Integrated Repetitive Transcranial Magnetic Stimulation and Acceptance and Commitment Therapy for Veterans with Chronic Pain and Depression

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April 17, 2023

Study Title: Integrated Repetitive Transcranial Magnetic Stimulation and Acceptance and Commitment Therapy for Veterans with Chronic Pain and Depression

Principal Investigator:

VA Facility: VA San Diego Healthcare System

Participant Name:	Date:

STUDY SUMMARY

You are being asked to participate in a research study. This section summarizes key information about this study to assist you, or your legally authorized representative, in understanding the reasons why you may or may not want to participate in the research. Your participation is voluntary. You may refuse to participate or withdraw at any time. You will not lose any services, benefits or rights you would normally have if you chose not to volunteer. Carefully review this section and the detailed information that follows before you agree to participate.

WHAT IS THE STUDY ABOUT AND WHY ARE WE DOING IT?

This study examines if the combination of Acceptance and Commitment Therapy (ACT) and transcranial magnetic stimulation (TMS) can help Veterans living with chronic pain and depression. Both ACT and TMS have shown promise to improve chronic pain and depression. This study will determine if TMS offers an additive benefit to ACT. It is being funded by the VA and UC San Diego.

WHAT DOES THE STUDY INVOLVE AND HOW LONG WILL IT LAST?

Each participant in this study will receive 8-sessions of ACT, delivered in 90-minute weekly sessions by a licensed clinical psychologist. Additionally, each participant will be randomized, similar to flipping a coin, to receive “active-TMS” or “sham-TMS”. Both forms of TMS will be delivered at the San Diego VA for 6 weeks, 4 times per week for 6 weeks, for a total of 24 TMS sessions. Total time participating in this study is about 10 weeks.

ACT is an evidence-based cognitive-behavioral treatment for chronic pain and depression. ACT will be provided by a licensed clinical psychologist virtually using a tablet provided by the VA. For the 6 weeks you receive TMS, you will complete the ACT sessions immediately after TMS in a private room within the VA. You will work with the study therapist to find a time during the week that works for both of you. You will be able to complete the last 2 sessions of ACT from your home if you wish.

For those randomized into the active-TMS condition, you will receive closely-monitored TMS over the dorsolateral prefrontal cortex (DLPFC), a brain region involved in depression and pain processing, at stimulation frequencies from 1 – 20 Hz. TMS involves the use of a magnet that delivers pulsed magnetic fields. These magnetic fields are of a similar type and strength used in magnetic resonance imaging (MRI) machines. During a TMS session, a qualified staff member will place the magnetic coil gently against your scalp, directing the magnetic fields produced by the coil at the DLPFC. Stimulation will occur as a series of “pulses”, indicating brief periods of time when the magnet is active. You’ll hear a clicking sound and feel a sensation on your scalp.

For those randomized into the sham-TMS condition, a magnetic coil will be placed against your scalp accompanied with a clicking sound, but the machine will not deliver any magnetic pulses. If you are randomized into this condition, you will be eligible for active-TMS following the completion of the study.

Approximately one week prior to scheduling your first visit at the San Diego VA, you will be asked to download a VA-approved smartphone application. This application will send a notification to your smartphone four times per day over the course of a week for a total of 28 notifications. After completing treatment, you will again receive four notifications per day over a week for an additional 28 notifications. Each notification will consist of about 10 questions about your pain, mood, and quality of life and take about 2 minutes per notification to complete.

Prior to beginning ACT and TMS, you will come to the La Jolla VA to complete your "baseline visit", which consists of questionnaires about your pain, mood, and quality of life, two game-based cognitive tasks with electroencephalography (EEG), and establish TMS parameters. One of these games examines how distractible you are by presenting different facial expressions on a computer screen and the other game examines how attentive you are to your breath. EEG is a non-invasive measure of the electrical activity of your brain. For this measurement, you will wear a cap that allows us to collect information about electrical signals produced by different parts of your brain. After you finish ACT and TMS, we will ask you to return to the La Jolla VA for your final "posttreatment visit", where you will complete similar questionnaires and complete once again the two game-based cognitive tasks with EEG. Each of these sessions will take about 2 hours.

