Protocol Title:	Real-time fMRI and Neurofeedback of Brain Networks Mediating Trauma Memory Recall in PTSD

Principal Investigator:	Keith Bush, PhD
Department:	Brain Imaging Research Center; Department of Psychiatry
Address:	4301 W. Markham # 554
Telephone:	526-8347
FAX:	526-8199
E-mail:	KABush@uams.edu

Sub- Investigator:	Clint Kilts, Ph.D.
Department:	Brain Imaging Research Center; Department of Psychiatry
Address:	4301 W. Markham # 554
Telephone:	526-8163
FAX:	526-8199
E-mail:	CDKilts@uams.edu

Sub- Investigator:	Andy James, Ph.D.
Department:	Brain Imaging Research Center; Department of Psychiatry
Address:	4301 W. Markham # 554
Telephone:	526-8345
FAX:	526-8199
E-mail:	GAJames@uams.edu

Location(s) of Study:	Brain Imaging Research Center Department of Psychiatry University of Arkansas for Medical Sciences 4301 W. Markham # 554 Little Rock, AR 72205

Table of Contents

I. Abbreviations

AFNI	Analysis of Functional Images
BIRC	Brain Imaging Research Center
fMRI	Functional Magnetic Resonance Imaging
PFC	Prefrontal Cortex
PTSD	Posttraumatic Stress Disorder
SCR	Skin Conductance Response

II. Protocol Summary

State of the art treatments for posttraumatic stress disorder (PTSD) are only associated with success rates of ~60% (Foa, et al., 1999; Foa, Rothbaum, Riggs, & Murdock, 1991; Schnurr, et al., 2007). The goal of this project is to test a novel means of boosting efficacy of exposure-based therapy for PTSD.

III. Background and Rationale

PTSD is characterized by intense emotional distress upon exposure to trauma reminders and avoidance of people and places that can trigger the trauma memory. Neurocircuitry models of PTSD that seek to explain symptoms of heightened emotional reactivity, hypervigilance for threat, and avoidance (Patel, Spreng, Shin, & Girard, 2012; Rauch, Shin, & Phelps, 2006) suggest abnormal activity of neural regions involved in emotional reactivity (e.g., amygdala) and cognitive control of emotional responding (e.g., ventral medial prefrontal cortex, anterior cingulate cortex). While knowledge exists about neurobiological abnormalities associated with PTSD, these data are cross-sectional in nature and ignore individual differences in both neural encoding and subjective aspects of the trauma itself (e.g., whether it elicits fear vs guilt vs disgust). Additionally, the manner by which existing psychological treatments alter these neural mechanisms mediating core PTSD symptoms is unknown. This is problematic, given that state-of-the-art treatment for PTSD is only effective ~60% of the time (Foa et al., 1991; Schnurr et al., 2007).

Here, we propose to utilize a novel computational modeling approach combined with state-of-the-art fMRI-based neurofeedback(S. LaConte, Strother, Cherkassky, Anderson, & Hu, 2005; S. M. LaConte, 2011; S. M. LaConte, Peltier, & Hu, 2007) to directly identify and modulate the idiosyncratic neural network encoding the trauma memory. Successful pursuit of these aims would 1) provide scientific support for the hypothesis that a distributed network including the amygdala, hippocampus, mediap PFC, lateral PFC, and anterior insula mediates emotional responding upon trauma memory recall, and 2) provide proof-of-concept evidence that neurofeedback modulation of this network can boost existing therapy efficacy.

IV. Hypothesis or Research Question /Specific Aims

Overall research goals: The overall goals of this research plan are to:

1) Develop a computational model that identifies idiosyncratic neural networks mediating emotional responding upon trauma memory recall. *Hypothesis*: Co-activation between amygdala, hippocampus, mediap PFC, lateral PFC, and anterior insula mediates emotional responding upon trauma memory recall.
2) Demonstrate that real-time fMRI neurofeedback of the identified idiosyncratic brain network modulates the activity of the brain network, which in turn corresponds with expected changes in objective measures of emotional arousal. *Hypothesis*: Neurofeedback increases or decreases activity of the identified neural network, resulting in increases or decreases in emotional arousal, respectively.

V. Trial Design

Overview

There are two stages to this experimental protocol: Pilot Stage and Implementation Stage. In the pilot stage, we would recruit healthy adult women (n=10). In the implementation stage, we would recruit adult women with a history of physical or sexual assault or trauma (n=17). The pilot stage will be used to refine the methodology prior to enrolling the more vulnerable assault sample in the implementation stage. All procedures between the different stages would be conceptually identical.

