

AWARD NUMBER: W81XWH-17-1-0619

TITLE: Neuroimaging Biomarker for Seizures

PRINCIPAL INVESTIGATOR: William Curt LaFrance, Jr., MD, MPH

CONTRACTING ORGANIZATION: Ocean State Research Institute
Providence, RI 02903

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Fort Detrick, Maryland 21702-5012

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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					
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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: 42%

Milestones: Recruitment and Follow-up

- Timeframe: Months 7-48
- Percent Completed: year 2: 93%; overall of 4 year study: 42%

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 2: 100%; overall of 4 year study: 42%

Milestones: Data summaries and analysis

- Timeframe: Months 6-48
- Percent Completed: 100% to date.

Major Goal 5: Prepare scientific manuscripts and follow-on research grant proposals; prepare and present results at conferences

- Timeframe: Months 13-48
- Percent Completed: 100% to date.

Milestones: submit results for publication

- Timeframe: Months 45-48
- Percent Completed: 0%, not started yet.

What was accomplished under these goals?

In year 1, we established multi-site infrastructure, obtained regulatory approval from all appropriate sites, and started enrollment. Also, in year 1, we developed the data analysis pipeline to be used for neuroimaging and neurobehavioral data.

During year 2, we encountered enrollment challenges and addressed them by problem-solving. We meet weekly via teleconference as a research team, to identify problems and develop solutions.

With respect to the study, since starting participant 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 treatment retention rate is above 80%. We have also completed pre/post fMRIs and evaluations for participants. We enrolled 111 participants as of 9/15/2019, and we have exceeded our to-date projected TBI control recruitment goal for both year 1 and 2.

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

We remain compliant with all research regulations. We have completed continuing reviews for all sites.

In addition, three posters were prepared for conference presentations.

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

MRI training for study staff (Goodman) included novel analytic approaches. In the year 1 startup phase, study clinicians (Drs. Gaston & Grayson) completed CBT-Sz treatment training and now continue treating participants in the study. Research staff (Tocco, Vogel, Martin) completed SCID-5 training and are in the process of MRI level 3 training.

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, including the Epilepsy Foundation. Dr. LaFrance lectures nationally discussing TBI, ES and PNES.

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

4. **IMPACT:**

What was the impact on the development of the principal discipline(s) of the project?

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 comprehensive neuropsychiatry approach, we are increasing dialogue between neurology and mental health practitioners. With this study, we are bridging clinical and research neuroscience, including neurology, psychiatry, neuroimaging, neurophysiology and biostatistics.

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 of ES, PNES, and TBI, people with these disorders often face stigma and skepticism about their condition. Patients with epilepsy still encounter stigma in the community because of lack of knowledge about seizures. Likewise, for PNES, we can reduce the misconception that nonepileptic seizures are “pseudo-” (meaning false or fake), by improving public knowledge through researching effective treatments for it. With new neuroimaging findings for both types of seizure disorders, and by expanding on the limited amount of research that has been done on treatments for PNES, the results of this project can have a profound contribution to research and ultimately an impact on the public’s attitude towards individuals with PNES and ES.

5. **CHANGES/PROBLEMS:**

Changes in approach and reasons for change

During year 2, we made changes to our participant compensation schedule. Originally PTE and PNES patients were compensated \$50 in total for completing each treatment session. We modified our language to compensate \$40 for completing each treatment session and \$10 for completing the session survey, so \$50 in total. This change was made to ensure we are able to collect weekly survey data from participants.

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

During year 2, we experienced some challenges that contributed to our delay in enrollment, as well as flow of treatment.

- Problem: One UAB therapist was out for maternity leave in 2018; The other UAB therapist was out on maternity leave May-August 2019. There was only one UAB therapist seeing patients during leave.
 - Plan: Dr. Jeff Wincze, PhD, from RIH, who co-wrote the Therapist Guide for the Workbook, will be seeing patients to help fill the UAB therapist gap.
- Problem: Limited MIR scanning time at UAB MRI –Booking participants 7-8 weeks out for 1st MRI.
 - Plan: Birmingham Coordinator has been attempting to schedule the 2nd MRI scan 13 weeks out for patients at their first treatment session. Also, MRI scan hours have become available on weekends to scan.