Of note, the spouse of a co-investigator on this project ([redacted]) owns the copyright to the software for the game-based cognitive tasks, and thus it is possible this research may affect the value of this copyright.

You will also have the option for opting into a pain assessment to help us better understand the impact of treatment on pain sensitivity. This assessment includes: 1) heat sensations, tested using a commercially available thermal sensory testing machine used widely in clinical and research purposes applied to your forearm; 2) pressure sensations, tested using a handheld device with a small rubber tip that will be applied to your trapezius (shoulder muscle); 3) mechanical sensation tests, tested by a handheld probe that has a small nylon tip to poke the back of your hand; and 4) combined pressure sensations and cold sensations, tested by assessing pressure sensations at the trapezius as described above before and after placing your non-dominant hand in a cold water bath. All of these procedures may produce mild to moderate pain. You will be able to stop any procedure at any time. If you choose to opt into the pain assessment, it will add about an hour to your baseline and posttreatment session.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

Your participation will help further research into improving chronic pain and mood treatments. In addition, being in this study may improve your chronic pain and your mood.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

You may not feel comfortable having your brain stimulated using TMS, brain activity recorded using EEG, or undergoing the pain assessment procedures. A complete description of risks is included in the Research Details Study Risks section. A complete description of risks is included in the Research Details Study Risks section.

Participation is voluntary and the alternative is to not participate. A complete description of alternate treatment/procedures is provided in the Research Details Alternatives section.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The person in charge of the study is [redacted] of the VA San Diego Healthcare System. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his contact information is: [redacted]

RESEARCH DETAILS

WHO IS CONDUCTING THIS RESEARCH AND WHY?

[redacted], PhD, is conducting this research. This study is being sponsored by the VA and Department of Psychiatry at UC San Diego.

The purpose of this research is to learn more about integrating ACT and TMS for chronic pain and depression. The device used to deliver the stimulation is FDA-cleared for depression but not chronic pain. The application of TMS for chronic pain is considered experimental. You are being asked to participate because you have chronic pain and depression. Approximately 40 people will take part in this research at this facility.

FOR HOW LONG WILL I BE IN THE STUDY?

It will take approximately 30 minutes to explain the study procedure, get participant consent and perform inclusion/exclusion assessments.

The duration of the study is approximately 10 weeks: 1-week of smartphone notifications, followed by 8-weeks of ACT and TMS, followed by 1-week of additional smartphone notifications.

At the baseline session, you will complete study questionnaires, the two game-based tasks with concurrent EEG, and establish TMS parameters, which will take approximately 90 minutes (20 minutes for questionnaires, 20 minutes to set up the EEG, 20 minutes to complete the game-based cognitive tasks, 30 minutes to establish TMS parameters). If you choose to opt into the pain assessment at the first and final TMS session, this will add an additional 30 minutes to the baseline session. For the posttreatment session, you will repeat these tasks (minus establishing TMS parameters).

For TMS sessions, it will take approximately 15 minutes to set up the TMS machine and approximately 20 minutes to a complete a TMS session. After one of your weekly TMS sessions, you will walk to a private room in the VA hospital and meet virtually with your study therapist for a 90-minute ACT session. Because there are a total of 8 weekly ACT sessions but the TMS protocol only lasts for 6 total weeks, you will do the last 2 weekly ACT sessions at home using your personal home computer or a tablet provided by the VA.

Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without penalty or loss of benefits to which you are entitled. If you decide that you no longer wish to continue in this study, please notify [redacted] or his research staff by calling [redacted] You will be told if any important new information is found during the course of this study that may affect your wanting to continue.

WHAT WILL HAPPEN AND WHAT CAN I EXPECT IF I TAKE PART IN THIS STUDY?

