AWARD NUMBER: W81XWH-17-1-0336

TITLE: The Imprint of Psychogenic Non-Epileptic Seizures on the Brain: A New Model and Imaging Biomarker

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REPORT DATE: October 2018

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2018	Annual	30 Sept 2017 – 29 Sept 2018

4. TITLE AND SUBTITLE

The Imprint of Psychogenic Nonepileptic Seizures on the Brain: A New Model and Imaging Biomarker

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-17-1-0336

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The goal of the project is to obtain evidence that supports a new mechanism that assumes that PNES are caused by a predisposition for enhanced synchronization/overshooting recruitment of brain regions involved in emotion control/processing of traumatic/stressful experiences. By assuming such a predisposition, the project implicitly assumes that PNES have a specific biological underpinning. The first year of the project was spent on finalizing questionnaires and report forms , obtaining IRB approval from all participating institutions, development and implementation of MR imaging protocol and image processing pipelines, hiring and training research personnel. The project got permission to enroll participants in 05/18. Since then 28 potential PNES patients have been screened and 1 PNES has been enrolled and has completed the assessments.

15. SUBJECT TERMS

Psychogenic non-epileptic seizure, fMRI, overshooting, brain imprint, emotion, PTSD, trauma, stress

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	16	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and*

Psychogenic non-epileptic seizures (PNES) are defined by the occurrence of seizure-like episodes that interfere with normal functioning but lack the characteristic ictal EEG manifestations of epileptic seizures. The overall goal of this application is to confirm a new PNES mechanism by identifying its characteristic signature in task-free fMRI data of PNES patients and demonstrating a relationship between PNES severity and the expression of this signature. The new mechanism assumes that PNES is associated with a predisposition for an overshooting recruitment. Overshooting recruitment describes a state that is characterized by an enhanced synchronization between brain regions normally involved in emotion control and by the additional recruitment of regions involved in abnormal emotion processing. Repeated or prolonged stress or traumatic experiences further reinforces this predisposition which renders the brain more susceptible for overshooting recruitment and leaves a characteristic imprint that is detectable in the individual's task-free fMRI even in the absence of stress. On the behavioral level, overshooting allows for aspects of pathological emotion processing, e.g. anxiety, to become apparent during mild stress and facilitates overshooting reactions severe enough to recruit the additional brain regions required to generate the individual's typical PNES, in moderate to high stress situations. The project is designed as a cross-sectional study and will enroll 40 PNES patients and 20 controls. All will undergo fMRI on a 3T magnet and a standardized assessment regarding PNES risk factors and psychiatric co-morbidities that will be used to calculate co-morbidity scores. A dynamic fMRI analysis approach will be used to capture the "overshooting signature" and to relate it to the severity of psychiatric comorbidity, seizure frequency and semiology at the group and individual level.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Psychogenic non-epileptic seizure, fMRI, overshooting, brain imprint, emotion, PTSD, trauma, stress.

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

Major Task 1 (Year 0-1). **Project Initiation**:
a. Hiring and training of study personnel
b. Setup databases and design study documents
c. Finalize imaging protocol
c. Writing IRB protocol
d. Obtain IRB approval UCSF, VA, DoD

Major Task 2 (Year 1-3): Patient Screening, Recruitment and Assessment incl imaging
a. Year 1: 8 PNES
b. Year 2: 26 PNES
c. Year 3: 6 PNES

Major Task 3 (Year 1-3): Control Screening, Recruitment and Assessment incl imaging
a. Year 1: 4 controls
b. Year 2: 13 controls
c. Year 3: 3 controls

Major Task 4 (Year 1-3): Data Processing
a. Compilation of clinical and psychiatric data, transfer into database
b. MRI preprocessing.

Major Task 5 (Year 2-3): Graph Analysis and cluster analysis to isolate PNES imprint
a. Data processing
b. Identification of PNES imprint/cluster
c. Correlation with psychiatric comorbidity score, seizure frequency, type
d. Imprint simulations
e. Additional analysis (requested during review): Proof that PNES imprint is not present in epilepsy patients. This subtask will use existing fMRI data from epilepsy patients and controls that has been acquired previously for another project.

