**AWARD NUMBER:** W81XWH-17-1-0619

**TITLE:** Neuroimaging Biomarker for Seizures

**PRINCIPAL INVESTIGATOR:** Dr. William LaFrance

**CONTRACTING ORGANIZATION:** Ocean State Research Institute, Inc.
Providence, RI 02908

**REPORT DATE:** October 2018

**TYPE OF REPORT:** Annual

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

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**6. AUTHOR(S)**
William Curt LaFrance, Jr., MD, MPH
Krista Tocco, BA

E-Mail: Krista.Tocco@va.gov

**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**
Providence VA Medical Center
Providence, RI 02908
University of Alabama at Birmingham;
Birmingham, AL 35233
Rhode Island Hospital
Providence, RI 02903

**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**
**USA Medical Research ACQ Activity**
U.S. Army Medical Research and Materiel Command
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**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**
The multi-site study will examine patients with epilepsy (ES) following head injury [i.e., posttraumatic epilepsy (PTE)] and posttraumatic Psychogenic Non-epileptic seizures (PNES) and will compare them to patients with traumatic brain injury (TBI) who do not have seizures. The research aims to investigate: 1. Differences in cerebral underpinnings of emotion and stress processing in PNES and PTE; 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 (Cognitive Behavioral Therapy for Seizures (CBT-Sz), a manualized behavioral therapy program) that result in neuroplasticity. This study aims to enroll 264 participants (Veterans and civilians) divided over the sites: 88 with PNES, 88 with PTE, and 88 with TBI without PNES or PTE. Over the past year, we established multi-site infrastructure, obtained regulatory approval, started enrollment and preliminary data analysis.

**15. SUBJECT TERMS**
Traumatic Brain Injury, Psychogenic Non-Epileptic Seizures, Post-Traumatic Epilepsy, Epilepsy, fMRI, Cognitive Behavioral Therapy, Seizures, Convulsion, Non-Epileptic, Post-Traumatic Stress Disorders, Conversion Disorder, Brain Injury, Somatoform Disorder

| 16. SECURITY CLASSIFICATION OF: U | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | USAMRMC |
| Unclassified | Unclassified | Unclassified | UU | 25 | 19b. TELEPHONE NUMBER *(include area code)* |

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## 1. INTRODUCTION:

The multi-site study will examine 88 patients with epilepsy (ES) following head injury [i.e., posttraumatic epilepsy (PTE)], 88 with posttraumatic Psychogenic Non-epileptic seizures (PNES), and will compare them to 88 patients with traumatic brain injury (TBI) who do not have seizures. The research aims to investigate the differences in cerebral underpinnings of emotion and stress processing in PNES and PTE using well established fMRI probes. We also aim to investigate the neuroimaging biomarker of PTE and PNES that predicts treatment outcome in order to inform effective non-pharmacologic treatments for seizures. Lastly, we are looking for evidence for a positive treatment response to the intervention (Cognitive Behavioral Therapy for Seizures (CBT-Sz), a manualized behavioral therapy program) that result in neuroplasticity.

## 2. KEYWORDS:

Traumatic Brain Injury, Psychogenic Non-Epileptic Seizures, Post-Traumatic Epilepsy, fMRI, Cognitive Behavioral Therapy, Seizures, Convulsion, Post-Traumatic Stress Disorders, Conversion Disorder, Brain Injury

## 3. ACCOMPLISHMENTS:

### What were the major goals of the project?

**Major Goal 1**: Refinement and finalization of fMRI, receive regulatory approval, establish data systems, and purchase materials.

- Timeframe: Months 1-3
- Percent Completed: 100%

**Milestones:** IRB approval and the completing of case report forms and the manual of procedures.

- Timeframe: Months 1-6
- Percent Completed: 100%

**Major Goal 2**: Participant recruitment, complete pre-post evaluations, and treatment as outlined in Aims 1 and 2 of the protocol.

- Timeframe: Months 4-48
- Percent Completed: 20%

**Milestones:** Recruitment and Follow-up

- Timeframe: Months 7-48
- Percent Completed: year 1: 90%; overall: 30%

**Major Goal 3**: Continuation of research regulatory compliance

- Timeframe: Months 7-48
- Percent Completed: year 1: 100%

**Major Goal 4**: Data Analysis and upload. *UAB is responsible for MRI data analysis. RIH, Providence, RI is responsible for behavioral data analysis. Each site completes their own data upload.*

- Timeframe: Months 3-48
- Percent Completed: year 1: 100%; overall: 20%

**Milestones:** Data summaries and analysis

- Timeframe: Months 6-48
- Percent Completed: overall 15%

**What was accomplished under these goals?**

In year 1, we have established multi-site infrastructure, obtained regulatory approval from all appropriate sites, and started enrollment. Also, we have developed the data analysis pipeline to be used for neuroimaging and neurobehavioral data. During year 1, we encountered enrollment challenges and problem-solved to address enrollment. We have meet weekly via teleconference as a research team, to identify problems and develop solutions. Since starting enrollment, we have provided participants with new tools to address seizures and comorbidities.

We began enrollment in February 2018 and have since established relationships with many seizure disorder and traumatic brain injury clinicians, clinics and foundations. Our retention rate is above 80%. We have also completed pre/post fMRIs and evaluations for participants. We have enrolled 43 participants up to 9/14/2018 and have exceeded our to-date projected TBI control recruitment goal.

All fMRI analysis procedures have been developed and tested and processing pipeline is in place.

We remain compliant for all research regulations. During year 1, we prepared and submitted a continuing review at the Providence VAMC and received approval from both the PVAMC IRB and HRPO. We also began to prepare for UAB and RIH's continuing review due in Year 2, quarter 1.

**What opportunities for training and professional development has the project provided?**

MRI training for study staff (Goodman) included novel analytic approaches.
In the startup phase, study clinicians (Drs. Gaston & Grayson) completed CBT-Sz treatment training.
Research staff (Tocco, Vogel, Martin) underwent training for administering the SCID-5.

**How were the results disseminated to communities of interest?**

To disseminate study information to community providers and organizations, we have engaged hospitals, clinics, clinicians, voluntary organizations and the Epilepsy Foundation.

**What do you plan to do during the next reporting period to accomplish the goals?**

We plan to continue our recruitment efforts in the next period. We will continue to develop more relationships with professional and community partners/clinics to aid in our recruitment efforts and will continue to maintain these and existing relationships with clinicians and stakeholders. We also plan to start developing abstracts and posters for upcoming conferences when sufficient preliminary data are available.

## 4. IMPACT:

This study, which is investigating mechanisms of psychogenic non-epileptic seizures (PNES) and post-traumatic epilepsy (PTE), will provide increased understanding of neural circuitry in PTE and PNES, which may identify PTE and PNES neurophysiology and inform treatments that could change clinical neurologic and psychiatric practice for PTE and PNES.

**What was the impact on other disciplines?**

With our neuropsychiatry approach, we are increasing dialogue between neurology and mental health practitioners.

**What was the impact on technology transfer?**

Nothing to Report.

**What was the impact on society beyond science and technology?**

Due to lack of public knowledge on PNES, people with this disorder often face stigma and skepticism about their condition. We can reduce the misconception that nonepileptic seizures are "pseudo" by improving public knowledge through researching effective treatments for it. By expanding on the small amount of research that has been done on treatments for this disorder, the results of this project will likely have a profound contribution to research and ultimately an impact on the public's attitude towards individuals with PNES.

## 5. CHANGES/PROBLEMS:

### Changes in approach and reasons for change

N/A

### Actual or anticipated problems or delays and actions or plans to resolve them

During the 2nd quarter, we delayed recruitment at the three sites due to a protocol change. To resolve we aimed to increase our monthly recruitment and enrollment numbers to achieve our year 1 goal of 48 participants. All together, we enrolled 43 participants. We are continuing to discuss recruitment efforts and plans each week on our research team

### 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.*

During year 1, we had a few delays, as well as favorable developments that have impacted our expenditures.

