown to be safe and generally do not to cause burns. On rare occasions, a mild burn or blister can occur over a small area where the probe is in contact with the skin. This is similar to a burn from a bad sunburn. We will call you after your participation to make sure you do not have any residual redness or discomfort. During this testing, you may be asked to rate pain (e.g. 0 to 10 scale), and/or perform behavioral, cognitive, or memory tasks while receiving the thermal sensation.

☐ Cold-Water Immersion and Pressor Test: Cold-water immersion involves having you place one or two limbs (hand, arm, foot, or leg) in a tank of cold water (>32 degrees F). Immersion may be for a fixed duration of time or for a variable amount of time based on tolerance, or how long you can keep the limb(s) in the water. This is referred to as the pressor test. You may remove your hand at any time for both the fixed and variable durations. For the variable duration (pressor test), you are encouraged to keep your hand submerged until you can no longer tolerate it. A circulating pump is used to ensure that the water remains a consistent temperature. This device is called a Micro-Jet pump (MC 450) made by Aquarium Systems. It is not currently approved as a medical device by the FDA, and is used mainly in aquarium

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systems. The pressor test takes about 5 minutes to perform and may be repeated up to 5 times during one session to obtain consistent results.

☐ Physical Examination: Additional tests include using a camel hair brush to assess sensitivity to touch, using a dolorimeter or manual pressure to assess joint pressure, and using a 128 Hz tuning fork to assess response to vibration. Also, blood pressure, skin temperature, height, weight, and range of motion may be assessed.

☐ Capsaicin: Before the experiment begins, a capsaicin cream may be applied to the area of your skin where the thermode will be attached, or to an alternate area. Capsaicin is made from chili peppers and increases sensitivity to heat where applied. This cream allows us to use lower temperatures with the thermode. The cream used may vary from .075 – 10% concentration of capsaicin. After the experiment is finished, the cream can be removed with a standard cleaning agent, polyethylene glycol. Then the skin will be washed with soap and water. If there is still an unpleasant burning sensation, a 5% lidocaine patch may be applied to the area.

- C. Behavioral tasks: You may be asked to complete behavioral tasks, such as responding to visual or other sensory stimuli, performing cognitive or memory tasks, and/or providing ratings of pain or other related phenomena. The research team will describe in detail each of the tests and instructions before beginning. Some tests may include viewing pictures relating to pain or pictures that may be pleasant, neutral, or unpleasant. You will be warned prior to viewing any graphic images as part of testing procedures. Behavioral tasks may be administered before, during, or after other experimental components (Psychophysical Testing, Neuroimaging, and/or Magnetic Stimulation).
- D. Questionnaires: You may also be asked to complete questionnaires regarding pain and other potentially relevant information (e.g. anxiety, mood, or personality). Questionnaires administered will depend on the sub-project as well as whether you are a chronic pain patient or a healthy control, for which some of the questionnaires regarding pain do not apply. We may call you to administer the questionnaires over the phone or to direct you to an online survey you may complete on your own.

Neuroimaging:

☐ MRI Scanning: Non-invasive structural and functional imaging of the brain and/or spinal cord may be acquired, at the 3 Tesla scanner at the Lucas Imaging Center. You will be screened for conditions contraindicated to MRI scanning. Assessments (including cold-water immersion, thermal testing, and behavioral tasks) and/or Magnetic Stimulation may be performed before, during, and/or after imaging.

MRI machines use a strong magnet and radiofrequency magnetic fields to make images of the body interior. The scanning procedure is very much like an X-ray or CT scan. You will be asked to lie on a long narrow couch for one to two hours while the machine gathers data. During this time you will not be exposed to x-rays, but rather a strong magnetic field and radiofrequency magnetic fields, which you will not feel. You will, however, hear repetitive tapping noises that arise from the Magnetic Resonance scanner. We will provide earplugs or headphones that you will be required to wear. You may also be fitted for a bite bar in order to keep your head from moving during the scans. A bite bar is a bar made of dental wax which you will hold in your

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mouth during the scans. This will assist you in keeping your head still. The space within the large magnet in which you lie is somewhat confined, although we have taken many steps to relieve the "claustrophobic" feeling.