Major Task 6 (Year 3): Stationary fMRI analysis to isolate PNES imprint
a. Data processing
b. Identification of PNES imprint/cluster
c. Correlation with psychiatric comorbidity score, seizure frequency, type

Major Task 7 (Year 3): Manuscript writing, result dissemination

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Major Task 1 (Year 0-1). Project Initiation
Tasks outlined in 1 were all accomplished. The data bases and report forms were developed, personnel hired and trained, the imaging protocol was developed and successfully tested on a healthy volunteer. The IRB approvals were obtained on:

- **03/08/2018: Approval of Study Protocol UCSF IRB**
- **03/09/2018: Protocol submitted to Human Research Protection Office (HRPO)**
- **03/22/2018: VA Clinical Research Workgroup initial protocol approval**
- **04/05/2018: Approval of study protocol by R&D/ACOS San Francisco**
- **04/11/2018: Approval of study protocol by HRPO**

The project started the screening of potential participants in 05/2018

Major Task 2 (Year 1-3): Patient Screening, Recruitment and Assessment incl imaging
a. Year 1: 28 potential PNES participants were screened, 1 PNES was enrolled and completely assessed. This is below the enrollment goal for Y1.

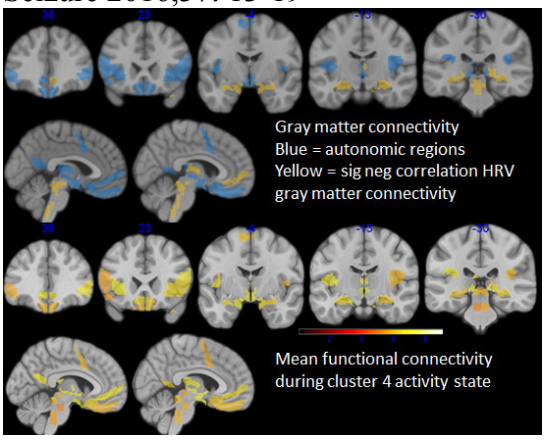
Major Task 3 (Year 1-3): Control Screening, Recruitment and Assessment incl imaging
a. Year 1: Enrollment of controls was delayed due since it is intended to recruit controls who are matched to the patients re age, gender and socio-economic background.

Major Task 4 (Year 1-3): Data Processing
An imaging data pre-processing pipeline was developed and implemented and has been successfully deployed for the pre-processing of 2 data sets.
The primary imaging outcome measure is a functional imprint of PNES that will be characterized by identifying functional connectivity states using dynamic analysis of task-free fMRI data. This analysis will be complemented by adding information re gray matter connectivity and white matter connectivity. Processing pipelines for these measurements were added to the fMRI processing pipeline.

Major Task 5 (Year 2-3): Graph Analysis and cluster analysis to isolate PNES imprint
a. Data processing
e. Additional analysis (requested during review): Proof that PNES imprint is not present in epilepsy patients: Preliminary Analyses:

