HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: Neurofeedback of amygdala activity for PTSD

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Version Date: 11/08/2022

(*If applicable*) ClinicalTrials.gov Registration #: NCT03574974

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

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SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

The primary purpose of this study is to investigate the efficacy of biofeedback (or neurofeedback; "NF") of real-time functional magnetic resonance imaging (rt-fMRI) data for reducing symptoms in patients with PTSD. The target mechanism for this intervention is control over amygdala activity following trauma recall. Namely, participants will be presented with rt-fMRI data that corresponds to amygdala activity in response to recalled trauma in order to help them improve control over this key region in the fear circuit. We hypothesize that improved control over the amygdala will reduce the core symptoms of PTSD and initiate a healthier clinical trajectory.

A secondary purpose of this study is to use fMRI as a method for investigating brain function in individuals with PTSD. This study approach provides a tool for probing the neurobiology of PTSD by (1) testing the critical role of the amygdala in this disorder and (2) examining how amygdala connectivity is related to both amygdala regulation and clinical symptoms.

In pursuit of the overarching goals of this study, we aim to:
- determine if our NF intervention increases control over the region of interest (the amygdala) more than sham feedback in which participants receive feedback that is unassociated with their PTSD symptoms
- determine if NF results in clinical improvements in PTSD symptoms, relative to sham feedback, and examine whether these improvements correlate with improved control over the amygdala
- determine if NF results in changes in resting state connectivity to the amygdala, and whether these changes correlate with symptom improvement and an improved ability to regulate the amygdala

Finally, we would like to relate genetic markers to brain patterns in PTSD subjects. Therefore, we have a created a separate consent form to allow us to collect, analyze, and relate genetic information to brain function.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

The initial R-61 phase (testing whether, when used by human participants, the proposed intervention alters the presumed biological signature/mechanism of action) will last two years. If in the R-61 phase, participants who receive NF demonstrate larger improvement in control over their amygdalae than sham patients, an R-33 phase (continued testing of the efficacy of the intervention) will be initiated, and last up to 8 years.

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

MRI methods can detect quite subtle changes in blood flow/oxygenation using T2* weighted images. These methods are often used to assess alterations in brain that occur with regional activation in response to external stimuli or tasks. The methods, known generally as functional magnetic resonance imaging (fMRI), are non-invasive and permit repeated performances of tasks in individuals as well as children. The resolution is similar to that of conventional anatomic MRI. There is firm evidence that this approach to the study of brain responses provides a higher quality of information, with much better spatial and temporal resolution, sensitivity and safety, and without the need for inter-subject averaging, than the best PET or SPECT studies of

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blood flow. For localization and quantitation of regional responses to stimuli, it is becoming increasingly clear that MRI will be the method of choice in experimental neuroscience. The preliminary results from other laboratories strongly suggest that this method is capable of providing unique information about the magnitude and location of the physiological response of the brain to specific stimuli [1,2].

More recently, there have been publications suggesting that real-time neurofeedback of functional imaging data can enable individuals to control brain activity in specific parts of their brain. One recent study reported that neurofeedback of anterior cingulate activity resulted in a decrease in pain in patients with chronic pain disorders as well as a decrease in the perception of pain associated with a painful stimulus in healthy control subjects [3]. Thus, real time neurofeedback of functional imaging data is new method with promising applications to many clinical conditions.

In the context of PTSD, real time fMRI neurofeedback may be effective at reducing symptom severity by targeting amygdala activity. Amygdala hyperactivity is a hallmark feature of PTSD, with a substantial body of literature revealing heightened amygdala responsivity in PTSD during the processing of both trauma-related and trauma-unrelated affective information [4]. Amygdala hyperactivity is also positively correlated with symptom severity in PTSD, making it an ideal target for neurofeedback aimed at producing clinical improvement (see Shin et al. for review) [4]. Moreover, amygdala activation is associated both with the risk of developing PTSD and with positive response to treatment, [5, 6], further highlighting the unique role of the amygdala in modulating PTSD. This study will target amygdala activity using a script paradigm first piloted by other groups [7, 8], in which individual trauma scripts are collected for each subject and later played in the scanner. This will allow us to localize and provoke amygdala activity to use as a target in the neurofeedback intervention.

One of the popular control conditions for studies using neurofeedback of real-time fMRI data is a form of sham feedback in which a subject receives a feedback signal based on a prior subject's performance during their (true) neurofeedback scan. Because the times at which subjects are told to increase or decrease activity in their brain are consistent across subjects, this type of sham biofeedback creates the impression in the subject that they are somewhat successful in controlling their brain activity. That is, to the extent that the previous subject was able to increase activity during increase periods and decrease activity during decrease periods, the subject receiving the sham feedback will appear to also be successful. This helps to control somewhat for the perception of success which can affect motivation or placebo effects. This form of sham, known as a yoked sham, will be used as the control intervention in this study.

References

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7. Lanius RA, Williamson PC, Densmore M, et al. "Neural correlates of traumatic memories in posttraumatic stress disorder: a functional MRI investigation." Am J Psychiatry **158**(11): 1920-1922, 2001.
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4. Research Plan: Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

A. Screening and Initial Clinical Assessment:

Prior to participation, subjects will be screened both over the phone and in-person at the West Haven campus of the VA Connecticut Health Care System to determine eligibility and to collect demographic and personal history data relevant to the study. If deemed eligible and willing to participate, subjects will attend an initial clinical assessment (see Figure 1 for flowchart of all patient visits). During this assessment, a clinical psychologist with experience with PTSD will evaluate the severity of the subject's symptoms of PTSD and other disorders via a structured clinical interview. If it would represent a significant burden to the participant to attend an initial in-person screening session due to distance or risk of infection by COVID19, a virtual screening will be offered. Assessments that may be collected remotely include the neurological and psychiatric evaluation interview, assessment of treatment history, and, for eligible subjects only, the scripting of life events and the strategy session. If subjects remain eligible after the initial session, they will be invited to continue in the study. Using virtual screening sessions will help to reduce burden on potential participants and staff, and limit in-person visits to only those subjects already determined to meet the psychiatric eligibility criteria.

In the Initial Clinical Assessment, if the subject meets clinical inclusion criteria for PTSD, the clinician will then collect information about the subject's traumas and stressful life events. The collection of life events will occur at the West Haven VA or virtually At this visit, participants who appear in person will be asked to wear a portable physiotracking watch to record their GSR and Heart rate during memory recall (E4 Wristband, Empatica Inc.) The information about events will later be used to create two types of provocative auditory stimuli: auditory trauma narratives (scripts) and clips of trauma-related noises. Briefly, and in collaboration with the subject, narratives of the subject's six most traumatic and stressful life events will be created and ranked from most to least traumatic. Then, two different scripts will be written for each trauma memory (i.e., different wordings, descriptions). These scripts will be rich in imagery, combining the subject's narrative accounts with descriptions of their emotional and physiological state at the time of the trauma (e.g., sweaty hands, tense muscles, etc.). Once written, scripts will be recorded by different voices and edited so that each

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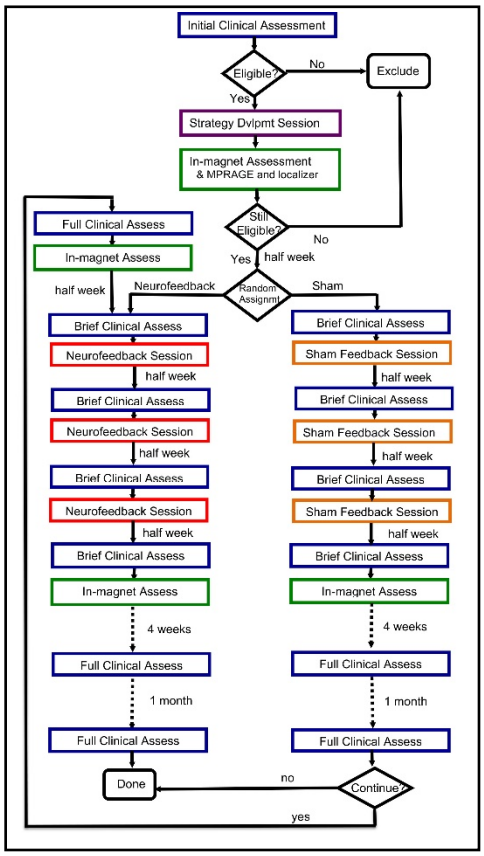