Participants would have two visits to the BIRC. On day 1, participants would undergo a structured clinical interview to assess trauma history and mental health diagnoses. Participants would also complete assessments and a standardized form for generating idiosyncratic trauma/stress scripts. Participants would return on Day 2 in order to complete the MRI scan. The MRI scan will consist of a resting state scan and neurofeedback scans. The neurofeedback scans will consist of two phases: model building and neurofeedback phases. During the model building phase, participants would be presented their stress/trauma scripts in concurrent visual and oral formats during fMRI while undergoing simultaneous measurement of physiological arousal (SCR). A computational model would be fit to this initial data to identify the brain regions that correspond with heightened emotional arousal during the stress/trauma script. Participants would then be given three neurofeedback phases (3 minutes each), during which they are given feedback to decrease, increase, and decrease activity in this network. A more detailed description is included in the following section.

fMRI Procedures

Prior to the MRI scan, subjects may have a training session in the MRI simulator to help habituate and train them to the MRI environment and MRI tasks. During this training session, subjects will also be allowed to practice some of the computer tasks. Per the MRI Policies and Procedures, the decision of who will be acclimated in the MRI Simulator will be made by the Research Coordinators and PI on a case-by-case basis. The PI for the study will have final say in this decision.

Before the MRI scan, participants will be given an explanation of the study's procedures and screened with the MRI Safety Form for metal objects and claustrophobia. Participants will also be screened with the SAFESCAN® ferromagnetic detector according to MRI Policy and Procedures. The participant will then lie supine in the scanner. Participants will wear noise-cancelling headphones for communication and view visual stimuli through a mirror attached to the imaging head coil. Participants will undergo an anatomic scan in addition to functional scans to facilitate alignment of images.

Script generation. Numerous studies have used script-guided imagery to induce emotional states, including creation of stress scripts, neutral scripts, and trauma scripts to induce generic emotional distress or emotiona distress specific to trauma memory recall vs neutral scripts (Cisler, et al., 2014; Orr, et al., 1998; Orr, Pitman, Lasko, & Herz, 1993; Pitman, Orr, Forgue, de Jong, & Claiborn, 1987; Rauch, et al., 1996; Shalev, Orr, & Pitman, 1992, 1993; Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006; Sinha, Lacadie, Skudlarski, & Wexler, 2004). Here, we would use this standardized methodology to activate a stress memory (pilot stage participants only) or a trauma memory (implementation stage participants only)) during fMRI. During the Day 1 assessments, participants will be asked to write a short narrative (including about 500 words) describing a stressfull/traumatic event using standardized methodology. This narrative will be displayed both on screen and via audio recording through headphones during the MRI scan. The pilot stage participants would create a non-traumatic stress script based on selecting a recent real-life stressful experience, while the implementation stage participants would create a trauma script describing their primary traumatic event. These procedures are consistent with our previous IRB approved protocols (133973 and 202715).

Real-time fMRI and neurofeedback.

Modeling building phase. The first phase of the MRI acquisition would consist of a single 3 min presentation of the stress/trauma script followed by a 3 min presentation of the neutral script (with the order counterbalanced across participants). In between the stress/trauma script and neutral script, there would be an emotion rating period, during which the participants indicate on a 9 pt Likert scale their anxiety and vividness of the imagery. Skin conductance response (SCR) will be recorded using BIOPAC's psychophysiological monitoring equipment. A series of electrodes placed on the participant's skin will measure SCR and provide an objective measure of physiological arousal. A subsequent reinforcement learning algorithm, fitted Q learning, would be applied to these joint fMRI and SCR data to identify distributed patterns of co-activated brain regions that specifically encode high emotional arousal (i.e,. high SCR) to the stress/trauma memory. The resulting idiosyncratic brain map would inform the neurofeedback phase in the next three runs. This phase will take approximately 6 minutes.

Neurofeedback phase. In this phase, participants would undergo three additional 3 min presentations of the stressful/traumatic script; however, they would also concurrently be given neurofeedback to up- or down-modulate the identified brain network. In this neurofeedback phase, participants would be given visual feedback of the current state of their brain with

respect to the desired brain state (based on the computational model). In order to demonstrate a causal relationship between the brain state and emotional arousal, we would alternate between instructions to decrease the brain state (during which we expect to see decreased SCR), increase the brain state (during which we expect to see heightened SCR), and then decrease the brain state again. The sequence of manipulations would always be decrease – increase – decrease so that participants always end during a phase attempting to decrease emotional arousal. Also note that other experiments have used neurofeedback to modulate pain and both increase and decrease pain in order to demonstrate experimental control of pain through manipulation of the identified brain regions (deCharms, et al., 2005). This phase will take approximately 18 minutes.

