Neuroimaging Biomarker for Seizures

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BACKGROUND

Seizures in patients with epilepsy (ES) or with psychogenic nonepileptic seizures (PNES) are often severely disabling, difficult to treat, and are frequently encountered in neurology, psychiatry, and emergency departments. Epileptic seizures (ES) and PNES have the same appearance clinically, but have significantly different etiologies and treatments. Epilepsy is caused by abnormal brain cell discharges. PNES is a conversion disorder caused by trauma and stress and manifests neurologically with seizure-like episodes. Both types of seizures are common and disabling among Veterans and civilians. Up to 400,000 people in the U.S. have PNES. A quarter of the 80,000 Veterans with seizures have PNES. Many people with PNES are misdiagnosed with epilepsy and undergo invasive procedures and are prescribed anti-epileptic drugs (AEDs), which do not treat PNES.

Even though PNES have been described in the medical literature for millennia, effective treatments are limited. Based on a psychotherapy developed and studied for patients with epilepsy,[1] in our treatment trials,[2, 3] we have developed and validated an innovative treatment, cognitive behavioral therapy (CBT) for PNES, which showed a significant reduction in PNES. Thus, we now can apply CBT to both, epilepsy and PNES, and call it CBT for seizures (CBT-Sz). Despite advances in understanding of the characteristics of patients with seizures, the neuropathophysiology of patients with PNES is less well understood. Understanding brain neurophysiology using neuroimaging in patients with seizure disorders will provide treatment targets for PNES/ES. This study will examine patients with epilepsy (ES) following head injury [i.e., posttraumatic epilepsy (PTE)] and posttraumatic PNES and will compare them to patients with traumatic brain injury (TBI) who do not have seizures.

OBJECTIVES

We will investigate:
1. Differences in cerebral underpinnings of emotion and stress processing in PNES and PTE using well established fMRI probes.
2. Neuroimaging biomarker of PTE and PNES that predicts treatment outcome in order to inform effective non-pharmacologic treatments for seizures; and
3. Evidence for a positive treatment response to the intervention (CBT-Sz) that results in neuroplasticity – i.e., the symptom change instantiated by actual physiologic change in the brain.

STUDY DESIGN OVERVIEW

Our plan is to investigate the cerebral underpinnings of emotion and stress processing in 88 individuals with confirmed PNES and 88 individuals with confirmed PTE and 88 individuals with a history of TBI without seizures (PNES or PTE) matched for psychiatric comorbidities (TBI control subjects – CS). In addition to the between group comparisons (PNES vs. PTE vs. CS), we will examine the changes in brains' response to fMRI probes after receiving treatment (CBT-Sz), a non-pharmacologic therapeutic approach that is used for the treatment of difficult to control seizures in patients with PNES and PTE. All participants in the 3 groups will receive fMRI scans at approximately 13 week intervals. Including CS in the neuroimaging and symptom surveys portion will allow us to determine the stability of signals between and within the individuals and to control for the effects of psychological and psychiatric comorbidities.

SPECIFIC AIMS

Specific Aim 1: To compare neural correlates of response to fMRI stimuli before and after cognitive challenge (CBT-Sz). Individuals with PNES and PTE will be compared to individuals with a history of TBI who do not have PTE/PNES in order to control for common comorbidities including depression, anxiety and PTSD, and to show fMRI signal stability between and within the individuals.

Hypothesis 1: We hypothesize, based on our preliminary data, that baseline fMRI in all groups will show aberrant responses to stress and abnormal emotional processing between those with seizures vs. those without seizure disorders, with differences predominantly observed in the medial frontal cortices and amygdala with these differences being most abnormal in the PNES group.

Specific Aim 2: To investigate changes in neural circuitry for emotional processing in individuals with seizures after receiving CBT-Sz and to correlate these changes with symptomatic improvement.

Hypothesis 2: We hypothesize that CBT-Sz will lead to changes in the fMRI signals and in amygdala connectivity as shown with DTI and fMRI. This change will, in turn, be predicted by the magnitude of clinical responses defined by seizure frequency improvement over time and secondarily by targeted behavioral measures.

Protocol Title: Neuroimaging Biomarker for Seizures

1.0 Study Organization and Administration

Investigators:
Principal Investigator: William Curt LaFrance, Jr., MD, MPH, Providence RI;
Collaborating Investigator- Jerzy P. Szaflarski, MD, PhD, Birmingham AL

Study Site Descriptions:
This is a multi-site study. The following institutions are involved

Providence, Rhode Island:
Providence VA Medical Center (PVAMC)
Rhode Island Hospital (RIH)

Birmingham, Alabama:
University of Alabama at Birmingham (UAB)
Referrals to UAB will also come from Birmingham VA Medical Center (BVAMC)

Study personnel:
Study personnel will be responsible for recruiting, advertising, enrolling, obtaining informed consent, administering the protocol, assessments and surveys, maintaining the case report forms and data entry. The PIs and their designated staff will be responsible for quality assurance and total study oversite, as well as the adherence to the CBT-Sz sessions and imaging protocols. Study personnel will be trained in the study modalities and measures required for this protocol.