Figure 5: Flowchart of study design. All patients are debriefed and unblinded after the final Full Clinical Assessment. Those who had the sham intervention will be offered the option of also participating in NF, but data obtained from unblinded crossover patients will not be used for any of our primary analyses.

lasts exactly 60 seconds. In addition, for each trauma memory described by the subject, recordings of relevant sounds will be collected and combined into 60 second audio clips of trauma-related noises. For example, for a veteran whose trauma involves a jeep under fire, we will concatenate jeep sounds, gun shots, heavy breathing, skidding sounds, moaning, etc. to create a 60s trauma-related sound clip. Both types of minute-long provocative sound files will be played during the scanning runs to provoke trauma recall and anxiety. The two different types of provocative sound clips ensure that we have many different stimuli so we don't need to repeat stimuli too many times (which could induce habituation or "tuning out" to that particular sound clip). Information regarding how these auditory clips are used during scans is outlined in more detail in the following paragraphs.

B. Strategy Development Session:

After the Initial Clinical Assessment, participants will meet in person or virtually with a clinician to take part in a strategy development session, the goal of which is to develop an individualized cognitive strategy for the subject that may provide them with some initial control over their amygdala activity. While strategies discussed during this session are intended to assist individuals in raising/lowering amygdala activity after trauma recall, they are meant only to engender an initial, limited ability to control the amygdala – a starting point for the feedback sessions. During the feedback sessions, subjects will have the chance to experiment with their cognitive strategies and receive direct feedback regarding what is more effective, thereby allowing subjects to develop increasing control over the amygdala in the way that best fits her/his individual style of coping. It is important to note that because this stage occurs before randomization, *all* subjects (NF and sham) participate in this session. Therefore, learning effects specific to the session are controlled for by group comparisons.

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C. MR Imaging:

At this point, subjects are ready to begin the MRI portion of the study, which consists of two in-magnet assessments and three neurofeedback or sham sessions, all taking place at the Magnetic Resonance Research Center in the Anlyan Center in New Haven, CT. The specific in-magnet procedures are described in more detail in the following sections *i. – iv.*

All subjects who take part in MR imaging are screened at each visit, using screening conventions that are standard for magnetic resonance studies, to ensure they do not have any metallic implants, shrapnel, pacemakers, etc. Subject will be screened to make sure they are not under the influence of illicit substances using urine analysis and a breathalyzer. Based on the results of the urine test and breathalyzer, the researchers will determine whether to run the participant through the study protocol that day or to postpone participation to a later date as to avoid a potential dampening of study effectiveness due to intoxication. Women of child-bearing age will only be included if they assure us they are not pregnant. A free urine pregnancy test will be offered to them to use privately if they wish.

Before each in-magnet assessment, subjects also undergo brief clinical assessments at the Yale Magnetic Resonance Research Center (MRRC). During these sessions, symptoms of PTSD and depression will be collecting using brief self-report checklists. Information regarding any adverse event will also be solicited and recorded.

Subjects will be escorted to and from the scanner by research personnel who will remain present throughout the entire assessment. Before each in-magnet assessment, participants will be required to fill out an MR Safety Questionnaire, endorsing no rule-outs for MR imaging, and walk through a metal detector to ensure they have no ferromagnetic metals on or in their person. The United States Food and Drug Administration (FDA) guidelines for magnet strength and exposure to radio waves will be carefully observed during all scanning sessions. During in-magnet assessments, MR imaging of the brain will record the three dimensional anatomy of the brain, using conventional 3D gradient echo sequence to obtain high-resolution slices of the brain. Images of the subject's brain will also be taken while subjects engage in a specific task (described in more detail in Section III.B.). Thousands of images will be obtained on each subject for each scanning session. This will provide enough information to calculate which regions alter their MRI signal during the activation, or to examine which regions vary in signal level in a correlated manner. We may also collect diffusion tensor imaging (DTI) data which is most commonly used to examine the integrity of white matter tracts. The total imaging time in a single scanning session will not exceed 90 minutes for any subject. During MR scans, components of the Siemens Physiologic Monitoring Unit will be used to take recordings of the subject's pulse (via a pulse-oximeter placed on their finger), respiration (via a pneumatic belt), and galvanic skin response (via sensors on the fingers). This equipment is designed to be completely MR compatible. The records of pulse and respiration will be used during data processing to remove physiologic noise from the images. In order to minimize subject head motion during the MR scans, we may place tape across the subject's forehead or chin. This provides tactile feedback about head motion.

Over the course of this procedure, subjects will be asked to report various aspects of their experience – this will include responding to questions regarding their perceived control over their brain activity.

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i. In-Magnet Assessment 1: MPRAGE, Resting State, Initial Control Runs, and Localizer. If time allows, DTI data will also be collected.

During the first in-magnet assessment, a high resolution structural image will be collected using an MPRAGE sequence. Functional resting state data will be collected, as well four control runs. During the resting state sessions spontaneous pupil dilation will be measured using a Eyelink 1000 system. As seen in Figure 2, control runs involve a resting period, exposure to a provocative audio clip, a period of down-regulation where participants try to bring down their amygdala activity, and a final resting period. In order to minimize anticipation and rumination regarding the upcoming or preceding stressor, resting periods are separated from the provocative audio clip and subsequent period of down-regulation by a 1-back memory task (seen in Figure 2 as "1-bk"). These memory tasks provide a cognitively-engaging distraction for the subject, preventing anticipatory and spill-over amygdala activity during resting periods and allowing for a more valid baseline to be established.

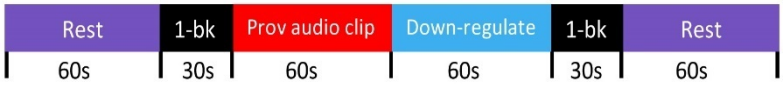

Figure 2: Schematic illustration of a control task run. Control assessed based on activity in the target region of the amygdala in the down-regulate blocks (relative to rest)

Three localizer runs will also be performed during this session. As seen in Figure 3, the localizer runs will involve a resting period, exposure to a provocative audio clip, and a final resting period. As in the control run, to ensure that resting periods are not affected by the symptom provocation, subjects will perform a 1-back working memory task between the rest periods and the provocative audio clips. In order to identify the part of the amygdala involved in trauma-related anxiety, activation during the trauma exposure will be compared to activity during the resting periods. The area of the amygdala located during this session will be used as the target for the brain activity that will be shown to subjects in future NF runs. As such, we must be able to identify adequate activation in the amygdala for NF to be possible – if no such activation can be identified, the subject will no longer be eligible for continuation of the study.

Figure 3: Illustration of a localizer run. Activity will be contrasted between provocation and rest blocks to identify region of peak amygdala activity.

ii. Randomization

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All subjects who remain eligible following the localizer will be randomized to receive either NF or sham feedback, subject to the restriction that there must always be at least as many subjects in the NF group as in the sham group. We will not explicitly describe the sham feedback procedure to subjects – rather, all subjects will be told that they will be randomly assigned to receive either an experimental intervention (that we hope will help symptoms, but that has not yet been demonstrated to be effective) or a control intervention (that we do not believe can help symptoms). Subject will be blind to their condition until study completion, at which point we will tell them which intervention they received. At that point, those who received the control intervention (sham) will be given the option of trying the experimental intervention (NF).