The visual representation of the brain network will be presented using each participant's stress/trauma stress. The script will be typed and presented to the participant whil laying in the scanner. During Run 1 (initial acquisition), participants will be instructed to focus on the memory and any thoughts or feelings associated with it. During Runs 2, 3, and 4, participants will be instructed to either increase or decrease emotional arousal, based on instructions given to them. The script will increase or decrease in brightness as activation of the brain state increases or decreases. Participants learn to control activation of their brain state, and thus the brightness of the script, through trial and error on their own. Figure 2 provides an overview of the experimental design while participants undergo fMRI.

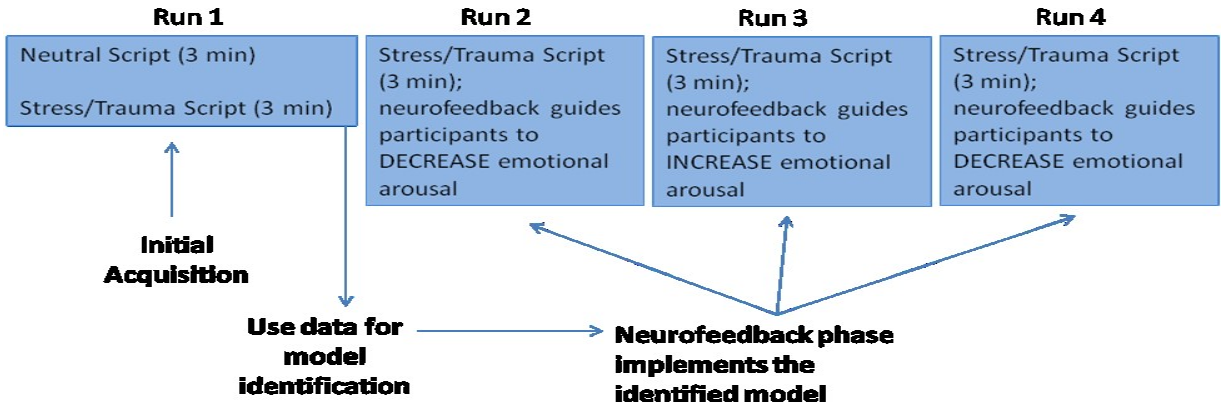

Figure 2. Diagram depicting Model-building and Neurofeedback Phases

Image acquisition is performed by a Philips Achieva 3T X-series MRI.

Assessments

Participants will complete several interviews and questionnaires to determine psychological and medical history, current life functioning, history of drug use, stress experiences, individual traits, family functioning, and demographic variables.

Structured Clinical Interview for DSM-IV: measures current psychological functioning and drug use history (First et al., 2002).

Data Collection Form: internal form used to collect study specific information such as handedness, age, race/ethnicity, medications, etc.

National Survey of Adolescent Trauma Assessment: assesses assaultive event exposure and other types of childhood adversity history and chronology (Kilpatrick, et al. 2000, Kilpatrick, et al. 2003).

Beck's Depression Inventory: measures the severity of current depression (Beck et al., 1961).

Childhood Trauma Questionnaire: measures histories of abuse and neglect during childhood (Bernstein, et al. 2003).

Difficulty in Emotion Regulation Scale: assesses multiple aspects of emotion dysregulation (Gratz & Roemer, 2004).

NEO Five-factor Inventory: measure of the Big Five personality traits (Goodwin and Friedman 2006).

Positive and Negative Affect Scale: measure of current (at this moment) affect (Watson et al., 1988).

Posttraumatic Stress Disorder Checklist- 5: assesses the 20 DSM-5 symptoms of PTSD (Weather et al., 2013).

Strategies to Increase and Decrease Emotions: provides information about various strategies participants may use to increase or decrease activation of brain states.

Stress Script Generating Forms: create narrative description of stressful/traumatic events (Pitman et al., 1987). This form is identical to forms used in previously approved projects (IRB#: 113160, 133973, and 202715).

