COVER PAGE:

STUDY TITLE:

HIRREM FOR MITIGATION OF PTSD SYMPTOMS IN MILITARY PERSONNEL

DATE OF DOCUMENT:

JANUARY 7, 2015

COMMENT:

THIS IS THE IRB-APPROVED INFORMED CONSENT DOCUMENT THAT WAS IN EFFECT WHEN ENROLLMENT FOR THIS PILOT STUDY BEGAN IN FEBRUARY, 2015. SUBSEQUENT AMENDMENTS HAVE:

1. ADDED COLLECTION OF BLOOD SAMPLES FOR EPIGENETIC MARKERS
2. EXPANDED THE SAMPLE SIZE TO AN ENROLLMENT OF UP TO 40 PARTICIPANTS
3. ADDED COLLECTION OF SELF-REPORT SYMPTOM INVENTORIES AT 6 MONTHS AFTER COMPLETION OF INTERVENTION (SO DATA COLLECTIONS NOW AT ENROLLMENT, IMMEDIATE COMPLETION OF INTERVENTION, AND 1, 3, AND 6 MONTHS AFTER COMPLETION OF INTERVENTION).

THERE HAVE BEEN NO OTHER SUBSTANTIVE CHANGES SINCE ENROLLMENT BEGAN. THERE HAVE TO DATE BEEN THREE CONTINUING REVIEWS BY THE IRB, WITH THE MOST RECENT CONTINUING APPROVAL BEING GRANTED ON 5/15/17.

Wake Forest®
School of Medicine

HIGH-RESOLUTION, RELATIONAL, RESONANCE-BASED, ELECTROENCEPHALIC MIRRORING (HIRREM) TO REDUCE SYMPTOMS ASSOCIATED WITH TRAUMATIC STRESS IN MILITARY PERSONNEL

Informed Consent Form to Participate in Research
Charles H. Tegeler M.D., Principal Investigator

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have military-related symptoms of insomnia, poor concentration, sadness, irritability, or hyper-alertness, associated with traumatic stress. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to determine the effects of a technique called High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM®), for symptoms associated with traumatic stress. Sometimes referred to as Brainwave Optimization® (BWO), HIRREM is a novel, noninvasive, electroencephalic-based feedback technology to facilitate relaxation and auto-calibration of neural oscillations by using auditory tones to reflect brain frequencies in near real time. HIRREM is not a medical device, and is not intended to treat, cure, heal, or diagnose any disease, mental illness or symptom, and individual results and duration of effects may vary. HIRREM technology was created by Brain State Technologies, LLC, and is FDA-exempt when used as biofeedback for relaxation and self-regulation. It is noninvasive, which means it will not cause pain or break the skin in any way. It is a computer-based technique that may help improve your symptoms by using auditory tones that are played back based on readings of your brain's electrical frequencies, to help achieve a more balanced brain pattern. Men and women who are on active duty in the military or recent veterans (2001 or after), are over 18 years of age, and have military-related symptoms associated with traumatic stress, with or without traumatic brain injury (TBI), are eligible to participate in the study.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Up to 12 people will be enrolled in this study at Wake Forest Health Sciences to achieve a target of 10 people completing the study. In order to identify the 12 subjects needed, we may need to screen as many as 100 individuals because some people will not qualify to be included in the study. All participants who are enrolled in this study will receive the HIRREM intervention.

WHAT IS INVOLVED IN THE STUDY?

If you choose to participate in this study you will be scheduled to be at Wake Forest School of Medicine for a two week block of time. The on-site period will require face-to-face presence on up to 12 days, and will include 2 data collection visits, 2 MRI brain scans, 2 collections of blood and saliva samples, and up to 24 HIRREM sessions. Visit #1 is an enrollment and baseline data

collection visit. It will take place on the first morning, and require a total of 3-4 hours. During this visit, the study will be explained to you in detail and any questions you have will be answered, your informed consent will be obtained, and a brief medical history will be obtained. At this visit, you will also complete some questionnaires, have your blood pressure and heart rate monitored, and will complete a reaction time test, a grip strength test, and a brainwave assessment. Instructions will also be given on how to record an online daily sleep diary. Following this, blood and saliva samples will be collected, and you will receive your first MRI scan. Each MRI scan session is expected to last about 90 minutes. Once you have completed the first MRI scan, you will then begin a course of HIRREM sessions, while also continuing your other usual care. HIRREM sessions will be administered over the two week period that follows. After your final HIRREM session you will complete Visit #2 to collect additional data, which includes having a second MRI brain scan and a second blood and saliva sample collection. A third and fourth data collection visit will be done by telephone, at one month, and three months after completion of the Visit #2.

