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, INC.
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REPORT DATE: October 2020

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
Oct 2020	Annual	9/15/2019 to 9/14/2020

4. TITLE AND SUBTITLE
Neuroimaging Biomarker for Seizures

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-17-1-0619

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)

OCEAN STATE RESEARCH INSTITUTE, INC.
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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
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 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	28	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: 61%

Milestones: Recruitment and Follow-up

- Timeframe: Months 7-48
- Percent Completed: year 3: 67%; overall of 4 year study: 61%

Major Goal 3: Continuation of research regulatory compliance

- Timeframe: Months 7-48
- Percent Completed:100% to date.

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 3: 100% for MRI data; 90% for behavioral data/session videos
    - Overall percent completed for 4 year study: 61% for MRI data; 51% for behavioral data/session videos

Milestones: Data summaries and analysis

- Timeframe: Months 6-48
- Percent Completed: 97% 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: 10%, primary outcome paper not started yet. Secondary abstracts and papers, under review and accepted. Three abstracts have been presented at conferences.

What was accomplished under these goals?

In year 1, we established multi-site infrastructure, obtained regulatory approval from all appropriate sites, developed our study database, and started enrollment. Also, in year 1, we developed the data analysis pipeline to be used for neuroimaging and neurobehavioral data. All fMRI analysis procedures have been developed and tested, and processing pipeline is in place.

During year 2, we completed pre/post fMRIs and evaluations for participants, as well as starting 8/12 month follow-ups. We established relationships with many seizure disorder and traumatic brain injury clinicians, clinics, and foundations. For data collection, we put in place target dates to ensure our database is up to date and appropriately reflects our progression in the study. In addition, we coordinated periodic data checks with the data manager for quality assurance.

In year 3, we continued making progress with the above accomplishments, while also achieving new goals. We established an annual data submission schedule, created a data mapping/validation process with FITBIR's ETL and imaging tools, and completed our first submission to the FTIBIR data respository. The data submission included baseline, endpoint, and MRI data for TBI controls and PTE participants.

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. We have enrolled 161 participants as of 9/15/2020. Despite the COVID-19 enrollment university mandated pause from March until June 2020 at the Unviersity of Alabama at Birmingham and until August 2020 at the Providence sites, we have enrolled 89% of our TBI control and 73% of our PNES year 3 enrollment goal. Our CBT-ip treatment retention rate is at 72%, currently. Our MRI completion rate for all arms is 84%, with some MRI visits pending re-scheduling due to COVID.

We continue to meet weekly via teleconference as a research team, to identify problems and develop solutions. We also remain compliant with all research regulations. We have completed continuing reviews for all sites.

Lastly, one manuscript was accepted for publication and published during year 3 and another manuscript is under review.

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.

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 (EF) of America and EF New England. Dr. LaFrance lectures regionally, nationally and internationally discussing TBI, ES and PNES, and he mentions the study in the lectures.

What do you plan to do during the next reporting period to accomplish the goals?
We will continue our recruitment efforts in the next study period. We 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. We are also planning for a no-cost extention to help meet recruitment goals for our PTE population.

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 clnical 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. For PNES, we can reduce the misconception that nonepileptic seizures are "pseudo-" (meaning false or fake), by improving public knowledge through researching evidence-based treatments for the disorder. With new neuroimaging findings for both epileptic and nonepileptic 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
Nothing to report.

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

During year 3, we experienced challenges that contributed to our delay in enrollment, as well as flow of treatment.

- Problem: COVID-19

Site Impacts:

- The Rhode Island Hospital's (RIH) Office of Research Adminstation advised all scheduled in-person interactions to be switched to remote interactions, whenever possible, on March 13, 2020.
- The Providence VA Medical Center (PVAMC) issued an administrative hold on non-critical, in-person interactions with human research subjects on March 18th.
    - The PVAMC site received approval to resume in-person visits at the VA on August 25, 2020.
- Brown Magnetic Resonance Facility (MRF), where the RIH and Providence VAMC participants are scanned, paused all human subject scans on March 16, 2020.
    - The RIH and PVAMC sites received approval to resume at the Brown MRF on August 4, 2020.
- Unversity of Alabama at Birmingham (UAB) was closed to in-person interactions with human subjects on March 16th, which included the Civitan International Neuroimaging Laboratory (CINL).
    - The study received approval to resume on June 22, 2020.