2.0 Introduction

Preliminary Studies

Cognitive Behavioral Therapy (CBT-Sz)
The PIs have extensive expertise in diagnosis and treatment of seizures, and both have studied and published extensively in the field. The preliminary data from the PIs' studies that are described below provide the necessary preparation for both, the intervention and the neuroimaging aspects of this study. Dr. LaFrance's work provides preliminary data for the efficacy of the intervention. Dr. Szaflarski's work provides the preliminary neuroimaging data. Both investigators have a long-standing history of collaboration including conducting the only randomized controlled trial of CBT for PNES.[2]

CBT-Sz is used for both ES and PNES, and is based on initial studies conducted in patients with epilepsy as described below. We have systematically examined the clinical trial methodology in PNES: first in an open label study of sertraline for PNES,[4] and then in a pilot placebo-controlled randomized controlled trial (RCT).[5] We also modified a psychotherapy initially used in epilepsy[6] for use in PNES or in epilepsy,[7] and we completed an open label non-pharmacologic intervention.[3] Next, we conducted a multi-center pilot RCT comparing CBT-Sz, sertraline, CBT-Sz and sertraline, and Standard Medical Care (SMC).[2]

To describe CBT-Sz developed for this study, we focus on two of our completed treatment trials that demonstrated a significant reduction in PNES and improvement in comorbidities.[2, 3] The treatment is an approach predicated on the observation that in patients with seizures, life experiences and trauma

result in maladaptive core beliefs (negative schemas) and they demonstrate cognitive distortions and somatic symptoms. The 12 weekly, 1-hour long, individual therapy sessions are specifically tailored for patients with PNES or epilepsy to address directly both the seizures and the comorbidities that commonly occur in seizure disorders and to promote behavioral change, self-control, and self-efficacy. This approach has the advantage of being validated and manualized, facilitating its use and evaluation in multicenter studies. CBT-Sz addresses connections between mood, cognition and the environment, as well as patients' automatic thoughts, catastrophic thinking, maladaptive schemas, and somatic misinterpretations.

Based on positive preliminary results, we conducted a multi-site randomized controlled trial (RCT), where 38 patients with video/EEG-confirmed, lone PNES were randomized to one of four treatment arms: Medication (sertraline) only, CBT-Sz only, CBT-Sz and Medication combined, or standard medical care (SMC).[2] The CBT-Sz arm showed >50% seizure reduction ($p<0.01$ with 33% of the participants seizure-free at study exit), improvement in functioning and in scores on symptoms scales. The combined treatment arm also showed improvements in seizures and functioning while the Medication arm showed a trend for seizure improvement. SMC showed no seizure reduction or improvement in any secondary outcomes. Similarly, the workbook-based therapeutic approach (CBT-E) showed reduction in patients with epileptic seizures.[6, 8, 9] Given that the intervention has been validated and manualized,[7] successfully disseminated to other sites, used in multi-center studies, and that it reduces seizures and comorbidities, this is the most logical next step to investigate its ability to induce cortical plasticity and a potential biomarker for treatment response.

Imaging

The past neuroimaging studies in PNES and ES have documented only a single time point in small groups of participants; none of them assessed neurophysiological or clinical changes over time or in response to a specific behavioral challenge (CBT-Sz).[10, 11] In PNES, it is widely accepted that structural imaging should be normal, which is not always the case.[12] While epidemiologic studies did not report specifically on imaging findings,[13, 14] other studies have found that up to 40% of patients with PNES have structural abnormalities on routine MRIs,[15-17] which is similar to patients with PTE related to mild or moderate TBI.[18, 19] Thus, while only a few studies performed such analyses, it is clear that imaging abnormalities are frequent in patients with PNES, and may have negative implications for outcomes[15] despite the fact that the lesions are not the direct cause of PNES.

Functional imaging in epilepsy and PNES

Pathological responses to stressors are the origin of Conversion Disorders (CDs), which are thought to be related to “repression of psychological conflict and its conversion into physical” symptoms.[20] Neuroimaging investigations of pathophysiologic mechanisms underlying CDs and PNES or epilepsy are scarce. In a motor CD study the authors explained the observed differences between patients with CD and comparable participants without CD as different utilization of emotion and stress neural circuits for processing stressful lifetime events.[21] Another study showed greater FC between right amygdala and right supplementary motor cortex indicating a possible mechanism underlying motor CD.[21] We recently compared emotion processing in patients with epilepsy and PNES without the preexisting TBI or without introducing an intervention (Szaflarski et al., HBM under review). We have shown that compared to ES, that patients with PNES exhibit increased fMRI response to happy and neutral emotions in cerebellar and fronto-temporo-parietal regions and to fear in bilateral inferior and middle temporal gyri and right middle occipital gyrus. Connectivity analyses comparing patients with PNES and ES identified substantial differences in functional connectivity to several brain regions, particularly to cerebellar, visual, and fronto-temporal regions. Resting state connectivity of the left and right amygdala to various brain regions including emotion regulation circuits was increased in patients with PNES when

compared to patients with ES. Additional analyses showed aberrant functional connections between left uncus and right hemispheric regions in PNES compared to both the ES and healthy control groups. In summary, we documented that patients with PNES exhibit altered emotion processing and increased amygdala functional connectivity compared to ES. These findings identified key differences in emotion processing reflective of potential neurophysiologic markers of neural circuitry alterations in PNES with their presence possibly underlying initiation and/or maintenance of PNES when compared to ES.