At Visit #1 (V1, enrollment, and baseline data collection):

- You will be asked to provide informed consent to participate in the study.
- You will be asked to complete some paper and pencil questionnaires as well as electronic questionnaires on a computer.
- You will be asked questions regarding your sleep pattern and medical history.
- You will complete a questionnaire where you will be asked questions that have no right or wrong answers. You will simply respond to how strongly you agree or disagree with something. It will be explained to you.
- You will be given a survey that asks views about your overall health. This information will help track how you feel and how well you are able to do your day to day activities.
- You will learn how to complete an online daily sleep diary.
- Your blood pressure and heart rate will be monitored for 10 minutes.
- Your reaction time will be tested by having you grasp a dropped wooden stick.
- Your grip strength will be tested by having you grip a hand dynamometer.
- A brainwave assessment will be obtained. This assessment will evaluate the electrical frequencies of your brain. For this assessment you will be sitting in a chair and the HIRREM Technologists will place sensors over multiple areas of your head to record data while the brain is at rest, or on task, with eyes closed, partially open, and open. The sensors look like pads that will be placed with special paste. It will not hurt. The sensors have tiny computer chips that will allow collection of data on the frequencies from the brain. This brainwave assessment takes about 45-60 minutes to complete.
- You will be asked to give a blood sample via a small catheter inserted into a vein in your arm and a sample of your saliva (spit) to check the level of different measures of inflammation.
- All activities for Visit #1 will take about 90-120 minutes to complete.

At Visit #2 (V2, for repeat data collection, which will occur before you leave, on the day you

complete the HIRREM sessions), the same questionnaires and tasks, except for the brainwave assessment, will be repeated.

- You will be asked to complete some paper and pencil questionnaires as well as electronic questionnaires on a computer.
- You will be asked questions regarding your sleep.
- You will complete a questionnaire where you will be asked questions that have no right or wrong answers. You will simply respond to how strongly you agree or disagree with something. It will be explained to you.
- You will be given a survey that asks views about your overall health.
- You will be reminded to continue the online daily sleep diary.
- Your blood pressure and heart rate will be monitored for 10 minutes.
- Your reaction time will be tested by having you grasp a dropped wooden stick.
- Your grip strength will be tested by having you grip a hand dynamometer.
- Your blood and saliva sample will be collected again similar to Visit #1
- All activities at Visit #2, including the MRI scan, are expected to take 2.5-3.5 hours.

MRI scans (with V1 and V2)

- You will lie quietly in the MRI scanner for about 60 minutes. A series of brain images will be taken. Each image lasts about 5 minutes.
- You will need to lie still and not move your head while each image is taken.
- While the images are being taken you will either lay with your eyes closed, your eyes open, or while completing simple sensory/cognitive tasks.
- No needles or injections are required for the MRI scan.

The brain images are taken for research purposes only. They are not the same type of image that is taken for clinical use. Therefore, most brain abnormalities are not seen on these images. However, you will be notified if any abnormalities are found. Abnormal findings my require you to get further evaluation by your personal doctor.

Telephone Follow-Up Data Collection (V3, 1 month after V2 is completed)

- You can now discontinue the online daily sleep diary.
- You will be asked questions regarding your sleep, overall health, and mood.
- This should take about 30 minutes.

Late Telephone Follow-Up Data Collection (V4, 3 months after V2 is completed)

- You will be asked questions regarding you sleep, overall health, and mood. This completes your involvement in the study, and will be exited from study
- This should take about 30 minutes.

All baseline measures, along with a brainwave assessment, will be obtained during the enrollment visit (V1), when you will also start a daily sleep diary, which will be maintained until the one month post-HIRREM follow-up phone call. The HIRREM sessions, will begin in the afternoon following V1 visit. The technologist will review the information gathered from your brainwave assessment, and plan for the first HIRREM session. You will receive up to 24 HIRREM sessions over the two weeks that follow. You will typically receive 2 HIRREM

sessions during a half day period. The sessions will typically be about 1.5-2 hours in length. For the sessions, you will be comfortably at rest, sitting or reclining, and sensors will be placed over the specific areas on the scalp corresponding with brain regions/lobes to be observed. During each session, the sensors may be moved into 4-10 different locations, with 6 to 40 minutes spent at each location. You will be able to read a book, do a word search, or just relax for some of these sessions.

During your two week stay in Winston-Salem, you will be provided lodging at the SECU Family House, 1970 Baldwin Lane, Winston-Salem, NC 27103.

Upon your request, we can send information about your study results to your personal health care provider. Even if you do not wish to have any information sent to your health care provider, you can still participate in this research study.

Do you request that we send information about your study results to your personal health care provider?

[ ] Yes [ ] No _____ Initials

HOW LONG WILL I BE IN THE STUDY?