General Impacts:

- Those who were actively in treatment at the PVAMC and UAB at the time could no longer come in person to continue their treatment.
- The closure of the Brown MRF and the CINL facility forced pausing enrollment of new participants at all sites, as the imaging piece is an inclusion criteria for the study.
- At the Brown MRF and CINL, participants are now asked to wear a mask throughout the entire scan appointment.
    - To date, we have had one participant decline coming in for a 2nd MRI scan due to wearing a mask.
- Additional safety procedures were put in place at all sites for screening and sanitization purposes. Participants who screen positive to any of the questions must cancel and reschedule their appointment after the 2 week quarantine period, or provide a negative test result.
- Due to COVID and following institution safety guidelines, there has been a greater number of cancelations and reschuling appointments by participants.
- In the past, we have had a number of participants travel from outside of Alabama and Rhode Island to enroll in the study, but due to travel/institution restrictions, this is not possible at all times.

Actions Taken/Future Plan:

- Throughout March to June/August, all sites continued to screen and contact eligible participants.
- For the participants who were already enrolled in the study, prior to the pause of in-person interactions, were able to continue receiving the treatment via telehealth.
- For new participants at the Providence VAMC, we were recently approved to

conduct consent procedures by video or phone (a wet signature is still required for documentation), which allows us to limit in-person interactions.
    - This is being discussed at the RIH and UAB site as well.

- Problem: We are not meeting our recruitment goals for our PTE population. We are finding many potential particpants do not meet our inclusion criteria of having a abnormal EEG to confirm the diagnosis of epilepsy.
    - Plan: Continue to establish relationships with neurology clinicians in the surrounding areas. In addition, we have taken extra steps to expand our recruitment efforts at sites:
    - 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.
    - Brown Neurology ECW

- Problem: Many patients with seizure disorders 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.
    - Plan: We are exploring transportation options for patients with driving limitations.

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.

Year 3:

- Due to enrollment pause and the site's MRI facility temporarily closed, limited participant reimbursement and no MRI funds from all sites were expendited from April-June, 2020.

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.

Year 3:

- 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, J.P., LaFrance, W.C. 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).
- Goodman, A.M., Allendorfer, J. B., Blum, A., Bolding, M., Correia, S., ver Hoef, L., Gaston, L., Grayson, L., Kraguljac, N., Lahti, A., Martin, A., Monroe, W., Philip, N. S., Vogel, V., Tocco, K., LaFrance Jr., W. C., & Szaflarski, J. P. White matter and neurite morphology differ in psychogenic non-epileptic seizures. *Annals of Clinical and Translational Neurology.* 2020:doi: 10.1002/acn3.51198. PMID: 32991786
- Balachandran, N., Goodman, A. M., Allendorfer, J. B., Martin, A. N., Vogel, V., Tocco, K., LaFrance Jr., W. C., & Szaflarski, J. P. (2019). Relationship between neural responses to stress and mental health symptoms in psychogenic nonepileptic seizures after traumatic brain injury. *Epilepsia*. 2020: under review

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):
Nearest person month worked: *2*
Contribution to Project: *No Change*

Name: Jerzy Szaflarski, MD, PhD
Project Role: *Site PI*
Researcher Identifier (ORCID ID):
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

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:

- Additional Positions and Employment
  - 2019-present Butler Hospital: Director of Psychology and Director of Research in the Memory & Aging Program
- Additional Other Experience
  - 2020-present Director, Care New England COVID-19 Employee Support Service
- Additional Professional Memberships
  - 2020-present Rhode Island Psychological Association
- Additional Contribution to Science
  - Barredo J, Bellone JA, Edwards M, Carpenter L, Correia S, & Philip N. (2019). White Matter Integrity and Functional Predictors of Response to Repetitive Transcranial Magnetic Stimulation for Posttraumatic Stress Disorder and Major Depression. Depression and Anxiety. 36(11): 1047-1057.
  - Asken BM, Thomas KR, Lee A, Davis JD, Malloy PF, Salloway SP, Correia S. (2019). Discrepancy-Based Evidence for Loss of Thinking Abilities (DELTA): Development and Validation of a Novel Approach to Identifying Cognitive Changes. Journal of the International Neuropsychological Society. Dec 11:1-16. Epub ahead of print.
- Additional Ongoing Research Support
  - Alzheimer's Association/National Institute on Aging Baker, L (multisite PI) 2020-2026
  - Protect Brain Health Through Lifestyle Interventions on Reduce Risk (U.S. POINTER)
  - Multi-domain lifestyle interventions to lower risk for Alzheimer's disease
  - Co-I: RI-New England Site

Co-I: Noah Philip, MD:

- Additional Positions and employment

        - Butler COBRE Center for Neuromodulation
            - Neuroimaging and Neuromodulation Core Co-Director
    - Additional Honors
        - 2020 Distinguished Fellow, American Psychiatric Association
        - 2020 Psychiatry Research Teaching & Mentoring Award, Brown Dept. of Psychiatry and Human Behavior
- Additional Contributions to science
    - Barredo J, Aiken E, van 't Wout-Frank M, Greenberg BD, Carpenter LL, **Philip NS**. Neuroimaging Correlates of Suicidality in Decision-Making Circuits in Posttraumatic Stress Disorder. Front Psychiatry. 2019 Feb 12;10:44. doi: 10.3389/fpsyt.2019.00044.
    - van't Wout-Frank M, Shea MT, Larson M, Greenberg BG, **Philip NS**. Combined Transcranial Direct Current Stimulation with Virtual Reality Exposure for Posttraumatic Stress Disorder: Feasibility and Pilot Results. Brain Stimulation. 2019 Jan - Feb;12(1):41-43.
    - **Philip NS**, Barredo J, Aiken E, Larson V, Shea MT, Greenberg BG, van't Wout-Frank M. Theta burst stimulation for posttraumatic stress disorder. American Journal of Psychiatry. 2019 Nov 1;176(11):939-948
    - Zandvakili A, Barredo J, Swearingen HR, Aiken E, Greenberg BD, Carpenter LL, and **Philip NS**. Mapping PTSD Symptoms to Brain Networks: A Machine Learning Study. Translational Psychiatry 2020 Jun 18;10(1):195. doi: 10.1038/s41398-020-00879-2.
- Additional Ongoing research support
    - US Dept. of Veterans Affairs, RR&D, IK1 RX003082, "Establishing Relationships and Developing a Therapeutic Target for Impulsivity and Suicidality Among Veterans with TBI and Co-Occurring Conditions" Role: **Mentor** (PI: Aaronson) 3/1/2020-2/28/2022. I am the neuromodulation mentor for Dr. Aaronson's CDA1.
    - NIMH, R01 MH120126, "Mechanistic circuit markers of transcranial magnetic stimulation outcomes in pharmacoresistant depression." Role: **Site Principal Investigator** (PI: Williams), 9/1/2019-10/31/2024, $415,001 (site total). This study characterizes neuroimaging correlates of therapeutic TMS.
    - VA RR&D I21 RX003338. "sTMS for Substance Use-Disordered Veterans" Role: **Co-Investigator** (PI: McGeary); $199,755; 7/1/2020-6/30/22. This study evaluates potential use of synchronized TMS in Veterans with substance use disorders.

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

- Additional Experience and Professional Memberships
    - Board Member, Functional Neurological Disorder Society
- Additional Contributions to science
    - Cheng Y, Pereira M, Raukar N, Reagan JL, Queseneberry M, Goldberg L, Borgovan T, LaFrance Jr WC, et al. Potential biomarkers to detect traumatic brain injury by the profiling of salivary extracellular vesicles. J Cell Physiol. 2019;234(8):14377-88.

University of Alabama at Birmingham Personnel

Co-PI: Jerzy Szaflarski, Md, PhD:

- Additional Honors
    - 2020 Graduate Dean's Award for Excellence in Mentorship, UAB
- Additional Contribution to science

- Espay AJ, Ries S, Maloney T, Vannest J, Neefus E, Dwivedi AK, Allendorfer JB, Wulsin L, LaFrance WC, Lang AE, Szaflarski JP "Clinical and neural responses to cognitive behavioral therapy for functional tremor" Neurology 2019; 93: e1787-e1798; PMID: 31586023

Co-I: Jane Allendorfer, PhD:

- Additional publications related to this project:
  - Goodman AM, Allendorfer JB, Heyse H, Szaflarski BA, Eliassen JC, Nelson EB, Storrs JM, Szaflarski JP (2019). Neural response to stress and perceived stress differ in patients with left temporal lobe epilepsy. Human Brain Mapping. 40(12):3415-3431. PMID: 31033120
- Additional Honors:
  - 2019 Clinical Investigator Training Program, University of Alabama at Birmingham, Birmingham, AL
- Additional Contributions to science:
  - Espay AJ, Ries S, Maloney T, Vannest J, Neefus E, Dived AK, Allendorfer JB, Wilson LR, LaFrance WC, Lang AE, and Szaflarski JP (2019). Clinical and neural responses to cognitive behavioral therapy for functional tremor. Neurology. 93(19): e1787-e1798. PMCID: PMC6946484

Co-I: Tyler Gaston, MD:

- Additional Contributions to science
  - Gaston TE, Szaflarski M, Hansen B, Bebin EM, Szaflarski JP. Quality of Life in Adults Enrolled in an Open-Label Study of Cannabidiol for Treatment-Resistant Epilepsy. Epilepsy & Behavior 2019; 95: 10-17.

