Treating Stimulant Addiction with Repetitive Transcranial Magnetic Stimulation

NCT04228276

November 28, 2023

IRB Use Only
Approval Date: November 28, 2023
Expiration Date: November 28, 2024

Title of Study: Treating Stimulant Addiction with Repetitive Transcranial Magnetic Stimulation	
Title of Consent (if different from Study Title):	
Principal Investigator: **Jong H. Yoon, MD**	VAMC: VA Palo Alto HCS

Are you participating in any other research studies? _____ yes _____no

You are invited to participate in a research study of stimulant use disorder. We hope to learn if repetitive transcranial magnetic stimulation (rTMS) can be an effective treatment for stimulant use disorder. rTMS is currently approved by the FDA for use in depression, and its use for other conditions is being researched.

Your participation in this study is voluntary, and you may withdraw your consent at any time. If you choose not to take part in this study, you may alternatively receive treatment as usual at the Addiction Treatment Service at the Palo Alto VA.

The duration of your participation is about three months, and will include rTMS treatment, fMRI scans, and clinical assessments. There are also additional procedures you may choose to take part in. You will continue to receive treatment as usual at the Addiction Treatment Service at the Palo Alto VA.

There may be some risks and discomforts associated with this study, including headache and fatigue. These are described in more detail below.

PURPOSE OF RESEARCH

You are invited to participate in a research study of stimulant use disorder. We hope to learn if repetitive transcranial magnetic stimulation (rTMS) can be an effective treatment for stimulant use disorder and to explore biomarkers that may guide patient selection for rTMS treatment and predict treatment response. Currently rTMS is not FDA approved for treatment of stimulant addiction. You were selected as a possible subject in this study because you are a Veteran with stimulant use disorder at the Addiction Treatment Service (ATS) at the VA Palo Alto. This study is being done together by researchers at VA Palo Alto and Stanford University.

If you decide to terminate your participation in this study, you should contact Dr. Jong Yoon at (650) 493-5000 ext. 69193.

This research study is looking for 48 people with stimulant use disorder, recruited through the ATS at the VA Palo Alto.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to

participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care you are entitled to.

DURATION OF STUDY INVOLVEMENT

Study participation will take place across three months: 8 treatment sessions with rTMS for two weeks, followed by weekly urine toxicology and a clinical assessment occurring three months after completion of rTMS treatment.

PROCEDURES

Patients who sign this informed consent form and meet study eligibility criteria will be enrolled into the study and will be randomized into one of the two treatment groups: active (real) rTMS or sham (placebo) rTMS. You will have a fifty percent chance of receiving the active treatment or a fifty percent chance of receiving the sham treatment. The rTMS active (real) treatment will use magnetic pulses to stimulate areas of the brain and the rTMS sham (placebo) treatment will simulate (sound and feel like) a real rTMS treatment, but will not use magnetic pulses or stimulate the brain in any manner. At the end of the study, participants who received sham rTMS may have the option to receive active rTMS, dependent upon staff and resource availability. It is possible that, based on information gained from this study, the researchers may have serious concerns (relating to matters such as severe depression, physical abuse, etc.) about your health and/or safety; in such a case, the researchers may contact you and provide a referral for your care.

If you choose to participate, the investigators will perform the following procedures:

1) Baseline in-person telephone or virtual clinical assessment and screening
2) Baseline experimental measurements
3) rTMS treatment
4) Midpoint assessments
5) Post-treatment clinical assessments
6) Post-treatment experimental measurements
7) 3-month follow-up assessments
8) Weekly toxicology tests over the course of the study

1) <u>Baseline in-person clinical assessment and screening:</u> You will meet with study staff for an in-person or telephone or virtual clinical assessment using approved Stanford Zoom video-conferencing software. You have the right to refuse to answer particular questions. The purpose of this clinical assessment will

be to confirm the diagnosis of substance use disorder and the absence of major psychiatric comorbidity, to obtain a medical history to ensure your safety, and to quantify your level of functioning and severity of stimulant use. This meeting is expected to take between 3 and 4 hours.