**Delays**

- At University of Alabama in Birmingham, a post-doctorate was hired in month 7 instead of the projected month 3.
- With the delay, our recruitment goals were slightly behind target, so projected participant payments and MRI fees have not been expended to date, but will be in the future.

**Favorable Developments**

- Throughout months 1-3, study materials and equipment were purchased. During this time many copyrighted study assessment measures (SCID, BDI, BAI, etc.) were purchased at a lower rate than what was budgeted, due to a research discount.

**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**

N/A

**Significant changes in use or care of vertebrate animals**

N/A

**Significant changes in use of biohazards and/or select agents**

N/A

## 6. PRODUCTS:

### Publications, conference papers, and presentations

### Journal publications.

Szaflarski, JP, LaFrance WC Jr. Psychogenic nonepileptic seizures (PNES) as a network disorder – evidence from neuroimaging of functional (psychogenic) neurological disorders. *Epilepsy Curr*. 2018;18(4):211-216. doi: 10.5698/1535-7597.18.4.211. PMID: 30254510 (no fed support).

### Books or other non-periodical, one-time publications.

**LaFrance Jr WC,** Schachter SC, Eds. Gates and Rowan's Nonepileptic Seizures. 4th Edition. Cambridge; New York: Cambridge University Press; 2018. (no fed support).

- **Other publications, conference papers and presentations**.

Nothing to Report.

### Website(s) or other Internet site(s)

Nothing to Report.

### Technologies or techniques

Nothing to Report.

### Inventions, patent applications, and/or licenses

Nothing to Report.

### Other Products

Nothing to Report.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

**What individuals have worked on the project?**

*Name:* W. Curt LaFrance, Jr., MD, MPH
*Project Role:* PI
*Researcher Identifier (ORCID ID):* 0000-0002-4901-3852
*Nearest person month worked:* 2
*Contribution to Project:* No Change

*Name:* Jerzy Szaflarski, MD, PhD
*Project Role:* Site PI
*Researcher Identifier (ORCID ID):* 0000-0002-5936-6627
*Nearest person month worked:* 1
*Contribution to Project:* No Change

*Name:* Jane Allendorfer, PhD
*Project Role:* MRI Data Manager – University of Alabama, Birmingham
*Researcher Identifier (e.g. ORCID ID):*
*Nearest person month worked:* 1
*Contribution to Project:* No Change

*Name:* Adam Goodman, PhD
*Project Role:* Postoctoral Fellow – University of Alabama, Birmingham
*Researcher Identifier (e.g. ORCID ID):*
*Nearest person month worked:* 3
*Contribution to Project:* No Change.

*Name:* Amber Martin
*Project Role:* Study Project Coordinator – University of Alabama, Birmingham
*Researcher Identifier (e.g. ORCID ID):*
*Nearest person month worked:* 3
*Contribution to Project:* No Change

*Name:* Krista Tocco, BA
*Project Role:* Study Project Coordinator, Providence, RI
*Researcher Identifier (e.g. ORCID ID):*
*Nearest person month worked:* 3
*Contribution to Project:* No Change

*Name:* Valerie Vogel, BA
*Project Role:* Research Assistant, Providence, RI
*Researcher Identifier (e.g. ORCID ID):*
*Nearest person month worked:* 3
*Contribution to Project* No Change

*If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been.*

**Providence VA Medical Center Personnel**

- Stephen Correia, PhD: nothing to report.
- Noah Philip, MD: nothing to report.
- William Curt LaFrance, Jr., MD, MPH:
  - Promoted to Professor of Psychiatry and Neurology, Brown University
  - Additional scholarly articles written:
    - Szaflarski JP, LaFrance WC Jr. Psychogenic nonepileptic seizures (PNES) as a network disorder – evidence from neuroimaging of functional (psychogenic) neurologicaldisorders. *Epilepsy Curr*. 2018;18(4):211-216. doi: 10.5698/1535-7597.18.4.211. PMID: 30254510

**University of Alabama at Birmingham Personnel**

- *PI: Jerzy Szaflarski, Md, PhD:*
  - Additional projects in completed research support:
    - Title: Harnessing neuroplasticity to promote rehabilitation: CI therapy for TBI (Sponsor: Department of Defense (PT 130232)); Role: Co-Principal Investigator (PI: Edward Taub, PhD); Award period: 9/1/2014-8/31/2017 Title: Post-stroke aphasia and rTMS treatment (PART) study (NIH R01 HD068488); Role: Principal Investigator; award period1/1/2012-12/30/2017
    - Title: Quality of Epilepsy Treatment and Costs in Older Americans by Race (QUIET CARE; NIH R01 NS080898); Role: Co-Investigator (PI: Maria Pisu, PhD); award period 10/1/2012-9/30/2016
    - Title: "Presurgical applications of fMRI in epilepsy" (NIH R01 NS035929); Role: Subcontract PI (PI: Jeffrey R. Binder, MD, Medical College of Wisconsin); award period 7/1/11-6/30/16; NCE 7/1/16-6/30/17.
  - Additional scholarly articles written:
    - Szaflarski JP, LaFrance WC Jr. Psychogenic nonepileptic seizures (PNES) as a network disorder – evidence from neuroimaging of functional (psychogenic) neurological disorders. *Epilepsy Curr*. 2018;18(4):211-216. doi: 10.5698/1535-7597.18.4.211. PMID: 30254510

- *Co-I: Jane Allendorfer, PhD*
  - Additional projects in completed research support:
    - UAB Faculty Development Grant Program Allendorfer (PI) 08/01/2015-07/31/2018; Project Title: Effects of exercise on memory deficits and brain network connectivity in patients with epilepsy; Role: PI
    - PT 130232 Taub (PI) 09/01/2014-08/31/2017; Department of the Army – USAMRAA; Project Title: Harnessing neuroplasticity to promote rehabilitation: CI therapy for TBI; Role:Co-I
  - Additional ongoing support:
    - UAB McKnight Brain Institute Pilot Grant Allendorfer (PI), Lubin (co-PI) 04/01/2018-04/01-2019; Project Title: Exercise-related effects on memory function and neural circuitry – a parallel clinical and preclinical investigation; Role: PI

- *Co-I: Tyler Gaston, MD*
  - Additional scholarly articles written:
    - **Tyler E. Gaston, MD**, E. Martina Bebin, MD, Gary R. Cutter, PhD, Yuliang Liu, PhD**,** Leslie P. Grayson, MD, and Jerzy P. Szaflarski, MD, PhD on behalf of the UAB CBD Program. Effect of Drug-Drug Interactions with Cannabidiol (CBD) on Seizure Frequency and Severity. Submitted for publication in Neurology July 2018.

- *Co-I: Leslie Grayson Perry*
  - Additional scholarly articles written:
    - Tyler E. Gaston, MD, E. Martina Bebin, MD, Gary R. Cutter, PhD, Yuliang Liu, PhD**, Leslie P. Grayson**, MD, and Jerzy P. Szaflarski, MD, PhD on behalf of the UAB CBD Program. Effect of Drug-Drug Interactions with Cannabidiol (CBD) on Seizure Frequency and Severity. Submitted for publication in Neurology July 2018.
    - Leslie Grayson, et al. "An Interaction between warfarin and cannabidiol, a case report." Epilepsy & Behavior Case Reports, 2018. 9:10-11.https://doi.org/10.1016/j.ebcr.2017.10.001
  - Additional review papers:
    - **Grayson, L.P.** & DeWolfe, J.L. Curr Sleep Medicine Rep (2018) 4: 125.
  - Additional abstracts
    - Effect of Pharmaceutical Formulation of Purified Cannabidiol (CBD) on Seizure Frequency and Severity is Independent of Drug-Drug Interactions with other AntiEpileptic Drugs (AEDs) Tyler Gaston, Gary Cutter, Yuliang Liu, **Leslie Perry**, E Bebin, Jerzy Szaflarski. AAN 2018.
    - Response to Pharmaceutical Formulation of Purified Cannabidiol (CBD) in Pediatric and Adult Patients with Treatment-Refractory Epilepsy. Jerzy Szaflarski, E Bebin, Tyler Gaston, **Leslie Perry**, Yuliang Liu, Gary Cutter. AAN 2018.
    - Behavioral Status after a Trial of Cannabidiol (CBD) in a Pediatric Sample of Pharmacoresistant Epilepsy. M.D. Thompson, E.M. Bebin, **L. P. Grayson**, G. Cutter, J.P. Szaflarski. AES 2018. Submitted by Thompson.
    - Inter-professional Patient Simulation Improves Clinical, Communication andInterpersonal Skills of Medical Students in the Real-World Clinical Setting. Womack H, Lin CP, Amara AW, Rinker JR, Register SJ, Peterson DT, Chitlangia AA, Vines BL, Patel M, Memon A, McCullough BA, Jones BA, Smelser BL, Benesh FS, **Perry LE**, Kaur M, MuhlhoferW,

- *Co-I: Mark Bolding, PhD*
- *Co-I: Lawerence Ver Hoef, PhD*: nothing to report.