You will be in the study for about three and a half to four months, to include an enrollment visit, with baseline data collection (V1), MRI #1, baseline blood and saliva collection, 2 weeks of HIRREM sessions, a second data collection visit after HIRREM sessions are completed (V2), MRI #2, repeat blood and saliva collection, a telephone call one month after V2, and a telephone call 3 months after V2. You will only be required to be on site for 2 weeks in order for you to have your enrollment, V1, MRI #1, baseline blood and saliva collection, to receive up to 24 HIRREM sessions, to complete the V2 data collection, and have MRI #2, and repeat blood and saliva collection. The two follow-up telephone calls can be conducted from anywhere.

You can stop participating at any time. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences.

WHAT ARE THE RISKS OF THE STUDY?

No known risks have been reported with HIRREM. Some individuals undergoing HIRREM have reported an apparent "release of emotions" or paradoxical effects especially during initial sessions, which can occur as brief periods of increased awareness of emotional states, both positive and negative. These experiences are typically transient, i.e. lasting intermittently over the course of one to several days. For example, some participants have cried as they reported feelings of joy, or of sadness. In the course of providing HIRREM to 275 individuals participating in one of four IRB-approved research studies at WFSM, such mild symptoms have been estimated to occur in less than ten percent of participants, and we have not seen prolonged or intense changes in emotional state. These have been relatively brief episodes not requiring additional treatment or causing discontinuation of sessions.

You may find some of the questions involved in the testing during data collection visits as stressful. If you feel uncomfortable please let your doctor or the research staff know about this.

We do not anticipate significant risk in performing the intravenous blood or saliva sampling or MRI scan. Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported to the IRB.

MR scanners have been in clinical use for about 30 years. During that time, no important side effects have been found with the use of standard clinical magnets. Unlike x-rays, CAT scans, and nuclear medicine studies, the MR machine does not use x-rays or other forms of radiation. The MR scanner uses a magnetic field and radio waves, and to the best of our knowledge, there are no risks to having an MR scan.

Because strong magnetic fields are used for scanning, patients with inserted devices or objects known to be sensitive to strong magnetic fields (i.e. metallic foreign bodies inside your head or in your eyes, incompatible medical implants, pacemakers, brain stimulators, blood vessel clips, etc.) will not be allowed to participate. The inside of the scanner is small. Some people feel nervous or anxious in such tight spaces. You will be able to stop the scan if you have these feelings. You will be in verbal communication with the study team at all times. In addition, you will be given a squeeze ball that you can use to set off an alarm any time if you feel the need to stop the scan. Claustrophobia is readily relieved by taking people out of the MRI scanner. If you need to be removed from the scanner, the study team will remove you at your request.

All of the MRI scans used in this study are done for research purposes, not to treat or diagnose medical illnesses. However, some of the brain images could suggest that you have a medical condition. In the unlikely event that our results do suggest a possible medical condition you will be told. Your doctor will also be told if you elect to have this information sent to him/her. Your doctor may tell you that you should have more tests. These tests will be recommended by your doctor and are not part of this study. Although it may be in the best interests for your health to have these additional tests, you do not have to have them as part of this study.

REPRODUCTIVE RISKS AND OTHER ISSUES TO PARTICIPATING IN RESEARCH
Due to unknown risks and potential harm of MRI scans to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a cervical cap or sponge. We encourage you to discuss this issue further with the study team if you have any questions.

The presence of metallic bodies is a significant risk if unrecognized and combined with an MRI scan. Shrapnel, bullets, and some medical implants are incompatible with the MRI machine. All participants must complete the MRI checklist included below in this consent form. This will be

evaluated by the study team and the MRI technologist. Those with contraindications will not be allowed to participate in the MRI imaging portion of the study.

With the collection of blood samples, you may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally some people become dizzy, lightheaded or feel faint. Infection may occur on rare occasions. Frequent donation of blood can result in low iron in your blood.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future. The benefits of participation in this study may be improvement in your symptoms associated with traumatic stress.

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study to receive treatment for your symptoms associated with traumatic stress. You should talk to your health care provider about all the choices you have. Your alternative is to not participate in this study.

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you, information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes but is not limited to, such things as your name, address, telephone number, and date of birth. Your personal health information includes all information about you which is collected or created during the study for research purposes. It also includes your personal health information that is related to this study and that is maintained in your medical records at this institution, or at other places such as other hospitals and clinics where you may have received medical care. Examples of your personal health information include your health history, your family health history, how you respond to study activities or procedures, test results, and information from study visits, phone calls, and surveys.

For the purpose of scheduling your study visits and HIRREM sessions, a medical record number for Wake Forest Baptist Health will be assigned when you enroll, and a record created in the WFBH electronic medical record (WakeOne). Other than your name, date of birth, a contact number, and the fact that you are participating in a research study, no personal health information regarding you, or this research study, will be entered. Only in the case of emergency will other personnel directly involved with your care have access to this information in WakeOne.

