COVER PAGE

Study consent as of 8/7/19, last reviewed/approved 4/1/2020, current as of 2/2/21

NCT04019054

University of California, Los Angeles

CONSENT TO PARTICIPATE IN RESEARCH

Title: **Transcranial Magnetic Stimulation (TMS) in Conjunction with Exposure Therapy for the Treatment of Spider Phobia**
IRB: **19-000218**

Name: _____ Date: _____

You are being asked to participate in a research study conducted by the Principal Investigator, Michael Leuchter, Marco Iacoboni, M.D., Ph.D., and colleagues from the Departments of Psychiatry and Biobehavioral Sciences and of Neurology, at the University of California, Los Angeles David Geffen School of Medicine. This study will enroll 40 participants over the course of 1 year. *YOUR PARTICIPATION IN THIS STUDY IS VOLUNTARY*

Key Information: The following is a short summary of this study to help you decide whether or not to be a part of this study. More detailed information is listed later on in this form. Please do not hesitate to contact us (contact information at the end of this form in ***"Who can I contact if I have questions about this study?"***) should you have any additional questions or concerns.

Why am I being invited to take part in a research study?

We invite you to take part in a research study because you have been found to have clinically-significant spider phobia, as determined by the results of your questionnaires in both pre-screening and earlier in this initial visit.

What should I know about a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

Spider phobia is an exceedingly common phobia throughout the world. The current standard treatment involves exposure therapy, which consists of a series of brief exposures of an individual to the thing they fear, in this case spiders. This study aims to examine the use of a neuromodulatory technology, transcranial magnetic stimulation (TMS), as a possible treatment option for spider phobia. TMS uses low-intensity electromagnetic energy to stimulate the brain, introducing energy into critical hubs of brain networks to "reset" their function and alleviate symptoms with very few side-effects. Prior work has shown TMS may alleviate symptoms in those with spider phobia.

How long will the research last and what will I need to do?

Participation will take a total of approximately 4 hours of varying lengths spread over 4 visits: Visit 1 (75-90 minutes), Visit 2 (30-45 minutes), Visit 3 (30-45 minutes), and Visit 4 (45-60 minutes)

On Day 1 of the study, you will be asked to complete a multi-step protocol that assesses the degree to which they feel comfortable approaching a live spider while we record both objective physiologic data and subjective measures. Next, you will be asked to engage in a series of short experimenter-guided exposure practices with a live spider, followed by a brief transcranial magnetic stimulation (TMS) treatment using intermittent theta burst stimulation (iTBS), a specific TMS protocol.

At the time of your initial visit, your treatment will be randomized to study treatment or a control treatment. For scientific reasons, this consent form does not include complete information about the study methodology, specifically the differences between the study and control treatments. You will not be informed to which group you are randomized, nor will you be informed of the differences between the study and control treatments. However, both the study and control treatments will involve the use of exposure therapy and iTBS stimulation, and carry similar risk. You will be fully debriefed following your participation in the research.
On Days 2 and 3 of the study, you will be asked to return to the lab to complete additional sets of experimenter-guided exposure practices with a spider and additional iTBS treatments.
On Day 4 of the study (5-7 days later), you will be asked to return to the lab to complete follow-up questionnaires and an identical protocol as was completed on Day 1 to reassess the degree to which you feel comfortable approaching a live spider.

More detailed information about the study procedures can be found under ***"What will happen if I take part in this research study?"***

Is there any way being in this study could be bad for me?

The potential risks of your participation in this study include those associated with TMS treatment and those associated with exposure therapy.

The most common side effects of TMS treatment are headaches, scalp discomfort at the site of stimulation, tingling, spasms or twitching of facial muscles, or lightheadedness. These side effects are mild and transient. While rare, the most serious risk associated with TMS treatment is that of a seizure. For this reason, you will be monitored throughout your TMS sessions, and it is important that you inform the research staff if you have any history of seizures or are at increased risk of a seizure.

You may also feel uncomfortable or distressed during the experimental procedures. For example, you may feel distressed when approaching a live spider and/or viewing images of spiders.

This study may also include risks that are currently unforeseeable. You may stop participation in the study at any time. You may tell the researchers about any distress you experience at any time before, during, or after the experiment, and the researchers will assist in helping you reduce any anxiety you experience at your request.

More detailed information about the risks of this study can be found under "***Are there any potential risks or discomforts that I can expect from this study?"***

Will being in this study help me in any way?