**Rhode Island Hospital Personnel**

- *Jeffery Wincze, PhD*: nothing to report.
- *PI: Andrew Blum, MD*: 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.*

***In-Kind Recruitment Support:***
Organization Name: Epilepsy Foundation of Alabama
Location of Organization: Mobile, AL
Organization Name: CURE (Citizens United for Research in Epilepsy)
Location of Organization: Chicago, IL
Organization Name: Birmingham VAMC
Location of Organization: Birmingham, AL
Organization Name: Alabama Head Injury Foundation
Location of Organization: Birmingham, AL

## 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.*

Quad chart uploaded.

## 9. APPENDICES

A. Jerzy Szaflarski Updated Biosketch
B. Psychogenic Nonepileptic Seizures (PNES) as a Network Disorder – Evidence From Neuroimaging of Functional (Psychogenic) Neurological Disorders

# BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

NAME: Szaflarski, Jerzy P.

eRA COMMONS USER NAME (agency login): szaflajp

POSITION TITLE: Professor of Neurology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

| INSTITUTION AND LOCATION | DEGREE (if applicable) | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Collegium Medicum (Bydgoszcz; Nicolaus Copernicus University, Torun/Poland | MD (7/91) | 9/1985-7/1991 | Medicine |
| University of Saarland Med. School, Homburg, Germany | | 10/1990-7/1991 | Medicine |
| Collegium Medicum (Bydoszcz); Nicolaus Copernicus University, Torun/Poland | PhD (11/97) | 11/1997 | Neuroembryology |
| The American Board of Psychiatry and Neurology | | 6/2000 (valid through 2020) | Neurology |
| The American Board of Psychiatry and Neurology | | 3/2003 (valid through 2023) | Clinical Neurophysiology |

**A. Personal Statement**

In this proposal we will investigate and thereby meet the intent of the ERP IDA mission:

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 development of an effective nonpharmacologic treatment for seizures (CBT-Sz); 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.

In order to systematically address these goals, with help of the American Epilepsy Society (AES), we have created a consortium for seizure disorders research, a coordinated, multicenter effort involving investigators from several institutions, organized into clinical, neuroimaging and data analysis cores. Given the neuropsychiatric nature of seizure disorders, progress in developing biomarkers requires a network of experienced researchers in various fields, ranging from neurology, psychiatry, neuroimaging, psychology, clinical trials, and biostatistics. This multifaceted approach requires leadership with a breadth of skills that is best handled by a close knit collaborative leadership team, rather than a single individual. This is the main reason why Dr. LaFrance and I decided to join our efforts. This project involves two PIs because it integrates two distinct areas of research, each within the expertise of one of the PIs. While Dr. LaFrance is a world-recognized expert in studying the neuropsychiatric aspects of PTE/PNES including the development and implementation of CBT-Sz, my expertise lies in MRI/fMRI data collection and analyses. In this study, I will oversee all other aspects of the study as they relate to the MRI/fMRI protocol implementation and data collection and analyses. As an expert in seizure disorders including diagnosis and management of PNES and PTE, EEG, clinical trials, TMS and neuroimaging (fMRI, EEG/fMRI and multimodality imaging) and I will devote a considerable amount of time to work with Dr. LaFrance and the teams from both institutions to achieve the goals of this study. I am committed to this project and will spend the necessary time to make this projects a success. My contributions to this field include:


1. **Szaflarski JP**, LaFrance WK "Psychogenic nonepileptic seizures (PNES) as a network disorder – evidence from neuroimaging of functional (psychogenic) neurological disorders" *Epilepsy Currents*; 2018, 18(4): 211-216; PMID: pending
2. **Szaflarski JP**, Allendorfer JB, Nenert R, LaFrance WC, Barkan H, Dewolfe J, Pati S, Thomas AE, Ver Hoef L "Facial emotion processing in patients with seizure disorders" *Epilepsy and Behavior* 2018, 79: 193-204; PIMD 29309953
3. Ritter AC, Wagner AK, **Szaflarski JP** et al. "Prognostic models for predicting post-traumatic seizures during acute hospitalization, and at 1 and 2 years following traumatic brain injury" *Epilepsia*; 2016; Sep:57(9): 1503-1514; PMID: 27430564
4. Ritter AC, Wagner AK, Walker WC, Fabio A, **Szaflarski JP** et al. "Incidence and Risk Factors of Post-Traumatic Seizures following Traumatic Brain Injury: A Traumatic Brain Injury Model Systems Study" accepted for publication in *Epilepsia*; PIMD: 27739577

5. **Szaflarski JP**, Dreer L, Nazzal Y "Post-traumatic epilepsy: current and emerging treatment options" *Neuropsychiatric Disease and Treatment*, 2014; 10:1469-1477; PMID 25143737

**B. Positions and Honors**

***Positions and Employment***

1991-1992 Internship, Collegium Medicum (Bydgoszcz); Nicolaus Copernicus University, Torun/Poland
1991-1992 Research and Teaching Associate, Dept. of Histology and Embryology, Collegium Medicum (Bydgoszcz) of the Nicolaus Copernicus University, Torun/Poland
1992-1995 Research Associate, Depts of Pediatrics and Neurology, University of Michigan, Ann Arbor, MI
1995-1996 Internship, Department of Internal Medicine, Easton Hospital, Easton, PA
1996-1999 Neurology Residency, Department of Neurology, UC COM, Cincinnati, OH
1999-2001 Clinical Neurophysiology and Epilepsy Fellowship, Department of Neurology, UC COM, Cincinnati, OH
2001-2007 Assistant Professor, Department of Neurology, UC COM, Cincinnati, OH
2002-2007 Assistant Director, Center for Imaging Research, UC COM, Cincinnati, OH
2003-2007 Director, Clinical Neurophysiology Fellowship, Department of Neurology, UC COM
2007-2009 Affiliate Faculty, Pediatric Neuroimaging Research Consortium, CCHMC, Cincinnati, OH
2007-2012 Associate Professor, Neurology, Neuroscience and Psychiatry, UC COM, Cincinnati, OH
2007-2012 Associate Director, Center for Imaging Research, UC COM, Cincinnati, OH
2009- Associate Professor, Psychology, UC COM, Cincinnati, OH (since 2012 voluntary)
2009-2012 Medical Director, Pediatric Neuroimaging Research Consortium, CCHMC, Cincinnati, OH
2012- Professor (w/tenure), Departments of Neurology and Neurobiology, UAB, Birmingham, AL
2012- Director, Epilepsy Center, Department of Neurology, UAB, Birmingham, AL
2014- Co-Director, University of Alabama CBD Program, Birmingham, AL
2014- Distinguished Fellow of the Collegium; The Kosciuszko Foundation Collegium of Eminent Scholars, New York, NY; http://www.thekf.org/kf/programs/eminentscientists/