It is important to note that all clinical assessments performed after randomization are carried out by a clinical psychologist who is blind to subject assignment.

iii. Neurofeedback and Sham Feedback

After randomization, subjects will undergo a total of 18 NF or sham feedback runs, carried out over three separate sessions one half of a week apart from one another. Each session tends to be composed of 6 NF or sham runs. However, extenuating circumstances (e.g., technical errors, subjects' schedules) may necessitate the 18 NF or sham runs to be spread out over more than three sessions.

In NF runs, an arrow at the top of the screen indicates the subject's current goal. A red arrow pointing upward prompts the subject to listen to the provocative auditory clip and *not* try to control their brain activity pattern. A blue arrow pointing downward prompts the subject to try to decrease activity in the target area. A white arrow pointing to the right indicates a rest period. In all blocks, a color-coded feedback line is presented below the arrow. The line is updated every 2 seconds throughout the scan to indicate activity in their target area. During the red block, a provocative audio clip is playing. Subjects are instructed not to try to control their activity during this period. The provocative auditory stimulus ends when the blue block begins, but subjects often have high activity in this period due to rumination. Their goal is to decrease this activity during the blue period. Before engaging in this task, subjects are given instructions about what to do during each block, and are informed that there is a 6-8 second delay between changes in activity in their target brain area and changes in the line graph due to the slow blood flow response and processing delays.

The sham feedback is identical to the NF, except for the fact that the feedback line displayed to the subject is taken from the amygdala time-course of a previous subject who received NF, rather than from the current level of amygdala activity of the present subject. This allows the sham subject to get a similar impression of success (or lack thereof) compared to the NF subject they were matched to, without receiving any true neurofeedback. While this does involve a degree of deception (as subjects will believe that the feedback they are receiving is based on their brain activity), subjects in the sham condition will be told at the end of the study that the feedback they received was a control intervention and will be offered the chance to receive the experimental neurofeedback intervention. It is important to note that although the feedback line in the sham condition comes from a past subject, the

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audio clips in sham runs will still be based on the sham subject's personal memories, and the onset and offset of provocative sound files is time-locked across subjects.

iv. In-Magnet Assessment 2: Resting State, Post-Intervention Control Runs, DTI (if time allows).

Upon completion of all 18 NF or sham runs, subjects will take part in a second in-magnet assessment where resting state data will again be collected and they will also complete four more control runs. During the resting state sessions spontaneous pupil dilation will be measured. These runs are identical in design to the initial control runs described in Section C.i. These final control runs will allow us to see how much control subjects gain over their amygdalae in the sham versus NF conditions. If time allows, DTI data may also be collected in this session.

v. Follow-Up Scan: Resting State, Long-Term Follow-Up Control Runs, DTI.

One month after the completion of In-Magnet Assessment 2, subjects will take part in an approximately hour-long scan where they will perform additional control task runs and where resting state and DTI data will be collected. During the resting state sessions spontaneous pupil dilation will be measured.

D. Clinical Assessments

During brief clinical assessments, symptoms of depression, PTSD, and other clinical conditions common in this population, such as tinnitus, will be collected using brief self-report measures. Subjects will also respond to a clinician-administered PTSD scale and will be queried regarding adverse events. These follow-ups do not always require the subject to be physically present, and will often be carried out over the phone or Zoom video conferencing. At 1 and 2 month/s post completion of the final feedback session, subjects will undergo a full clinical assessment. Similar measures will be collected during these assessments, in addition to the Clinician Administered PTSD Scale for DSM-V (CAPS-5).

E. Genetic Testing

Adult PTSD patients will be asked via a separate consent form (see below for more details) to provide DNA and RNA samples. Both DNA and RNA will be collected in order to conduct sequencing of DNA and RNA. Analyses will focus on genes best supported by the PTSD literature at the time of analysis. Genetic data collected may be related to the imaging data to examine, for example, whether genetic markers are associated with learning over the course of the neurofeedback protocol. See below for more details on genetic testing. The genetic component of the present study will occur in collaboration with a pre-existing protocol that examines the genetics of neuropsychiatric disorders (HIC0301024156; “Genetic and molecular studies of developmental neuropsychiatric disorders associated with cognitive and behavioral impairment”). All participants who choose to provide DNA and RNA samples will be consented under this protocol, and all genetic data collected by these means will be shared with personnel associated with this protocol.

5. Genetic Testing (continued)

A. Describe

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i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned.

Both DNA and RNA will be collected in order to conduct sequencing of DNA and RNA. Analyses will focus on genes best supported by the PTSD literature at the time of analysis. Genetic data collected may be related to the imaging data to examine, for example, whether genetic markers are associated with learning over the course of the neurofeedback protocol. On the genetics-specific consent form associated with HIC0301024156, subjects will be able to choose whether they want their specimen to be stored for future testing.

ii. the plan for the collection of material or the conditions under which material will be received.

Genetic data will be collected in accordance with HIC0301024156. Participants will be consented under this protocol using a separate, genetics-specific consent form.

iii. the types of information about the donor/individual contributors that will be entered into a database.

Both DNA and RNA will be collected in order to conduct sequencing of DNA and RNA. As outlined in HIC0301024156, subjects will also be asked to give permission to their health care providers to release copies of their relevant medical and psychiatric records.

iv. the methods to uphold confidentiality.

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with the permission of the subject or as required by U.S. or State law. The personal information obtained from subjects will be de-identified at the earliest reasonable time after it is received. The principal investigator will keep a link that matches subjects to their coded information, and this link will be kept secure and available only to the PI or selected members of the research team. The link to any personal information will be kept only 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.

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?

The genetic data collected in association with this study will be shared with the PI and research personnel of HIC0301024156. This data may also be shared with the U.S. Department of Health and Human Services (DHHS) agencies, representatives from Yale University/the Yale Human Research Protection Program/the Yale Human Investigation Committee, co-investigators and other investigators, study coordinators and members of the research team, and Data and Safety Monitoring Boards and others authorized to monitor the conduct of the study. Any transfer of data will occur in a HIPAA-compliant manner using a secure network and encryption when necessary. De-identified data, including data on participant sex/gender, race, ethnicity, and age, may be included in reports to NIH, in manuscripts, or on websites, or made otherwise publicly available. Subjects will be asked to allow their de-identified genetic data and questionnaire data to be submitted to the NIH dbGaP (database of Genotypes and Phenotypes) and/or similar restricted-access scientific databases. The research data

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collected in the database(s) will be used by scientists for the benefit of medical research. All information will be de-identified prior to submission to the NIH dbGaP and/or other similar restricted-access scientific database(s). Information that will be sent may include: age at sample collection, gender, race, relevant clinical diagnosis and laboratory values.

All health care providers subject to HIPAA are required to protect the privacy of subject 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 subject 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 subject information in ways not mentioned in this protocol. However, to better protect subject health information, agreements are in place with these individuals and/or companies that require that they keep subject information confidential.

C. Is widespread sharing of materials planned?

Not the genetic data. Although other data collected in this study may be uploaded to the National Database for Clinical Trials, genetic data will not be included in the upload. Other de-identified data, including data on participant sex/gender, race, ethnicity, and age, may be included in reports to NIH, in manuscripts, or on websites, or made otherwise publicly available. Subjects will be asked to allow their de-identified genetic data and questionnaire data to be submitted to the NIH dbGaP (database of Genotypes and Phenotypes) and/or similar restricted-access scientific databases. The research data collected in the database(s) will be used by scientists for the benefit of medical research. All information will be de-identified prior to submission to the NIH dbGaP and/or other similar restricted-access scientific database(s). Information that will be sent may include: age at sample collection, gender, race, relevant clinical diagnosis and laboratory values.