- Problem: Many seizure disorder patients do not have transportation.
 - Plan: We have developed a telehealth system for all sites to use to reach patients in surrounding states and those without access to reliable transportation.
- In addition, we have taken extra steps to expand our recruitment efforts at both sites:
 - In Alabama, we received approval for Birmingham VA as a recruitment-only site.
 - At our Providence site, we received access to a large database containing the names of Veterans who have had a seizure related visit in all of VISN 1.

Changes that had a significant impact on expenditures

Delays

Year 1:

- At Providence, RI: both the research coordinator and the research assistant were projected to start full time by month 2. Both staff members were hired by month 2, but did not start until 2 months later due to delays in the VAMC hiring process.
- 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.

Year 2:

- Nothing to report.

Favorable Developments

Year 1:

- 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.

Year 2:

- Nothing to report.

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

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.

- Balachandran, N., Goodman, A. M., Allendorfer, J. B., Martin, A. N., Vogel, V., Tocco, K., LaFrance Jr., W. C., & Szaflarski, J. P. (2019). Altered Neural Response to Stress is Related to Mental Health Symptoms in Psychogenic Nonepileptic Seizures Following TBI. Poster to be presented at the Annual Meeting of the American Epilepsy Society. Baltimore, MD, December 2019.
- Goodman, A. M., Allendorfer, J. B., LaFrance Jr., W. C., & Szaflarski, J. P. (2019) White Matter Integrity and Neurite Morphology are Related to Patient Profiles in Psychogenic Nonepileptic Seizures Following TBI. Poster presented at the Annual Meeting of the Organization for Human Brain Mapping. Rome, Italy.
- Goodman, A. M., Allendorfer, J. B., Baird, G., Blum, A., Bolding, M., Correia, S., ver Hoef, L., Gaston, L., Grayson, L., Kraguljac, N., Lahti, A., Martin, A., Monroe, W., Philip, N. S., Skidmore, F., Tocco, K., Vogel, V., LaFrance Jr., W. C., & Szaflarski, J. P. (2019) Axonal integrity and neurite morphology in psychogenic nonepileptic seizures following TBI. Poster to be presented at the Annual Meeting of the American Epilepsy Society. Baltimore, MD, December 2019.
- **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: Postdoctoral 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

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Providence VA Medical Center Personnel

Co-I: Stephen Correia, PhD: nothing to report.

Co-I: Noah Philip, MD: nothing to report.

CO-PI: William Curt LaFrance, Jr., MD, MPH:

- Changes to Ongoing Research Support
 - Removed: Seed Grant, A Biomarker in Veterans with mTBI (7/1/15-6/30/16 n.c.e)

University of Alabama at Birmingham Personnel

Co-PI: Jerzy Szaflarski, Md, PhD:

- Additional Positions and Honors
 - Professor, Department of Neurosurgery; University of Alabama at Birmingham, Birmingham, AL
 - Member, Alabama State Medical Cannabis Study Commission (nominated by Governor Kay Ivey)
 - Member, National Coordinating Center for Epilepsy under the HRSA / Maternal and Child Health Bureau (MCHB) – joint committee of AAN and AAP
- Additional Ongoing Research Support
 - Title: Effects of perampanel (PER) on inflammation in human epilepsy – MRS-thermometry (MRS-t) study; Eisai; Role: Principal Investigator; Award period 11/1/2019-10/31/2021
 - Title: Cognitive and Neural Basis of Functional Communication Deficits in Post-Stroke Aphasia NIH R01DC017137; Role: Co-Principal Investigator (with Daniel Mirman, PhD, University of Edinburg); Award period 9/1/2019-8/31/2024
 - Title: A preliminary study of the neurobiology of AAC-induced language recovery in post-stroke aphasia (R15/NINDS); Role: Mentor (PI: Aimee Dietz, PhD; University of Cincinnati); Award period 8/1/2018-7/31/2021
- Additional Completed Research Support
 - 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
 - Title: Relationship between serum CBD levels and seizure control; Serina Therapeutics Inc; Role: Principal Investigator; Award period 10/1/2017-12/31/2018
 - Title: Perampanel as a neuroprotective and antiepileptic compound in animal model of TBI (Eisai, Inc.); Role: Principal Investigator; Award period: 7/1/2016-12/31/2018