VI. Study Population

Participant recruitment

We plan to enroll a total of 27 healthy adults (all women), aged 21-50, into this study: 10 healthy women for the pilot stage and 17 women with a history of physical or sexual assault for the implementation stage. Given known sex differences in brain reactivity to stress and in neural correlates of PTSD (Felmingham, et al., 2010; Seo, et al., 2011), we focus on only women to maximize statistical power. In order to achieve these enrollment goals, up to 110 adults could be recruited and screened for eligibility. The participants would be recruited from local advertisements and flyers in public places. Additionally, we may recruit participants from previous or ongoing IRB-approved BIRC studies, provided they have consented to be recontacted for other studies by the study team.

Inclusion criteria for the healthy pilot stage participants will be no current Axis I psychological diagnoses, between the ages of 21-50, English speaking (due to lack of validated measures for non-English speaking populations), and medically healthy. Participants endorsing any of the following conditions will be excluded from the study: 1) current serious medical condition, 2) any internal metal objects, 3) under the age of 21 or over the age of 50, and 4) any current psychological disorder or psychiatric medication including acute suicidality or major depression. Any subjects that are at high risk or unstable (e.g. self-cutting, comorbid addiction) will also be excluded from the study.

Inclusion criteria for the implementation stage participants will be a history of physical or sexual assault, between the ages of 21-50, and medically healthy. Participants endorsing any of the following conditions will be excluded from the study: 1) current serious medical condition, 2) any internal metal objects, 3) under the age of 21 or over the age of 50, and 4) a psychotic disorder or developmental disorder including acute suicidality or major depression. Any subjects that are at high risk or unstable (e.g. self-cutting, comorbid addiction) will also be excluded from the study.

Due to safety concerns, participants with these conditions will be ineligible to participate:

- Claustrophobia, or the inability to lie still in a confined space
- Major medical disorders (e.g., HIV, cancer)
- Magnetic metallic implants (such as screws, pins, shrapnel remnants, aneurysm clips, artificial heart valves, inner ear (cochlear) implants, artificial joints, and vascular stents), as these may heat, pull, or twist in the strong magnetic field of the MRI scanner
- Electronic or magnetic implants, such as pacemakers, as these may stop working
- Permanent makeup or tattoos with metallic dyes
- A positive pregnancy test (for females), since the effect of strong magnetic fields on the developing fetus remains unknown and inconclusive. (We will conduct a pregnancy test for all female participants of childbearing potential on the day of the MRI scan.)
- A self-reported history of loss of consciousness (greater than 10 minutes)
- Physical disabilities that prohibit task performance (such as blindness or deafness)
- Psychotic disorders (e.g., schizophrenia)
- Any other condition that the investigator believes might put the participant at risk

Due to their effects on image quality, participants with the following MAY be ineligible to participate per Principal Investigator's judgment:

- Medications which may affect image quality (e.g., water pills)
- Nonremovable dental implants, such as braces or upper permanent retainers, as these will distort the MRI images we collect (note: filings, crowns, and silver or gold teeth are OK)
- Any other condition, medication, or implant that the investigator believes would degrade image quality or render data unusable

VII. **Investigational Plan**

Participant screening, consenting and assessments

Participant assessment will occur in two parts. First, a phone screening will be conducted to ensure a high probability that participants are eligible for the study. This phone screening will assess self-report of whether the individual has a current mental health disorder, medical disorders, internal metal, claustrophobia, and transportation capability to UAMS. The phone-screening will be conducted by a trained research coordinator. If the participant meets probable inclusion criteria, the research coordinator will schedule the participant for part two of the assessment process.

Upon arrival to the BIRC for part two, the participant will first be given a written and verbal description of the study and informed consent. The PI or designated staff will discuss the informed consent form with the subject volunteer. The consent process will take place in a quiet and private room. Subjects may take as much time as needed to make a decision about their trial participation and may take the document home if desired. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and follow-up requirements of the study. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. No research related procedures will be performed prior to obtaining informed consent. All signatures and dates will be obtained. A copy of the signed consent will be given to the participant. The informed consent process will be documented in each subject's research record.