***Honors***

1990-1991 Individual Mobility Grant awarded by Trans-European Mobility Scheme for University Studies (Commission of the European Communities awards this grant to the best students so that they can study in another country)
1998 American Neurological Association travel grant "Residents' Program in Academic Neurology: Preparing for the Future." 123rd Annual Meeting; 10/1998, Montreal, Canada
1999 "Annual Meeting Scholarship for Residents" 51st AAN Meeting; 4/1999, Toronto, Canada
1999 Neurology Resident Teacher of the Year Award (UC COM, Cincinnati, OH)
2003 "40 under 40: People to watch at the UC Medical Center," UCCOM, Cincinnati, OH
2005 Excellence in Neuroscience Award to Mark DiFrancesco, PhD (Research Fellow under mentorship) UC COM, Cincinnati, OH
2006- Editorial Board Member, *Epilepsy and Behavior*
2006 Donald M. Palatucci Advocacy Leadership Forum, AAN, St. Paul, MN
2006 National Institutes of Health K-23 Award (1K23 NS052468)
2007 Elected to "Best Doctors in America"
2008- Ad-hoc reviewer, NIH, Israel Science Foundation, and British Medical Council (participated in multiple review cycles with all 3 agencies)
2009- Elected to "Best Doctors in America"
2010-2014 Editorial Board Member, *Journal of Epileptology*
2013- Associate Editor, *Restorative Neurology and Neuroscience*
2015- Associate Editor, *Journal of Epileptology*
2015- Contributing Editor, *Epilepsy Currents*

***Contributions to science:***

In addition to the investigations eluded to in my personal statement, my contributions to science have been focused into four areas all tied together with a common theme of neuroimaging: 1). Investigation into the effects of intervention (rehabilitation) on language and motor recovery after acute brain insult, 2). Investigation of patterns of language localization and lateralization in health and diseased states including language development, 3). The intersection between measurable brain physiology, such as measured by functional magnetic resonance imaging (fMRI) and electrophysiologic measures of brain activity (EEG), and 4). Investigations into the relationship between functional neurological disorders (e.g., psychogenic non-epileptic seizures or psychogenic movement disorders) and cognitive performance including memory processes, stress, and quality of life. I will discuss these areas of research interest in turn.

1). Investigations into the effects of intervention (rehabilitation) on language and motor recovery after acute brain insult have resulted in several discoveries. For example, we have shown that modified constraint-induced motor therapy (mCIMT) may significantly improve motor performance in patients with post-stroke motor deficits who have failed standard therapies; we have also observed similar results when rehabilitating patients with post-stroke aphasia using constraint-induced aphasia therapy (CIAT), a therapy based on forcing the patient to use verbal rather than non-verbal communication abilities. Further, application of non-invasive stimulation to patients with post-stroke aphasia have resulted in significant improvements in their linguistic performance and concomitant changes in structural connectivity. Selected relevant publications from an extensive list are included below:

1. **Szaflarski JP**, Griffis JC, Vannest J, Allendorfer JB, Nenert R, Amara A, Sung VW, Walker H, Martin AN, Mark V, Zhou X "A feasibility study of combined intermittent theta burst stimulation and modified constrain-induced aphasia therapy in chronic post-stroke aphasia" *Restorative Neurology and Neuroscience* 2018; 36(4): 503-518; PIMD 29889086
2. Griffis JC, Nenert R, Allendorfer JB, **Szaflarski JP** "Interhemispheric plasticity following intermittent theta burst stimulation in chronic post-stroke aphasia" *Neural Plasticity Article ID 4796906 vol. 2016*; PMID 26881111
3. Griffis JC, Allendorfer JB, **Szaflarski JP** "Voxel-based Gaussian naïve Bayes classification of ischemic stroke lesions in individual T1-weighted MRI scans" *Journal of Neuroscience Methods*; 2016; 257: 97-108; PMID 26432931
4. **Szaflarski JP**, Ball AL, Vannest J, Dietz A, Allendorfer JB, Martin AN, Hart K, Lindsell CJ "Randomized, blinded, and controlled pilot trial of constraint-induced aphasia therapy for the treatment of post-stroke aphasia" *Medical Science Monitor*; 2015; 21:2861-2869; PMID: 2630481
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2). Investigation of patterns of language localization and lateralization in health and diseased states including language development have resulted in several significant contributions. For example, studies in left- and right-handed children and adults showed that in right-handers during maturation there is a gradual shift of the language centers to the left hemisphere with maximum left lateralization around the ages 20-25 years and later gradual redistribution of language representation to both hemisphere during aging a process that appears to be associated with concomitant changes in white matter structural connectivity; this process appears to be similar in left-handers. Selected relevant publications from an extensive list are included below:

1. Nenert R, Allendorfer JB, Martin AN, Banks, C, Vannest J, Holland SK, **Szaflarski JP** "Age-related language lateralization assessed by fMRI: The effects of sex and handedness" *Brain Research*; 2017, 1674: 20-35; PMID 28830770
2. Allendorfer JB, Hernando KA, Hossein S, Nenert R, Holland SK, **Szaflarski JP** "Arcuate fasciculus asymmetry has a hand in language function but not handedness" *Human Brain Mapping*; 2016; Sep;37(9): 3297-309; PMID 27144738
3. Madhavan KM, McQueeny T, Howe SR, Shear P, **Szaflarski JP** "White matter microstructure and language functioning in healthy aging" *Brain Research* 2014: 1562: 11-22; PMID: 24680744
4. **Szaflarski JP**, Rajagopal A, Altaye M, Byars AW, Jacola L, Schmithorst VJ, Schapiro MB, Plante E, Holland SK "Left-handedness and language lateralization in children" *Brain Research* 2012; 1433: 85-97; PMID: 22177775
5. **Szaflarski JP**, Schmithorst VJ, Altaye M, Byars AW, Ret J, Plante E, Holland SK "A longitudinal fMRI study of language development in children age 5-11" *Annals of Neurology* 2006,59(5):796-807; PMID: 16498622

3). The intersection between measurable brain physiology, such as measured by functional magnetic resonance imaging (fMRI) and electrophysiologic measures of brain activity (EEG). In order to investigate the issue of pharmacoresistance in genetic generalized epilepsies (GGEs) I have applied EEG combined with fMRI (EEG/fMRI) to the evaluation of the sources of brain signals associated with spike and wave discharges. The main goal was to verify the hypothesis that the spike and wave generators in patients with pharmacoresistant GGEs are localized in the frontal lobes (predominantly in the medial regions) and in patients with GGEs controlled with medications in subcortical/thalamic regions. We were able to demonstrate that the cortical and subcortical regions generate and maintain spike and wave discharges, but the frontal lobes are the source of epileptic seizures in patients with difficult to control genetic generalized epilepsies. The results of our research question theories that support the central (thalamic) onset of generalized epilepsies with genetic etiology. Selected relevant publications from an extensive list are included below:

1. Bowman AD, Griffis JC, Visscher KM, Dobbins AC, Gawne TJ, DiFrancesco M, **Szaflarski JP** "Relationship between alpha rhythm and the default mode network: An EEG-fMRI study" *Journal of Clinical Neurophysiology* 2017, 34(6):527-533; PIMD 28914659
2. Kay B, Holland SK, Privitera MD, **Szaflarski JP** "Differences in Paracingulate Connectivity Associated with Epileptiform Discharges and Uncontrolled Seizures in Genetic Generalized Epilepsy" *Epilepsia* 2014: 55(2): 256-263; PIMD 24447031
3. Kay BP, DiFrancesco MW, Privitera MP, Gotman J, Holland SK, **Szaflarski JP** "Reduced default mode network connectivity in treatment-resistant idiopathic generalized epilepsy" *Epilepsia* 2013: 54(3): 461-470; PIMD 23293853
4. **Szaflarski JP**, Kay BP, Gotman J, Privitera MD, Holland SK "The relationship between the localization of the generalized spike and wave discharge generators and the response to valproate" *Epilepsia* 2013: 54(3): 471-480; PIMD 23294001
5. **Szaflarski JP**, DiFrancesco MD, Hirschauer T, Banks C, Privitera MD, Gotman J, Holland SK "Cortical and subcortical contributions to absence seizure onset examined with EEG/fMRI" *Epilepsy & Behavior,* 2010,18(4):404-413; PMID: 20580319

