rTMS in alleviating Pain and Co-morbid symptoms in GWVI

NCT04046536

January 3, 2024

Study Title: rTMS in alleviating Pain and Co-morbid symptoms in Gulf War Veterans

Principal Investigator: Dr. Albert Leung

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 choose 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 is about treating headaches and pain in Gulf War veterans. You have been asked to participate in this study because you are a veteran who has served in the Persian Gulf War from 1990-1. It is being funded by the Department of Veterans Affairs. By doing this study, we hope to assess the effectiveness of non-invasive magnetic stimulation to the brain, also known as repetitive transcranial magnetic stimulation (rTMS), in alleviating headache and pain symptoms in Gulf War veterans.

WHAT DOES THE STUDY INVOLVE AND HOW LONG WILL IT LAST?
You will be asked to attend a total of 15 research visits over the course of 12 weeks. Each visit will take approximately 2 hours or less and will consist of cognitive assessments, rTMS treatments, or magnetic resonance imaging (MRI).

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?
There may or may not be a direct benefit to you from these procedures. The investigator, however, may learn more about assessing the effect of rTMS in treating GWI related headaches and co-morbid symptoms.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?
You may choose not to participate in the study because of the requested time commitment or perceived risks in participating. However, scheduling can be accommodated to suit both the research staff and the prospective subject and a complete description of risks is included in the Research Details Study Risks section for review.

Participation is voluntary and the only known alternative would be to speak to your Primary Care Physician to discuss alternate methods of pain management or treatments. 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 Dr. Albert Leung 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: 858-552-8585 ext. 3331

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RESEARCH DETAILS

WHO IS CONDUCTING THIS RESEARCH AND WHY?

Dr. Albert Leung and his colleagues (investigators) at the VA are conducting a research study to find out more about treating headaches and pain in Gulf War veterans. You have been asked to participate in this study because you are a veteran who has served in the Persian Gulf War from 1990-1. This study plans to enroll approximately 360 total participants from the VA San Diego, VA Palo Alto and the VA Atlanta with 200 subjects anticipated at this facility. The purpose of this study is to assess the effectiveness of magnetic stimulation to the brain, also known as repetitive transcranial magnetic stimulation (rTMS), in alleviating headache and pain symptoms in Gulf War veterans. The rTMS device uses a non-invasive technology to produce small electrical currents in specific regions of the brain. No anesthetic is required when rTMS is provided. The device consists of an insulated coil that will be held in contact with the head. A current is passed around the coil and a magnetic field passes through the scalp and skull, and into the first few millimeters of the brain. A figure eight coil is commonly used because it gives a precise localization. All procedures are done for research purposes.

FOR HOW LONG WILL I BE IN THE STUDY?

Your individual participation will take approximately 12 weeks. There are 15 visits involved, each lasting 2 hours or less. After Visit 1 and the first MRI, the study treatment that utilizes rTMS will take place, those are 10 visits that are expected to take place within a 2-5 week window. After that will be the follow-up visits.

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

If you agree to be in the study, and you are a patient with GWI related headache and pain, the following will happen to you:

a. **Screening:** After you have signed the informed consent and agreed to study participation, you will be screened for the study enrollment. If you meet the study inclusion and exclusion criteria, you will be provided with a daily HA diary to rate your average daily HA level on a 0-10 Numerical Pain Scale and return one week later for the study Visit 1. If the time before your Visit 1 exceeds 28 days, the medical questions of the screening will be repeated during that visit to ensure you are still eligible for the study. If you are a female at child bearing age, a urine pregnancy test will be issued and the PI will check the result prior to the study. You will be ineligible to participate in the study if you are pregnant.

   During the study, you will be asked to rate the intensity of HA, muscle and joint pain in a diary provided to you. You will also be asked to record the duration of your headache and the severity of interference of your headache on your daily activities. The only information that will be stated into your medical record through CPRS is that you came in for a research study visit, none of the data or identifying information will be recorded in CPRS. Each of the visits will be conducted at the VA San Diego Healthcare System in

Building 23, Room 105 or 108 except for the MRIs which will be done at the neighboring UCSD Keck imaging center.

b. **Visit 1:** The investigators will further evaluate your HA with the following surveys: Headache Impact Test and Neurobehavioral Inventory. Joint pain will be assessed through the McGill Pain Questionnaire short form and your muscle pain with the Fibromyalgia Impact Questionnaire. In addition, an intensity rating will be obtained on a sliding scale and your overall pain with a Brief Pain Inventory survey.

In addition, the investigators will also assess your mood through the Hamilton Scale for Depression and the Columbia Suicide Severity Rating Scale (CSSRS). A test called CAPS will also be used to assess any Post Traumatic Stress Disorder (PTSD) related symptoms. Assessments will also be conducted to assess your sleep pattern and chronic fatigue symptom. Several questionnaires will be required of you to include the Veteran RAND 36-item Health Survey and the Gulf War and Exposures Worksheet. The assessments will take approximately two hours to complete at this visit. Keep in mind, you may skip any question that makes you uncomfortable and you can stop at any time.