Following the obtainment of consent, part two will entail an in-person interview with a trained clinical research coordinator who will administer the BIRC Data Collection form, SCID, trauma assessment, questionnaires, and script generation forms. The research coordinator has a bachelor's level education in psychology and has received training in administering structured clinical interviews. A Clinical Research Nurse with over 20 years experience in structured clinical interviews will train the research coordinator on the SCID. The PI will supervise the research coordinator. Participants' trauma history will be assessed with an adapted version of the trauma assessment interview utilized in the National Women's Study (Resnick et al., 1993) and National Survey of Adolescents (Kilpatrick et al., 2000). Participants will additionally complete a battery of questionnaires, including the Posttraumatic Stress Disorder Checklist (PCL), Beck Depression Inventory (BDI), Childhood Trauma Questionnaire (CTQ), Positive and Negative Affect Scale (PANAS), and Difficulty in Emotion Regulation Scale (DERS). Mental health functioning will be assessed with the Structured Interview for DSM-IV Disorders (SCID-IV). This interview is expected to last approximately 3 hours. If the participant meets inclusion criteria for the study following the assessment, they will then be asked to complete the Stress/Trauma Script Generator Form . If the participant does not meet inclusion criteria following the assessment, they will not be allowed to be enrolled in the study, and they will be compensated and thanked for their time. For additional information on these forms, see Assessments section.

NOTE: Some participants from past BIRC studies or patients of the Women's Mental Health Program (WMHP) may have completed one or more of the clinical interviews used in the current project. If the participant has completed these interviews in the past, they may consent to use of these forms for the current project, provided the interviews were completed within the past year.

MRI

Upon arrival to the BIRC for the fMRI scanning session, the participant will be given instructions for what they will be asked to do in the scanner. Prior to the scan, participants will complete the Strategies to Increase and Decrease Emotions form. Following the training, the participant will be screened for internal metal and claustrophobia. The participant will also be screened using the SAFESCAN® ferromagnetic detector per MRI Protocol and Procedures. The fMRI data will be acquired on a 3T Achieva X-series head-dedicated MRI scanner (Philips Healthcare, USA). The lead MRI coordinator has had extensive experience with high field imaging systems. Training on the current system was given to the coordinator by a Philips education specialist. A similar training was given to the back-up coordinator as well. Each MRI session will start with a localizer and reference scan to optimize head placement. Experimental tasks will be programmed with commonly used software (Presentation), and the images will be projected onto a translucent screen via a projector situated in an adjacent room. Anatomic fMRI scans will be acquired on all subjects for image alignment purposes.

Assessing participant well-being: The PI will be present at each scan. A clinical psychologist with significant PTSD experience will assess the participant's emotional well-being in person immediately following the scan with a private and informal clinical interview. Referral information about treatment options and contact information will be provided to participants who need it. Additionally, a trained research coordinator will contact the participants approximately one week later by phone to assess well-being.Referral information about treatment options and contact will be given to participants who need it. This research coordinator will have access to the clinical psychologist for questions regarding participants' clinical status.

Compensation

Participants will be compensated for their time and participation. They will receive $25 for the interview and $25 for the fMRI scan. Participants will also receive $15 for travel to scheduled appointments. Travel will be only compensated one time at the completion of the first visit. Participants driving themselves to UAMS for the study will have their parking validated. Bus tokens may also be provided to participants utilizing the Central Arkansas Transit (CAT) system.

VIII. Adverse Events: Adverse Events Reporting and Evaluation

In adverse event reporting, all areas which mention the investigator refer to the PI and/or the PI's designee. All adverse events occurring during the course of the clinical study will be recorded on the Adverse Event Case Report Form. For all adverse events, the investigator must provide an assessment of the adverse event, its treatment and resolution, and its relationship to

the investigational drug or device. Special reporting procedures are required for certain adverse events.

Identification of Adverse Events

An adverse event is defined as any new medical problem, or exacerbation of an existing problem, experienced by a subject while enrolled in the study, whether or not it is considered device-related by the investigator.

Serious Adverse Events

Each adverse event will be assessed for its seriousness using the criteria outlined below. The term serious adverse event is not synonymous with a “severe” adverse event, which may be used to describe the intensity of an event experienced by the subject. An adverse event will be classified as serious if it meets any of the following criteria:

• Results in, or contributes to, a death
• Life-threatening (i.e., the subject was, in the opinion of the investigator, at risk of death at the time of the event, but it does not include an event that, had it occurred in a more severe form, might have caused death)
• Results in permanent disability or incapacity (i.e., permanent impairment of a body function or permanent damage to a body structure)
• Requires in-subject hospitalization or prolongs hospitalization
• Necessitates medical or surgical intervention to preclude a permanent disability or incapacity
• Results in a congenital anomaly or birth defect

Non-serious adverse events are all events that do not meet the criteria for a “serious” adverse event. If serious adverse event occurs, the investigator will promptly notify the reviewing IRB of such an event as soon as possible, but no later than ten (10) working days after first learning of the event.