4). Investigations into the relationship between functional neurological disorders (e.g., psychogenic non-epileptic seizures or psychogenic movement disorders) and cognitive performance including memory processes, stress, and quality of life – the goals of this line of investigation are several-fold. One is to develop interventions that will afford patients with seizure disorders improved seizure control and better utilization of their cognitive resources. This research has so far resulted in several publications documenting the specific detrimental effects of seizures on QOL, memory processes, the effects on memory localization in the brains of patients with seizure disorders. We have recently developed and are implementing an intervention for memory improvement in patient with seizure disorders. Further, our investigations have shown that the emotional processing in patients with seizure disorders including white matter structural (DTI) connectivity is severely affected resulting in an impaired quality of life and recent preliminary fMRI results indicate altered emotion processing including hyper-focused emotional state in PNES that is exacerbated by mood state (manuscript in preparation). Selected relevant publications from an extensive list are included below:

1. Espay AJ, Maloney T, Vannest J, Norris M, Eliassen J, Neefus E, Allendorfer J, Chen R, **Szaflarski JP** "Dysfunction in emotion processing underlies functional (psychogenic) dystonia" *Movement Disorders* 2018, 33(1): 136-145; PMID 29124784
2. Espay AJ, Maloney T, Vannest J, Norris MM, Eliassen JC, Neefus E, Allendorfer JB, Lang AE, **Szaflarski JP** "Impaired emotion processing in functional (psychogenic) tremor *NeuroImage Clinical* 2018, 17: 179-187; PMID 29085776
3. Lee ST, Allendorfer JB, Griffis J, Gaston TE, Hernando KA, Knowlton R, **Szaflarski JP**, Ver Hoef LW "Investigation of white matter integrity in patients with psychogenic non-epileptic seizures" in print *Brain Research*; PMID 25979311
4. Hernando KA, **Szaflarski JP**, Ver Hoef LW, Lee ST, Allendorfer JB "Uncinate fasciculus connectivity in patients with psychogenic non-epileptic seizures: a diffusion tensor tractography study" in print *Epilepsy and Behavior* 2015; 45(7): 68-73; PIMD 25868002
5. LaFrance WC Baird GL, Barry JJ, Blum AS, Frank-Webb A, Keitner GI, Machan JT, Miller I, **Szaflarski JP** "Multicenter pilot treatment trial for psychogenic nonepileptic seizures" *JAMA Psychiatry* 2014: 71(9): 997-1005; PMID 24989152

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**D. Ongoing Research Support (clinical trials not included)**

Title: Neuroimaging biomarker for seizures; DoD/USAMRAA; Role: MPI (w/Curt LaFrance); Award period 9/30/2017-9/30/2021

Abstract: The goal of this project is to examine the neural circuitry that underlies response to stress in patients with post-traumatic seizures and the role of this circuitry in response to treatment (CBT).

Title: Understanding hippocampal internal architecture in human temporal lobe epilepsy – from MRI to epigenetics; NIH R01 NS094743; Role: Co-Investigator (PI: Lawrence W. Ver Hoef, MD); Award period 8/1/2016-7/31/2021

Abstract: The goal of this grant is to examine the structural and epigenetic etiology of medication resistance and response to surgical intervention in patients with treatment-refractory temporal lobe epilepsy.

Title: RII Track – 2 FEC: Probing and Understanding the Brain: Micro and Macro Dynamics of Seizure and Memory Networks; National Science Foundation (NSF) – OIA-1632891; Role: UAB Principal Investigator (PI: Leon Iasemidis, PhD, Louisiana Technical University); Award period 9/1/2016-8/31/2020

Abstract: The goal of this multicenter study is to evaluate the network dynamic in seizure onset propagation in animal and human models of epilepsy and to determine the interactions between the seizure and memory networks.

Title: Perampanel as a neuroprotective and antiepileptic compound in animal model of TBI (Eisai, Inc.); Role: Principal Investigator; Award period: 7/1/2016-12/30/2018

Abstract: The goal of this project is to evaluate antiepileptogenic and neuroprotective properties of an antiepileptic drug perampanel in a rodent model of closed head injury using electrophysiologic measures.

Title: UAB CBD Program (State of Alabama General Fund); Role: Co-Principal Investigator with E. Martina Bebin, MD); Award period: 10/1/2014-present (5 years anticipated)

Abstract: The aim of this project is to provide rigorous evaluation of clinical properties of Cannabidiol for the treatment of treatment-resistant epilepsies in children and adults.

Title: Glutamate, brain connectivity and duration of untreated psychosis (NIH R01 MH 102951); Role: Co-Investigator (PI: Adrienne Lahti, MD); Award period 7/1/2014-6/30/2019

Abstract: The goals of this study are to evaluate neuroimaging biomarkers of treatment response in patients with new onset schizophrenia and untreated psychosis.

Title: "Neural correlates of stress in patients with temporal lobe epilepsy" (Pamela and Charles Shor Foundation for Epilepsy Research); Role: PI (Jane Allendorfer, PhD – Co PI)

Abstract: The aims of this study are to provide preliminary evidence regarding aberrant neural circuitry and hormonal responses to stress in patients with left temporal lobe epilepsy who report increased seizures in response to stress.

**E. Completed Research Support (last 3 years only; clinical trials not included)**

Title: Harnessing neuroplasticity to promote rehabilitation: CI therapy for TBI (Sponsor: Department of Defense (PT 130232)); Role: Co-Principal Investigator (PI: Edward Taub, PhD); Award period: 9/1/2014-8/31/2017

Title: Post-stroke aphasia and rTMS treatment (PART) study (NIH R01 HD068488); Role: Principal Investigator; award period 1/1/2012-12/30/2017

Title: Quality of Epilepsy Treatment and Costs in Older Americans by Race (QUIET CARE; NIH R01 NS080898); Role: Co-Investigator (PI: Maria Pisu, PhD); award period 10/1/2012-9/30/2016

Title: "Presurgical applications of fMRI in epilepsy" (NIH R01 NS035929); Role: Subcontract PI (PI: Jeffrey R. Binder, MD, Medical College of Wisconsin); award period 7/1/11-6/30/16; NCE 7/1/16-6/30/17.

Title: Psychogenic tremor: Functional magnetic resonance study on emotional processing" (NIH K23 MH092735); Role: Mentor (PI: Alberto Espay, MD, MS); award period 7/1/11-6/30/16

Title: Wireless transcranial magnetic stimulation in magnetic resonance imaging (NIH R21 MH103828); Role: Consultant (PI: Shumin Wang, PhD; Auburn University); award period 7/1/2014-6/30/2016

Title: Imaging the effect of centrotemporal spikes and seizures on language in children" (NIH R01 NS065840); Role: Subcontract PI (PI: Jennifer Vannest, PhD, Cincinnati Children's Hospital Medical Center); award period 9/15/11-7/31/16

Title: FMRI of language recovery following stroke in adults (NIH R01 NS048281; Role: PI; Award period 8/1/08-7/31/14; NCE 7/31/2015)

EPILEPSY CURRENTS

CurrentReview
In Clinical Science

# Psychogenic Nonepileptic Seizures (PNES) as a Network Disorder-EvidenceFromNeuroimagingofFunctional (Psychogenic) NeurologicalDisorders

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In the past decade, there has been a significant growth in the literature with a focus on neuroimaging of psychogenic nonepileptic seizures (PNES). The expectation of this work is theidentificationofbiomarkers for diagnosis, treatment response, and prognosis of PNES. With different studies identifying different potential regions of interest, one critique of the nascent literature is that some studies seemingly contradict otherstudies,showingdivergentresultsinsimilarpopulations. Although the current findings of neuroimaging literature are not helpful to diagnose PNES in individuals, they provide a foundation for postulating neurobiological underpinnings of PNES. Examining the available PNES neuroimaging data and supplementing them with data from studies of other functional neurological disorders (FNDs)/conversion disorders (CDs) to derive commonalities allows for proposing and providing the initial structure of a network model involved in generation and maintenance of PNES (see Figure). This comparison may allowus to identify availableclues andfuturegoals to address existingdeficienciesinthecurrentscience,therebyprovidinga well-supported and unified theory of FNDs/CDs.