Co-I: Leslie Grayson Perry, MD:

- Additional publications related to this project:
  - Adam M. Goodman, Jane B. Allendorfer, Grayson Baird, Andrew S. Blum, Mark Bolding, Stephen Correia, Larry ver Hoef, Tyler Gaston, Leslie Grayson, Nina Kraguljac, Adrienne C. Lahti, Amber N. Martin, William S. Monroe, Noah S. Philip, Frank Skidmore, Krista Tocco, Valerie Vogel, W. Curt LaFrance, Jr & Jerzy P. Szaflarski. White matter integrity and neurite morphology in psychogenic non-epileptic seizures following TBI. Accepted to Annals of Clincial and Translational Neurology 8/2020.
- Additional Contributions to science:
  - Leslie P. Grayson, et al, "Longitudinal Impact of Epidiolex on EEG Measures in Subjects with Treatment Resistant Epilepsy," submitted to Epilepsy Research 6/2020.
  - Leslie P Grayson, Jurriaan M Peters, et al, "Pilot study of neurodevelopmental impact of early epilepsy surgery in tuberous sclerosis complex" accepted for publication to Pediatric Neurology 4/2020
  - Maaike Nijman, Edward Yang, Camilo Jaimes, Ana K. Prohl, Mustafa Sahin, Darcy A. Krueger, Joyce Y. Wu, Hope Northrup, Scelling S. Stone, Joseph R. Madsden, Aria Fallah, Jeffrey P. Blount, Howard L. Weiner, Leslie Grayson, E. Martina Bebin, Brenda E. Porter, Simon K. Warfield, Sanjay P Prabhu, and Jurriaan M. Peters. Structural MRI Markers of the Epileptogenic Zone in Young

Children with Tuberous Sclerosis Complex undergoing Epilepsy Surgery. Being prepared for submission to AJNR 6/2020.

- MD Thompson, R.C. Martin, L.P. Grayson, S.B. Ampah, G. Cutter, J.P. Szaflarski and E.M. Bebin, Cognitive Function and Adaptive Skills after a One-Year Trial of Cannabidiol (CBD) in a Pediatric Sample with Treatment-Resistant Epilepsy. Accepted to Epilepsy & Behavior 6/2020.
- Tyler Gaston, Jane Allendorfer, Sangeeta Nair, E. Martina Bebin, Leslie P. Grayson and Jerzy P
- Szaflarski. Effects of Highly Purified Cannabidiol (CBD) on fMRI of Working Memory in Treatment Resistant Epilepsy. Epilepsy & Behavior. Volume 112. November 2020. https://doi.org/10.1016/j.yebeh.2020.107358
- Rodolphe Nenert, Jane B Allendorfer, Kathleen Hernando, E Martina Bebin, Tyler E Gaston, Leslie E Grayson, James T Houston, Jerzy P Szaflarski. Cannabiol normalizes resting-state functional connectivity in treatment-resistant epilepsy. Epilepsy & Behavior. Volume 112. November 2020. https://doi.org/10.1016/j.yehbeh.2020.107297

Co-I: Mark Bolding, PhD:

- Goss, A. M., Dowla, S., Pendergrass, M., Ashraf, A., Bolding, M., Morrison, S., Amerson, A., et al. (2020). Effects of a carbohydrate-restricted diet on hepatic lipid content in adolescents with non-alcoholic fatty liver disease: A pilot, randomized trial. Pediatric obesity, e12630. PMCID: pending

Co-I: Lawerence 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.