Severity

Each adverse event will be assessed for its severity, or the intensity of an event experienced by the subject, using the following:

1. **Mild:** Discomfort noticed, but no disruption to daily activity.
2. **Moderate:** Discomfort sufficient to reduce or affect normal daily activity.
3. **Severe:** Inability to work or perform normal daily activity.

Deaths

The investigator will notify the sponsor and IRB as soon as possible, preferably within 24 hours but in no event later than 48 hours, of learning of subject’s death, regardless of whether the death is related or unrelated to the investigational drug and/or device. The investigator will attempt to determine, as conclusively as possible, whether the death is related to the device. The cause of death and the investigator’s discussion regarding whether or not the death was drug- or device-related will be described in a written report.

Pre-existing conditions

Pre-existing conditions will not be reported as an adverse event unless there has been a substantial increase in the severity or frequency of the problem which has not been attributed to natural history.

Annual Reporting to IRB (Continuing Review)

An annual report will be compiled and sent to the IRB to report on number of subjects enrolled in the study, safety events, and accrual schedule.

IX. Risks and Benefits

Potential risks

Internal metal during MRI scanning: One potential safety concern is participant internal metal during MRI scanning, which can be painful and dangerous.

Assessment of mental health and traumatic event exposure: One potential psychological risk of the proposed study is the possibility that some participants might experience distress or become offended when asked questions pertaining to victimization and mental health history. Many people assume that asking such questions produces substantial distress, particularly in research settings. However, the empirical literature suggests that this risk is minimal, and that individuals with traumatic event histories actually report obtaining positive benefits from their participation in studies where traumatic event history is assessed (Griffin, Resick, Waldrop, & Mechanic, 2003; Newman, Walker, & Gefland, 1999).

Assessment of suicidal ideation: During the clinical interview (SCID) in the depression module, questions regarding suicidal ideation are asked. This may elicit distress from participants; however, there is a specific protocol should a participant report suicidal ideation, intent, or plan, and a protocol to decrease distress, described below. Individuals meeting criteria for current major depression will be excluded from the study, further decreasing the likelihood of reported suicidal ideation.

Distress during the stress/trauma imagery task: Another potential risk is that the script-guided imagery procedure will elicit anxiety/distress, in addition to the MRI environment itself. Participants are able to quit the task at any time by indicating to the MRI coordinator(s) that they wish to do so.

Personal health information/Loss of confidentiality: With all research participation, there is a risk that personal information obtained from research participants will be mishandled, and confidentiality may be compromised.

Protections Against Risks

This study will be conducted according to good clinical practice (GCP) guidelines and with utmost concern for the participant's well-being. Appropriate safeguards will be used to minimize pain or discomfort associated with study participation and involve careful subject screening and monitoring. Procedures to minimize risks identified in the previous section are outlined below.

Internal metal during MRI scanning: The MRI Safety Screening Form will be used to screen for any internal or external ferromagnetic objects. If not removable, such objects would represent a basis for study exclusion. Participants will also be screened using the SAFESCAN® ferromagnetic detector to assure that they have no metal on or in their persons.

Assessment of traumatic event exposure: Participants will be instructed that they are free to refuse to respond to any items if they are not comfortable discussing them Additionally, the trauma assessment interview (NSA) is worded with dichotomous questions so that the participant only has to answer yes or no to a series of questions. Additionally, if in ascertaining a participant's current condition, the need for clinical intervention is determined, the appropriate mental health referral will be arranged.

Procedures for suicidal participants: Individuals who are actively suicidal, defined as intending to hurt or kill themselves in the acute time frame, will be referred to the UAMS ER. The treatment response may include hospitalization. These participants will be ineligible for further study participation.

Distress during the stress/trauma imagery task: First, any history of claustrophobia would be assessed with participants acclimated to the scanner environment using a MR simulator to assess and minimize anxiety. Participants will be instructed that they are free to withdraw from study participation at any time, with their refusal to continue having no effect on medical care associated with UAMS. Second, numerous past studies have used script-driven imagery procedure for generic stress induction or trauma-specific stress induction, and while the protocol is successful in inducing either generic or trauma-specific distress, the distress is temporary and no adverse events have been noted. Third, participants are instructed that they can stop the task at any time without negative consequence to them.