Co-I: Jane Allendorfer, PhD:

- Additional publications related to this project:
 - Allendorfer JB, Nenert R, Hernando KA, DeWolfe JL, Pati S, Thomas AE, Billeaud N, Martin RC, Szaflarski JP (2019). fMRI response to acute psychological stress differentiates patients with psychogenic non-epileptic seizures from healthy controls - A biochemical and neuroimaging biomarker study. *Neuroimage Clinical*. 24:101967. PMID: 31446314

Co-I: Tyler Gaston, MD:

- Additonal manuscripts:
 - Gaston TE, Bebin EM, Cutter GR, Ambah SB, Liu Y, Grayson, LP, Szaflarski JP, UAB CBD Program. Drug-drug interactions with cannabidiol (CBD) appear to have no effect on treatment response in an open-label Expanded Access Program. *Epilepsy Behav.* 2019 Sep; 98(PtA): 201-206. doi: 10.1016/j.yebeh.2019.07.008.
 - Szaflarski JP, Hernando K, Bebin EM, Gaston TE, Grayson L, Ampah S, Moreadith R. Higher Cannabidiol Plasma Levels are Associated with better seizure response following treatment with a pharmaceutical grade cannabidiol. *Epilepsy & Behavior* 2019; 95: 131-136.
 - Allendorfer JB, Nenert R, Bebin EM, Gaston TE, Grayson LE, Hernando K et a. fMRI Study of Cannabidiol-induced changes in attention control in treatment-resistant epilepsy. *Epilepsy & Behavior* 2019; 96: 114-121

Co-I: Leslie Grayson Perry, MD:

- Personal statement updated
- Additional manuscripts:
 - Leslie P Grayson, Jurriaan Peters M Peters, et al, “Neurodevelopmental impact of early epilepsy surgery in Tuberous Sclerosis Complex,” planning submission to *Epilepsia* pending completion of ongoing review by TACERN physicians
 - Leslie P. Grayson, et al, “Longitudinal Impact of Epidiolex on EEG Measures in Subjects with Treatment Resistant Epilepsy,” planned submission to *Epilepsia* upon completion of review by authors
 - Gaston TE, Bebin EM, Cutter GR, Ambah SB, Liu Y, Grayson, LP, Szaflarski JP, UAB CBD Program. Drug-drug interactions with cannabidiol (CBD) appear to have no effect on treatment response in an open-label Expanded Access Program. *Epilepsy Behav.* 2019 Sep; 98(PtA): 201-206. doi: 10.1016/j.yebeh.2019.07.008.
 - Szaflarski JP, Hernando K, Bebin EM, Gaston TE, Grayson L, Ampah S, Moreadith R. Higher Cannabidiol Plasma Levels are Associated with better seizure response following treatment with a pharmaceutical grade cannabidiol. *Epilepsy & Behavior* 2019; 95: 131-136.
 - Allendorfer JB, Nenert R, Bebin EM, Gaston TE, Grayson LE, Hernando K et a. fMRI Study of Cannabidiol-induced changes in attention control in treatment-resistant epilepsy. *Epilepsy & Behavior* 2019; 96: 114-121
- Additonal posters
 - “Longitudinal Impact of Cannabidiol on the EEG,” Hernando, **Grayson** et al. 2019. Annual Epilepsy Society meeting in Baltimore, MD 12/2019
 - “Neurodevelopmental Impact of Early Epilepsy Surgery in Tuberous Sclerosis Complex: Updated Results and Future Considerations.” **Grayson**, et al. 2019 Annual Epilepsy Society meeting in Baltimore, MD
 - “Structural MRI Markers of the Epileptogenic Zone in Young Children with TSC undergoing Epilepsy Surgery.” Nijman, Yang, Jaimes, Prohl, **Grayson**, et al. 2019 Annual Epilepsy Society meeting in Baltimore, MD
 - “Effects of Highly Purified Cannabidiol (CBD) on fMRI of Working Memory in Epilepsy.” Gaston TE, Allendorfer JB, Bebin EM, **Grayson L**, Houston JT, Szaflarski JP. The Organization for Human Brain Mapping, June 2019, Rome, Italy.

