YALE UNIVERSITY SCHOOL OF MEDICINE–YALE-NEW HAVEN HOSPITAL

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

PROJECT TITLE: Neurofeedback of amygdala activity for PTSD

PRINCIPAL INVESTIGATOR: Ilan Harpaz-Rotem, Ph.D.

STUDY SPONSORS: Departments of Psychiatry and Radiology and Biomedical Imaging, Yale School of Medicine, National Center for PTSD, and National Institutes of Health (pending)

Invitation to Participate and Purpose of the Study

You are invited to be a subject in a research study using magnetic resonance imaging (MRI) of the human brain. You have been invited because you have post-traumatic stress disorder (also known as PTSD). The purpose of the study is to learn more about PTSD and the effects it has on the human brain by taking pictures of your brain, showing you patterns of brain activity in areas associated with PTSD symptoms, and asking you to try to control this brain activity. This study is expected to last up to 8 years but your participation will only be for 2-3 weeks, with additional follow-up phone calls 1 month and 2 months after you finish the scanning portion of the study.

This study is a clinical trial in which we compare an experimental intervention to a control intervention. We hope the experimental intervention may help symptoms, but this has not been demonstrated. The control intervention we do not believe has any potential to help symptoms. By choosing to participate you are agreeing to be randomized to receive either the control or experimental intervention. You will not be told which one you received until the intervention, including all follow-up assessments, has been completed. At that point, if you received the control intervention, you will be given the option of receiving the experimental intervention. Both types of interventions involve MR scanning sessions in which you hear trauma related audio clips and attempt to control your brain activity patterns, as described in more detail below.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed judgment. This consent form gives you detailed information about the research study. A member of the research team will also discuss this information with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

Your participation in this study will involve the following procedures:

1. Initial Clinical Assessment: During this session, you will meet one-on-one with a clinician, who will ask you questions regarding the severity and characteristics of your symptoms. This session will last between 4 and 5 hours. If it not feasible for you attend this session in person due to physical distance or risk of infection from COVID-19, a remote session over Zoom conferencing may be arranged.

2. Trauma Script Collection: During this session, you will be asked to describe in detail your stressful and traumatic life events. The detailed descriptions you provide will then be used to produce audio recordings narrating what happened to you during those events, as well as audio clips containing noises related to the events. Later in the study, you will be asked to listen to these personalized audio clips during the scans when you are trying to control your brain activity patterns. You will be asked to wear a portable physiological tracking watch that will record your body's heart rate and sweat levels during this session. This session will last between 4 and 5 hours. A remote session over Zoom for this study procedure can also be arranged.

3. Strategy Development Session: Either in a one-on-one meeting or over the phone or Zoom, a clinician will discuss with you strategies for controlling your brain activity

patterns that you can try during the neurofeedback sessions. This session will last between 30 and 60 minutes.

4. Randomization: You will be randomly assigned to one of two interventions: the experimental intervention, which we hope may help symptoms (although this has not been demonstrated), and the control intervention, which we do not believe has any potential to help symptoms. You will not be told which intervention you received until the intervention – including all follow-up assessments – has been completed. At that point, if you received the control intervention, you will be given the option of receiving the experimental intervention. Both types of interventions involve MR scanning sessions in which you hear trauma related audio clips and attempt to control your brain activity patterns, as described in more detail below.

5. Imaging: All imaging will be done at the Magnetic Resonance Research Center (MRRC) in the Anlyan Center at the Yale Medical School. In this part of the study we will take pictures of your brain with a magnetic resonance imaging machine (also known as an "MRI"). The pictures of your brain will give us information about the structure and activity level of different parts of your brain, and information about how brain areas are connected. We are particularly interested in understanding how different parts of the brain work together to do different tasks and whether you can control the activity patterns in specific parts of your brain. Prior to the scan, you will receive a urine test and a breathalyzer test. Based on the results of these tests (i.e., if you are intoxicated), you may be asked to reschedule the scan. You will not be scanned if there is any possibility you may be pregnant. A free pregnancy test will be available by request for you to use privately before the scan.

You will be escorted to the machine by research personnel, who will remain for the duration of the scan before escorting you out of the building. The machine will make loud drumming noises when the pictures are being taken. You will either be given headphones to wear, or ear plugs to muffle the sounds of the machine, or both, and you will be asked to lie flat on a narrow bed. You may have a clip placed on your finger to monitor your pulse, and a belt placed across your abdomen to monitor your breathing

patterns. Your head may have tape placed across it to help you keep it still throughout the study. We will also record your pupil dilation to assess your stress levels. You will then be moved on the bed into the MR magnet, which is shaped like a large tube.