Personal health information/Loss of confidentiality: To protect the identity of research volunteers, contact information will be stored in a separate file and in a locked cabinet from experimental data forms. All experimental data will be de-identified using an alphanumeric study code rather than a name or other identifying information. All data collection forms will be stored in a password-protected cabinet behind a locked office. Computer data records will be stored in password-protected network drives. Data will be stripped of all identifiers, including the stripping of facial features from the anatomical MRI data. All participants will receive a Notice of Privacy Practices, outlining the procedures UAMS investigators use, when they sign informed consent and the HIPAA agreement.

Potential benefits of the proposed research to the subjects and others

There are no direct health benefits to participating subjects. However, the potential benefits of this research to society are major in terms of improving the ability to consolidate fear extinction learning memories.

Importance of the Knowledge to be Gained

The goal of this program of research is to better understand how the brain encodes emotional distress upon exposure to trauma reminders and provide proof-of-concept data that neurofeedback can modulate this network and potentially boost existing therapy efficacy.

X. Outcome Measures

Data will be collected from living human participants through clinical interview, self-report questionnaires, behavioral measures, and MRI scanning. Data for the project will be obtained specifically for research purposes.

XI. Data Handling and Recordkeeping

The PI will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and the integrity of the study. All study subject material will be assigned a unique identifying code or number. The key to the code will be kept in a locked file in the principal investigator's office. Only Drs. Clint Kilts, Andrew James and Keith Bush and the appropriate research coordinators will have access to the code and information that identifies the subject in this study.

XII. Statistical Plan

Power analysis

A sample size of 10 for the pilot stage will provide sufficient preliminary data and experience implementing this technology to proceed to the implementation stage. Assuming large effect sizes, a sample size of 17 during the implementation stage should provide power > .8 to detect the hypothesized within-subject effects (i.e,. changes in brain activity and emotional arousal between the decrease – increase – decrease neurofeedback phases.

Data analysis

Image processing will be performed in AFNI. Standard preprocessing steps (motion correction, slice timing correction, noise filtering) will be applied, and then analyses will test hypotheses.

We would use a data-driven, model-free, approach towards identifying idiosyncratic brain mechanisms mediating emotional arousal upon exposure to trauma cues. This would using the whole-brain (i.e., voxel-wise) feature space (~50,000 voxels) in the fitting the computational model. The fitted Q iteration algorithm (Reidmiller, 2005) would be fit to these data, such that the timeseries of activity for each voxel are used as input features with which to predict subsequent values of SCR. Cross-validation within- and across-particiapants would identify the

non-linear combination of the voxels whose timecourse of activity scales with the magnitude of the concurrent SCR response. In the neurofeedback phase, this fitted model would be computed on the observed brain states to provide feedback of the participant's current brain state with respect to the modeled target brain state. We would compare mean brain state activation and SCR response during neurofeedback phases using repeated measures GLMs for the within-subject manipulation of instruction (decrease – increase – decrease). Cluster level thresholding would be used to correct for multiple comparisons during the fMRI analyses, FDR would control for multiple comparisons during the SCR analyses.

XIII. **Dissemination of Data**

All data will be deidentified. Publication of results will only include group level statistics: data will not be reported separately for any individual.

XIV. **References**

Cisler, J. M., Steele, J. S., Lenow, J. K., Smitherman, S., Everett, B., Messias, E., et al. (2014). Functional reorganization of neural networks during repeated exposure to the traumatic memory in posttraumatic stress disorder: An exploratory fMRI study. *Journal of Psychiatric Research, 48*(1), 47-55.

deCharms, R. C., Maeda, F., Glover, G. H., Ludlow, D., Pauly, J. M., Soneji, D., et al. (2005). Control over brain activation and pain learned by using real-time functional MRI. *Proceedings of the National Academy of Sciences of the United States of America, 102*(51), 18626-18631.

Felmingham, K., Williams, L. M., Kemp, A. H., Liddell, B., Falconer, E., Peduto, A., et al. (2010). Neural responses to masked fear faces: sex differences and trauma exposure in posttraumatic stress disorder. *J Abnorm Psychol, 119*(1), 241-247.

Foa, E. B., Dancu, C. V., Hembree, E. A., Jaycox, L. H., Meadows, E. A., & Street, G. P. (1999). A comparison of exposure therapy, stress inoculation training, and their combination for reducing posttraumatic stress disorder in female assault victims. *J Consult Clin Psychol, 67*(2), 194-200.