This is what will happen at each visit if you participate in this study:

- You will download a VA-approved application to your smartphone. This application will send notifications to your smartphone, with each notification consisting of approximately 10 brief questions. You will complete these notifications 1-week prior and 1-week following ACT and TMS sessions.
- At the baseline visit, you will complete questionnaires about your background (e.g., age, gender, race/ethnicity, etc.), pain, quality of life, and mental health, including thoughts and feelings of depression and anxiety. Some of the questions may be personal in nature and you can choose to not answer them. You will complete a similar set of questionnaires at the posttreatment visit. These questionnaires will take approximately 20 minutes.
- At the baseline visit, you will establish TMS parameters. For this part of the study, [redacted] the study physician, will establish the location and stimulation parameters for your TMS treatment. This will take approximately 30 minutes.
- At the baseline and posttreatment visit, you will also complete two game-based tasks with concurrent EEG. Including setting up the EEG, this will take approximately 40 minutes.
- If you opt into the pain assessment, this will add approximately 30 minutes to the first and final session.
- You will complete 8 90-minute sessions of ACT virtually with a licensed clinical psychologist.
- You will receive 24 sessions of TMS brain stimulation. You will be randomly assigned, similar to flipping a coin, to receive 24 sessions of active-TMS or sham-TMS. Your group assignment will be fixed for the entire 24 sessions.
- We will obtain clinical information from your medical record to relate the cognitive and brain activity measures to clinical information.

WHICH PROCEDURE/S OR TREATMENT/S ARE DONE FOR RESEARCH?

All aspects of this study are done for research.

WHAT POSSIBLE RISKS OR DISCOMFORTS MIGHT I HAVE IF I TAKE PART IN THIS STUDY?

Any procedure has possible risks and discomforts. The procedures in this study may cause all, some, or none of the risks or side effects listed. Rare, unknown, or unexpected risks also may occur.

ACT
It is possible that the ACT intervention will produce some discomfort including feelings of anxiety or frustration.

TMS
1. Some participants may experience tapping or painful sensations at the treatment scalp site, muscle contractions, as well as headaches or neck stiffness after TMS.
2. Some participants may find the loud click that accompanies the stimulation unpleasant.
3. Seizures (also called convulsions or fits) have been known to occur as a consequence of TMS stimulation. You have about a .003% (1/30,000) chance of having a seizure related to this TMS treatment. Certain medications, drugs of abuse and medical diagnoses (such as seizure disorder) increase the chances of having a seizure. A doctor associated with this research will review your medical history to assess your level of risk and will discuss this with you.
4. TMS should not be administered to anyone who has magnetic-sensitive metal in their head or magnetic- sensitive metal within 12 inches of the TMS coil that cannot be removed. Failure to follow this restriction could result in serious injury or death. Objects that may have this kind of metal include:
- Aneurysm clips or coils
- Carotid or cerebral stents
- Implanted stimulators
- Electrodes to monitor your brain activity
- Ferromagnetic implants in your ears or eyes
- Bullet or shrapnel fragments
- Other metal devices or objects implanted in the head
- Pellets, bullets, or metallic fragments

If you have any of the above, you should not participate in this study.

Game-based cognitive tasks with EEG.
It is possible some participants may experience frustration or fatigue while completing the game-based cognitive tasks. EEG involves no risk, but you may experience some physical discomfort from wearing the EEG cap.

Pain assessment
The pain assessment precures may be uncomfortable or unpleasant. You will experience some temporary discomfort from the heat, pressure, mechanical, and cold pain testing; you can stop any of the procedures at any time. There is a very low risk that the heating device may produce a burn. In addition, there is a low risk the pressure and mechanical testing may produce bruising. Finally, the study procedures could cause a temporary increase in your blood pressure.

Potential loss of confidentiality, including both information you provide to the research staff as well as information obtained from CPRS records.

There is always a chance that any procedure can harm you. In addition to the risks described above, you may experience a previously unknown risk or side effect.

There are no risks to the reproductive system or a developing fetus.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

It is possible that being in this study can positively impact your chronic pain and mood. Additionally, the information we get from this study may help us learn more about the nature of chronic pain and depression and how to best treat it.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO JOIN THIS RESEARCH STUDY?

The alternative to participation in this study is not to participate. If you have chronic pain and depression, you can get other treatments (including medications and other forms of brain stimulation). Please discuss these options with your doctor.

WILL I BE TOLD NEW INFORMATION ABOUT THIS STUDY?

While you are a participant in this study, you will be notified if any important new information is found that may affect your willingness to continue. If the results of this research might influence your medical care after your participation, the investigators will contact you to let you know these results.