3.0 Study Procedures

3.1 Study Design

In this multi-site study, participants may be enrolled at PVAMC, RIH, and UAB. UAB will also receive referrals from BVAMC. This study aims to enroll 264 participants across the sites: 88 with PNES, 88 with PTE, and 88 with TBI without PNES or PTE. To meet recruitment goals, we will enroll both Veterans and civilians participants. Civilians will be seen at Rhode Island Hospital. All participants will be imaged at 2 time points and will complete self-reports, assessments and symptom measures as detailed in this protocol. The PNES and PTE participants will receive 12 sessions of CBT-Sz.

3.2 Recruitment Methods

Referrals to the study will come from the VA hospital systems for Veteran participants, and civilian participants will be referred from clinicians in the respective catchment areas. We plan to use multiple recruitment strategies to reach potential participants. In order for the findings to be applicable to Veterans and civilians with seizures, referrals from both cohorts will be accepted. All recruitment documents and language for recruitment documents will be reviewed and approved by each site's appropriate IRB prior to release. As required, outside press releases, advertisements and media postings, Facebook, Twitter and Craigslist.com will go through the appropriate site's Public Affairs Officer. We will also register the study on clinicaltrials.gov and will post study info the American Epilepsy Society (AES) studies list (https://www.aesnet.org/research/clinical_research/clinical_trials_site).

Physicians, rehabilitation, mental health, nursing and other professionals as appropriate at the associated site's VA's and hospitals, CBOCs and the Veteran Centers will be educated about this study. They will be asked to share information about this study with potential participants. If their patient is interested in hearing more about the study, the clinician will give them a copy of the IRB approved study brochure so the patient can contact the study staff directly. The clinician will also have the option to ask the potential participant if they would like their name to be shared with the study PI, so study staff can contact them. If the potential participant agrees for their name to be shared, the professional will document this in their record and provide the participant's contact information to the PI or his designated research staff through the study site's approved method (i.e. encrypted email, calling the research staff directly on their site associated phone extension, medical record referral process as available). After the referral names are received, the research staff will send the potential participant a letter. The letter will state which provider shared their name and the fact that they were interested in hearing more about the study. The letter will include information about when the research staff would be calling them.

We will also advertise using IRB approved language through brochures, fliers or PowerPoint advertisement posted throughout the sites, the CBOCs, Veteran Centers and in other community locations and events likely to be visited by Veterans and their families. We will issue

press-releases to the site's local news outlets and may submit to online posting sites, such as Craig's List, each site's Research Service website, and their Twitter and Facebook accounts

We may also advertise through Veteran Associated Newsletters and magazines and local newspapers as well as through staff wide email sent through the public relations or the director's office as locally approved and available. We will also use our medical record with a waiver for screening prior to enrollment to identify potential participants and send them an IRB approved letter telling them about the study and informing them of a date when research staff will call them to see if they are interested.

See the addendum for the study recruitment language, brochures, fliers and PowerPoint ads.

3.3 Informed Consent Procedures

Prior to conducting of any of the study procedures, eligible potential participants will be required to provide informed written consent. Potential participants that are deemed eligible on pre-screen and are interested in the study will be asked to come to the PVAMC main building or building 32 in a room as assigned for review of the consent form and HIPAA before any study procedures are performed. The PI or study staff will review the consent form with the potential participant and assure understanding of the study involvement. Participants will be given adequate time to review and comprehend all study activities, and ask questions prior to being asked if they agree to participate. If they agree, then they will sign the consent form. If needed participants may be asked to sign releases of information to gather additional clinical information from their health care providers for this study.

Participants will be told that they may refuse participation without any negative consequences, and if they decide to participate, they will be free to withdraw from the study at any time. They will be reminded that their decision to enroll in this study will not affect their relationship with their healthcare providers or the care they receive now or in the future at the PVAMC.

3.4 Inclusion/Exclusion Criteria

<u>Inclusion criteria for PNES, ES and TBI (w/o PNES or ES) participants</u>

- Individuals with history of documented TBI (any severity)
- Males and Females ages 18-60 years
- Women of child bearing potential, if currently using appropriate contraception

<u>Inclusion criteria of PNES and ES participants</u>

- Diagnosed by video/EEG with lone PNES or by EEG with lone ES
- Patients must have at least 1 PNES or 1 ES during the year prior to enrollment.

<u>Exclusion Criteria of PNES, ES and TBI (w/o PNES or ES) participants</u>

- Current or past year self-injurious behavior
- Current suicidal intent (BDI suicide question 9 score of >1)
- Current or past year psychosis
- Pending litigation or current application for long term disability

● Active substance or alcohol use disorders (dependence), at the discretion of the investigator if they preclude participation in the study
● Serious illness requiring systemic treatment or hospitalization; the participant either completes therapy or is clinically stable on therapy, for at least 30 days prior to study entry
● Inability to fill out the self-report surveys
● Women who are or/are attempting to become pregnant during the study
● Ineligible or unwilling to complete MRI imaging
● Inability to document TBI

Exclusion Criteria for PNES and ES participants

● Inability or unwillingness to participate in CBT and assigned homework
● Currently enrolled in cognitive therapy aimed at PNES (Current CBT or other psychotherapy may be administered)
● Concurrent mixed ES/PNES or equivocal video/EEG findings in discerning between ES and PNES will not be enrolled.