☐ Near Infrared Spectroscopy (NIRS): NIRS is also a non-invasive way to scan your brain or spinal cord activity. You will have small probes attached to your scalp that will send out light to measure changes in blood flow in your brain. Assessments (including cold-water immersion, thermal testing, and behavioral tasks) and/or Magnetic Stimulation may be performed before, during, and/or after imaging.

☐ Electroencephalography (EEG): EEG involves the recording of electrical signals from the brain. Recording electrodes are placed on the scalp of your head, and EEG may be performed in the MRI scanner or separately. Assessments (including cold-water immersion, thermal testing, and behavioral tasks) and/or Magnetic Stimulation may be performed before, during, and/or after EEG.

Magnetic Stimulation Procedures:

☐ Magnetic Stimulation of Brain (Transcranial Magnetic Stimulation): Transcranial Magnetic Stimulation (TMS) is a non-invasive method for stimulating the brain. TMS is currently FDA approved for the treatment of depression. Electrical current flows through a coil placed on the scalp, generating a magnetic pulse in the brain. You will be screened for conditions contraindicative to TMS administration. Assessments (including cold-water immersion, thermal testing, and behavioral tasks) and/or Neuroimaging may be performed before, during, and/or after Magnetic Stimulation. Some participants might be randomized (like flipping a coin) to receive sham TMS (no actual stimulation). The effects of TMS depend in part on frequency of stimulation, and one or more of the following frequency parameters may be used:

- ☐ Single-pulse TMS (one stimulus at a time)
- ☐ Paired-pulse TMS (pairs of stimuli separated by a brief interval)
- ☐ Low Frequency rTMS (trains of stimuli delivered at 1 Hz or less)
- ☐ High Frequency rTMS (trains of stimuli delivered at more than 1Hz)
- ☐ Theta Burst (repeated bursts of 20-50 Hz stimuli)
- ☐ Repeated Theta Burst (multiple sessions of repeated bursts of 20-50 Hz stimuli)
- ☐ Sham TMS (Inactive TMS to serve as a control stimulation)

You will be asked to come to our research office for **a minimum of 1-2 treatments within a week or up to 5 sessions per week**. Treatment may be stopped early by the research team for safety reasons. You may also stop the treatment at any time.

At each treatment session, the researcher may inquire about your medical history, perform a physical exam and/or psychophysical tests described within. You may also be asked to fill out questionnaires at each session. Each treatment session may last up to 2 hours. We may call or

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email you after each treatment session to ensure you do not have any residual symptoms or discomfort.

☐ **Daily or** ☐ **Weekly Pain Reports:**

No matter what group you are in, you will be asked to complete a brief daily or weekly pain questionnaires for a period of up to 6 weeks to be specified by your research team. This short questionnaire may be filled out online or alternatively be completed over the phone or via a handheld device. It is important that you complete the pain report survey every day so that we can gather information and track your pain.

☐ **Magnetic Stimulation of Spinal Cord and Peripheral Nerves:** Magnetic Stimulation is also a non-invasive method for stimulating the spinal cord and peripheral nerves. Electrical current flows through a coil placed over spinal cord or peripheral nerves, generating a magnetic pulse for neuronal stimulation. You may or may not receive actual stimulation. You will be screened for conditions contraindicated to administration of Magnetic Stimulation. Assessments (including cold-water immersion, thermal testing, and behavioral tasks) and/or Neuroimaging may be performed before, during, and/or after Magnetic Stimulation.

☐ **Electromyography (EMG):** Electrodes may be placed on the skin to measure small voltage changes, typically from muscle activity. This is a routine procedure often used to determine to appropriate amount of magnetic stimulation (motor threshold). Data may be acquired during Assessment, Neuroimaging, and/or Magnetic Stimulation.

WOMEN OF CHILDBEARING POTENTIAL

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not participate in some of the procedures included in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk due to the fMRI scanner.