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include a reduction in psychological symptoms of spider phobia (e.g. distress in the presence of spiders). This benefit is possible but is not guaranteed. Should you experience this benefit during the course of this study, it is not guaranteed that this benefit will continue after the study. The information collected as part of this study is being obtained for research purposes only. The data are not being collected for clinical purposes and will not be provided to you unless there are clinically relevant findings that may be reviewed by a study physician or provided to you to take to your primary care physician.

The results of the research may further development of new treatment options and improvement of existing options for spider phobia. Given the widespread suffering and disability associated with anxiety disorders and specific phobias, as well as the financial burden of treating them, the anticipated societal benefit is a greater understanding of both the processing of fear-based memory as well as the mechanisms and utility of TMS in the treatment of anxiety disorders, especially phobias.

What happens if I do not want to be in this research?

Participation in research is completely voluntary. You can decide to participate or not to participate. Should you decide not to participate in this experiment, you can participate in other research experiments or complete class assignments per course instructions. If you wish to seek independent help for an anxiety or phobic disorder, a referral list will be provided.

Detailed Information: The following is a more comprehensive overview of this to help you decide whether or not to be a part of this study. Please do not hesitate to contact us (contact information at the end of this form in "***Who can I contact if I have questions about this study?"***) should you have any additional questions or concerns.

What will happen if I take part in this research study?

Participation in this study involves four visits to our lab at UCLA. Prior to participating in the study, you will have completed a questionnaire concerning your current fear and behavior toward spiders.

On the first day of the study, once you have reviewed and signed the consent form, you will be asked to complete a demographics and eligibility questionnaire. You may choose to abstain from answering any demographics questions without it affecting your participation in the study, though you will need to answer the eligibility questions to proceed. You will also undergo screening for anxiety, depression, and suicidality in form of questionnaires as a part of the eligibility screening. The experimental procedures that will take place will be explained to you in detail by a trained research assistant, and you will have the opportunity to ask questions and express any concerns. Next, you will complete a multi-step protocol that assesses the degree to which you feel comfortable approaching a live spider. Psychophysiological measures will be recorded during this assessment via electrodes placed on two of your fingertips and two electrodes placed on opposite sides of your chest, and you will be asked to rate your confidence and distress at each step. You are not required to complete any given step during this portion of

the study and discontinuing will not affect further participation in the study. Next, you will be randomized to either a study or control group. You will not be informed to which group you are randomized nor will you be informed of the differences between the two groups; both groups carry similar risk. You will then be asked to engage in a series of short exposure practices, where you will be asked to place your ungloved hand inside a spider's terrarium for 30 seconds at a time, for a total of ten trials. After, you will be asked to undergo a 3-4 minute TMS treatment session.

The second visit will occur the following day, and you will be asked again to undergo exposure therapy and a TMS session. The same protocol will occur the following day for the third visit.

The fourth visit will occur five to seven days after the third visit. During the fourth visit, you will be asked to return to the lab to complete two questionnaires about your current fear of spiders, as well as an identical multi-step protocol as was completed at the first visit to assess the degree to which you feel comfortable approaching a live spider. Afterwards, you will complete a final questionnaire regarding your experience with the study.

More information on exposure therapy, TMS, and clinical data below

Exposure Therapy: Exposure therapy is the current standard of care for treatment of phobias, and it involves exposing an individual to his or her feared stimulus in an effort to generate new non-fear associations with that stimulus. Treatment benefit with exposure therapy is observed in 70-75% of individuals compared to placebo. In this case, exposures therapy will consist of a series of 10 short exposures of placing your hand inside the terrarium away from the spider for a duration of 30 seconds each.

Transcranial Magnetic Stimulation (TMS): In 2008 and 2015, the first TMS treatment system and Magstim Rapid^2 Therapy System, respectively, were approved by the US Food and Drug Administration (FDA) for use with depression, so the treatment itself is not experimental, though the application to the study of phobias is investigative. A TMS treatment session is conducted using devices such as the Magstim Rapid^2 Therapy System or MagVenture MagPro R30 (also FDA approved) to provide electrical energy to a "treatment coil" or magnet that in turn delivers pulsed magnetic fields. These magnetic fields are the same type and strength as those used in magnetic resonance imaging (MRI) machines that can provide pictures of the brain and other parts of the body.

Clinical Data: Your clinical and demographic information will be gathered from your completed questionnaires. The following information will be stored: date of birth, gender, contact information, screening questionnaire data, TMS treatment dates, TMS treatment settings (such as the stimulation site and pulse parameters), exposure therapy treatment dates, exposure therapy treatment durations, behavioral assessment test scoring, behavioral assessment test physiologic data including heart rate variability and skin conductance, and spider phobia severity ratings over the course of treatment. This information will be coded, meaning that the information extracted cannot reasonably identify you. Only the research staff will have access to your coded information. Your information collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies. The data will not be used in future research, and will be erased within one year of completion of the study.