As mentioned previously, genetic data will also be shared with the collaborating HIC0301024156 – the protocol under which genetic material will be collected.

D. When and under what conditions will materials be stripped of all identifiers?

The personal information obtained from participants will be de-identified at the earliest reasonable time after it is received. If subjects do not opt in to long-term storage of their genetic material, their sample will be destroyed after the genetic information about PTSD-relevant genes has been determined.

E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?

Subjects can withdraw their material at any time before the link to their personal information has been destroyed, after which it will not be possible for study staff to identify their material for withdrawal.

i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

The principal investigator will keep a link that matches subjects to their coded information, and this link will be kept secure and available only to the PI or selected members of the research team. If the subject requests their material be withdrawn from the study while this link exists,

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their material will be discarded, and any records of their genetic information destroyed. The link to any personal information will be kept only 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.

F. Describe the provisions for protection of participant privacy.

As mentioned above, any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with participant permission or as required by U.S. or State law. The personal information obtained from participants will be de-identified at the earliest reasonable time after it is received. The principal investigator will keep a link that matches subjects to their coded information, and this link will be kept secure and available only to the PI or selected members of the research team. The link to any personal information will be kept only 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. Any information sent to the NIH dbGaP or any other restricted-access scientific database will be de-identified prior to submission.

G. Describe the methods for the security of storage and sharing of materials.

Genetic samples will be stored in a locked cabinet that only the necessary research staff have access to, and will only have coded study number information on them, no personally identifying information. When the material is taken out to be analyzed for genetic information, there will never be personal information attached, only study numbers. A record associating patient names and study numbers will be kept confidentially in paper form in a locked file cabinet to be seen only by the researchers. Personal information obtained from subjects during screening will be kept only on paper in a locked file cabinet. Electronically stored information regarding genetic information will be stored on a secure, encrypted server with a study number rather than any personal identifiers. As mentioned above, any transfer of data will occur in a HIPAA-compliant manner over a secure network and using encryption when necessary.

6. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.

This study will seek out subjects of all sexes, ages 18 and up. Inclusion criteria include an active and primary diagnosis of chronic PTSD, as established by the Clinician Administered PTSD Scale for DSM-V (CAPS-5). The subjects must be able to give signed, informed consent and follow instructions in English and have normal or corrected-to-normal vision. Subjects must be unmedicated or on a stable dose of SSRIs for 2 months prior to enrollment in the study, and must not have initiated cognitive-behavioral therapy or any other evidence-based therapy for PTSD within the past 3 months. What's more, subjects must have no intention of changing their medication or psychotherapy, or enrolling in another research study testing an experimental intervention, during the 2.5-month period of the intervention. However, if unforeseen changes in clinical condition occur during the study, we will not discourage subjects from withdrawing from the study to seek new treatments. Subjects with any primary psychiatric diagnosis of a current mood disorder, psychotic disorder, autism, mental retardation, or DSM-5 substance use disorder will be excluded from participation. Subjects with any history of psychosis or mania will also be excluded. While comorbid mood and anxiety disorders will be permitted if they are not the primary focus of clinical attention, active suicidality within the past year or a history of suicide attempt in the past 2 years will result in exclusion. As this study involves MRI, any subjects with contraindications to MR scanning (e.g., pregnancy, ferromagnetic metal in body, severe claustrophobia) will be unable to participate. Finally, any subjects with a history of unstable medical

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or neurological condition, or history of brain surgery, epilepsy, or other brain injury will be excluded from participation.

7. **Subject Classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

None of the populations listed below will be specifically recruited for enrollment.

☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

8. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion:

- Ages 18 and up
- Diagnosis of chronic PTSD, as established by the Clinician Administered PTSD Scale for DSM-V (CAPS-5) Ability to give signed, informed consent in English
- Normal or corrected-to-normal vision
- Participants who are on a stable dose of SSRI antidepressants for 2 months (3 months if they are on sertraline), or who have been un-medicated for at least 2 months, will be allowed to participate in this study
- At the time of recruitment, patients must have no intention of changing their medication or psychotherapy during the 2.5 month period of the intervention.
- Resarch group must be able to identify a trauma-related target region in or immediately adjacent to the amygdala

Exclusion:

- Any primary psychiatric diagnosis of a current major mood disorder, psychotic disorder, autism, mental retardation, or DSM-5 substance use disorder of mild or greater severity (2 or more symptoms) in the past 30 days. Comorbid mood and anxiety disorders will be permitted if they are not the primary focus of clinical attention.
- Any history of psychosis or mania
- Active suicidality within past year, or history of suicide attempt in past 2 years
- Any contraindication to MRI scanning (severe claustrophobia, ferromagnetic metal in body, etc.)
- Pregnancy
- Any unstable medical or neurological condition
- Any history of severe past drug dependence (i.e., a focus of clinical attention or a cause of substantial social or occupational difficulty)
- Any history of brain surgery, of penetrating, neurovascular, infectious, or other major brain injury, of epilepsy, or of other major neurological abnormality (including a history of

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traumatic brain injury [TBI] with loss of consciousness for more than 24 hours or posttraumatic amnesia for more than 7 days).
- Significant hearing loss or severe sensory impairment
- Any psychotropic medication other than a stable dose of SSRIs
- Any change in accepted psychotropic medication within the past 2 months
- Active engagement in cognitive-behavioral therapy or any evidence-based PTSD psychotherapy (CPT, PE, EMDR) initiated within the past 3 months (continuation of established maintenance supportive therapy will be permitted)
- Enrollment in another research study testing an experimental/clinical/behavioral intervention intended to affect symptoms initiated within the last 2 months, or intended enrollment within the next 2.5 months

9. How will eligibility be determined, and by whom?

Eligibility will first be determined during a brief phone screen carried out by research personnel, where potential subjects will answer questions about diagnosis, symptom, and medication history. Subjects will also answer questions regarding any contraindications for MR research. Individuals with obvious exclusion criteria will not be invited for an in-person assessment. Following the phone screen, subjects will attend an in-person assessment at the West Haven campus of the VA Connecticut Health Care System to determine eligibility and to collect demographic and personal history data relevant to the study. During this assessment, a clinical psychologist with experience with PTSD will evaluate the severity of the subject's symptoms of PTSD and other disorders via a structured clinical interview. This assessment may be conducted remotely via a virtual meeting with the study clinician, if an in-person assessment would present a hardship to the participant.

10. Risks: Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

The screening procedure is practically never associated with any risks. However, some of the questions participants will be asked to answer will be personal and may be upsetting.

Magnetic resonance (MR) is a technique that uses magnetism and radio waves – not x-rays – to acquire images of the brain. However, there are still some risks associated with this technique due to the size of the scanner or the strength of the magnetic field and radio waves. First, some people may feel uncomfortable or anxious during the scans due to the tight quarters of the scanner (especially if they have a history of claustrophobia) or due to other factors such as the noises that the scanner makes. There are also some very minor side effects that stem from exposure to magnetic fields and/or radio waves that can occur on rare occasions – some people might feel dizzy, get an upset stomach, have a metallic taste, or feel tingling sensations or muscle twitches during scans. However, these sensations are rare and usually go away quickly. Subjects will also be able to communicate with research staff about any issues that arise during the course of the scan. Because of its use of powerful magnetic fields, MR imaging carries more pressing risks for certain people. For example, individuals with pacemakers or other ferromagnetic metal objects inside their bodies might be harmed by the magnetic field. To avoid this risk, all subjects will be screened prior to participation for any MR contraindications – only individuals with no ferromagnetic metal in or on their person will be able to enter the room containing the magnet. Another risk inherent to MR research is the possibility of metal objects being pulled into the magnet and hitting research personnel or the subject. To prevent any accidents, no metal can be brought into the magnet room at any time.