Background: Heart rate variability (HRV) is a surrogate marker of autonomous nervous system function. Brain regions involved in HRV control overlap with brain regions showing abnormalities in PNES ,e.g. cingulate, insula, orbitofrontal cortex, and even more so in patients suffering from focal epilepsy, insula, cingulate, brainstem, hippocampus, amygdala. HRV abnormalities have been described in PNES and epilepsy patients with the former having a higher sympathetic tonus in the interictal state and the latter in the ictal state (1,2). Based on these findings, it is expected that patients with epilepsy and patients with PNES show differences of gray matter and functional connectivity within the autonomic network. The aim of this pilot study was to develop the methods to investigate the autonomic network in epilepsy patients.
Methods: The study population consisted of 11 controls and 18 patients with non-lesional focal epilepsy (LRE) in whom heart rate variability (HRV) measurements and a 3T MRI (T1 in all subjects, task-free fMRI in 7 controls/ 12 LRE) had been acquired. Dynamic task-free fMRI analysis was done using a slightly modified approach (inclusion of brainstem ROIs), gray matter connectivity was assessed using newly developed approach.
Results: Epilepsy patients had a lower heart rate-adjusted HRV than controls (-0.176 (1.014) vs. 0.318 (0.941), p = ns). Significant ($p<0.05$) negative associations between increased negative strength and lower HRV indicating a negative effect on the function/structure relationship of the autonomic network were found in bilateral hippocampus/amygdala, left septum/ventral thalamus, right pregenual cingulate, median thalamus and all brainstem ROIs in the patient group. In controls, significant HRV brain structure associations were restricted to brainstem ROIs. Dynamic task-free fMRI analysis identified 17 states. The strength within the functional autonomic network during state 4 was positively associated with HRV ($r =-0.55$, $p = 0.038$). Reduced gray matter connectivity within the autonomic network (beta = -0.5, $p<0.05$) and functional connectivity within the autonomic network (beta = 0.3, $p<0.05$) explained 86% of the HRV variability in this population. Reduced structural and functional brainstem connectivity together only explained 55% of the HRV variability.
.

Conclusion: Reduced HRV in LRE is associated with an altered structural and functional network structure of the autonomic system. 1. Epilepsy & Behavior, 2017, 70: 204-211, 2. Seizure 2016,37: 13-19



What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

1. The results reported in the previous section were presented as a Poster at the Partners Against Mortality Meeting in Alexandria, VA, in June 2017. This meeting focus on sudden death in epilepsy (SUDEP) . SUDEP is a condition in which a dysfunction of the autonomic system is supposed to play a major role. The meeting is attended by researchers but also by epilepsy patients and relatives of SUDEP victims.
2. Presentation of project at the 2018 meeting of the Northern California Epilepsy Consortium to raise awareness and prompt referrals by neurologists and epileptologists.

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Year 2 will focus on recruitment and assessment of eligible patients. The goal is to raise the number of patients that are enrolled in this period to meet the recruitment milestones specified in the SOW. The following is planned:
1. Revision of inclusion/exclusion criteria to identify those that were responsible for the high percentage of patients that were screened but not enrolled and eliminate/modify them.
2. Add UCSF Epilepsy Center as a referral site. IRB modification submitted and approved by UCSF and SFVA on 09/21. Modification submitted to HRPO on 09/24, decision still pending.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:
- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

1. IRB approval (UCSF, VA, HRPO) took longer than expected. 2. Patient recruitment is lagging behind. UCSF Epilepsy Center will be added as 3rd referral site. 3. Approval of IRB protocol modification by HRPO takes longer than expected.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

1. Software up-grade (VD13A – VE11C) scheduled for Dec 2018. The development of the imaging protocol was adapted accordingly by choosing sequences that are available in both versions and were not modified in the new release.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

None

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

UCSF Epilepsy Center added as a referral site. IRB modification submitted and approved by UCSF and SFVA on 09/21. Modification submitted to HRPO on 09/24, decision HRPO approval still pending.

Significant changes in use of biohazards and/or select agents

None

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report.

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

  Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Poster presentation at the PAME meeting in Alexandria, VA. June 2018

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding,

prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Name:	*Susanne Mueller*
Project Role:	*PI*
Researcher Identifier	*(e.g. ORCID ID): 0000-0002-5515-4432*
Nearest person month worked:	*0.3*
Contribution to Project:	*Development of IRB protocol, development of reporting documents, questionnaires, training of study personnel, setting up study logistics, finalizing imaging protocol, development of processing pipelines, testing of processing pipelines. Analysis of preliminary data, subject enrollment, scheduling of assessments*