Are there any potential risks or discomforts that I can expect from this study?

Exposure Therapy:

The potential risks of your participation in this study include the possibility of feeling uncomfortable or distressed during the experimental procedures. For example, you may feel distressed when approaching a live spider and/or viewing images of spiders. There is also a risk of physical contact with spiders. This study may also include risks that are currently unforeseeable. You may stop participation in the study at any time. You may tell the researchers about any distress you experience at any time before, during, or after the experiment, and the researchers will assist in helping you reduce any anxiety you experience at your request. A referral list will additionally be available at the end of the study if you wish to seek independent help.

Due to the risk of physical contact with spiders, it is important that you notify the investigators if you are allergic to bees, insects, or spiders.

Transcranial Magnetic Stimulation (TMS):

- ***IMPORTANT INFORMATION ABOUT iTBS THERAPY:***
    - iTBS stands for "Intermittent Theta Burst Stimulation". iTBS Therapy is a medical procedure. An iTBS treatment session is conducted using the Magstim or MagVenture TMS Therapy system. The device provides electrical energy to a "treatment coil" or magnet that delivers pulsed magnetic fields for TMS therapy. These magnetic fields are the same type and strength as those used in magnetic resonance imaging (MRI) machines that can provide pictures of the brain and other parts of the body.
    - The durability of response to iTBS Therapy is unknown.
- Participants who receive iTBS using the research device are subject to the same risks as FDA-approved iTBS treatment. Generally, iTBS is considered safe and well-tolerated. However, it can cause some side effects. They may include headaches, scalp discomfort at the site of stimulation, tingling, spasms or twitching of facial muscles or lightheadedness. Serious side effects are rare and may include seizures, mania particularly in people with bipolar disorder or hearing loss if there is inadequate ear protection during treatment.
- Participants who receive single pulse TMS using our research or clinical device may experience discomfort from the individual or paired pulses and/or a minor muscle twitch during the pulse. There is no risk of seizure with single pulse TMS.
- The Magstim Research System (Super Rapid^2 Plus^1 device) differs from Magstim's Rapid^2 device, which is FDA-cleared for the treatment of depression, by virtue of having two additional power supply units. The TMS System will be configured to perform iTBS treatment.

To minimize risks, you should not undergo TMS if you are someone who is at greater risk of having a seizure, or for whom the consequences of having a seizure may be greater. For this reason, you will be asked some questions about your and your family's medical history and you will be excluded from the study if you have any of the following:

- Are mentally or legally incapacitated, unable to give informed consent
- Are pregnant
- Have an infection or poor skin condition over the forehead where the device will be positioned
- Have current substance abuse disorder in the 6 months prior to enrollment
- Have been exposed to VNS treatment in your life

- Have increased risk of seizure because of family history, stroke, or currently use medications that lead to increased risk for seizure
- Have epilepsy, cerebrovascular disease, dementia, history of repetitive or severe head trauma, or tumors in the central nervous system
- Have an intracranial implant including cochlear implant, implanted electrodes/stimulators, aneursym clips or coils, stents, bullet fragments; implanted cardiac pacemaker, defibrillator, vagus nerve stimulator, deep brain stimulator; or other implanted devices or objects contraindicated by product labeling.

For your safety, it is essential that you inform the investigator if any of these above situations apply to you.

Throughout the TMS procedure, your hand muscles will be electrically and visually monitored and your face will be visually monitored for any signs of activity spreading beyond the stimulated area and your participation in the study will be discontinued by the investigator if any such signs are observed. In case of a seizure, you will receive emergency treatment and the seizure will be documented. A seizure may result in disturbance of sensation, loss of consciousness, convulsive movement, or some combination of these features. Short term effects of a stimulation-induced seizure may include mild memory deficits and EEG abnormalities. Both short-term effects are known to disappear within two days. There are no known long-term physical risks associated with stimulation-induced seizure. However, it is conceivable that the occurrence of a seizure could be misinterpreted or deliberately used as a pretext for the denial of employment or medical insurance. In this case, the investigator will provide, at your request, documentary support of your claim that a provoked seizure carries no adverse prognosis.