Co-I: Mark Bolding, PhD: nothing to report
Co-I: Lawrence Ver Hoeft, PhD: nothing to report

Rhode Island Hospital Personnel

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

What other organizations were involved as partners?

In-Kind Recruitment Support:

Organization Name: Epilepsy Foundation, New England

Location of Organization: Massachusetts

Organization Name: CURE (Citizens United for Research in Epilepsy)

Location of Organization: Chicago, IL

Organization Name: Boston VAMC Epilepsy Program – Harvard Epilepsy Program

Location of Organization: Boston, MA

Organization Name: West Haven VAMC – Yale Epilepsy Program

Location of Organization: West Haven, CT

Organization Name: Brain Injury Association

Location of Organization: East Providence, Rhode Island

Organization Name: Brown Synapse: Brain Injury Support Group

Location of Organization: Providence, Rhode Island

Organization Name: Care New England System

Location of Organization: Providence, Rhode Island

8. SPECIAL REPORTING REQUIREMENTS

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

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)

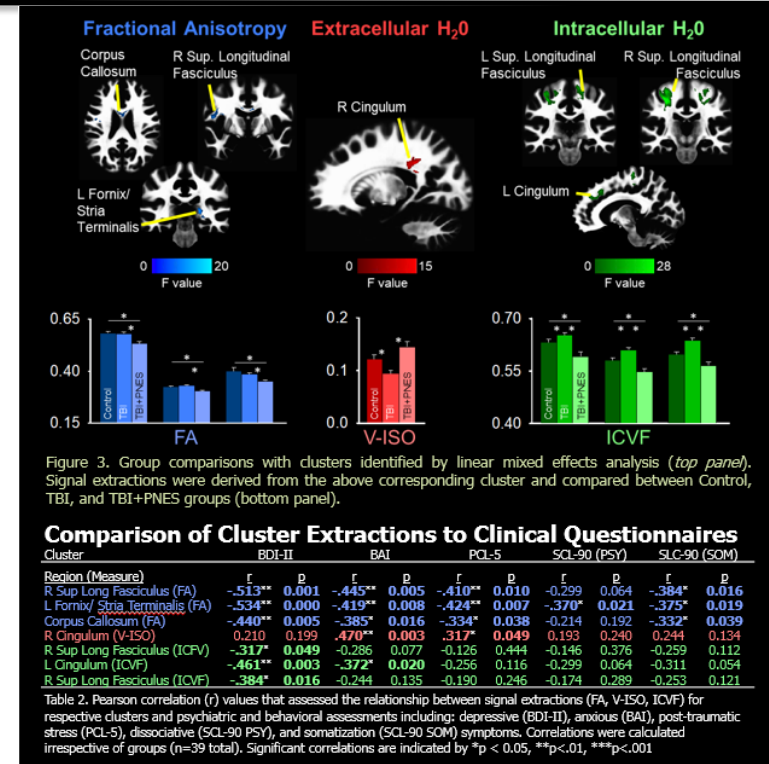
- Aim 1:** To compare neural correlates of response to emotional and stressful stimuli in 88 participants with PNES and 88 participants with PTE before and after cognitive challenge, CBT for Seizures (CBT-Sz). Participants with PNES and PTE will be compared to 88 participants with a history of TBI who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

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



Accomplishments: Axonal integrity and neurite morphology in psychogenic nonepileptic seizures following TBI poster to be presented at the Annual Meeting of the American Epilepsy Society.

Goals/Milestones

Major goal 5 was started and to date three posters have been prepared for conference presentations.

Comments/Challenges/Issues/Concerns

We recruited and enrolled 68 participants in year 2. We continue to discuss and develop plans to reach our recruitment goals for year 3.

Budget Expenditure to Date

Projected Expenditure for Year 2: \$904,178.00

Actual Expenditure to September 30: 858,282.16 (residual to carryover to Yr3)