The aim of this review is to provide an increased understanding of the macro- and submacroscopic neuroimaging abnormalitiesthatarepresentinpatientswithPNES.Thus,we will explore the idea that PNES/FNDs are a network, rather than afocaldisorder, with avarietyofknownpsychologicalprofiles (1–3)andvariableclinicalsemiologies(4,5),bothofwhichmay depend on which part of the network is affected. Further, we willalso examineevidenceinsupportofspeculations provided in some studies regarding their findings and the relationship between the findings and the disorder itself (6).

## Structural Neuroimaging Data

Several studies have examined (either specifically or as part of the investigation) the presence/incidence of structural neuroimaging abnormalities in patients with PNES. While these studieshavefocusedmostly on"visible"abnormalities (e.g., corticalmalformations,cavernous angiomas,periventricular white matterdisease, or posttraumatic lesions), otherstudies provide additional evidence for submacroscopic abnormalities (differencesincorticalthickness, corticalatrophy, orchanges in the integrity of the white matter tracts). Overall, it is widely acceptedandexpectedthatstructuralimagingin PNESshould be—but does not need to be—normal. Moreover, it is well established that the presence of seemingly epileptogenic abnormalities in patients with new onset or ongoing seizures does not necessarily predict that the patient has or will develop epilepsy (7, 8).

## Lesion Studies

Whileearlyepidemiologic studies of PNES did not reportspecifically onimaging findings (9, 10), otherstudieshavefound thatupto40%ofpatientswithPNEShavestructuralabnormalities on routine MRIs (11–14). Thus, while only a few studies have specificallydescribedMRI abnormalities,it isclear thatstructural imaging abnormalities are prevalent in patients with PNES andmayhavenegativeimplicationsforoutcomes,despitethe factthatthelesionsarenotthedirectcauseof PNES (12). One oftheearlierstudies foundsignificantlyhigherprevalenceof nondominanthemisphericlesionsinpatientswithPNES(15). The findingofthenondominanthemisphericstructuralabnormalities, combined with the notion that regulation of certain emotions is predominantly right-hemispheric, has led Devinsky andcolleaguestohypothesizethatthiscombinationmaybefacilitating the development of conversionsymptomatology(15).

## Volumetric Structural Analyses

MRI studies have also utilized volumetric analyses of regions ofinterestto identifystructuralabnormalities in patientswith PNES.The presence ofthe aforementionedright-hemispheric asymmetry in cerebral pathology in PNES was recently supportedbyanotherstudy thatshowed rightwards asymmetryofthe uncinatefasciculus(UF;structuralconnectivity)inPNESandpostulated a relationship between this finding and thesymptoms

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of depression and anxiety that are frequently present in this population(3,16,17).Further,thisstudyshowedanassociation between the age at PNES onset and the degree of UF asymmetry (16). However, this study didnotexaminetherelationship between UF asymmetryand anyother neuropsychiatricfindings.

Anotherstudydocumenteddecreasedcorticalthickness in the right motor and premotor regions. Here, also, while a relationshipbetweencorticalthicknessanddepressedmood was observed, a comparison to controls with similar mood disorders was not performed, questioning whether the findingsarerelatedtodepressionorPNES(18).Otherstudiesdid notconfirm therightwards structural findings (11, 19). In fact, studies have documented that at least some of the structural findings are present more so in the left than in the right hemisphere. For example, one study documented widespread bilateral cortical thickness, surface area, and sulcal depth abnormalities in areas involved in emotion processing, includingthe insula, orbitofrontal, andprecentralregions(20). In this particular study, in addition to various positive and negative correlations between right medial orbitofrontal cortical thickness and neuropsychological tests, the authors observed increased thickness of the left inferior (ventral) anterior insula (20). A few studies that involved not only patients with PNES butalso other FND semiologies (e.g., functional motor disorders[FMDs]) describedstructuraldifferences between patientsandcontrolsthatappearto becommonacross FNDs. Forexample, one studydescribedreducedcorticalthickness of the left anterior cingulate in patients versus controls, while within-groupanalysesshowedpositivecorrelationsbetween personality trait testing and anterior cingulateand right lateral corticalthickness (21). Anotherstudyfoundinverse associations between left insular volume and functional neurological symptoms with childhood abuse burden in women (22). Also in this study, when men were included in the analyses, associations were notedbetweenthesymptoms of PTSD andanterior cingulate volume (22). Finally, one report linked, in univariateanalyses,increasinghippocampalgraymattervolume and 6-monthmentalhealthoutcome in patients with FNDs (predominantly functional [psychogenic] movement disorders, PNES, andfunctionalweakness); these correlationsdid not survive correction for anxiety and life events scores (23).

### Diffusion Tensor Imaging

Afewneuroimagingstudiesexaminedstructuralconnectivity among brain regions. A diffusion tensor imaging (DTI) study showed predominantly left-hemispheric white matter tract changes connecting left UF, left superior temporal gyrus (STG), andleft subcorticalstructures (24).The previouslymentioned study(16)documentedasymmetryinUFinpatientswithPNES compared tocontrols that was related to the age of onset. Another DTI study described changes in small-worldness in PNES when compared to controls with a shift towards more regular organization of the network specifically in the attention, sensorimotor, subcortical, and default-mode networks (25). Finally, a recent meta-analysis indicated that the area that may be semi-consistentbetweensomestudiesisaspecificareainthe left anterior inferior insula—labeled in the study more broadly as left temporal lobe (6). The findings from the last study are in agreement with a study in patients with FNDs that found reduced left anterior insula volume in volumetric analysis in patients who reportedthe mostsevereimpairmenton SF-36; the authors also observed a relationship between reduced amygdala volumes and reduced mental health (26). These seemingly inconsistentandincongruentfindings suggest that thestructuralabnormalitiesin PNES maybemultifocaland, in conjunction with thevariablesemiological presentationsofthe PNES, indicatethatabnormalitiesinvariousareasofthe brain may result in similar clinical phenotypes. This notion is supported by the recent finding of higher incidence of multifocal neuroimaging findings in PNES versus epilepsy (11).

### Neurometabolic Studies

Several metabolic studies inpatients with PNES supportthe aforementioned multifocal structural findings. One single photon emission computed tomography (SPECT) study documented brain hypoperfusion in 3 of 11 participants, one of each: bilateralparietal, right temporal, or righthemispheric (27). Another SPECT study showed similarly multifocal abnormalities in 3outof10 patients with PNES (28). Finally, inamore recent SPECT study, 2 of 3 participantsshowedsubtraction ictal SPECTco-registered to MRI (SISCOM) hypoperfusion in 1 participant in the left insula and in the right insula and lateral frontal lobe in the second participant (29). Overall, interictaland ictal SPECT findings in over 100 patients (some with comorbid epilepsy) includedin the above and otherstudies indicatethat 10 to 20 percentmay havefocal hypoperfusion. However, a single cerebral structure with ictalhypoperfusion that correlates with the PNES onsetlocation has notbeen identified (29).

In contrast to SPECT studies where comparisons have been madetopatients with epilepsy, arecent PET studycompared patients with PNES tohealthycontrols to identifytwo areas of hypometabolism: right inferior parietal and centralregion, and bilateral anteriorcingulate (30). The consistent finding from thesestudies is that the metabolic abnormalities are present in the minority of investigated patients in various brain areas and notnecessarilyina singlespecificbrainregion. Nevertheless, manyof thestudies indicate involvementofbrainregions thatare partof, orare responsiblefor,emotion processingand motor control, both of which are postulated to be involved in initiation and maintenanceof PNES. Tothe bestofourknowledge, innoneofthese studies was correlation with neuropsychiatric variablesperformed.