You will be able to talk with the researchers operating the MR system while you are in the magnet, when the machine is not collecting pictures. If you need to rest, you can tell us, and the session will stop until you are ready to continue. You will be able to see a mirror above your head, on which pictures will be projected for you to see at different times during the study.

When the study starts we will begin taking pictures of your brain. You will know when a picture is being taken because the machine will make a short burst of noise. It is important for the quality of the images that you lie as still as possible.

You will take part in the following imaging sessions as a part of this study, each about one half week apart from each other. Each session takes between 1 and 1.5 hours to complete.

A) Set-Up Session: First, we will take your basic brain picture. After that, you will be asked to do several different tasks. For some of these tasks you will just be able to rest, but will be asked to stay alert and to keep still. You will also be asked to perform simple memory tasks where you hear a list of letters and press a button if the current letter matches the previous one. In other tasks, you will be exposed to two types of trauma-related stimuli: auditory trauma narratives (scripts that describe your stressful/traumatic memories) and clips of trauma-related noises (e.g., gunshots), each lasting exactly 1 minute. Both types of stimuli will be auditory only (i.e., there will be no associated video footage), and will be custom-made to fit your personal experiences. You will be asked at times to try to control your stress after being exposed to these stimuli. These stimuli are designed to be stressful - and may affect your emotions or your clinical symptoms - in order to produce brain activity in a specific region and see if you are able to learn to control this stress-related activity. This session will help us determine which part of your brain responds to the stressful stimuli and see if you are able to control your stress without having had any practice.

B) Intervention Sessions: Like in the Set-Up Session, we will start by taking basic brain pictures. Next, you will be exposed to more trauma-related stimuli and asked to try

to control your stress in response to them. In order to help you do this, we will provide you with a visual stimulus (a line that updates over the course of the scan) indicating how well you are producing the desired brain activity pattern. It is important for the study that you do your best during these tasks. However, it is all right if you are unable to complete this task. Like before, you will also be asked to perform simple memory tasks. You will take part in 3 Intervention Sessions, with each session involving 6 run-throughs of these tasks. However, if there are technical issues or if we run out of time, we may try to schedule extra Intervention Sessions to make sure you have finished 18 run-throughs in total.

C) Follow-Up 1: In this session, we will take more basic brain pictures, then ask you to do several different tasks. In addition to the memory tasks, you will be exposed to more trauma-related stimuli and asked to control your stress – this time without any visual feedback about your brain activity (i.e., there will be no line corresponding to your brain activity). This will help us determine how much you learned during the Intervention Sessions.

D) Follow-Up 2: In this session, we will take more basic brain pictures, then ask you to do several different tasks. For some of these tasks you will just be able to rest, but will be asked to stay alert and to keep still. Like in the previous scan, in addition to performing memory tasks, you will be exposed to more trauma-related stimuli and asked to control your stress without any visual feedback about your brain activity.

6. Clinical Assessments: Before each Intervention Session and before the Final Session, you will speak with a clinician who will ask you questions about your symptoms. This will also occur at 1 month and 2 months after you complete the Final Session, and will take between 30 minutes and 1.5 hours. If you are unable to attend the follow-up clinical sessions, we may ask you to answer questions about your symptoms either by telephone or Zoom video conferencing.

7. Debriefing: Upon completion of the final Clinical Assessment, you will be fully debriefed by study personnel, who will explain more thoroughly the purpose of the study and answer any questions you may have. It is important to note that you may decide to

withdraw from the study or have your data removed at any time over the course of the study.

Risks and Inconveniences of the Procedures

Below are descriptions of the risks associated with the study procedures destroyed above. In general, while you are enrolled in this study, we ask that you refrain from participating in other research studies. We would prefer if you do not enroll in this study if you plan to change your medication or therapy before study completion. If a change in symptoms or situation arises during the study so that you wish to change your medication or therapy, this will be fine, but please let us know. We may remove you from the study as a result of the change.

Imaging:

Magnetic resonance (MR) is a technique that uses magnetism and radio waves, not x-rays, to take pictures of various parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines.

You will be watched closely throughout the MR study. Some people may feel uncomfortable or anxious. If this happens to you, you may ask to stop the study at any time and we will take you out of the MR scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly but please tell the research staff if you have them.