Other mild side effects may occur. Muscles and nerves near the stimulating coil are activated by TMS. This may cause discomfort and pain. In the interest of tolerability, the treatment stimulation will start less intense and ramp up to the full treatment stimulation. In susceptible individuals, repetitive TMS may cause tension-type headaches. The headaches usually respond well to mild analgesics (e.g. Aspirin or Tylenol). The TMS coil makes a loud click during stimulation, suggesting a possible risk of hearing loss. One study carried out to test this possibility did not find any evidence of hearing loss associated with TMS. Nevertheless, for your protection, you will be given earplugs to wear during these procedures. In studies of the effect of TMS on immune system function, one study showed a temporary change in on measure of immune function that was roughly equivalent in size to the normal fluctuations seen over the course of a day or in response to mild stress or the menstrual cycle. In subjects with history of fainting, TMS may cause fainting. Because this is an investigational instrument, there may be risks that are currently unforeseeable.

The primary risk of this treatment protocol is the potential for lack of clinical improvement. Subjects may suffer some fluctuation or worsening of symptoms during treatment. As a safety precaution, your symptoms will be monitored during your treatment.

Seizure Risks:

- Generalized seizures have been reported with the use of TMS in the clinical trial literature. No seizures were been reported with use of the original TMS System (the first FDA-approved TMS device) in over 10,000 treatment sessions in trials conducted prior its FDA clearance. Since the introduction of both it and other TMS devices (including the MagStim Rapid^2 and MagVenture devices, the only devices used in this study) into clinical practice, seizures have been rarely reported. The estimated risk of seizure under ordinary clinical use is approximately 1 in 30,000 treatments (0.003% of treatments) or 1

in 1000 patients (0.1% of patients). Nevertheless, all TMS Systems should be used with caution in patients who have a history of seizures.

- Having a seizure includes a potential effect on your future employability, insurability, and ability to drive. Should you experience a seizure that is related to magnetic stimulation, your doctor will provide you with a letter stating that the seizure was produced under experimental conditions and that there is no reason to expect another occurrence.

***Clinical Data*:** Potential risks include a breach of confidentiality and privacy. We will take all precautions to secure and store subject data as to minimize this risk.

Will I be paid for participating?

If you are enrolled in a psychology course, you will receive 1 course credit for your class for each of the in-lab visits, for a total of up to 4 course credits. You may discontinue participation at any time or refuse to answer any questions you do not want to and still receive credit(s) for the visit(s) you completed. If you are participating for financial compensation, you will receive $50 for your participation via check mailed to you at your specified mailing address.

Will information about me and my participation be kept confidential?

The researchers will do their best to make sure that your private information is kept confidential. Information about you will be handled as confidentially as possible, but participating in research may involve a loss of privacy and the potential for a breach in confidentiality. Study data will be physically and electronically secured. As with any use of electronic means to store data, there is a risk of breach of data security. All identifiable information about you will be replaced with a code. A list linking the code and your identifiable information will be kept separate from the research data.

All research data and records will be maintained in a secure location at UCLA.
Only authorized individuals will have access to it. Some research data and records will be stored on a laptop computer that is has encryption software. All research data and records will be stored electronically on a secure computer and network with password protection.

The research team, authorized UCLA personnel, the study sponsor, and regulatory agencies such as the Food and Drug Administration (FDA), may have access to study data and records to monitor the study. Research records provided to authorized, non-UCLA personnel will not contain identifiable information about you. Publications and/or presentations that result from this study will not identify you by name.

What are my rights if I take part in this study?

- You can choose whether or not you want to be in this study, and you may withdraw your consent and discontinue participation at any time.
- Whatever decision you make, there will be no penalty to you, and no loss of benefits to which you were otherwise entitled.
- You may refuse to answer any questions that you do not want to answer and still remain in the study.

Who can I contact if I have questions about this study?

- **The research team:**
  If you have any questions, comments or concerns about the research, you can talk to the one of the researchers. Please contact:
  Principal Investigator: Michael Leuchter, 310-890-6943 or mkleuchter@mednet.ucla.edu
  Faculty Supervisor: Marco Iacoboni, M.D., Ph.D. at iacoboni@ucla.edu
  Co-investigators:
  David Krantz, M.D., Ph.D. at dkrantz@ucla.edu
  Benjamin Rosenberg, Ph.D. Candiate, at benrosenberg@g.ucla.edu

- **UCLA Office of the Human Research Protection Program (OHRPP):**

  If you have questions about your rights as a research subject, or you have concerns or suggestions and you want to talk to someone other than the researchers, you may contact the UCLA OHRPP by phone: (310) 206-2040; by email: participants@research.ucla.edu or by mail: Box 951406, Los Angeles, CA 90095-1406.

You will be given a copy of this information to keep for your records.
SIGNATURE OF STUDY PARTICIPANT

_____
Name of Participant

_____ _____
Signature of Participant Date

SIGNATURE OF PERSON OBTAINING CONSENT

_____ _____
Name of Person Obtaining Consent Contact Number

_____ _____
Signature of Person Obtaining Consent Date