### Functional MRI Task Data

The available functional imaging data are even more complicatedand difficult to interpret. However, claritystarts to emerge, assomeofthe studies correlate neuropsychiatricvariables withneuroimaging results. ThefMRI studies have been largely conducted using task (fMRI) and resting state fMRI (rs-fMRI), and theirresultsareschematicallydepictedintheFigure,wherethe atpresentidentifiednodes of the network are derivedfrom the structural studies and theconnections betweenthe nodes are derived fromthestructuralandfunctionalconnectivitystudies.

One study did not find any differences between healthy controls and patients with PNES for either one of two fMRI tasks: encodingofpictures with highsentimental value and Stroop color naming (testing for dissociation; 31). Of interest,

these authors reported that their entire sample of 11 patients with PNES was free of any comorbid psychopathology, which occurs in less than 5% of PNES populations (31). In this study, the dissociation scale scores were correlated with rs-fMRI (see following). Other fMRI studies examined activation patterns in PNES using various versions of the emotion processing task (called "valence task" in some studies). One study compared the involvement of the emotion-processing circuits (emotional faces fMRI task) in PNES to matched healthy controls to show differences in responses to various facial emotions in frontal, parietal, and motor regions as well as in cerebellar, orbitofrontal/frontopolar, and insular regions (32)

Since there are currently very few fMRI studies in PNES, we supplemented the PNES data by reviewing activation patterns from other FND populations, with the understanding that FMDs (functional atasia-abasia, etc.) and FNDs/CDs (including PNES) are different semiologic expressions of the same psychopathological somatoform disturbance (33–36). In one study of patients with FMDs, the facial emotion processing fMRI task showed increased response in amygdala in FMDs compared to controls (37). In another study, the same authors showed that an action selection task activates the motor and emotion circuit differentially among patients with various FMDs and healthy controls (38). Finally, the same group analyzed data focusing on motor initiation in patients with FMD to document hypoactivation in the temporoparietal junction (TPJ), suggestive of deficits in multisensory integration in FMDs (39). In two other FMD fMRI activations studies, the authors compared patients with well-defined psychogenic dystonia or psychogenic tremor to controls, using emotional faces and intense emotion fMRI tasks (40, 41). In the first study, no differences were demonstrated among the groups in the activation patterns for standard motor tasks, indicating that the motor generators involved in the production of voluntary movement are the same in functional dystonia and healthy controls. They documented differential activations, however, in temporal gyrus, precuneus and inferior frontal gyrus with the faces task, while the intense emotion task also induced functional activation differences in insula, motor cortex, and fusiform gyrus (40). In the second FMDs study, patients with psychogenic tremor had differential activations in response to the emotional faces task in the paracingulate and left Heschl's gyrus, while there were no differences in the intense emotion task between the groups (41). Finally, two other FMD studies need to be mentioned briefly (42, 43): In the first study, the authors showed that motor inhibition in patients with FMDs is mediated by the inferior frontal gyrus with extension to the anterior insula, with clear differences between patients with FMDs and feigning subjects, especially in the medial prefrontal regions (42). The second study, using a combination of passive movement and emotional stimulation, resulted in amygdala hyperactivity, while connectivity analysis showed increased interaction between the amygdala and subthalamic nucleus/SMA (43). These studies document both similarities and differences between specific brain regions' involvement among various FNDs. Unfortunately, in most of the FNDs studies, correlations with neuropsychiatric measures or comparisons to participants matched for psychopathology are performed infrequently, leaving the psychopathological inferences of some of the studies speculative.

**Functional Connectivity Data**

Functional connectivity analyses provide some additional and necessary insights into alterations of the brain networks associated with PNES. Several studies have been conducted to date in patients with PNES, so studies in other FNDs are discussed only briefly. Four studies published on the same group of subjects addressed various aspects of resting state connectivity; although Structured Clinical Interview for DSM-IV (SCID) was conducted in the participants to exclude active psychopathology, correlations of comorbidities with neuroimaging were not performed. The first study assessed neural connectivity by the means of functional connectivity density mapping (FCDM) to show that, in comparison to 20 healthy controls, 18 patients with PNES had abnormal FCDM in frontal, sensorimotor, and occipital cortex in addition to insula and occipital cortex (44). In the second study, the authors combined DTI and rs-fMRI, to analyze connectivity differences between PNES and controls using graph theory (25, 45). As noted, the patients with PNES exhibited altered small-worldness in the structural and functional networks and altered nodal characteristics, which were thought to be related to the unstable cognitive–emotional and motor systems in PNES. Their third study duplicated the above results, performing a third type of analysis: fractional amplitude of low-frequency fluctuations (fALFF; 46). In the final manuscript, they examined the connectivity of the insula after dividing it into three subregions (ventral anterior insula [vAI], dorsal anterior insula [dAI], and posterior insula [PI]; 47). Interestingly, they found differential connectivity patterns of insular subregions: vAI was connected to the other insula, cingulate, SMA, and frontal and temporal gyri; dAI was connected with the other insular subregions as well as cingulate, precentral and supramarginal gyri, and parietal region; the PI was connected with the other insula, as well as cingulate and STG (47).

Overall, the findings of these four studies indicate altered functional connectivity within various parts of the networks that may be involved in PNES generation and maintenance. These network regions include executive control, frontoparietal, sensorimotor, and default mode networks that were shown to be significantly associated with dissociation symptomatology in one PNES study (31,48). This study (31) supports the notion that while insula may be very involved in this generation and maintenance of PNES, the participation of its various parts may reflect their functional separation (49). Another study indicated differences in connectivity between specific brain regions between PNES and controls—inferior temporal gyrus and parahippocampal gyrus/uncus, between parahippocampal gyrus/uncus and middle temporal gyrus, and between STG and paracentral regions (32). Of importance is that the previously mentioned meta-analysis of all available neuroimaging studies of PNES points towards anterior inferior insula as the potential common structural and functional substrate of PNES (6)

The findings in PNES correspond well with findings from other FND fMRI studies. For example, one study identified increased connectivity and directionality of the information flow from the right amygdala to the supplementary motor cortex (SMC), indicating the possibility of greater interaction between these structures in FMDs and a mechanism for an upstream control and modulation of motor activity (37). Another study of life events in patients with CDs indicated differences in DLPFC