To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study if the protocol director deems it necessary. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the Risk that pregnancy could still result despite the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

SUBJECT'S RESPONSIBILITIES

You should:

- Arrive when scheduled. If it is necessary to miss a scheduled scan time, please contact the Protocol Director or research study staff to reschedule as soon as you know you cannot make the agreed upon time.

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- Follow protocol directions as outlined by the Protocol Director.
- Do your best to lie as still as possible while in the MR scanner.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the Protocol Director or research staff if you believe you might be pregnant.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

You will have to sign this consent and Authorization form if you want to participate in this research study.

While participating in this research study, you should not take part in any other research project without approval from all of the Protocol Directors. This is to prevent our study procedures from interfering with other study procedures. Please let the researcher know if you are currently enrolled in any other research studies.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you chose to withdraw from the study there will be no adverse side effects or risks. Please contact Dr. Sean Mackey at (650) 725-9636 if you choose to withdraw from the study.

The Protocol Director may also withdraw you from the study without your consent for one or more of the following reasons:

- Inability to perform the tasks or to remain immobile during the scan
- Scheduling is incompatible
- Failure to follow instructions
- The Protocol Director decides that continuing the study could be harmful to you.
- Pregnancy
- The study is cancelled.
- Other administrative reasons
- Unanticipated circumstances

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director, Dr. Sean Mackey, if you have any questions. The known risks of each procedure are described below. There may be risks that are not currently known or have not been anticipated.

☐ **Thermal Testing:** The mildly painful thermal stimulation from the thermode should not be damaging to your skin or tissue. The thermode is used routinely in the clinical setting. On

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rare occasions, subjects have experienced a minor burn or blister where the thermode is in contact with the skin. This is similar to a burn you might get from a bad sunburn and it may cause scarring, pigmentation abnormalities, or keloid scarring. If there is a burn, please contact the Protocol Director, Dr. Sean Mackey. If an injury occurs, you will come in for a follow-up appointment with Dr. Mackey or another physician affiliated with the lab to ensure the burn is healing properly.

☐ **Cold-Water Immersion and Pressor Test:** Cold-Water testing generally does not cause injury, and risk is minimized by using temperatures and exposure durations that have been shown to be safe. You may remove your limb(s) at any time if the discomfort is too great.

☐ **Risk of Tactile Stimulation:** The weighted pin prick device is designed to not puncture your skin or tissue. On rare occasions, with repeated use of the heavier weighted pins (256mN & above), skin puncture may occur with a risk of bleeding and infection. Weighted pins are disinfected before use and if skin puncture occurs, the area will be cleaned with alcohol to minimize the risk of infection. Pressure applied using a pressure plunger may cause discomfort or short-term tenderness to the area where pressure is applied. You will be able to stop the test at any time if the pain becomes too intense. The researcher conducting the test will remove the pressure being applied if you find it too discomforting.

☐ **Risks of Capsaicin:** Capsaicin is a skin irritant, and consequently should be kept away from the eyes, nose and mouth. It is possible that participants may be allergic to this substance, although this is rare and unexpected. Capsaicin is the spicy ingredient in chili peppers, but it is used frequently in clinical and research settings. After you have completed the study, the capsaicin will be removed with polyethylene glycol, and your arm will be washed with soap and water. Still, there is a chance that some capsaicin will remain on your arm. You may experience lingering discomfort for up to 24 hours.

You should avoid touching the area to which capsaicin was applied so that you do not accidentally spread it to your eyes, nose and mouth. The capsaicin cannot do any damage to these areas but may be unpleasant. If capsaicin gets into your eyes, flush your eyes with water. If capsaicin gets on other sensitive areas of your body, wash the areas with warm (not hot) soapy water. If this occurs, please contact Dr. Sean Mackey at (650) 725-9636.

If you experience a burning sensation after the capsaicin is removed, we can apply a 5% lidocaine patch. This is a safe, commonly used local anesthetic. It is possible, however, that some participants may be allergic to this medication.

The area to which we apply capsaicin could be red for up to 24 hours. This is normal. If the area swells or spreads, this may indicate a rare allergic reaction. If this occurs, you should contact Dr. Sean Mackey at (650) 725-9636.