Name:	*Thomas Neylan*
Project Role:	*co-investigator*
Researcher Identifier (e.g. ORCID ID):	*NA*
Nearest person month worked:	*0.05*
Contribution to Project:	*supervision psychiatric evaluation*
Name:	*Nina Garga*
Project Role:	*co-investigator*
Researcher Identifier (e.g. ORCID ID):	*NA*
Nearest person month worked:	*0.05*
Contribution to Project:	*Screening and referral of PNES subjects*
Name:	*Kenneth Laxer*
Project Role:	*co-investigator*
Researcher Identifier (e.g. ORCID ID):	*NA*
Nearest person month worked:	*0.05*
Contribution to Project:	*Screening and referral of PNES subjects*
Name:	*Jennifer Hlavin*
Project Role:	*study co-ordinator SFVAMC mental health*
Researcher Identifier (e.g. ORCID ID):	*NA*
Nearest person month worked:	*0.05*
Contribution to Project:	*logistics of mental health assessment*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

The Imprint of Psychogenic Nonepileptic Seizures on the Brain: A New Model and Imaging Biomarker

Log No: EP160051

Award No: W81XWH-17-1-03360

PI: Susanne G. Mueller **Org:** NCIRE **Award Amount:** $500,000 Directs + $219,010 F&A

Study Aims

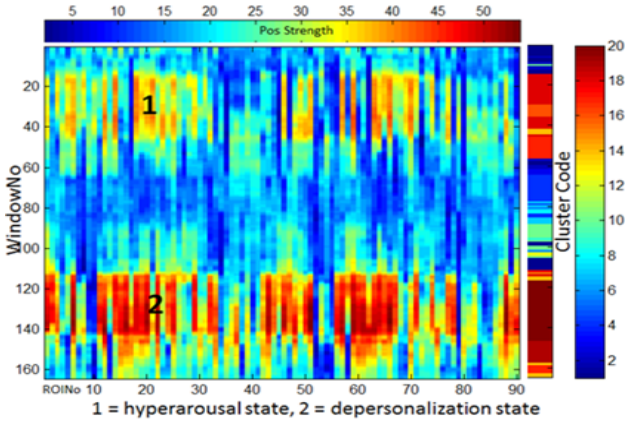
Specific Aim 1. PNES is associated with phases of overshooting recruitment between regions involved in emotion processing whose configuration reflects aspects of the individual's pathological emotion processing and PNES semiology.

Specific Aim 2. PNES is characterized by increased stationary connectivity in prefrontal-limbic regions involved in emotion control.

Approach

The overall goal of this 3 year cross-sectional project is to confirm a new model of PNES by identifying its characteristic signature (abnormal synchronization) in the resting state data in 40 veteran and civilian PNES patients and demonstrating its absence in 20 controls.

Fig 1. Pos Strength Fluctuations in highPDEQ PTSD subject



1 = hyperarousal state, 2 = depersonalization state

Accomplishment Y1/Q4: Enrolled and completed assessment of one patient, screened 28 potential patients. Reasons for non-enrollment were concomitant diseases, living to far from SFVAMC, age, language, brain lesions.

Timeline and Cost

Activities / CY	17-18	18-19	19-20
Major Task 1: Project Initiation	■		
Major Task 2: Patient recruitment, assessment	■	■	■
Major Task 3: Control recruitment, assessment	■	■	■
Major Task 4: Data processing	■	■	■
Major Task 5: Dynamic data analysis & signature	■	■	■
Major Task 6: Stationary data analysis			■
Estimated Budget ($K)	165	166	169

Updated: 10/24/18

Goals/Milestones)

CY 17-18

■ **Major Task 1:** Project Initiation

□ **Major Task 2:** Patient recruitment, assessment

□ **Major Task 3:** Control recruitment, assessment

CY 18-19

□ **Major Task 2:** Patient recruitment, assessment

□ **Major Task 3:** Control recruitment, assessment

□ **Major Task 4:** Data processing

□ **Major Task 5:** Dynamic data analysis & signature simulations

CY 19-20

□ **Major Task 2:** Patient recruitment, assessment

□ **Major Task 3:** Control recruitment, assessment

□ **Major Task 4:** Data processing

□ **Major Task 5:** Dynamic data analysis & signature simulations

□ **Major Task 6:** Stationary data analysis

Comments/Challenges/Issues/Concerns: IRB approval slower than expected

Budget Expenditure to Date

Direct Costs	9/30/2017	9/24/2018
Projected	$	164,980.00
Actual	$	112,136.48
Difference	$	52,843.52