The usage of opioid medication of your headaches will also be assessed. The investigators will also assess your overall pain problems and how they affect your quality of life.

MRI Visit: If you are asked to continue with the study, your brain anatomical imaging will be recorded in a magnetic resonance machine. This visit will be conducted at the UC San Diego KECK Center.

Optional: The investigators may ask you to participate in a functional magnetic resonance imaging (fMRI) study while intermittent thermal heat pain stimulation will be delivered via a thermode controlled by a computer at your left calf area for about 10 minutes, and you are lying restfully in the scanner for 5 minutes. During that time the resting state fMRI will be conducted. You will receive additional compensation if you choose to participate in the fMRI studies. The overall process will take less than one hour. Prior to the scanning, the investigators will also assess your temperature sensing threshold with a thermal probe at your left calf area. The process will take about 15 minutes.

c. **Visit 2:** Study procedure. In preparation for the study procedure, one of your fingers will be connected to a recording device to record electrical potentials generated by your muscle cells with a test TMS. However, the rTMS study procedure will be given at an intensity, which will not cause any hand muscle movement. We will then determine the optimal scalp location for the study procedure.

Next, you will receive either active rTMS or sham (false study procedure that seems real) study procedure. Depending on your subject number, you will receive the study procedure at one of the two different brain areas that are being tested for the study. Once the enrollment numbers have been met for the primary brain area being studied, then study participants will receive the study procedure at the secondary brain area being studied. Within the study procedure location you are in, you will be assigned to either active rTMS or sham study procedure by chance, like the flip of a coin. You will not be told which group you are

in until the study is over. During the research, you and the researchers) will not know which group you are in. (The researcher can find out in case of an emergency). About half of the subjects will be randomly selected to receive the sham instead of the rTMS procedure. During the study, subjects will not be told whether the real or sham procedure is received. The first study procedure visit will take approximately 30 min. to complete.

d. **Visit 3-10:** Study procedures. Each of the ten study procedure visits will take approximately 30 min to complete and all ten visits must be completed within 2-5 weeks. You will be asked to rate your HA intensity prior to and after each of the study procedures.

e. **Visit 11:** On your last study procedure visit, which will take approximately 30 minutes, you will be provided with a second daily HA diary to rate your worst daily HA level on a 0-10 NPS and to record the duration of the worst HA episode every night until your next visit.

f. **Visit 12:** One-week follow-up where HA intensity, pain, sleep and depression will be reassessed. The same assessments conducted at Visit 1 will be repeated at this time and will take approximately two hours to complete.

Optional: If you have participated in the fMRI at Visit 1, you may be asked to return to the scanner for another session of fMRI after the assessments at Visit 12. This will take no more than one hour.

g. **Visit 13:** One-month follow-up and Maintenance Treatment. This visit will last about one hour during which surveys and questionnaires previously used in Visit 1 and Visit 12 will be conducted. During this visit you will receive a maintenance rTMS procedure as part of the study protocol. This will take approximately 30 minutes.

h. **Visit 14:** Two-month follow-up and Maintenance Treatment. The visit will last about one hour during the surveys and questionnaires previously used in Visit 1, Visit 12 and Visit 13 will be conducted. During this visit you will receive a maintenance rTMS procedure as part of the study protocol. This will take approximately 30 minutes.

i. **Visit 15:** Three-month follow-up. The visit will last about one hour during which the surveys and questionnaires previously used in Visit 1, Visit 12, Visit 13, and Visit 14 will be conducted. This will be the end of the study.

As this is a treatment study, rTMS will be available at the end of the study if the subject would like to continue the treatment sessions. Clinically relevant research results, including individual research results, will be disclosed to subjects once the final analysis has been completed and the publication is available to the public.

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As a participant your responsibilities and expectations for this research study include:

-Keep your study appointments. If you miss an appointment, please contact the investigator or research staff to reschedule as soon as you know you will miss the appointment.

-Tell the investigator or research staff if you believe you might be pregnant or might have gotten your partner pregnant.

-Fill out your headache and pain logs as instructed.

-Complete your questionnaires as instructed.

-Ask questions as you think of them.

-While participating in this research study, do not take part in any other research project without approval from the investigators. This is to protect you from possible injury from things such as extra blood drawing, extra X-rays, or potential drug interactions. Taking part in other research studies without first discussing it with the investigators of this study may invalidate the results of this study, as well as that of the other studies.

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

All procedures are done for research purposes only and are not part of standard of care.

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

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.

A. Common
- A potential side effect of rTMS is a mild headache, resulting from muscle stimulation on the scalp. Typically, the headache will resolve spontaneously a few hours after the study procedure or with a dose of acetaminophen.
- Some patients may experience sleep disturbance during the course of rTMS or a feeling of increase/decrease of energy level.
- The thermal pain testing will induce some discomfort/pain. The temperature range of the thermal analyzer is internally set at 32 to 122 ºF, which is known not to cause any risk of skin injury. The use of varying temperatures further minimizes the risk of skin damage.
- Assessments and questionnaires may cause emotional discomfort, frustration or boredom. However you are not obligated to complete them all and can terminate the session if you would like.