3.5 Diagnosis and Study Enrollment Procedures
The diagnosis of lone PNES or lone PTE, and TBI without PNES or PTE will be clinically established prior to study enrollment. All pre-screening, prior to consent, of potential participants will be done with an IRB-approved waiver or signed release of information.

3.6 Study intervention behavioral challenge (CBT-Sz)
CBT-Sz will be given to 176 participants (88 with PNES; 88 with ES) by a trained therapist in 12 individual weekly one-hour sessions (the first CBT-Sz session is called the Introduction session, followed by 11 more sessions). Study sessions will be administered according to the manualized protocol. Participants will have weekly homework to complete between the sessions that may take up to 1 hour to complete. Missed CBT-Sz sessions will be made up, if possible, during the same week of the scheduled appointment or by scheduling the session the following week. If that is not possible, the session is counted as a missed appointment of the 12 sessions. The CBT-Sz therapist will document the missed sessions and report them to the research coordinator. Clinical experience suggests that the more appointments attended by the participant, the more response to the intervention. Participants will continue CBT-Sz sessions regardless of the number of missed sessions.

Participants who are unable to attend the CBT-Sz office appointments due to transportation limitations can have sessions over the telephone. The feasibility and safety of the tele-CBT has been demonstrated in our CBT-PNES trial[3] and other CBT trials.[22-26] Initial sessions, if possible, will take place in-person to establish patient-therapist rapport, and to provide the patient with the treatment packet (forms, modules, mailing envelopes, etc.) that will be used, if needed, in any future telephone sessions. If not, materials will be provided to participants at the baseline or 1st MRI visit. Tele-CBT follows the format and duration of face-to-face sessions and can be completed by any trained IRB approved study therapist at either the Providence VAMC, Rhode Island Hospital, and University of Alabama, Birmingham. Therapy sessions will be digitally recorded to ensure therapy adherence and competence.

3.7 Study Evaluations

Clinical Evaluations: The Schedule of Evaluations in Table below includes all clinical study evaluations for the PTE and PNES participants. TBI participants will also complete the study

evaluations at baseline, endpoint, and Month 8 and 12. A mark in a cell indicates that a particular evaluation is to be performed at a particular study visit.

	Pre-Screening	**Entry**	**Baseline** After consent day 0 up to day 14	**Every week** (beginning Day 14 from consent). Introduction plus Session 1 through Session 11 (exit)	**Interval Assessments** Sessions- 6,("Midpoint") 10 ("Endpoint")	**Month 8 and 12**
Informed Consent		RS				
MRI Safety		RS			RS, prior to 2nd MRI	
EEG Report Diagnosis Validation	X	N*				
Neurological Exam	X	N*				
SCID-5-RV (Axis I)			RS			
SCID-5-PD (Axis II)			RS			
TLEQ (Trauma history)			P			
MRI			RS will coordinate		RS will coordinate At least 13 weeks after first MRI and within the 2 weeks after the last session	
Cognitive Bhvrl Th (CBT-Sz)				Psy		
Seizure Calendar Review (log)			For the month retrospective before consent	RS		
MoCA (v8.1 and v8.2)			RS or Psy		RS or Psy	
Adverse Events /Side Efx			P		P	
Med review			RS	RS		
Adherence Assessments				RS	RS	
CGI-S/I (Global impress.)			RS		RS	
GAF / OHS (Function/disability)			RS		RS	
LIFE-RIFT (Work/social function)			RS		RS	
BDI-II (Depression)			P	P	P	P
BAI (Anxiety)			P		P	P
PCL-5 (PTSD sxs, severity)			P		P	
FAD (family functioning)			P		P	
MFS (Modified Fear Survey)			P		P	
BIS-11 (Impulsivity)						
SCL-90 (Gen sxs severity)			P		P	

QOLIE-31 (quality of life)			P		P	
NSI (TBI symptoms)			P		P	
ESTXFU						RS

Legend - X –referring physician, N- Neurologist, P-Participant, RS- Research Staff, Psy-Psychiatrist or Psychologist.

Neurological Examination: which documents a complete history, medical and neurological examination based on NINDS Common Data Elements (CDE), will be documented from chart extraction.

***** If neurological examination was not performed within 36 months prior to enrollment into the study, it will be obtained by the study neurologist after consent is obtained. This routine exam will take about 30 minutes and will include mental health, medical, family, social and developmental history and will be assessed during the baseline period.

Symptom Surveys: Self-report questionnaires assessing psychiatric symptoms, family functioning and social functioning will be administered during baseline (within the 2 weeks after consent and validation of diagnosis) prior to the initiation of the CBT-Sz intervention, as well as at Session 6 (called "midpoint") and Session 10 (called "endpoint"). "Endpoint" surveys are collected at Session 10 rather than at the final session to maximize data collection. To monitor depressive signs and symptoms, the Beck Depression Inventory self-report will be given at each session. Seizure calendars will be reviewed at each session. The participant self-reports will take approximately 45 to 75 minutes to complete. The SCIDs can take up to 180 minutes. After the sessions end, the participants will have two follow-up interviews at months 8 and 12 from the first CBT-Sz session to assess functional status, symptoms and seizures. These follow-up assessments will take about 30 minutes.