APPROVED BY THE YALE UNIVERSITY IRB 12/7/2022

Due to the trauma-related stimuli presented to subjects in the scanner, there is a risk that their PTSD symptoms will flare-up. These stimuli include personalized scripts and sound effects that relate to the subjects' traumatic experiences (see section *I.4. Research Plan* for more detail on these audio clips), and are intended to provoke subjects' symptoms. While the subjects' goal is to learn to control these symptoms with the help of neurofeedback, exposure to upsetting audio clips will no doubt be a difficult and stressful experience. If subjects feel they are at risk of an intense reaction (such as a panic attack or psychotic episode), they are encouraged to let the investigators know immediately. During piloting of this study under a different protocol, a clinician was physically present during the scans involving symptom provocation. No adverse events occurred during these scans. As such, a clinician will be on-call at all times during the symptom provocation sessions rather than physically present. If subjects have a problem following the session, whereby they cannot stop thinking and feeling upset about the stimuli, they are encouraged to contact a collaborating researcher and clinician during normal work hours or the Biostudies on-call physician for emergency treatment after normal work hours.

11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.

During screening, participants can choose not to answer any questions and can choose to leave the study at any time without incurring any sort of penalty. If participants feel upset when asked about military trauma during the PTSD assessment (CAPS-5) or while making the trauma narratives, trained study staff will assist. A psychologist in the Mental Health Clinic will also be available to speak with the participant. The clinician can employ crisis intervention techniques, assist with healthy coping, and provide debriefing and clinical referrals, as necessary. During study debriefing, additional resources will be provided, such as the Veterans Crisis Line and information about the VA Connecticut PTSD Firm services. In the event that the assessment will indicate an acute emotional distress associated with suicidal thoughts, a psychiatrist or psychologist will be readily available to evaluate and talk to the participant. If imminent danger to self or other persists it may result in psychiatric hospitalization against the participant's will. If a subject experiences a significant worsening in their psychiatric symptoms during the course of the study but after the subject leaves the site, one of the study clinicians will be available to meet with them to address these issues. Subjects will be told that if they have an issue following the session, whereby they cannot stop thinking and feeling upset about the stimuli, or if they have any other research-related complaints, concerns, or questions, they will be encouraged to call Dr. Harpaz-Rotem [(203) 494-5454] during normal work hours. If it is after-hours and the subject is concerned that they may have a panic attack or a psychotic episode, they are to contact the Biostudies on-call physician for emergency treatment by calling the VACHS operator at (203) 932-5711, extension 0.

In terms of the MRI procedure, the United States Food and Drug Administration (FDA) guidelines for magnet strength and exposure to radio waves will be carefully observed during all scanning sessions. Subjects will be closely monitored during the scans and will be able to openly communicate with research staff whilst in the magnet. Subjects will be able to request to be removed from the scanner at any time during the session if they feel uncomfortable for any reason or decide to discontinue participation. All subjects will be thoroughly screened for any MR contraindication prior to participation by carefully filling out an MR Safety Questionnaire in the presence of research personnel and by passing through a metal detector. To minimize the risk of metal objects being pulled into the scanner, *all* individuals – not just participants – who enter into the room with the magnet will first ensure that they have no ferromagnetic material on their person. Once the subject is in the scanner, the door to the room containing the scanner will be closed and remain closed for the duration of the session. To protect the subject from the loud noises associated with running an MR scan, subjects will wear both earplugs and headphones (the latter also allowing subjects to communicate with

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the research personnel in the adjoining room, as mentioned above, and to hear the auditory stimuli during scans).

Although provocation of symptoms in PTSD engenders clinical risks, they are manageable. Exposure therapy, which involves extensive symptom provocation, is the first-line intervention recommended by the Institute of Medicine (IOM), DoD, and VA. In the context of NF, we have had no clinical issues arise in years of symptom provocation for our OCD study. Moreover, in our PTSD pilot studies, all 4 participants tolerated the intervention well. For these reasons, we expect participants to tolerate the intervention without adverse reactions. However, for the sake of caution, we will always closely monitor the patients' symptoms and a psychiatrist or clinical psychologist will be available to speak with them and intervene should symptom exacerbation occur. Namely, if subjects feel they are at risk of an intense reaction (such as a panic attack or psychotic episode), they are encouraged to let the investigators know immediately. As previously mentioned, during piloting of this study under a different protocol, a clinician was physically present during the scans involving symptom provocation. No adverse events occurred during these scans. As such, a clinician will be on-call at all times during the symptom provocation sessions rather than physically present. If subjects have a problem following the session, whereby they cannot stop thinking and feeling upset about the stimuli, or have any other research-related complaints, concerns, or questions, they are encouraged to contact the PI (Dr. Ilan Harpaz-Rotem -ilan.harpaz-rotem@yale.edu / (475) 434-2943) during normal work hours. If it is after-hours and subjects are concerned that they may have a panic attack or a psychotic episode, they are encouraged to contact the Biostudies on-call physician for emergency treatment by calling the VACHS operator at (203) 932-5711, extension 0.

12. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)

a. What is the investigator's assessment of the overall risk level for subjects participating in this study?

Moderate risk associated with symptom provocation for PTSD patients, other aspects of the study involve minimal risk.

b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?

N/A

c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates

Neurofeedback of amygdala activity for PTSD
Data and Safety Monitoring Plan (DSMP)
420 FR.1

Greater Than Minimal Risk DSMP

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1. Personnel responsible for the safety review and its frequency:

Dr. Ilan Harpaz-Rotem (the principal investigator), Dr. Michelle Hampson, and their research personnel (postdoctoral and postgraduate associates) will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at a minimum of every 6 months (including when re-approval of the protocol is sought). More specifically, Dr. Ilan Harpaz-Rotem will have primary responsibility for patient well-being during the protocol and for maintaining clinical data in a secure manner. Dr. Michelle Hampson will be responsible for maintaining confidentiality of the neuroimaging data in a secure manner and for ensuring safety during MR scanning. During the review process, the principal investigator, in consultation with Dr. Hampson, will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. In addition to the two primary investigators (Drs. Harpaz-Rotem and Hampson) and research personnel, an Independent Monitoring Committee has been established to ensure the proposed study's safety and efficacy. This committee consists of two experts in the field of PTSD: Professor Steven Southwick, M.D., and Robert Pietrzak, Ph.D. of VACT and Yale School of Medicine. Either of the primary investigators, the IRB, or the Independent Monitoring Committee have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed greater than minimal but less than high for the following reasons:

1. We do not view the risks associated with the exposure to trauma-related stimuli as minimal risks.
2. Although provocation of symptoms in PTSD engenders clinical risks, they are manageable. Exposure therapy, which involves extensive symptom provocation, is the first-line intervention recommended by the Institute of Medicine (IOM), DoD, and VA. In the context of neurofeedback, we have had no clinical issues arise in years of symptom provocation for our OCD study. Moreover, in our PTSD pilot studies, all 4 participants tolerated the intervention well. For these reasons, we expect participants to tolerate the intervention without adverse reactions. As such, given the now-established safety and validity of the current experimental treatment in our prior work, we do not view the proposed study as high risk.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

As previously mentioned, Dr. Harpaz-Rotem will have primary responsibility for patient well-being during the protocol and for maintaining clinical data in a secure manner. Dr. Hampson will be responsible for maintaining confidentiality of the neuroimaging data in a secure manner, and for ensuring safety during MR scanning. Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with the permission of the subject or as required by U.S. or State law. The personal information obtained from subjects will be de-identified at the earliest reasonable time after it is received. The principal investigators will keep a link that matches subjects to their coded information, and this link will be kept secure and available only to the PIs or selected members of the research team. The link to any personal information will be kept only 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. Personal information obtained from subjects during screening will be kept only on paper in a locked file cabinet. Any other data that is collected during the study (i.e., DICOM data) will be stored on a secure, encrypted server with a study number rather than any personal identifiers. The record associating patient names and study numbers will be kept confidentially in paper form in a locked file cabinet to be seen only by the researchers. Any transfer of data will occur in a HIPAA-compliant manner over a secure network, using encryption when necessary.