☐ **Risks of Near Infrared Spectroscopy (NIRS):** There is a possibility of slight discomfort from the NIRS cap and sensor/detectors on scalp.

☐ **Electroencephalography (EEG):** There is a possibility of slight discomfort from the EEG recording electrodes on scalp.

☐ **Risks of MRI:**

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Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electronic devices. If you have a cardiac pacemaker or any other biomedical device in or on your body, it is very important that you tell the operator/investigator immediately. As metallic objects may experience a strong attraction to the magnet, it is also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. All such objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed. In addition, watches and credit cards should also be removed as these could be damaged. You will be provided a way to secure these items. If you have any history of head or eye injury involving metal fragments, if you have ever worked in a metal shop, or if you could be pregnant, you should notify the operator/investigator.

There is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is expected and should not be painful.

Some of the RF imaging coils, imaging software and devices being used in your scan are not approved by the FDA but are similar to counterparts that have been approved by the FDA. There is a small risk of heating from the cables associated with these devices. Please report any heating sensation immediately.

Dizziness or nausea may occur if you move your head rapidly within the magnet.

If you feel discomfort at any time, notify the operator and you can discontinue the exam at any time.

The scans performed in this study are for specific research purposes and are not optimized to find medical abnormalities. The investigators for this project may not be trained to perform medical diagnosis. The investigators and Stanford are not responsible for failure to find existing abnormalities with these MRI scans. However, on occasion the investigator may notice a finding on an MRI scan that seems abnormal. When this occurs, a physician will be consulted as to whether the findings merits further investigation, in which case the investigator will contact you and your primary care physician and inform you of the finding. The decision as to whether to proceed with further examination or treatment lies solely with you and your physician. The investigators, the consulting physician, and Stanford are not responsible for any examination or treatment that you undertake based on these findings. Because the images collected in this study may not comprise a proper clinical MRI scan, these images will not be made available for diagnostic purposes.

☐ **Risks of Magnetic Stimulation Procedures:**

- A. Magnetic Stimulation of Brain (Transcranial Magnetic Stimulation): Transcranial Magnetic Stimulation (TMS) is a non-invasive method for stimulating the brain. Electrical current flows through a coil placed on the scalp, generating a magnetic pulse through the scalp/skull to the brain. TMS has been used in research since the mid 1980's, and High Frequency rTMS was approved by the FDA in 2008 as a therapy for treatment-resistant depression. A consensus paper regarding the safe use of TMS was published in 2009 (Rossi, et al., 2009). Seizures are a concern with TMS (<1% of High frequency rTMS), but can be reduced by following safety guidelines, screening patients, and having a response protocol in place. Reported seizures are typically brief (<60 s) and typically can be managed by preventing complications (such as laying the individual in a position

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to assist breathing). Screening individuals for neurotropic medications, neurological conditions, and metal items near site of stimulation also reduces risks. Syncope, or a brief loss of consciousness, is also possible as an epiphenomenon (i.e., not related to direct brain effects). The type and frequency of side effects depends on the type of stimulation being used. Below, we describe the possible risks for each type of stimulation:

☐ (1) Single-pulse TMS (one stimulus at a time): The potential of seizure induction is rare and has only been reported in individuals with a family history of seizure, structural brain pathology, or using a medication that makes seizure more likely. There is a possibility of transient headache (mild to severe, which may occur with or without symptoms of nausea and vomiting), local pain (e.g. scalp soreness), neck pain, toothache, and parasthesia (a feeling of tingling, prickling, or numbness). In most individuals, these discomforts self-resolve quickly after stimulation. An oral analgesic such as acetaminophen or ibuprofen can be helpful if pain symptoms persist. There are possible hearing changes, and hearing protection will be provided to reduce possible risk.