B. Occasionally
- Skin irritation, scalp discomfort or burn can occur. This occurrence will be assessed by a qualified physician and treated with ointments or by other required means.

C. Rare
- Although rare seizure occurrences were reported in the past with other rTMS study procedure settings, to the best knowledge of the investigators, no seizure occurrences have been reported in recently published studies using the current study procedure setting.

- Noise or hearing loss during the study procedure may also be a concern. However, you will be required to wear earplugs during the study procedure session.
- There are no major known risks, dangers or side effects associated with fMRI. Some people report temporary fatigue or headache. fMRI is not proven to be safe during pregnancy. The magnet at the center of the procedure may affect, or be affected by, any person fitted with a pacemaker, hearing aid, or other electrical device. Therefore any persons with metallic implants or patches are not permitted inside the fMRI. All removal metal objects must be removed prior to entering the MRI scan room.

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.

Risks of the usual care you receive are not risks of this study. Those risks are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

Photographs, audiotaping, or videotaping: There will be no photographs, audio tapes, or video tapes made of you as part of this study.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

We do not know if you will get any benefits from taking part in this research study. However, possible benefits may include a decrease in depressive symptoms, improvement in quality of life and alleviation of headache, muscle or joint pain.

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

The only option if chosen to not participate it so confer with your Primary Care physician to discuss alternative methods of pain management. You may be able to receive rTMS on a clinical protocol if your Primary Care provider recommends it. Please consult your doctor for options.

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 you complete 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.

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If you should have a medical concern or get hurt or sick as a result of taking part in this study, call:

DURING THE DAY:
Study Coordinator at [redacted]

AFTER HOURS:
Dr. Albert Leung at (858)642-3292

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. Please let the Study Coordinator or Principal Investigator know that you choose to discontinue so that we properly update our records as well as ensure your safety.

Data already collected prior to your withdrawal may continue to be reviewed but cannot collect further information, except from public records, such as survival data.

RIGHT OF INVESTIGATOR TO TERMINATE MY PARTICIPATION

It is the right of the Investigator to terminate your participation if it is in the best interest of yourself to be withdrawn from the study. In addition, if you are not compliant with the requirements of the study, you may be withdrawn from the study.

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

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 Dr. Albert Leung.

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?

In compensation for your time and travel, you will receive $30 for each visit. There are a total of 15 visits, adding up to $450. You will receive an additional $50/scanning if you are asked and agree to participate in the fMRI part of the study, making the total $550 for those eligible.

This payment will be made directly to your bank account using electronic funds transfer. If you currently have a debt to the Federal Government, your debt may be subtracted from your funds transfer payment for study participation.

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 the Study Coordinator at [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]

HOW WILL MY PRIVATE INFORMATION BE PROTECTED?

Participation in this study may involve a loss of privacy, but information about you will be handled as confidentially as possible. If you are not already a VA patient, a medical record including your name and Social Security number will be entered in the VA Computerized Patient Record System. If you are a patient of the investigators, your medical record will be reviewed based on the need of medical care either with or without participating in the study. If you are not a patient of the investigators, your medical record will not be reviewed until you have signed a consent to be screened and to participate in the study. Research records will be kept confidential to the extent allowed by law. Information regarding the study will be stored in the PI's office inside locked cabinetry, in a locked room. Sensitive Information will only be identified with initials and assigned subject numbers in the data sheets. You will only be assessed by the PI, and other approved study personnel.

In the event of a real or suspected breach of security, the VA police, the VA information Security Office, and the VA Privacy Officer will be notified as soon as possible. Sensitive Information will be accessed, stored, and destroyed according to a data security plan that will promote security and privacy. The raw data will be destroyed in accordance with RCS-10 and under the direction of VASDHS Records Control Manager.

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. Identifiers might be removed from the identifiable private information that are collected. After that removal, the information could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative.

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If the study procedures have any implication on the patient's care, the study team is required to put any details about the subject's participation that are relevant to their care providers in the patient's medical record and the following statement must be included:

We will include information about your study participation in your medical record.

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, the Food and Drug Administration, and federal compliance officers may look at or copy portions of records that identify you.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Disclosure of Results. While this study is being conducted, you will not 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.

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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 and/or Principal Investigator 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.

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

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

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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 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, address, date of birth, and information from your medical records such as medical history and mental health treatments as it relates to your eligibility for the study.

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 Cooperative Studies Program (CSPCC); CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC); CSP Site Monitoring; Auditing and Review Team (SMART); CSPCC's Human Research Committee (HRC) and the VA Office of Research Oversight (ORO); Institutional Review Board, Food and Drug Administration (FDA), Office of Human Research Protections (OHRP), and the Government Accountability Office (GAO); VA Palo Alto and Atlanta VA.

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:

VA San Diego Healthcare System (151)
3350 La Jolla Village Dr.
San Diego, CA 92161

If you revoke this authorization, Dr. Albert Leung and his 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 not 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.

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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

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

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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.