APPROVED BY THE YALE UNIVERSITY IRB 12/7/2022

At every clinical assessment, including brief ones, we collect the Beck Depression Index (BDI; Beck et al. 1961), which monitors suicidality, as well as information regarding adverse events and worsening of symptoms. These assessments are scheduled to occur at approximately half week intervals during the active part of the intervention and at month intervals during follow-up. If any issues arise, Dr. Harpaz-Rotem will be notified and will review the data. The guidelines of our IRB will be followed in the case of all adverse events. In the case of worsening symptoms or endorsement of suicidal ideation on the BDI (as indicated by a score of 2 or higher on question 9), Dr. Harpaz-Rotem will arrange an in-person assessment of the participant. As required by law, if needed, Dr. Harpaz-Rotem will admit the participant into Yale-New Haven hospital for further monitoring. In the case of difficult decisions, Dr. Harpaz-Rotem will consult the Independent Monitoring Committee.

As mentioned above, the Independent Monitering Committee consists of Drs. Southwick and Pietrzak. Every six months, the members of this committee will receive reports from the study team about the occurrence of adverse events, the progress of recruitment, the demographic characteristics of enrolled participants, the number of dropouts and participants' reasons for dropping out, as well as any protocol amendments. They will also be consulted if any difficult situations arise or if there are any serious and unanticipated adverse events that are possibly, probably, or definitely related to the study. These two committee members are extremely experienced in the assessment and the outpatient and inpatient management of all psychiatric emergencies, with particular expertise in PTSD and related disorders. They will be an ideal sounding-board and resource for the resolution of any challenging clinical situations that may arise during the conduct of this research. In the unlikely event that Dr. Harpaz-Rotem and the committee members have differing opinions as to the appropriate clinical choice for a particular patient, decisions made by the committee will be determinative, on the presumption that their external perspective will most appropriately weight the patients' well-being.

3. Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures/design by the principal investigators. As previously mentioned, Dr. Harpaz-Rotem will have primary responsibility for any adverse events of clinical significance or that involve overall patient well-being. Dr. Hampson will be responsible for any adverse events that occur during MR scanning. These events will be attributed to the study procedures/design according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s).
b.) Probable: Adverse event is likely related to investigational procedures(s).
c.) Possible: Adverse event may be related to investigational procedures(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s).

No possibly, probably or definitely related adverse events are expected for this intervention. We will query subjects at every clinical assessment for such events. If any occur, we will consult with the Independent Monitoring Committee who will have authority to terminate the study, remove patients from participation, etc.

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe adverse event

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5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:

In addition to grading the adverse event, the PIs will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PIs to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigators will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented. In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

APPROVED BY THE YALE UNIVERSITY IRB 12/7/2022

Adverse events will be reported to Yale University in a timely manner, according to the IRB guidelines. Any serious and possibly, probably, or definitely related events as will be reported within 48 hours of discovery to both the Yale IRB and the Independent Monitoring Committee. All adverse events (whether possibly related or not) will be summarized for NIH in the yearly renewal report.

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

X All Co-Investigators listed on the protocol.
□ Yale Cancer Center Data and Safety Monitoring Committee (DSMC)
X National Institutes of Health
□ Food and Drug Administration (Physician-Sponsored IND #_____)
□ Medical Research Foundation (Grant_____)
□ Study Sponsor
X Independent Monitoring Committee (as outlined above)

Every 6 months, Drs. Hampson and Harpaz-Rotem will conduct a review of all adverse events. After evaluating the frequency and severity of the adverse events, the PIs will determine if modifications to the protocol or consent form are required.

References

Beck, A. T., Ward, C.H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*, 561-571.

d. For multi-site studies for <u>which the Yale PI serves as the lead investigator</u>:

Not applicable (not a multi-site study)

13. <u>Statistical Considerations</u>: Describe the statistical analyses that support the study design.

This study will be divided into two phases: the R61 phase, which focuses on testing the mechanism of action of an intervention, and the R33 phase, which is contingent on the findings of the R61 phase and focuses on testing the associations between a change in the target, mechanisms of treatment response, and clinical outcome. The statistical analyses that support the study design are described below using the above two phases as organizing principles, including a section that covers offline neuroimaging data analysis that will be performed prior to analyses in both phases of the study.

A. Offline Neuroimaging Data Analyses:

i. *Preprocessing:* Data will be motion corrected using SPM (http://www.fil.ion.ucl.ac.uk/spm/) and all subsequent analyses will be done using Yale BioImage Suite software package.

APPROVED BY THE YALE UNIVERSITY IRB 12/7/2022

ii. *Registration:* The Montreal Neurological Institute (MNI) brain will be used as a reference coordinate system. Functional imaging data for all subjects will be transformed to the space of the MNI brain via a series of registrations (functional → anatomical → MPRAGE → MNI space) that have all been visually inspected.

iii. *Localizer analyses:* The localizer run (see section *I.4. Research Plan*) will be used to define the target region for NF. First, a whole brain "t-map" will be computed by calculating voxel-wise t-tests contrasting activity during the trauma script exposure period to activity in the resting periods, after adjusting for hemodynamic delay. This is not a true t-map due to autocorrelation, but is useful for identifying the voxels with peak activation in the amygdala. The 30 peak voxels (subject to a cluster filter of 4) falling in the amygdala will be defined as the target area.

iv. *Control task activation analyses:* Control over the amygdala target region will be computed by running voxel-wise regression analyses separately for the two categories of traumas – trained (traumas with which the subject engaged in NF) and untrained (traumas that the subject was not exposed to during NF). Four regression analyses will be run per subject – one per category from each of the two assessment sessions. Regressors will be defined for the task periods using boxcar functions convolved with a canonical hemodynamic response function. Three regressors will be used, corresponding to the provocation block, the down-regulate blocks of interest, and the 1-back periods (the lattermost being included to remove the effects of the 1-back periods and make contrasts relative to the rest blocks). Resulting maps of beta values for the regulate and provocation blocks will be transformed to a common space (see above section I.b.) and masked with the target region (also transformed to common space). Average value in the target region will be computed separately from beta maps for the provocation and down-regulate blocks to yield estimates of activation in the amygdala in each condition of each assessment session for the trained and untrained trauma memories. All analyses outlined in the following sections will use data from the regulation blocks of the untrained traumas unless otherwise noted.

v. *Resting state analyses:* In addition to the offline neuroimaging data analyses described above in section I., resting state data collected during each In-Magnet Assessment will be low-pass filtered (0.1 Hz), motion parameters, and the average time-courses of the ventricles and white matter will be regressed from the data. Seed maps of connectivity to the amygdala will then be computed. First, the time-courses of voxels in the target area will be averaged to yield a reference seed region time-course. This time-course will be correlated with the time-course of activity measured at every voxel in the brain to yield a whole-brain map of r-values. The r-values will be transformed to Gaussian variables via Fisher's transform. The resulting seed region connectivity maps for each In-Magnet Assessment of each subject will be entered into group-level analyses after transformation to common space (see above section ii.).

B. R61 Phase:

i. *To determine if NF increases control over amygdala more than sham feedback*: Activation in the target region of the amygdala in the down-regulate blocks (computed as described in above section A.iv.) will be compared across groups to see if mean activation is larger in the NF group than the sham feedback group, with an effect size of the group difference $d > 1$. If so, this will satisfy "Go" criteria and the study will proceed to the R61 phase. If not, the decision will be "No Go".