WHAT WILL HAPPEN IF I AM INJURED BECAUSE OF MY BEING IN THE STUDY?

The VA will provide necessary medical treatment should you be injured as a result of participating in this study and following study procedures. You will be treated for the injury by the VA at no cost to you or your insurance but no additional compensation is available.

DO I HAVE TO TAKE PART IN THIS STUDY?

Taking part in this research study is your decision. Your participation in this study is voluntary. You do not have to take part in this study, but if you do, you can stop at any time. You have the right to choose not to participate in any study activity or completely withdraw from continued participation at any point in this study without penalty or jeopardy to the medical care you will receive at this institution or loss of benefits to which you are entitled.

WHAT ARE THE COSTS TO ME IF I TAKE PART IN THIS STUDY?

Study Title: Integrated Repetitive Transcranial Magnetic Stimulation and Acceptance and Commitment Therapy for Veterans with Chronic Pain and Depression

Principal Investigator:

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There will be no costs to you or your insurance for any procedures or testing done only as part of this research study. If you receive a bill for services that you think could be related to your participation in this study, you should contact [redacted].

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.

WHAT COMPENSATION WILL I RECEIVE IF I TAKE PART IN THIS STUDY?

You will be paid $1 per smartphone notification that you complete, providing up to $56 compensation. You will be compensated $100 for your effort completing study questionnaires and the two game-based tasks with concurrent EEG at the first and final session for up to $200 compensation. If you choose to take part in the pain assessment at the first and final session, you will be compensated $100 for each, providing an additional $200 compensation.
Thus, you can receive up $456 for participation in this study.

WHO DO I CONTACT ABOUT THIS STUDY IF I HAVE QUESTIONS?

If you have any questions, complaints, or concerns about the research or other related matters, you may contact [redacted].

If you have any questions or concerns about your rights as a research subject, the validity of a research study, or research personnel you can contact the Research Compliance Officer at 858-642-3817, VA Research Service at 858-642-3657, VA Regional Counsel at 858-642-1540, or the VASDHS Institutional Review Board at 858-642-6362. This is the Board that is responsible for overseeing the safety of human participants in this study.

If you have study related questions or concerns you can contact the research team at [redacted]

FUTURE USE OF DATA AND RE-CONTACT

All electronic data collected will be stored on a password protected computer server. All direct identifying information such as name, phone number and medical record number will be separately stored in a password protected file. Only study investigator, [redacted] will have access to the file that links your name with a
subject number. All electronic assessment data (i.e. from cognitive and brain assessments and questionnaires) will be linked to a non-identifying participant ID that is only accessible to authorized research staff personnel.

We may contact you for future research opportunities by phone.

☐ **Yes, I may be contacted for future research opportunities as described**. _____(initial)

A copy of this document will be provided to the research participant.

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☐ **No, I do not wish to be contacted for future research opportunities as described**. _____(initial)

HOW WILL MY PRIVATE INFORMTION BE PROTECTED?

Participation in this study may involve a loss of privacy, but information about you will be handled as confidentially as possible. Your SSN will be collected only for your medical record review. Your research records will be labeled with a code number. The list that matches your name with the code number will be kept in a locked file in the research team's office. Any research records that identify you will be kept only as paper records in a secure VASDHS location, or as files behind the secure VASDHS computer firewall.

The data from the cognitive games and EGG will be analyzed outside the VA at UC San Diego. Disclosure to the analysis site will exclude subject identifiers.

Identifiers will be removed from the identifiable private information that is collected. After that removal, the information could be used for future research studies without additional informed consent from you or your legally authorized representative.

We will keep confidential all research and medical records that identify you to the extent allowed by law. However, you should know that there are some circumstances in which we may have to show your information to other people. For example, the Federal Office of Human Research Protections, the General Accounting Office, the VASDHS R&D Committee, the VASDHS Institutional Review Board and federal compliance officers may look at or copy portions of records that identify you.

While this study is being conducted, you will have access to your research related health records. This will not affect your VA healthcare including your doctor's ability to see your records as part of your normal care and will not affect your right to have access to the research records after the study is completed.