2) Baseline experimental measurements: The main measure will be functional magnetic resonance imaging (fMRI) which will take place at Stanford University after signing a separate consent form, but you may also elect to undergo, actigraphy as described below.

Actigraphy: Actigraphy is a non-invasive technique used to assess cycles of activity and rest. A small actigraph is worn on the wrist like a watch and measures activity through movement. The actigraph will be worn for about one month after the start of rTMS treatment.

You will be told the results of tests that are part of your clinical care, but you will not be told the results of the research tests, including any future research tests.

3) **Repetitive transcranial magnetic stimulation (rTMS):** rTMS involves applying pulses of rapidly changing magnetic field to induce electrical currents within a targeted brain region, which modulates its function. High frequency rTMS is a FDA-approved procedure for medication-resistant depression. Through this indication, rTMS is becoming widely adopted in psychiatry and undergoing testing for a variety of conditions, including substance use disorders. A small handful of controlled studies have shown promising results for rTMS in the treatment of stimulant use disorder. In this study, we hope to learn if rTMS can be an effective treatment for stimulant disorder. You will receive 8 sessions of rTMS over two weeks. Each session will last about 15 minutes and will take place at the Palo Alto VA.

4) Midpoint assessments: These clinical assessments will quantify your level of functioning, severity of stimulant use, and symptoms after half of the rTMS treatment sessions have been completed.

5) Post-treatment clinical assessments: Post-treatment clinical assessments will quantify your level of functioning, severity of stimulant use, and symptoms after all of the rTMS treatment sessions have been completed.

6) Post-treatment experimental measures: The procedures will include fMRI at Stanford University and optionally actigraphy very similar to the baseline procedures at the VA Palo Alto. Descriptions of these procedures can be found in section 2, Baseline Procedures.

7) 3-month follow-up assessments: These clinical assessments will quantify your level of functioning, severity of stimulant use, and symptoms three months after the last rTMS treatment session is completed.

8) Weekly toxicology: You will also undergo weekly urine toxicology tests during the course of this study, the rTMS treatment, and for three months after rTMS treatment is completed. These toxicology tests occur routinely for people enrolled in the Addiction Treatment Service.

By signing this consent form, you are agreeing to participate in clinical assessments, rTMS, and fMRI scans.

By checking the boxes below, please indicate which additional components of the study you are willing to participate in:

☐ Actigraphy

Video and/or Audio Recording

You may consent to be video- and/or audio-recorded so that members of the research team and collaborating researchers can review and analyze content to increase diagnostic reliability and improve diagnostic methods. You may also consent to allow recordings to be used for educational purposes (e.g., lectures to students or trainees).
Consent for video/audio recording is not required for study participation.

Circle One: YES | NO I consent to be videotaped for review and analysis by lab and collaborators to improve diagnostic methods and reliability.

Circle One: YES | NO I consent to allow video recordings to be used for educational purposes outside of this lab.

Circle One: YES | NO I consent to be audio-recorded for review and by lab and collaborators to improve diagnostic methods and reliability.

Circle One: YES | NO I consent to allow audio recordings to be used for educational purposes outside of this lab.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the investigators and study staff.
- Attend the rTMS treatment sessions as instructed.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the investigators or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the investigators or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the investigators or research staff if you believe you might be pregnant or gotten your partner pregnant.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Tell the investigators or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are **free to withdraw** your consent and stop your participation at any time. If you decide to withdraw from the study, you will not lose any benefits to which you would otherwise be entitled and your decision will not affect your ability to receive medical care for your condition.

If you want to stop being in the study you should tell the investigators or study staff. You can do this by phone by calling the principal investigator Dr. Jong Yoon at 650-493-5000 x69193.

The investigators may also withdraw you from the study and the study medication may be stopped without your consent for one or more of the following reasons:

- Failure to follow the instructions of the investigators and/or study staff.
- The investigators decide that continuing your participation could be harmful to you.
- Pregnancy.
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

This study involves the following risks, discomforts, and possible inconveniences:

Repetitive transcranial magnetic stimulation (rTMS)
Your study investigator will be monitoring you during your participation to see if you are experiencing side effects. It is important that you promptly report any side effect to study staff. If you feel, or your study investigator feels, that the side effects are not well tolerated, treatment may be stopped altogether and you may be withdrawn from the study.