We will make every effort to keep your Protected Health Information private. We will store

records of your Protected Health Information in a cabinet in a locked office or on a password protected computer. Only the following people or organizations will be granted access to your Protected Health Information:

1) The study investigator and his/her staff, or others at Wake Forest University Health Sciences who oversee research.

2) Other people or laboratories providing services for this research project on behalf of Wake Forest Health Sciences and Wake Forest Baptist Medical Center.

3) Representatives from government agencies such as the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS).

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it might no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept indefinitely. This authorization does not expire. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.

You can tell Dr. Charles H. Tegeler that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Charles H. Tegeler, M.D.
Department of Neurology
Medical Center Boulevard
Winston-Salem, NC 27157-1078

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

This authorization does not expire.

WHAT ARE THE COSTS?

There are no costs to you for taking part in this study. All costs related directly to study procedures, including the HIRREM sessions and MRI scans, will be paid for by the study. The study will also pay for the cost of lodging at the SECU House, during the two weeks you are in Winston-Salem. Other costs for travel to and from Winston-Salem, food, and local transportation during your stay, as well as and your regular medical care, not related to this research study, will be your own responsibility. In the event that the MRI brain scans suggest abnormalities, any costs related to further testing or evaluation are your responsibility.

WILL YOU BE PAID FOR PARTICIPATING?

You will receive no payment or other compensation for taking part in this study

The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation or for you to share in any profits if this should occur.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by the Enabling Technology Section of the Office of the Secretary of Defense, via a contract with the US Special Operations Command. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not hold a direct financial interest in the sponsor, or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at (336) 716-3467.

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Charles H. Tegeler, MD at 336-716-9482.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because you failed to follow instructions, your condition worsened or the study has been stopped.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Dr. Charles H. Tegeler at (336) 716-9447.

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at (336) 716-4542.

You will be given a copy of this signed consent form.

Females of childbearing age please answer the following questions:

1. Do you think that you might currently be pregnant? yes no (circle one)

2. Are you currently attempting to become pregnant? yes no (circle one)

All participants must review and complete the following questions:

Weight (in pounds):_____

You have been selected to participate in a Magnetic Resonance (MR) scan for a research study. The MR machine does not use x-rays, but rather a magnetic field and radio waves to take pictures inside your body. In some cases, the research study may be aided by the use of recently developed or investigational new MR techniques available at our university medical center. At no time, however, will the scanner be operated in a fashion that will pose any significant risk to you.

The MR room contains a very strong magnet. Before you are allowed to enter, we must know if you have any metal in your body. Several metal objects can interfere with your scan and can even be dangerous. So please answer the following questions carefully.

1. Do you have a cardiac pacemaker? Yes _____ No ___

2. Do you have a cerebral aneurysm clip (a clip on a blood vessel in your brain)? Yes _____ No _____

3. Have you ever worked with, or been hit in the eye with a piece of metal? Yes _____ No _____
   If so, is there any chance that a metal fragment may still be in your eye? Yes _____ No _____

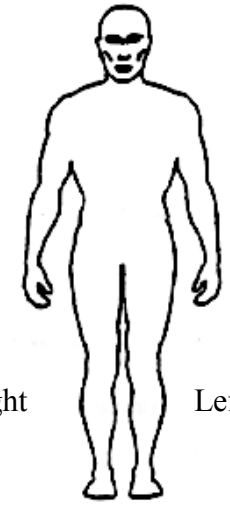
4. Are you pregnant, possibly pregnant, or breast-feeding? Yes _____ No

5. Please list all major operations you have had with approximate dates:

6. Do you have any metal objects or devices implanted in your body? Yes _____ No _____
   If yes, please list and show in diagram to the right:

7. Do you have any of the following items in/on your body?

Yes	No	Cardiac valve, wires, or defibrillator
Yes	No	Electrical stimulator for nerves or bone
Yes	No	Eye or ear implants
Yes	No	Bullets, BB's, or pellets
Yes	No	Metallic shrapnel or fragments
Yes	No	Infusion pump
Yes	No	Coil, filter, or wire in blood vessel
Yes	No	Orthopedic hardware (plates, screws, pins, rods, wires)
Yes	No	Surgical clips, staples, mesh or sutures
Yes	No	Eyelid tattoo
Yes	No	False teeth, partial plate, retainers, or magnetic braces
Yes	No	Hair pins, barrettes, wigs, rings, earrings, jewelry
Yes	No	Hearing aid
Yes	No	Drug delivery patch (smoking, estrogen, nitroglycerine)



NOTE: Do not carry loose items, such as safety pins, money, pens, pencils, keys, coins, watches, pocket knives, or artificial limbs/prostheses into the scanning room. They may become damaged or cause injury.

As a reminder, firearms are not allowed on Wake Forest School of Medicine property.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to

ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed): _____

Subject Signature: _____ Date: _____Time: _____ AM PM

Person Obtaining Consent: _____ Date: _____Time: _____ AM PM