Assessment of seizure frequency via seizure calendar: Participants will confirm they have had at least 1 seizure in the past year. Baseline seizures will be documented retrospectively for the 1 month prior to enrollment on the seizure calendar (referred to as "seizure log"); The participant will then fill out one seizure log per week, prospectively. Participants will be trained to complete the log so seizures are correctly and consistently logged. Participants can ask family members to assist in supplementing information for completion of calendars. The clinician will review the calendar with the participant to confirm documentation. Research staff will review the seizure calendar with the participant to assure it is complete and nothing has been left out, in order to validate the reported numbers.

Assessment of Comorbidities: Psychiatric and Symptom Assessments:
Interval assessments will be performed by Research Staff. Self-report scales will be completed by the participant. (Scales are included in the appendix)
The following will be administered:
●The Structured Clinical Interview for DSM-5 Axis I (SCID-5-RV) [27], and
●The Structured Interview for DSM-5 Personality (SCID-5-PD) [28]
●Beck Depression Inventory-II (BDI-II)
●Beck Anxiety Inventory (BAI)
●Posttraumatic Scale Checklist-5 (PCL-5),
●Modified Fear Survey (MFS),
●Barratt Impulsivity Scale (BIS-11)
●Traumatic Life Events Questionnaire (TLEQ)

The SCIDs and clinician rated symptom scales will be performed by a rater who has been trained and assessed for reliability by an expert in psychiatric diagnostic nosology. All scales administered have established reliability and validity.

Assessments of Quality of Life and functioning:
●Montreal Cognitive Assessment (MoCA): v8.1 at baseline and v8.2 at endpoint
●The Quality of Life in Epilepsy-31 Scale (QOLIE-31)
●Family Assessment Device (FAD)
●Longitudinal Interval Follow-Up Evaluation Range of Impaired Function (LIFE-RIFT)
●Symptoms Checklist–90 (SCL-90)
●Oxford Handicap Scale (OHS)
●Global Assessment of Function (GAF)
●Clinical Global Impressions Scale (CGI)
●Neurobehavioral Symptoms Inventory (NSI)

Follow-up assessment:
The PNES/ES follow-up questionnaire (ESTXFU) is used after the treatment portion of the study and will be used for secondary longitudinal analysis. There will be 2 follow up sessions (months 8 & 12 after the participant's first CBT-Sz session) the interviewer will ask participants questions regarding the seizure frequency and treatments using this questionnaire (ESTXFU). These sessions will be conducted by research staff either in person or via phone call.

Participants with TBI without PNES or PTE will complete/have:
●The consent process (giving written permission to take part in the study)
●MRI Safety screening
●Diagnosis validation
●Baseline and endpoint measures at the time of fMRI's (the same as Seizure participants)
●Two MRI brain scan approximately 13 weeks apart
● Follow-up at 8 and 12 months from the first fMRI with the TBI follow up survey (TBITXFU) (this assessment will ask about symptom frequency and treatments and will be conducted by research staff either in person or via phone call).

Allowable windows:
Research staff will aim for participants to meet the desired timeline, unexpected events occur in people's lives, therefore, for this study the researchers will allow for up to a 3 day window on either side of the desired timeline for completion of the study procedures and assessments before identifying them as a deviation. The CBT-Sz sessions may also be completed in up to 16 weeks.

Neuroimaging assessment:
After consent and eligibility has been completed. All participants will have a functional MRI at 2 time points, after consent within the 2 weeks before the start of the first CBT-Sz session, and at least 13 weeks after the first MRI (within 2 weeks after the last CBT-Sz session). The fMRIs take approximately 60 minutes. The functional MRIs will be conducted at either the Providence VA Medical Center Neuroimaging Suite or the Brown University MRI Research Facility (MRF).

These Functional MRI (fMRI) tasks were previously developed and tested in healthy controls and patients with epilepsy and PNES.[10, 29-31]

The fMRI emotional faces task: Participants will be presented a pseudo-randomized series of faces with different emotional expressions.[32] Unique facial images are displayed followed by a screen with a "+" in the center. In order to monitor attention to the task, participants will be asked to respond to the gender of the face using a response button held in their right hand. Immediately after fMRI, participants are asked to indicate the expression on each of the previously presented faces. Activations with this task are robust and the task allows for evaluating several types of emotions.[31] This task will occur at both fMRI's.

The fMRI stress task:

The fMRI task elicits mild-to-moderate level of stress similar to the level of stress experienced in everyday situations.