Seizure
There is little evidence of risk of seizures using rTMS the way it will be used in this study. A few patients among tens of thousands have had a seizure while receiving rTMS. All of the reported seizures resolved promptly on their own and none had any lasting effects or adverse impact on the patients. However, stimulant use may decrease the seizure threshold. If you are taking any drugs that may increase the risk of having a seizure, please notify the research staff.

In the unlikely event that a seizure does occur, you will be closely monitored and treated for any medical or psychological consequences. A physician will see you as soon as possible, and we will conduct an assessment, order labs, and recommend further assessment or treatment as warranted. The facility where the rTMS studies are being performed is fully equipped to safely handle a seizure. You will be given a letter regarding the seizure to share with your primary health care provider. The letter will indicate that the seizure during rTMS does not increase your risk for future seizures.

Headache
rTMS treatment can result in mild to moderate headaches in as many as 30 out of 100 patients. Some people also report discomfort at the site of rTMS stimulation. This occurs in around 15 out of 100 patients. Headaches and site discomfort usually respond readily to acetaminophen or ibuprofen. Painfulness improves over time or goes away. Often patients fall asleep in the second week while receiving the same treatment that on the first day was reported as very painful.

Dental pain
There is a small risk of dental pain with rTMS, during or immediately after the treatment. If this occurs, tell your study doctors and nurses know and they may be able to move the rTMS coil position or provide you with a bite block to reduce or prevent the pain.

Tingling and numbness
rTMS treatment may produce movement or tingling in the arm, leg, face, or scalp. You may also experience a temporary feeling of numbness in the face.

Hearing Loss
There is a possible risk of hearing loss due to the light clicking sounds made by the device. You will wear ear protection during your rTMS sessions. This should greatly reduce the possibility of hearing loss. The rTMS operator will monitor you for ear protection, coil placement, and seizure activity during all sessions.

Mania
In some people, rTMS can cause increased energy, no need for sleep, and rapid racing thoughts. This is called mania. If you notice these changes, notify your primary physician and the study team.

Long-term risks
The possibility of long-term risks is unknown. In previous studies, animal and human brains have shown no evidence of any kind of damage from rTMS. As with any experimental treatment, there may be unforeseen risks associated with this device. You will be informed of any new information that is developed during the study that might affect your willingness to continue your participation.

Women of childbearing potential
For safety reasons, pregnant women will not be allowed to participate in this study. This is because the effects of rTMS on an unborn child are unknown. There may be unforeseeable (unanticipated) risks to the participant (or to the unborn child) if the participant is pregnant or becomes pregnant during the study.

You will have a urine pregnancy test within 7 days prior to your starting study treatment.

You must agree to use a medically acceptable form of birth control while participating in the study. Acceptable forms of birth control are:

- Complete abstinence (not having sexual intercourse with anyone)
- An oral contraceptive (birth control pills)
- Norplant
- Depo-Provera
- A condom with spermicide
- A cervical cap with spermicide
- A diaphragm with spermicide
- An intrauterine device
- Surgical sterilization

If you become pregnant during the treatment phase of the study, you will not be able to continue the study treatments. You will also be referred to a Women's Health Clinic. If you become pregnant during the follow-up phase of the study, you will continue to come in for all remaining follow-up phase visits and complete all assessments as you normally would.

If you become pregnant at any time during the study, you will be asked to sign a release of information form for study staff to access medical records to obtain information regarding the outcome of your pregnancy. No pediatric records will be reviewed.

There is no likely effect on sperm count or motility or other reproductive risks associated with fathering a child, although this has not been formally tested in humans. Likewise there are no known risks on sperm and ova (eggs).

rTMS treatment may involve the additional risks to you, which are currently unforeseeable as it is a new possible treatment for substance abuse disorder.

IF YOU FEEL DISCOMFORT AT ANY TIME, NOTIFY THE OPERATOR AND YOU CAN DISCONTINUE THE EXAM AT ANY TIME.