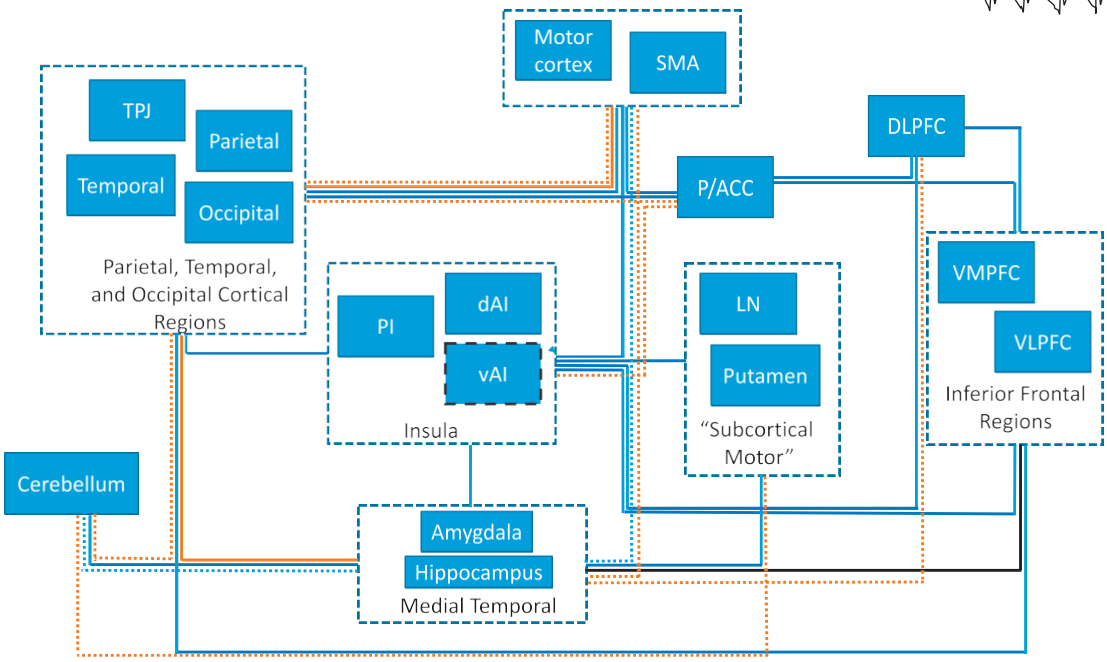


**FIGURE.** Schematics of possible nodes of the network underlying development and maintenance of psychogenic nonepileptic seizures (PNES) derived from structural neuroimaging studies of patients with PNES and other functional neurological disorders/conversion disorders (FND/CDs) and possible connections between those nodes derived from functional and structural connectivity studies. Colors indicate from which studies the connections were derived: BLUE = resting state connectivity; BLACK = structural findings/structural connectivity (dashed line around vAI is derived from the meta-analysis of some of the neuroimaging studies of PNES; 6); ORANGE = task-related functional connectivity; DASHED BLUE = connectivity noted in other FNDs/CDs, in addition to the connectivity in PNES; DASHED ORANGE = task-related functional connectivity (various tasks).

and hippocampal connectivity during the performance of an escape task that was associated with increased fMRI activity in the TPJ and SMA (50). Other previously mentioned studies in patients with FMD sindicated changes in connectivity between left amygdala and left middle frontal gyrus (41)

## Conclusion

In summary, the findings from a number of neuroimaging studies indicate that the submacroscopic abnormalities present in patients with PNES/FNDs are multifocal and, in some cases, associated with specific neuropsychiatric findings. The overlap among the networks involved in the generation and maintenance of PNES and other FNDs indicates that FNDs in general (and PNES in particular) are network disorders, and the symptoms associated with the disruption of various parts of the networks may result in the observed variation in the clinical symptoms (51). Unfortunately, the quality of the available studies specific to PNES is overall low, with very few studies examining the neuropsychiatric findings in conjunction with the neuroimaging findings or controlling for the neuropsychiatric abnormalities that are so prevalent in patients with PNES/FNDs.

Another major drawback of the currently available studies is the small sample size that does not allow comparison of patients with PNES/FNDs to controls matched for neuropsychiatric conditions. Finally, approaches to the investigations vary among centers and investigators and depend on availability of subjects and expertise in methods used to analyze the data.

To overcome these limitations, large studies are needed that specifically control for neuropsychiatric comorbidities. Further, the experiences of the seizures in patients with PNES are in many ways similar to experiences of patients with epilepsy (52, 53). Thus, comparisons to patients with epilepsy, such as the one recently performed (32), are needed to better delineate the network abnormalities that are specific to PNES and where an overlap with neuroanatomically based brain disorders—including multifocal, such as traumatic brain injury—is present. While treatments for seizures exist (54), understanding the functional neuroanatomy of PNES may, in turn, provide better targets for interventions for these patients and allow a more personalized approach.

## Abbreviations

SMA – supplementary motor area
ACC – anterior cingulate cortex
DLPFC – dorsolateral prefrontal cortex
SCmotor–subcortical motor (striatum/putamen)
VMPFC – ventromedial prefrontal cortex
VLPFC – ventrolateral prefrontal cortex
PI – posterior insula
dAI – dorsalanterior insula
vAI–ventralanterior insula
TPJ – temporoparietal junction
PCC – posterior cingulate cortex
LN – lentiform nucleus

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# Neuroimaging Biomarker for Seizures

Log Number: EP160028

Award Number: W81XWH-17-1-0619

**PIs:** William Curt LaFrance, Jr., MD, MPH, Providence RI; Jerzy P. Szaflarski, MD, PhD, Birmingham AL; Andrew Blum, MD, Providence, RI

**Org:** Ocean State Research Institute,Inc. **Award Amount:** $3,687,750

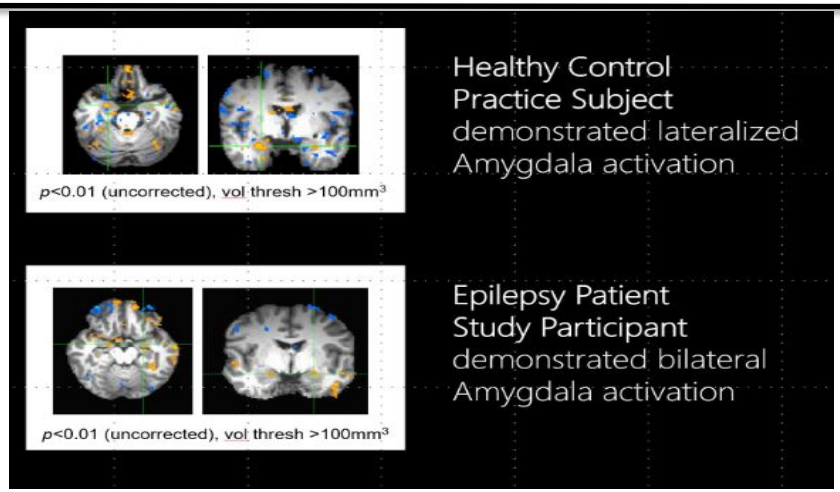
## Study/Product Aim(s)

• **Aim 1:** To compare neural correlates of response to emotional and stressful stimuli in 88 participants with PNES and 88 participants with PTE before and after cognitive challenge, CBT for Seizures (CBT-Sz). Participants with PNES and PTE will be compared to 88 participants 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.

• **Aim 2:** To investigate changes in neural circuitry for emotional processing and stress response in the participants with seizures, after receiving CBT-Sz, and to correlate these changes with symptomatic improvement.

## Approach

We are performing longitudinal fMRI and detailed neuropsychiatric assessments in patients with PNES or with PTE who undergo CBT-Sz, while controlling for common comorbidities in this population. Participants are recruited from the Providence VA Medical Center, Rhode Island Hospital, and University of Alabama, Birmingham (UAB).




**Accomplishments:** MRI data pre-processing analysis pipelines have been designed. Pre/post fMRIs have been completed within our proposed 13 week timeframe.

## Timeline and Cost

| Activities | 17 | 18 | 19 | 20 | 21 |
|---|---|---|---|---|---|
| **Major Task 1**: Refinement and finalization of fMRI, regulatory approval, and establish data systems, purchase materials. | | | | | |
| **Major Task 2:** Participant recruitment, pre-post evaluation, treatment, Aims 1 and 2. | | | | | |
| **Major Task 3**: Continuation of research regulatory compliance. | | | | | |
| **Major Task 4:** Data analysis and uploads. | | | | | |
| **Major Task 5:** Prepare scientific manuscripts and follow-on research grant proposals; Present results at conferences. | | | | | |
| **Estimated Budget** | $935,820 | | $905,080 | $914,054 | $882,879 |

**Updated: October 2018**

## Goals/Milestones – CY18 Goals (Months 7-9)

**Goals proposed in Year 1:**

- ❑ **Regulatory approval, multi-site infrastructure, development of analysis procedures**
- ❑ **Recruitment**
- ❑ **Baseline and Post Treatment Assessment**
- ❑ **Treatment and Retention**
- ❑ **Ongoing Study Meetings**
- ❑ **Prepare for annual regulatory audits/compliance**
- ❑ **Start fMRI and behavioral preliminary data analyses**

**Comments/Challenges/Issues/Concerns**

We recruited and enrolled 43 participants in year 1. We have discussed and developed plans to reach our recruitment goals for year 1 and year 2.

**Budget Expenditure to Date**

*Projected Expenditure for Year 1: $935,819.10*

*Actual Expenditure to Date*: *$502,786.28 (residual to carryover to Yr2)*