For both fMRIs, the stress tasks consists of a control math task (CMT) designed to be non-stressful and a stress math task (SMT) intended to induce a moderate amount of psychosocial stress. The SMT is based on the Trier Social Stress Task [33] and the Montreal Imaging Stress Task.[34] All participants perform the CMT followed by the SMT. All instructions (during practice and fMRI) are scripted to assure uniformity of the experimental conditions. CMT includes subtraction problems in which participants have to select the correct answer from two choices by pushing the corresponding button on the response box. Throughout the task, participants hear different pre-recorded messages that provide positive evaluative feedback regardless of actual performance. After completing the CMT and prior to SMT initiation, participants are told that "researchers" will be evaluating their performance and will give them feedback during the task, that for each question they have a variable time of 1-5 seconds to respond in order for their answer to count, and for their data to be used and to be reimbursed the full compensation of $100, they needed to achieve an unspecified number of correct answers based on the average score for people of their age and level of education (i.e., deception is used to induce mild-to- moderate stress response).[29] During the SMT, Participants perform more difficult subtraction problems than the CMT with three answers to choose from. Participants also hear different pre-recorded messages, all of which provide negative evaluative feedback regardless of actual performance (mild-to- moderate psychosocial stress). Both tasks also include instances of a tone condition where participants are instructed to press "1" or "2" on the response box while hearing a train of tones. The tone condition was designed to monitor attentiveness during the task regardless of actual performance. At the end of the imaging session each participant will be debriefed and informed that they earned the maximum amount of reimbursement irrespective of their performance.

This stress task target the emotion processing (limbic) circuits, including medial-frontal and medial- temporal regions.

MRI tasks scanning protocol

See appendix - MRI tasks and scanning protocol.
These tasks and instructions are currently in use at the UAB Imaging Center in studies that involve patients will be implemented at each study's imaging center.

Retention strategies

The retention/attrition-minimization strategies for this study will include weekly reminder contacts and utilizing tele-medicine visits when travel is restricted, which will be used as needed. Participants with

ongoing seizures cannot drive; therefore we will aim to a) assure that they have appropriate transportation or b) will conduct sessions via telephone.

Adherence and Competency (A&C): Treatment adherence and competency of intervention measures will be closely monitored by session review and digital-audio/video. To ensure that the therapists are conducting sessions in a highly competent fashion, rating scales designed to assess therapist competence and adherence will be utilized. Measures of therapist competence will be used to: a) verify therapist competence prior to treating study patients and b) to monitor sessions for quality assurance. The therapist competence in the sessions will be rated using the Clinical Management Scale of the Collaborative Study Psychotherapy Rating Scale (CSPRS) developed by the Collaborative Psychotherapy of Depression.[35] For CBT adherence, a modified Cognitive Therapy Scale (CTS)[36] that was designed and validated for CBT.

In addition to the above scales, each session will be rated as "acceptable" or "unacceptable." Ratings will be done by study staff reviewers at RIH. Potential problems or deviations will be noted by the reviewer for discussion with the therapist.

Risks/Benefits Assessment

Potential Risks to Participation

Assessment risks: Completing self-reports, questionnaires and the emotional processing MRI task could result in feelings of anxiety, depression, or psychological distress.

MRI risks: MRI imaging is generally considered to be safe but accidents, injuries, and even deaths have occurred during MRI procedures in the past. These events are extremely rare if all safety precautions are followed. Serious injuries can also occur if participants wear metal objects, like jewelry, eyeglasses, metallic cards, or clothing or eyeshadow with metal; these must be removed before the MRI process. If participants have metal pacemakers, metallic dust in the eyes (from metal eye injuries or history of metal work), or other metal implants that make them ineligible for MRI procedures, they will not participate in the study due to safety reasons. All childbearing age female participants will be required to be using birth control until completing the second MRI and to undergo a pregnancy test prior to each MRI, and those who test positive prior to their first MRI will not be allowed to participate in the study due to safety reasons. Research staff and the MRI technician will ensure that all proper screening is completed before deciding MRI eligibility and safety. All safety procedures will be carefully monitored according to standard MRI procedures and local MRI policy.

Treatment risks: A risk of participating in this study is that the treatment may not be as helpful as hoped. It is unlikely, but some parts of the treatment may lead to increased symptoms and possible need for hospitalization. Discussing distressing situations during the sessions may also temporarily increase symptoms.

Loss of privacy: Another possible risk is loss of privacy. Every effort will be taken to protect the confidentiality of participation in this study.

Safety Monitoring Plan

The Principal Investigator will have primary responsibility for day-to-day monitoring of participant safety, and the quality of operations in all data collection, data cleaning and transfer activities.

All adverse events (AEs) occurring during the course of the study will be collected, documented, and reported to the PI. The study investigators will follow all AEs to the point of a satisfactory resolution. A study participant may be withdrawn from the study if the medically responsible investigator determines it is the best decision in order to protect the safety of a participant. All AEs will be assessed to determine if they meet criteria for a Serious Adverse Event (SAE). SAEs will be reported to each IRB according to their policy. In the event that a participant either withdraws from the study or the investigator decides to discontinue their participation due to a SAE, the participant will have appropriate follow-up medical monitoring. Monitoring will continue until the problem has resolved or stabilized with no further change expected, or it is deemed to be clearly unrelated to participation in the study.

If during the study participants are found to develop suicidal intent, medical or other mental health problems they will be triaged for appropriate care, according to good clinical practice and the safety protocol.

This multi-site study includes a Data Monitoring Committee (DMC). See Addendum F for the DMC plan.

Risk management and emergency response:
The study's safety and seizure protocol is attached in the Appendix.