Incidental Findings

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 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. If this occurs, a doctor will be asked to look at the images to see if any medical follow-up is needed. If so, the investigator will contact you and recommend you inform your doctor about the findings. Because the images are taken using research settings they will not be made available for clinical purposes.

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 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.

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. 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.

Cognitive tasks and clinical assessments

There are virtually no risks involved in the cognitive task and psychosocial assessments other than the anxiety that can be associated with any test. However, these questions may bring on uncomfortable thoughts, feelings, and lead to recalling troubling memories. It is possible that you might become tired or frustrated by some of the testing. You may find answering the questionnaires annoying boring, or repetitive. If this happens, please tell us and we will take a break or continue the questions another day.

Blood draw

Drawing blood is a routine procedure involving the possibility of slight bruising and/or infection at the needle puncture site. There may be some discomfort during insertion of the tube for withdrawing blood. On rare occasions, some patients have fainted while having their blood drawn. A clot could also form in the vein, resulting in temporary or tenderness in the area where the tube was placed. Infection is rare. To minimize these risks, experienced medical personnel will handle all the blood drawing procedures. There is also a risk of scarring at the site of needle insertion with individuals having more pigmented skin having a greater risk of this occurring.

Actigraphy

The risks of actigraphy are akin to those wearing any kind of watch. That is, there is a risk of contact dermatitis (skin redness). If this occurs, we recommend that you apply lotion on the affected skin and move the actigraph to the other wrist. This is a greater risk in older participants.

POTENTIAL BENEFITS

We cannot promise that you will get any benefits from taking part in this research study. However, possible benefits may include improvements to your stimulant use disorder. The information that is obtained during this study may be scientifically useful and may lead to greater knowledge about the treatment of stimulant use disorder.

ALTERNATIVES

You may choose not to participate in this study. The alterative is to not take part in this study and receive treatment as usual at the Addiction Treatment Service at the Palo Alto VA.

PARTICIPANT'S RIGHTS

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

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.

ClinicalTrials.gov

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

CONFIDENTIALITY

Identifiers might be removed from identifiable private information and/or identifiable specimens and, after such removal, the information and/or specimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

We will keep your name and all the information about you used in this study as confidential as possible. We may publish the results of this study for others to read about, but you will not be identified in any articles about the study by name, social security number, address, telephone number, or any other direct personal identifier. Also, other federal agencies as required, such as the VA Office of Research Oversight and the VA Office of the Inspector General may have access to your information.

Because this study involves an investigational device, the Food and Drug Administration may also have access to information about you collected in this study.

The responses to questions concerning illegal drug use could be self-incriminating and harmful to you if they become known outside the study. As explained in the confidentiality statement of the consent, we do not intend to disclose this information.

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

Health Information Portability and Accountability Act (HIPAA)

There are rules to protect your private health information. Federal and state laws and the federal medical law, known as the HIPAA Privacy Rule, also protect your privacy. By signing this form, you provide your permission called your 'authorization,' for the use and disclosure of information protected by the HIPAA Privacy Rule.

How will my health information be used in the study?

This study utilizes repetitive transcranial magnetic stimulation (rTMS) in the treatment of stimulant use disorder. Information about your stimulant use and experimental measures will be used to learn about the efficacy of rTMS in the treatment of stimulant use disorder and its effect on brain function.

What Personal Health Information Will Be Used or Shared?

The following health information, linked to you by identifiers such as your name, SSN, date of birth, and medical record number, will be used for this research:

- *Demographic Information such as name, age, race*
- *Video or Audio Recordings*
- Medical history and physical examination information
- Laboratory Test Results on blood and urine
- MRI scans
- Behavioral Activity (actigraphy)
- Survey/Questionnaire responses
- Psychological test results and other clinical assessments
- Drug use related information
- Alcoholism or alcohol use related information
- Electronic medical record entries indicating level of contact with clinicians and types of VA services utilized

Who May Use or Share Your Health Information?