Foa, E. B., Rothbaum, B. O., Riggs, D. S., & Murdock, T. B. (1991). Treatment of posttraumatic stress disorder in rape victims: a comparison between cognitive-behavioral procedures and counseling. *J Consult Clin Psychol, 59*(5), 715-723.

Goodwin, R. D. and H. S. Friedman (2006). "Health status and the five-factor personality traits in a nationally representative sample." Journal of Health Psychology 11(5): 643-654.

Griffin, M. G., Resick, P. A., Waldrop, A. E., & Mechanic, M. B. (2003). Participation in Trauma Research: Is There Evidence of Harm? *Journal of Traumatic Stess, 16*, 221-227.

LaConte, S., Strother, S., Cherkassky, V., Anderson, J., & Hu, X. (2005). Support vector machines for temporal classification of block design fMRI data. *Neuroimage, 26*(2), 317-329.

LaConte, S. M. (2011). Decoding fMRI brain states in real-time. *Neuroimage, 56*(2), 440-454.

LaConte, S. M., Peltier, S. J., & Hu, X. P. (2007). Real-time fMRI using brain-state classification. *Human Brain Mapping, 28*(10), 1033-1044.

Newman, E., Walker, E. A., & Gefland, A. (1999). Assessing the ethical costs and benefits of trauma-focused research. *General Hospital Psychiatry, 21*, 1-10.

Orr, S. P., Lasko, N. B., Metzger, L. J., Berry, N. J., Ahern, C. E., & Pitman, R. K. (1998). Psychophysiologic assessment of women with posttraumatic stress disorder resulting from childhood sexual abuse. *J Consult Clin Psychol, 66*(6), 906-913.

Orr, S. P., Pitman, R. K., Lasko, N. B., & Herz, L. R. (1993). Psychophysiological assessment of posttraumatic stress disorder imagery in World War II and Korean combat veterans. *J Abnorm Psychol, 102*(1), 152-159.

Patel, R., Spreng, R. N., Shin, L. M., & Girard, T. A. (2012). Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews, 36*(9), 2130-2142.

Pitman, R. K., Orr, S. P., Forgue, D. F., de Jong, J. B., & Claiborn, J. M. (1987). Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. *Arch Gen Psychiatry, 44*(11), 970-975.

Rauch, S. L., Shin, L. M., & Phelps, E. A. (2006). Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research--past, present, and future. *Biol Psychiatry, 60*(4), 376-382.

Rauch, S. L., van der Kolk, B. A., Fisler, R. E., Alpert, N. M., Orr, S. P., Savage, C. R., et al. (1996). A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Arch Gen Psychiatry, 53*(5), 380-387.

Reidmiller, M. (2005). *Neural Fitted Q Iteration - First Experiences with a Data Efficient Neural Reinforcement Learning Method.* Paper presented at the Proceedings of the European Conference on Machine Learning.

Schnurr, P. P., Friedman, M. J., Engel, C. C., Foa, E. B., Shea, M. T., Chow, B. K., et al. (2007). Cognitive behavioral therapy for posttraumatic stress disorder in women: a randomized controlled trial. *JAMA, 297*(8), 820-830.

Seo, D., Jia, Z., Lacadie, C. M., Tsou, K. A., Bergquist, K., & Sinha, R. (2011). Sex differences in neural responses to stress and alcohol context cues. *Human Brain Mapping, 32*(11), 1998-2013.

Shalev, A. Y., Orr, S. P., & Pitman, R. K. (1992). Psychophysiologic response during script-driven imagery as an outcome measure in posttraumatic stress disorder. *J Clin Psychiatry, 53*(9), 324-326.

Shalev, A. Y., Orr, S. P., & Pitman, R. K. (1993). Psychophysiologic assessment of traumatic imagery in Israeli civilian patients with posttraumatic stress disorder. *Am J Psychiatry, 150*(4), 620-624.

Sinha, R., Garcia, M., Paliwal, P., Kreek, M. J., & Rounsaville, B. J. (2006). Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. *Arch Gen Psychiatry, 63*(3), 324-331.

Sinha, R., Lacadie, C., Skudlarski, P., & Wexler, B. E. (2004). Neural circuits underlying emotional distress in humans. *Annals of the New York Academy of Sciences, 1032*, 254-257.

Weathers, F.W., Litz, B.T., Keane, T.M., Palmieri, P.A., Marx, B.P., & Schnurr, P.P. (2013). The PTSD Checklist for DSM-5 (PCL-5).