Any presentations or publications from this information will not identify you.

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

You have been informed that you do not have to take part in this study, and your refusal to participate will involve no penalty or loss of rights to which you are entitled. You may withdraw from this study at any time without penalty or loss of VA or other benefits to which you are entitled.

The study coordinator has explained the study to me. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me. I have been given the chance to ask questions and obtain answers.

By signing this document below, I voluntarily consent to participate in this study. I also confirm that I have read this consent, or it has been read to me. I will receive a copy of this consent after I sign it.

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I agree to participate in this research study as has been explained in this document.

_____ _____
Participant's Signature Date

_____ _____ _____
Signature of Researcher obtaining consent Name (print) Date

Please indicate whether you would like to opt in to the pain assessment:

☐ **Yes, I would like to opt into the pain assessment**. _____(initial)

☐ **No, I do not wish to opt into the pain assessment**. _____(initial)

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 document, you provide your permission called your 'authorization,' for the access, use, and disclosure of information protected by the HIPAA Privacy Rule.

The research team working on the study will collect and use information learned from the procedures described in this consent form. They may also collect other information including your name, phone number and medical record number.

The research team may also need to share your health information and the information it collects to other entities as part of the study progress. Other VA entities may include the VA Office of Research Oversight (ORO). You also give your permission for the research team to disclose your information to non-VA entities such as Institutional Review Board, Food and Drug Administration (FDA), Office of Human Research Protections (OHRP), and the Government Accountability Office (GAO).

Your health information disclosed outside the VA as described in this authorization may no longer be protected by Federal laws or regulations and may be subject to re-disclosure by the recipient.

You can revoke this authorization, in writing, at any time. To revoke your authorization, you may (a) write to the Release of Information Office at this facility; (b) ask a member of the research team to give you a form to revoke the authorization; or (c) send your written request to the Principal Investigator for this study at the following address: [redacted] VA San Diego Medical Center, 3350 La Jolla Village Drive, San Diego, CA 92161.

If you revoke this authorization, [redacted] and his or her research team can continue to use information about you that was collected before receipt of the revocation. The research team will not collect information about you after you revoke the authorization.

While this study is being conducted you will have access to your research-related health records.

Treatment, payment or enrollment/eligibility for benefits cannot be conditioned on you signing this authorization.

Unless you revoke (take back) your permission, your authorization to allow us to use and/or disclose your information will expire at the end of this research study; any study information that has been placed into a repository to be used for future research will not expire.

AGREEMENT TO AUTHORIZE USE AND RELEASE OF INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION

By signing this document below, I give my authorization (permission) for the use and disclosure of my

individually identifiable health information as described in this document. This authorization has been explained to me and I have been given the opportunity to ask questions. If I believe that my privacy rights have been compromised, I may contact the VHA facility Privacy Officer to file a verbal or written complaint. I will be given a signed copy of this document for my records.

Participant's Signature	Last 4 of SSN	Date

Legally Authorized Representative (print)

This page is required for VA San Diego research and optional for other VA facilities with the understanding that the contact information would be corrected as applicable to the facility.

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Principal Investigator: [redacted]

VA Facility: VA San Diego Healthcare System

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

You have been asked to participate as a subject in medical research. You have the right to know:

1) The nature and purpose of the study.
2) The procedures in the study and any drug or device to be used.
3) Discomforts and risks reasonably to be expected from the study.
4) Benefits reasonably to be expected from the study.
5) Alternative procedures, drugs, or devices that might be helpful to you and their risks and benefits.
6) Availability of medical treatment should complications occur.
7) You may ask questions about the study or the procedure.
8) You may quit the study at any time without affecting your future care at the VA.
9) You should be given a copy of the signed and dated written consent form for the study.
10) Your consent to participate must be given freely, without being obtained through deceit, force, or coercion.

If you have any questions or concerns about your rights as a research subject please contact the VASDHS Research Compliance Officer at (858) 642-3817 or RCO@vapop.ucsd.edu. You may leave an anonymous comment at the VASDHS research compliance hotline at 858-642-6311.

REF: California HSC 24170-24179.5

A copy of this document will be provided to the research participant.