By signing this document, you allow the following individuals and entities to obtain, use and share your health information for this research study:

- The Principal Investigator Dr. Jong Yoon and members of the VA research team.
- Departments within the VA Health Care System responsible for the oversight, administration, or conduct of research.
- The Stanford University Administrative Panel on Human Subjects in Medical Research and other Stanford University Officials responsible for the oversight, administration, or conduct of research.

Who May Receive and Use Your Health Information

The investigators may share your health information with the following individuals as part of this research study.

- Stanford University collaborating investigators and research staff.
- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- The Rehabilitation Research and Development Service of the Department of Veterans Affairs.
- Other outside individuals or entities hired by the VA Palo Alto Health Care System to do certain work in support of the VA Health Care System
- The Food and Drug Administration

We will protect your health information as required by all laws, however health information shared with others may no longer be protected by Federal laws or regulations and might be shared by the parties above.

Do I have to sign this form?

No. Signing this form is voluntary. The VA may not condition treatment, payment, enrollment or eligibility for benefits based on signing this form. If you decide not to sign the form, you will not be able to take part in this study or receive any research-related treatment.

If I sign now, can I decide later not to continue in the study?

Yes. You are free to take back your permission and stop being in the study. The investigators will not collect any more information about you after you take back your permission, but they can continue to use your information that was collected before you took back your permission.

Your request to take back your permission must be done in writing. Either give your written request to the investigator or send it by mail to Principal Investigator Dr. Jong Yoon at the address 3801 Miranda Ave, Building 4, Room A-236l, Palo Alto, CA 94304.

Does My Permission for the use my Personal Health Information Expire?

Yes. Your information cannot be used forever. Your permission related to the use and sharing of your health information expires when this research study is completed or on December 31, 2035.

HIPAA regulations require you to give separate written permission (signature) for the use of your protected health information.

_____ _____

Signature of Adult Participant Date

FINANCIAL CONSIDERATIONS

Payment/Reimbursement for Participating in Core Elements of the Study

	Baseline	Post-Treatment	Follow-Up	
Clinical Assessment	$20	----	$20	
fMRI	$60	$60	----	
rTMS	-----	$20	----	
Completion Bonus			$100	
Payment/Subject	$80	$80	$120	**Total:** $280

Payment/Reimbursement for Participating in Actigraphy

	Baseline	Post-Treatment	Completion Bonus	
Actigraphy		$10	$10	
Payment/Subject		$10	$10	**Total:** $20

Payments will be made in the form of checks or other forms of direct payment at three timepoints-- after completion of baseline assessment, post-treatment, and follow-up. If you drop out before these timepoints, you will receive prorated reimbursements for your participation. If you complete the research study through the 3-month follow-up, you will receive a $100 bonus. Participants who complete all core components of the study will be reimbursed $280. Participants who complete additional components of the study may receive up to $20 additionally.

You may need to provide your social security number to receive payment.

Costs

There will be no costs to you for any of the treatment or testing done as part of this research study. However, medical care and services provided by the VA that are not part of this study (e.g., normal hospital and prescription expenses which are not part of the research study) may require co-payments if your VA-eligibility category requires co-payment for VA services.

Sponsor

The Rehabilitation Research and Development Service of the Department of Veterans Affairs is providing financial support for this study.

COMPENSATION for Research Related Injury

If you are injured as a direct result of being in this study, medical treatment will be available. If you are eligible for veteran's benefits, the cost of such treatment will be covered by the VA. If not, the cost of such treatments may still be covered by the VA depending on a number of factors. In most circumstances, the treatment must be provided in a VA medical facility. No other form of compensation for injuries is available. However, by signing this form you have not released the VA from liability for negligence.

CONTACT INFORMATION

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 principal investigator, Dr. Jong Yoon at 650-493-5000 x69193. 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.

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 arise;

- 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.

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

_____ _____
Signature of Participant Date

_____
Print Name of Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Print Name of Person Obtaining Consent

HIPAA regulations require the participant to give separate written permission (signature) for the use of their protected health information.

Person Obtaining Consent HIPAA Authorization confirmation:

☐ Confirm the participant signed the VA HIPAA Authorization section of this consent form.