Potential benefits
Individuals who receive CBT-Sz may receive the benefit of reduction of seizures and or increased quality of life. There is no other direct benefit to participants. Participants may contribute to the scientific understanding of the effects of CBT-Sz on the brain which may lead to more understanding about the brain in individuals with seizures and for researchers to learn the best non-drug treatment for seizures which may help other individuals with seizures.

Participant Compensation
Compensation will be according to each site's acceptable local policy, i.e. gift cards or (ETF) electronic transfer of funds, etc. Compensation will be based on study visit time and effort and to help with transportation/parking costs. PNES and ES participants will receive up to a total of $800 for study involvement. Compensation will be $100 per fMRI (for scan and testing/tasks at the fMRI session) which will be given after the completion of the fMRI and up to $600 at the last CBT-Sz session ($50 for completion of each of the 12 sessions).

The TBI controls will receive up to $200 for their time and effort. They will receive $100 for each fMRI session (for scan and testing/tasks at the fMRI session) which will be given after the completion of the fMRI.

4.0 Data Analysis
Each site will administer, score, code and enter the data. Evaluators will be trained in the administration of the scales and cross-site interrater reliability will be established in the startup phase. Staff will enter identifiable behavioral, demographic, and other non-neuroimaging data in the secure site REDCap hosted at RIH through participant permission (HIPAA).Neuroimaging data will be transferred to a secure site hosted at UAB (behind firewall) via secure uplink and/or by secure shipment of the imaging disc that will include the participant's study code and date of the fMRI.

4.1 Power analysis
Our power analysis is based on our preliminary neuroimaging and clinical data, and data regarding number needed to be evaluated in neuroimaging studies to reliably demonstrate differences between

groups in cognitive studies.[2, 37] Based on our preliminary data for the fMRI stress task (Szaflarski, unpublished), given the large effect size (Cohen's d) of 0.88, when the sample size is 14 people per group, a *t*-test of two related samples with 5% two-sided significance will have about 85% power to reject the null hypothesis that there is no difference in pre-intervention and post-intervention fMRI measures in limbic structures (medial frontal cortices and amygdala). In a recently analyzed study of the emotional faces fMRI task, 12 participants per group were sufficient to show significant differences between participants with PNES, ES and controls in emotion control brain circuits. (Szaflarski, et al, HMB, under review) It is possible that the effect size may not be as large in ES as it is expected in PNES. For this study, we expect 25 participants per group to be sufficient to account for the possibility of a more conservative effect size (e.g., 0.65). With the expected 50% responder rate to the cognitive challenge (CBT-Sz), 50 per each group (PNES, PTE, controls) will allow to test the within groups and between groups differences. Adding additional 24 participants per group will allow controlling for two most frequent comorbidities in our patients (12/condition; depression / anxiety and PTSD; 50+24=74). With anticipated attrition rate of up to 20% (74*0.2 = 14 to 15 per group) a sample of 88 Veterans with PNES, 88 Veterans with PTE, and 88 Veterans with TBI but no PNES/PTE can address the study hypotheses and control for the confounders including comorbidities.

Imaging data analyses

We will employ a multilevel approach to data analysis (1) image analysis (post-processing), (2) statistical hypothesis testing and modeling using summary imaging measures and clinical variables (these two analyses will use a summary parameterization of the fMRI and DTI data, which are the presence or absence of activation within the prescribed regions of interest (ROIs) defined for each modality (e.g., amygdala or medial prefrontal cortex for fMRI data) or integrity of white matter tracts connecting amygdala and medial frontal regions (e.g., number of white matter fibers or FA values) which will be based on the composite MRI data, and (3) image analysis that allows for modeling changes over time while considering the effect of covariates in hierarchical linear modelling (HLM). Our analyses will be corrected for multiple comparisons at a $p<0.05$ level to limit the possibility of false positives while maintaining sufficient power to detect effects of interest.

4.2 Quality Control and Data Management:

The accuracy and reliability of MRI data from each site are paramount to the success of this study. Quality control and quality assurance (QA) are essential in this process. A periodic QA review process will occur quarterly with the study QA staff and the research staff.

4.3 Withdrawal of Participants

Protocols are established to address and contain any high risk aspects of the proposed works, including increase in seizures or depressive symptoms. If during the study participants are found to develop medical or mental health problems, they will be referred for appropriate treatment, as indicated in the safety protocol. If clinically indicated, he/she will be withdrawn from the study. If a participant develops nonepileptic psychogenic status (NEPS) or status epilepticus, the participant will be referred to the local emergency department for observation, and if clinically indicated, will be withdrawn from the study.

Participants who decide that they do not want to start or finish the CBT-Sz sessions will be asked to continue completing self-reports and assessments and the second fMRI, in order to compare completers with any non-completers.

5.0 Reporting

The Principal Investigators will have primary responsibility for day-to-day monitoring of participant safety, and the quality of operations in all data collection, data cleaning and transfer activities. The research protocol will be approved by the following appropriate Institutional Review Boards: Providence VA Medical Center, UAB, RIH, and USAMRMC ORP Human Research Protections Office before any data collection begins. All Adverse Events (AEs) will be assessed continuously and reported to the local PIs immediately. The PVAMC study team will also be notified of all AEs that take place at each participating study sites. Adverse Events and unanticipated events will be submitted to each participating IRB according to local policy.