There are some risks with an MR study for certain people. If you have a pacemaker or some metal objects inside your body, you may not be in this study because the strong magnets in the MR scanner might harm you. Another risk is the possibility of metal objects being pulled into the magnet and hitting you. To reduce this risk, we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. We also ask all people involved with the study to walk through a detector designed to detect metal objects. It is important to know that no metal can be brought into the magnet room at any time. Also, once you are in the magnet,

the door to the room will be closed so that no one from outside accidentally goes near the magnet.

We want you to read and answer very carefully the questions on the MR Safety Questionnaire related to your personal safety. Take a moment now to be sure that you have read the MR Safety Questionnaire and be sure to tell us any information you think might be important.

This MR study is for research purposes only and is not in any way a clinical examination. The scans performed in this study are not designed to find abnormalities. The primary investigator, the lab, the MR technologist, and the Magnetic Resonance Research Center are not qualified to interpret the MR scans and are not responsible for providing a diagnostic evaluation of the images. If a worrisome finding is seen on your scan, a radiologist or another physician will be asked to review the relevant images. Based on his or her recommendation (if any), the primary investigator or consulting physician will contact you, inform you of the finding, and recommend that you seek medical advice as a precautionary measure. The decision for additional examination or treatment would lie solely with you and your physician. The investigators, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any examination or treatment that you receive based on these findings. The images collected in this study are not a clinical MR exam and for that reason, they will not be made available for diagnostic purposes.

Clinical and Neuropsychological Assessments:

You may find some of the questions being asked to be uncomfortable, and stressful. You do not have to answer any question that you do not want to answer.

Strategy Development Sessions:

You may find some of the strategies being taught to you to be stressful or not useful at all.

Trauma Script Collection:

Due to the trauma-related stimuli presented to you in the scanner, there is a risk that your symptoms will flare-up. If you feel you are at risk of an intense reaction (such as a panic attack or psychotic episode), it is important to let the investigators know immediately. You may experience temporary psychiatric symptoms' exacerbation when recalling or listening to your traumatic memories, which is normal and expected in the course of exposure treatment for PTSD. A clinician (a psychiatrist or a psychologist) will be on-call at all times during the symptom provocation sessions. If you experience a significant worsening in your psychiatric symptoms in the course of the study days after the scripting, one of the study clinicians will be available to meet with you to address these issues at your request. If you have a problem following the session, whereby you cannot stop thinking and feeling upset about the stimuli, or if you have any other research-related complaints, concerns, or questions, we encourage you to call Dr. Harpaz-Rotem [(203) 494-5454] during normal work hours. If it is after-hours and you are concerned that you may have a panic attack or a psychotic episode, please contact the Biostudies on-call physician for emergency treatment by calling the VACHS operator at (203) 932-5711, extension 0.

Risks Associated with Neurofeedback Sessions:

You may also experience a temporary psychiatric symptoms' exacerbation when confronted with their traumatic memories during the neurofeedback sessions, this is normal and expected in the course of exposure treatment for PTSD. If you experience prolong and significant worsening in your psychiatric symptoms in the days following the neurofeedback session, one of the study clinicians will available to meet with you to address these issues if needed.

In Case of Injury

If you are injured as a result of your participation in this study, treatment will be provided to you. However, you or your insurance carrier will be responsible for the cost of such treatment in the forms of copays and/or deductibles. You do not waive any of your legal rights by signing this form.

Benefits

This study was not designed to benefit you directly. It will allow us to study how effective our neurofeedback intervention is for treating PTSD and how brain patterns are related to PTSD symptoms. You may gain some control over your PTSD symptoms by learning to control activity patterns in your brain. It is important to note, however, that you may be receiving either the true experimental intervention (that we hope can help improve symptoms) or a control intervention (that we do not believe has any potential to improve symptoms/cognitive function). If you receive the control intervention, you will be given the option of receiving the true experimental intervention *after study completion*.

Economic Consideration

For your participation, you will be paid:

- $80 for each MR imaging session
- For sessions outside of the scanner, you will be paid $20 for strategy development sessions (these may take up to one hour), and $20 per hour for clinical and neuropsychological assessments.
- You will be paid $50 per hour for sessions involving the collection of PTSD trauma scripts.

You will be paid for any session you participate in regardless of whether or not you complete the study. According to the rules of the Internal Revenue Service (IRS), payments that are made to you as a result of your participation in a study may be considered taxable income.