APPROVED BY THE YALE UNIVERSITY IRB 12/7/2022

C. R33 Phase:

i. *To determine if NF increases control over the amygdala significantly more than sham feedback:* Activation in the amygdala in the down-regulate blocks (computed as described in above section A.iv.) will be entered into a 2x2 ANOVA with factors time-point (2 levels: pre and post) and group (2 levels: NF and sham). If there is a significant interaction of group by time-point at a $p < 0.05$ level, a two-sample t-test will be used to see if the improvement in control was greater in the NF subjects than the sham subjects.

ii. *To determine if NF improves symptoms more than sham feedback and to correlate symptom changes with control over the amygdala:* A 2x2 ANOVA with factors group (2 levels: NF and sham) and time-point (2 levels: pre-intervention and first post-intervention) will be run on the past-month scores from the clinician-administered symptom checklist collected during the Full Clinical Assessment sessions. If there is a significant group-by-time-point interaction and post-hoc t-tests reveal a significantly greater improvement in symptoms in the NF group than the sham group, we will conclude the NF does improve clinical symptoms more than the sham. The change in score will also be correlated across NF subjects with the change in control over the brain area (computed as described above in section A.iv.). We hypothesize a decrease in score (indicating improvement in PTSD symptoms) will be correlated with an increase in control. A secondary analysis will be run using all 3 time points of scores collected (pre, 1 month post, and 2 month post intervention) to explore the long-term clinical effects. A linear mixed model analysis with group (NF or sham) by time-point (pre, 1 month post, and 2 month post intervention) will be used to capture the longitudinal effect of the clinical intervention. Finally, if the intervention does appear to reduce symptoms, we will explore whether these changes are greatest for scores on PTSD criterion B (intrusion) and criterion E (alteration in arousal reactivity) as these are expected to be most closely related to successful amygdala regulation.

iii. *To determine if NF changes resting connectivity to the amygdala and if these changes are correlated with symptom improvement and improved ability to regulate the amygdala:* After transforming the resting connectivity maps to the reference space (see above section A.v.), we will subtract the seed region connectivity map of the resting data collected pre-intervention from that collected in the post-intervention to yield a map of change in amygdala connectivity for each subject. Two-sample voxel-wise t-tests will be computed across subjects comparing these maps in the NF and sham groups. The resulting group difference map will be cluster corrected, using a non-parametric permutation test to identify those areas of the brain "rewired" by NF. For each locus surviving cluster correction, we will also examine whether the change in amygdala connectivity in this locus for each NF subject is correlated with their symptom improvement or their improvement in control over the amygdala.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

B. DEVICES ☒N/A

APPROVED BY THE YALE UNIVERSITY IRB 12/7/2022

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects…

   a. Targeted for enrollment at Yale for this protocol: 60
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: 60

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers	☒ Internet/web postings	☐ Radio
☒ Posters	☐ Mass email solicitation	☐ Telephone
☒ Letter	☒ Departmental/Center website	☐ Television
☐ Medical record review*	☒ Departmental/Center research boards	☒ Newspaper
☐ Departmental/Center newsletters	☒ Web-based clinical trial registries	☒ Clinicaltrails.gov
☒ YCCI Recruitment database	☒ Social Media (Twitter/Facebook):	
☒ Other: collaborating sites (Connecticut Mental Health Center, VA CT Healthcare system, Yale New Haven Hospital); bus ads; Trialfacts (a company that helps with study recruitment)		

All recruitment material, including that which is generated by Trialfacts, will be submitted to the IRB as an amendment upon creation. Only recruitment material that has passed IRB review will be disseminated.

* Requests for medical records should be made through JDAT as described at
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

We will recruit participants from four sources: (1) The CT Mental Health Center (CMHC) – the largest provider of mental health services in the community; (2) The VA CT Healthcare system, where mental health services are provided to those who were exposed to psychological trauma either in an urban war setting or at war overseas. We are currently recruiting veterans from the CT VA for two ongoing projects – more than 150 veterans have already participated in our studies and many have expressed interest in returning for additional studies; (3) Yale New Haven Hospital, which serves as a major trauma center for central Connecticut. The Hospital treats a large number of individuals exposed to urban trauma such as physical abuse and gunshots; (4) As a large number of individuals who are exposed to trauma do not seek mental health treatment, we will also recruit from the larger community. We will use flyers and brochures that will be put on bulletin boards in the New Haven area, bus advertisements, advertisements in the newspaper and through Craigslist.

Additionally, we will commission the services of Trialfacts (trialfacts.com) – a recruitment service for research studies, with whom a Business Associate Agreement (BAA) and a Professional Services and Consulting Agreement (PSCA) have been reached. Trialfacts will post online advertisements (which will be

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submitted to the IRB upon creation) that funnel potential subjects into an online pre-screening survey. Responses from subjects who pass this survey and are interested in further screening will be shared with the investigators via Yale Secure Box, after which point they will be contacted in the manner described below. This process has been reviewed and approved by Yale ITS. No subject data obtained as a result of their subsequent participation in this study will be shared with Trialfacts.

b. Describe how potential subjects are contacted.

Participants will first express their interest by contacting the phone number or email that are listed on the advertisement/recruiting material. The research team will then reach out to them to describe the study in more detail and determine whether they would be willing to be contacted for an initial 10 to 15-minute phone screen. If so, subjects will be asked to provide a phone number and a good time at which to contact them. The research team will then carry out a 10 to 15-minute phone screen that queries for treatment and diagnosis history, symptoms of PTSD or other mental disorders, and any MRI contraindications. If there are any obvious rule-outs, the patients will be informed that they are not eligible for participation and will be given information regarding other possible resources they may be interested in (e.g., if they are seeking treatment). All subjects who do not have obvious rule-outs will be contacted and scheduled for an in-person screening at the West Haven VA. From this point forward, subjects will follow the procedure outlined in section *I.4. Research Plan*.

c. Who is recruiting potential subjects?

(1) Research personnel at the CT Mental Health Center (CMHC), the VA CT Healthcare system, Yale New Haven Hospital; (2) flyers/brochures that will be put on bulletin boards in the New Haven area, bus advertisements as well as advertisements in the newspaper, on buses, and on Craigslist; (3) the recruitment company Trialfacts (online advertising).

4. Assessment of Current Health Provider Relationship for HIPAA Consideration: Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects
☒Yes, some of the subjects
☐No

If yes, describe the nature of this relationship.

It is possible that subjects recruited through the VA CT Healthcare system may have an existing clinical relationship with Dr. Ilan Harpaz-Rotem.

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study
☒ For recruitment/screening purposes only
☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

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i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:

Authorization will be obtained for the study itself. However, it would be impracticable to try to acquire this information during the brief initial phone screen. Verbal consent will be obtained from participants prior to recording PHI. If patients remain eligible following the phone screen, they will undergo a more formal authorization process before data collection.

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data:

Signed authorization will be obtained for all participants. Only the brief phone screening of potential participants will be conducted without signed authorization (see above).

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

During the initial phone screens, research personnel will give an overview of the nature of the screening questions and obtain verbal consent from the subject before beginning the collection of any sensitive information/PHI. Subjects will be informed that this information will be put into a database and that they will be able to request that this data is removed and destroyed at any point. All subjects enrolled in the study will read over and sign full consent forms prior to clinical assessments and scanning sessions, with a member of the research team present and available to answer any questions they may have. This will occur at the Connecticut VA, the CMHC, or the Magnetic Resonance Research Center. Subjects will be knowledgeable about the study at this time and understand its risks and benefits, having had the procedure described to them in detail on both the consent form and by a member of the research team. The only part of the procedure that will be actively withheld from the subject is their condition (experimental or sham). However, the subject will be informed that they are being randomized into one of the two conditions and that their condition will be revealed to them upon study completion or termination, at which time subjects in the sham condition will be offered a chance to engage in real NF.

7. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

Research personnel obtaining consent will make sure that the subject is well informed on the research process. This means that they will describe the study in detail in largely non-scientific, layman's terms, making sure that the subject understands the procedure, its risks, and its benefits. The research personnel will also

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answer any questions the subject may have, and offer an ongoing dialogue about the experiment and the subject's role therein. This will ensure that the subject is both informed and motivated to engage in research, and is able to understand their role in the process. If the subject is unable to understand the research or changes their mind after hearing about the procedure in more detail, they will be deemed unable or unwilling to give consent and will not participate further in the study.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

As per the eligibility criteria, subjects must be able to understand and follow directions in English. This is due to the highly instructional nature of neurofeedback. Subjects will be asked to develop strategies, follow detailed instructions, and adapt their regulation techniques over the course of the study – all of which require active communication between the subject and researchers. For this reason, subjects must be comfortable with English to be able to participate fully in this study. For those who are proficient in English but for whom English may not be a first language, research personnel will take extra care to ensure that such subjects understand the nature of the study and are able to communicate effectively in English, especially during the consenting process.

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐Not Requesting any consent waivers

☒Requesting a waiver of signed consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study (Note that an information sheet may be required.)

APPROVED BY THE YALE UNIVERSITY IRB 12/7/2022

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☒
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☒ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO☒
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☒

☐ Requesting a waiver of consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

For a full waiver of consent, please address all of the following: N/A

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☐ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☐
- Why would the research be impracticable to conduct without the waiver? *Write here*
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *Write here*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Protected health information collected from the subject will include clinical information acquired during the phone screen and in-person assessments (including diagnostic and treatment history, symptom information, etc.). Structural and functional brain data will also be collected and used for research. If they consent to the additional genetic testing, genetic data will also be collected.

2. How will the research data be collected, recorded and stored?

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with subject 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). The personal clinical information obtained from subjects during screening will be kept only on paper in a locked file cabinet – the one exception being information collected during phone screens which will be kept in a REDcap database accessed only on encrypted devices connected to secure servers. Any other data collected during the study (such as structural and functional brain data or genetic data) will be de-identified and will be stored with a study number rather than

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any personal identifiers. A record associating subject name and study number will be kept confidentially in paper form in a locked file cabinet to be seen only by members of the research team. The research team will only give this coded information to others to carry out aspects of the present study. The link to 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.

De-identified data will be shared with ClinicalTrials.gov and with the NIMH National Database for Clinical Trials (NDCT).

3. How will the digital data be stored? ☒CD ☒DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☒ Laptop Computer ☒Desktop Computer ☒Other – locked-in-place hard drives for backing up data on secure servers/encrypted laptops

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

As mentioned above, any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with subject permission or as required by U.S. or State law. The personal clinical information obtained from subjects during screening and collected during study visits will be stored either on paper in a locked file cabinet or in a REDCap database accessed only on encrypted devices connected to secure servers. Any other data collected during the study (such as structural and functional brain data) will not be stored with any personal identifiers, but rather with a study number. A record associating subject name and study number will be kept confidentially in paper form in a locked file cabinet to be seen only by members of the research team. The research team will only give this coded information to others to carry out aspects of the present study. The link to 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. All analyses involving personal subject information will be performed on encrypted devices connected to a secure network.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

   The link to personal information will be kept in a locked file cabinet until the study is complete and all data analyses have been conducted and published, after which time the link will be destroyed by members of the research team and the data will become anonymous. The data will be kept in this anonymous form indefinitely. All analyses involving personal subject information will be performed on encrypted devices connected to a secure network.

6. If appropriate, has a Certificate of Confidentiality been obtained? *Yes.*

SECTION V: POTENTIAL BENEFITS

APPROVED BY THE YALE UNIVERSITY IRB 12/7/2022

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

It is important to note that this study was not designed to benefit the subject directly. Rather, this study will allow us to explore the neurobiological mechanisms of PTSD. If we are successful in identifying a target mechanism of action that works in treating PTSD, this study could open the door to the development of other interventions and potential treatments for what can be a highly debilitating disorder.

This study also seeks to validate neurofeedback as a feasible intervention for PTSD. A growing body of literature points to the efficacy of NF across multiple disorders, and this study could help to expand on past knowledge of both NF as a technique and of PTSD as a disorder. NF is a cutting-edge intervention that can bridge the gap between patients and technology by actively putting a powerful tool (fMRI) in the hands of the individual. In other words, rather than acting as a diagnostic tool, MRI in the context of a NF-based treatment would be able to be implemented as a patient-driven treatment in its own right. Due to the engaging and empowering nature of NF, adherence to a NF-based treatment may be better than other interventions. NF may also prove to be an effective alternative for individuals who don't respond to interventions such as exposure therapy, as it is designed to engage an independent mechanism of clinical improvement: a strengthening of emotion regulation circuitry via feedback learning. Therefore, if this intervention proves effective, it has potential as a frontline treatment for PTSD.

While this study was not designed to directly benefit the subject, subjects may gain some control over their emotion regulation circuitry and may see improvement in their clinical symptoms. While this improvement is by no means guaranteed, it is hypothesized that individuals in the experimental group (who are receiving real NF) will, on average, receive some benefit from the intervention. Subjects in the sham feedback group are not expected to receive any benefits, but will be invited to engage in real NF upon completion of the study.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?

Subjects who are seeking treatment for their PTSD or other disorders will be referred to meet with the appropriate clinicians in a non-research environment, if they so choose. The research personnel will facilitate discussions with subjects and individuals who reach out about study regarding treatment options, ranging from psychoeducation, psychotherapy, to medication. Any subjects interested in research who are not eligible for the present study will be matched to other research studies if possible, and/or referred to other research groups if the subject so chooses.

2. Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

Subjects will be paid $80.00 per scan, $20.00 per strategy development session, $20.00 per hour for clinical assessments, and $50.00 per hour for the script collection sessions. Subjects will be paid the corresponding amount at the end of each visit, in cash. Subjects who complete assessments over the phone or Zoom will have the option to either receive compensation via Visa or Amazon gift card, or have the appropriate amount of money held for them to pick up either at the MR center or the West Haven VA. As

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payments are made at the end of each visit, subjects who are unable to complete the entire study will be paid in an amount proportional to their participation.

3, Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

Subjects are responsible for transportation to the appropriate facilities. This may incur costs due to gas, bus tickets, and the like. In special circumstances (e.g., subjects traveling from NYC), travel reimbursement may be offered.

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

a. Will medical treatment be available if research-related injury occurs?

Yes.

b. Where and from whom may treatment be obtained?

Participants may contact a clinician (contact information provided in new attachment with title "Contact Information for Neurofeedback of Amygdala Activity for PTSD" that we would like to give to patients at consent time). Patients will not be charged for phone consultation. If more care is needed, the clinician they have phoned will refer them to either the CMHC or the emergency room of the Yale-New Haven Hospital, or, for veterans enrolled through the VA, to a VA medical facility.

c. Are there any limits to the treatment being provided?

Only what is limited by the subject's ability to pay for the costs of care provided. For veterans enrolled through the VA, the following text in the VA protocol applies: "If you are injured as a direct result of your participation in this research study, VA will provide necessary medical treatment at no cost to you. Except in very limited circumstances, this medical treatment will be provided in a VA Medical facility. There are no plans to provide compensation for your disability or other losses occurring over the long term or if any injury becomes apparent after your participation in the study has ended. However, by agreeing to participate in this research study, you are not waiving or giving up any legal rights to seek compensation."

d. Who will pay for this treatment?

For veterans enrolled through the VA, costs will be covered by the VA (as described above). For other participants with PTSD, the subject and/or the subjects' insurance will p ay.

e. How will the medical treatment be accessed by subjects?

They will be referred by a study clinician (or via the crisis/acute service hotlines).

APPROVED BY THE YALE UNIVERSITY IRB 12/7/2022

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities?
Yes ☐ No ☒

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

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