Special reporting guidelines for USAMRMC Funded Research:

The following study events will be promptly reported to the HRPO by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) or mail to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

(1) All unanticipated problems involving risk to participants or others.
(2) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies.
(3) Any instances of serious or continuing noncompliance with the federal regulations or IRB requirements.
(4) The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this clinical investigation or research.
(5) The issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any government regulatory agencies.

6.0 Privacy and Confidentiality

Participants will be asked to sign a HIPAA giving permission for their individually identifiable personal health information to be shared with the other sites in this study. PHI will only be shared after any required Data Transfer Agreements (DTAs) are in place and the participant signs the Authorization for Use and Release of Individually Identifiable Information Collected for Research (HIPAA).

The consent form for this study details the specifics of what personal health information will be shared and/or transferred outside the PVAMC and how long it will be stored at the other sites, as follows:

●Video/audio- will include participant's face, voice, study code and date of the recorded session.
●fMRI-will include participant's study code and date of the fMRI
●RIH study data base REDCap- identifiable information will be entered into the RIH's REDCap web based database which will include demographics, and study data. RIH's REDCap will store participant demographics separately from the study data.
●MRI Safety Screen: will include the participant's study code and date of screening. This form will be reviewed by the Brown MRI technicians if the MRI occurs at the Brown MRF and will not be maintained there, but will be returned to PVAMC.

●Federal Interagency Traumatic Brain Injury Research (FITBIR) repository: Participant's name will not be used; data will be identified by a study code. RIH research staff will be responsible for transferring the research data into the FITBIR repository

Participant's MRI data will be transferred through a secure method and shared with study researchers at the University of Alabama at Birmingham for analysis; these researchers will keep a copy of the

MRIs for 7 years after the study is completed and closed. Study data entered into the Rhode Island Hospital research database (RIH REDCap) will kept for 7 years after the study is completed and closed. The audio/video recordings of the study therapy sessions will be shared through a secure method with the study research staff at Rhode Island Hospital for expert review so it can be assured that participants are receiving therapy according to the study. Rhode Island Hospital researchers will keep a copy of these recordings for 7 years after the study is completed and closed.

See this protocol's Information Privacy and Security Addendum for more specific details.

7.0 Communication Plan

All local site IRB and R&D (as needed) approvals will be obtained prior to initiating this research study. All engaged sites will receive notification(s) when there are changes to the study protocol. All unanticipated events will be reported as per protocol. No research will be conducted at any facility that is not engaged. Study staff will receive training, through online and/or in-person training sessions prior to engaging in study activities to ensure that the research is conducted according to IRB-approved protocol. A minimum of monthly telephone meetings will be held with key study staff during the data collection phase. The site PIs and site RAs will meet on a bi-weekly teleconference to review enrollment and study administration.

8.0 References

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9.0 Abbreviations

VA -Veterans Administration
PI -Principal Investigator
C-PI - Collaborating PI
TBI- Traumatic Brain Injury
PTE - Post-Traumatic Epilepsy
PNES -Psychogenic nonepileptic seizures
ES -Epileptic seizures
CD - Conversion disorder
CS - Control Subjects
PTSD -Post traumatic stress disorder
CBT - Cognitive Behavioral Therapy
CBT-Sz - Cognitive Behavioral Therapy for Seizures
CBT-E - Cognitive Behavioral Therapy for Epilepsy
CBT-PNES - Cognitive Behavioral Therapy for Psychogenic Nonepileptic Seizures
CTS - Cognitive Therapy Scale
AED -Antiepileptic Drug
DTI -Diffusion Tensor Imaging
fMRI- Functional Magnetic Resonance Imaging
QOL - Quality of life
RCT -Randomized controlled trial
SMC - Standard Medical Care
BDI -Beck Depression Inventory
SCID -structured clinical interview for diagnosis
TLEQ - Traumatic Life Experience Questionnaire
CGI - Clinical Global Impression
S/I - Severity/Improvement
GAF - Global Assessment of Functioning
OHS -Oxford Handicap Scale
LIFE-RIFT -Longitudinal Interval Follow up Range of lmpaired Function Test
BAI -Beck Anxiety Inventory
FAD -Family Assessment Device
MFS -Modified Fear Survey
BIS -Barret Impulsivity Scale
SCL - Symptoms Check List
SAE - Serious adverse event
QOLIE - Quality of Life in Epilepsy
ESTXFU -Epilepsy treatment follow up survey
TBITXFU -TBI follow up survey
EMU -Epilepsy Monitoring Unit
NEPS -nonepileptic psychogenic status
EEG -Electroencephalogram
vEEG -Video Electroencephalogram
QA- Quality Assurance
CMT - Control Math Task
SMT - Stress Math Task
CPT-END -continuous performance task with emotional and neutral distracters
DoD -Department of Defense
NINDS -National Institute of Neurological Disorders and Stroke

CDE -Common Data Elements
RIH -Rhode Island Hospital
PVAMC -Providence Veterans Affairs Medical Center
UAB -University of Alabama at Birmingham
BVAMC -Birmingham Veterans Affairs Medical Center
USAMRMC ORP – US Army Medical Research Acquisition Activity
HRPO – Human Research Protection Office