Confidentiality and Privacy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If

you decide to be in this study, the researchers will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name and contact information. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify you will remain confidential. The personal information we obtained from you during screening will be kept only on paper in a locked file cabinet or in a secure database at the VA health center. Any other data we collect from you during the study (such as your brain scan) will not be stored with any personal identifiers, but rather with a study number. A record associating your name and that number will be kept confidentially in paper form in a locked file cabinet to be seen only by the researchers. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept until the study is complete and all data analyses have been conducted and published, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

The information about your health that will be collected in this study includes:

- *Research study records – including all data collected in this study (including, but not limited to functional and structural brain images, personal health history, and assessments of symptom severity).*
- *Records of your study visits*

This research is covered by a Certificate of Confidentiality from the National Institutes of Health (NIH). The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be

disclosed to anyone else who is not connected with the research, except if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases), if you have consented to the disclosure (including for your medical treatment), or if it is used for other scientific research as allowed by federal regulations protecting research subjects.

The Certificate of Confidentiality cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the NIH, or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document. Information about you and your health which might identify you may be used by or given to:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- The Principal Investigator
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Technicians who run the MR scanners
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the study
- Neuroradiologists at the MRRC

De-identified data, including data on sex/gender, race, ethnicity, and age, may be included in reports to NIH, in manuscripts, or on websites, or made otherwise publicly available. De-identified information means that all personal information about research participants such as name, address, and phone number is removed and replaced with a code number.

De-identified data will be uploaded to ClinicalTrials.gov. De-identified data will also be uploaded to the National Institute of Mental Health (NIMH) National Database for Clinical Trials (NDCT), a branch of the NIMH National Data Archive (NDA). The NDA is a data repository run by the (NIMH) that allows researchers studying mental health and substance use to collect and share de-identified information with each other. A data repository is a large database where information from many studies is stored and managed. With an easier way to share, researchers hope to learn new and important things about mental illnesses more quickly than before.

During and after the study, the researchers will send de-identified information about your health and behavior and in some cases, your genetic information, to NDA. Other researchers nationwide can then file an application with the NIMH to obtain access to your de-identified study data for research purposes. Experts at the NIMH who know how to protect health and science information will look at every request carefully to minimize risks to your privacy.

You may not benefit directly from allowing your information to be shared with NDA. The information provided to NDA may help researchers find better treatments. NIMH will also report to Congress and on its web site about the different studies that researchers are conducting using NDA data. However, you will not be contacted directly about the data you contributed to NDA.

You may decide now or later that you do not want to share your information using NDA. If so, contact the researchers who conducted this study, and they will tell NDA, which can stop sharing the research information. However, NDA cannot take back information that was shared before you changed your mind. If you would like more information about NDA, this is available on-line at http://data-archive.nimh.gov.

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine, the West Haven VA, and the Connecticut Mental Health Center are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies. However, by deciding to take part in a single or double blinded treatment study and signing this permission form, you will not be allowed to look at or copy your study related information until after the research is completed.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

If you have consented to participate in other human research protocols here at Yale, we may share your data across studies in order to relate data collected under one study to data collected under another.

This study is a registered clinical trial. A description of the 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, though de-identified results will be uploaded, as outlined above. You can search this website at any time.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing from the Study

If you do become a subject, you are free to stop and withdraw from this study at any time during its course.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments (if applicable).

The researchers may withdraw you from participating in the research if necessary. This may be the case if they feel that you should receive a treatment that is not allowed while participating, if they feel that your participation is in any way detrimental to your health, if in the course of participating, it is discovered that you do not satisfy inclusion criteria for the study (for example, if an excluded neurological condition is discovered on a brain scan), or if you do not comply with study requirements (such as showing up on time for sessions). If you are removed from the study due to concerns that participation may be making your symptoms worse, you will be offered counseling.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with the Child Study Center, the VA, or the Yale OCD Research Clinic. You may withdraw or take away your permission to use and disclose your health information at any time. You may withdraw your permission by telling the study staff or by writing to Ilan Harpaz-Rotem at ilan.harpaz-rotem@yale.edu.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully - as long as you feel it is necessary - before you make a decision.

Authorization:

I have read this form and decided that I, _____,

(name of subject)

will participate in the project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

_____

Signature

_____

Date

_____ _____

Signature of Research Staff Who Obtained Consent Telephone

If you have further questions about this project or if you have a research-related injury, please contact the principal investigator, Ilan Harpaz-Rotem, at ilan.harpaz-rotem@yale.edu / (475) 434-2943. If you have questions about your rights as a research subject, please call the Yale Human Investigation Committee at (203) 785-4688.