☐ (2) Paired-pulse TMS (pairs of stimuli separated by a brief interval): There are no reports of seizure with paired-pulse TMS. There is a possibility of transient headache (mild to severe, which may occur with or without symptoms of nausea and vomiting), local pain (eg. scalp soreness), neck pain, toothache, and parasthesia (a feeling of tingling, prickling, or numbness). In most individuals, these discomforts self-resolve quickly after stimulation. An oral analgesic such as acetaminophen or ibuprofen can be helpful if pain symptoms persist. There are possible hearing changes, and hearing protection will be provided to reduce possible risk.

☐ (3) Low Frequency rTMS (trains of stimuli delivered at less than 1Hz): Seizures with Low Frequency rTMS are rare, and such stimulation is typically thought to be protective from seizures given the inhibitory characteristics. There is a possibility of transient headache (mild to severe, which may occur with or without symptoms of nausea and vomiting), local pain (eg. scalp soreness), neck pain, toothache, and parasthesia (a feeling of tingling, prickling, or numbness). In most individuals, these discomforts self-resolve quickly after stimulation. An oral analgesic such as acetaminophen or ibuprofen can be helpful if pain symptoms persist. There are possible hearing changes, and hearing protection will be provided to reduce possible risk.

☐ (4) High Frequency rTMS (trains of stimuli delivered at more than 1Hz): Seizures with High Frequency rTMS are possible (< 1% in normal individuals). Transient hypomania (feeling hyperactive, irritable, or having an elevated mood) is also possible following left prefrontal stimulation. Transient headache (mild to severe, which may occur with or without symptoms of nausea and vomiting), local pain (eg. scalp soreness), neck pain, toothache, and parasthesia (feeling of tingling, prickling, or numbness) are frequent. In most individuals, these discomforts self-resolve quickly after stimulation. An oral analgesic such as acetaminophen or ibuprofen can be helpful if pain symptoms persist. There are possible hearing changes, and hearing protection will be provided to reduce possible risk.

☐ (5) Theta Burst and Repeated Theta Burst (single or multiple sessions of patterned bursts of 50Hz stimuli delivered at a rate in the 5Hz range): There is limited data on these forms of stimulation. Seizure induction is possible, with one reported occurrence.

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Transient headache (mild to severe, which may occur with or without symptoms of nausea and vomiting), local pain (eg. scalp soreness), neck pain, toothache, and paresthesia are possible. In most individuals, these discomforts self-resolve quickly after stimulation. An oral analgesic can be helpful if pain symptoms persist. Transient impairment of working memory has been reported.

☐ (6) Sham TMS (Inactive TMS to serve as a control stimulation): There is a possibility of temporary headache (mild to severe, which may occur with or without symptoms of nausea and vomiting), local pain (eg. scalp soreness), neck pain, toothache, and paresthesia (a feeling of tingling, prickling, or numbness). In most individuals, these discomforts self-resolve quickly after stimulation. An oral analgesic such as acetaminophen or ibuprofen can be helpful if pain symptoms persist. There are possible hearing changes, and hearing protection will be provided to reduce possible risk. If you experience a headache or local pain as a result of the TMS device, the lab has over-the-counter oral analgesics available such as Naproxen (Aleve), Ibuprofen (Advil), and Acetaminophen (Tylenol). You should not take these medications if you have a known allergy or a previous adverse reaction to any of these medications or to aspirin, and you should follow the instructions on the package for use. Ibuprofen and Naproxen are non-steroidal anti-inflammatory drugs (NSAIDS). The most common side effect of NSAIDS is gastrointestinal upset, including nausea, abdominal pain, and heartburn. There is also the risk of stomach bleeding; you should not take this medication if you have taken another NSAID recently, if you have stomach bleeding problems or ulcers, or if you take a blood thinning agent or steroid drug. NSAIDS also have cardiovascular risks and you should not take this medication if you have any cardiac problems, such as high blood pressure or palpitations. You should not take Acetaminophen if you have liver damage.

☐ B. Magnetic Stimulation of Spinal Cord and Peripheral Nerves: Magnetic Stimulation has been used for stimulation of the spinal cord and peripheral nerves. We are not aware of any adverse events with such stimulation, although there is limited safety information. Risk are minimized by screening participants (particularly for metal near site of Magnetic Stimulation), administering Magnetic Stimulation by appropriately trained personnel, and monitoring for signs of adverse effects.

☐ **Risks of Electromyography (EMG):** No known risks.

☐ **Other Risks:** There is a risk you may feel uncomfortable answering some of the questions on the questionnaires. You have the right to refuse to answer particular questions. There is a risk that some of the behavioral tasks may cause discomfort. Some of the visual stimuli presented may include graphic images. You will be warned prior to being shown these images and you have the option to not participate in the task or to stop any of the testing at anytime if you ever feel too uncomfortable or find the testing too distressing.

It is possible that, based on information gained from this study, the investigators may be required to report information (e.g., information relating to suicide, physical or sexual abuse) to the appropriate authorities.

The testing, as with any testing, may be an inconvenience or uncomfortable, but the tests are not known to cause undue distress. These procedures may involve risks to the subject, which are currently unforeseeable.

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POTENTIAL BENEFIT

WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOU WILL RECEIVE ANY BENEFITS FROM THIS STUDY. However, data from this study could help us understand how the brain processes pain and help us work towards designing more effective treatments for chronic pain.

Patients and subjects should not consider information provided from any member of the experimental team in connection with this study or otherwise as medical advice. For medical advice patients and subjects should rely exclusively on their treating physicians.

ALTERNATIVES

Your alternative is to not participate in this study.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction.

If you decide not to participate, tell the Protocol Director. You will not lose care for your disease and any benefits to which you would otherwise be entitled.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

You have the right to refuse to answer particular questions.

CONFIDENTIALITY

Your identity will be kept as confidential as possible as required by law. Except as required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Your research records may be disclosed outside of Stanford, but in this case, you will be identified only by a unique code number. Information about the code will be kept in a secure location and access limited to research study personnel. The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your identity will not be disclosed.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The information gathered in this study may be combined with information gathered from other studies you are participating in.

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Protocol Title: TMS and Pain – Piloting Consent

USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION**Authorization To Use Your Health Information For Research****Purposes**

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

The purpose of this research study is to determine how chronic pain and experimental pain for healthy adults is processed in the brain. Your health information may be used in scientific publications.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must contact: Sean Mackey, M.D., Ph.D. at 1070 Arastradero Road, Suite 200, Palo Alto, CA, 94304

What Personal Information Will Be Used or Disclosed?

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Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to your pain threshold, MRIs, results of TMS, and answers to questionnaires.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director Sean Mackey, M.D., Ph.D.
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary.
- The research team

Who May Receive / Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- The Food and Drug Administration (FDA)
- The National Institutes of Health (NIH)

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?

Your authorization for the use and/or disclosure of your health information will expire January 1, 2050.

Signature of Subject_____
Date_____
Printed name

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FINANCIAL CONSIDERATIONS

PAYMENT: You will be paid \$30 for each in-person visit for up to three rounds of treatment.

COSTS: There will be no cost to you for participation in this study.

SPONSOR: This study is being funded by the John and Dodie Rosekranz Endowment for Pain Research, by the Redlich Endowment for Pain Research, by the National Institute of Health, and by the Wu Tsai Neuroscience Translate award.

CONTACT INFORMATION

Appointment Contact: If you need to change your appointment, please contact a member of the research team at (650) 724-0522.

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Dr. Sean Mackey at (650) 725-9636. You should also contact him at any time if you feel you have been hurt by being a part of this study.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650) 723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

Additionally, Stanford is not responsible for research and medical care by other institutions or personnel participating in this study. You do not waive any liability rights for personal injury by signing this form.

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EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should rise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form;
- and be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about other studies that may be of interest to you? We may also send you a participant newsletter with updates on this and other studies in appreciation of your participation. You may choose to be removed from our contact list at any time.

☐ YES☐ NO

Signing your name means you agree to be in this study and that you were given a copy of this consent form.

SIGNATURE OF SUBJECT_____
Date_____
PRINTED NAME_____
SIGNATURE OF PERSON OBTAINING CONSENT_____
Date_____
PRINTED NAME