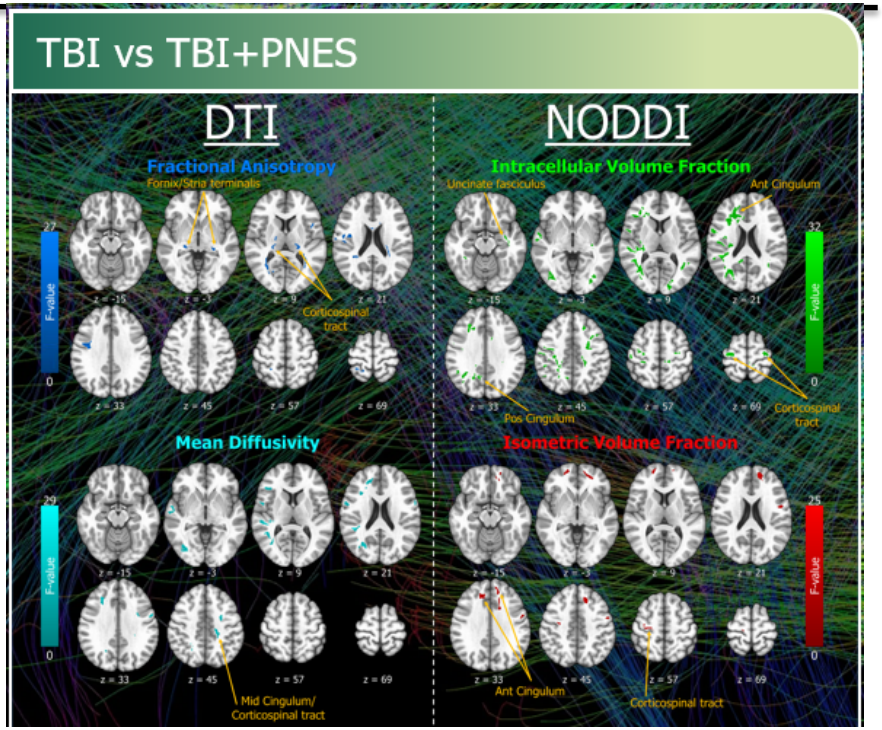
Approach

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

Updated: September 2020



Accomplishments: Results from the 5 linear mixed effects analysis that survived the cluster correction volume threshold ($p<0.01$ uncorrected, $p<.05$ corrected, NN-3). Volume extent thresholds (Monte Carlo simulation) were determined separately for FA (443mm3); MD (460mm3); ODI (437mm3); ICVF (548mm3);and V-ISO (612mm3) based on whole-brain spatial noise distributions for each index. No clusters survived group-level analysis for ODI measures. Clusters that fell within pathways identified a pri ori tracts of interest are identified with yellow arrows and labels.

Goals/Milestones

Major goal 5 was started and to date one manuscript was accepted for publication in the Annals of Clinical and Translational Neurology.

Comments/Challenges/Issues/Concerns

We recruited and enrolled 50 participants in year 3. Due to COVID-19, enrollment was paused from March 12020 to June 2020 (UAB site) and Sept (RIH and PVAMC sites).

Budget Expenditure to Date

Projected Expenditure for Year 3: $ $871,390.00
Actual Expenditure to September 30: $741,531.76 (residual to carryover to Yr4)

ANNALS of Clinical and Translational Neurology
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RESEARCH ARTICLE

White matter and neurite morphology differ in psychogenic nonepileptic seizures

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Funding Information
This research was supported by the US Department of Defense [DOD EP160028 (W81XH-17-0619)]. PIs: LaFrance Jr, WC, and Szaflarski, JP.

Received: 14 May 2020; Revised: 10 August 2020; Accepted: 24 August 2020

doi: 10.1002/acn3.51198

Abstract

Objective: To further evaluate the relationship between the clinical profiles and limbic and motor brain regions and their connecting pathways in psychogenic nonepileptic seizures (PNES). Neurite Orientation Dispersion and Density Indices (NODDI) multicompartment modeling was used to test the relationships between tissue alterations in patients with traumatic brain injury (TBI) and multiple psychiatric symptoms. **Methods**: The sample included participants with prior TBI (TBI; N = 37) but no PNES, and with TBI and PNES (TBI + PNES; N = 34). Participants completed 3T Siemens Prisma MRI high angular resolution imaging diffusion protocol. Statistical maps, including fractional anisotropy (FA), mean diffusivity (MD), neurite dispersion [orientation dispersion index (ODI)] and density [intracellular volume fraction (ICVF), and free water (i.e., isotropic) volume fraction (V-ISO)] signal intensity, were generated for each participant. Linear mixed-effects models identified clusters of between-group differences in indices of white matter changes. Pearson's r correlation tests assessed any relationship between signal intensity and psychiatric symptoms. **Results**: Compared to TBI, TBI + PNES revealed decreases in FA, ICVF, and V-ISO and increases in MD for clusters within cingulum bundle, uncinate fasciculus, fornix/stria terminalis, and corticospinal tract pathways (cluster threshold $\alpha = 0.05$). Indices of white matter changes for these clusters correlated with depressive, anxiety, PTSD, psychoticism, and somatization symptom severity (FDR threshold $\alpha = 0.05$). A follow-up within-group analysis revealed that these correlations failed to reach the criteria for significance in the TBI + PNES group alone. **Interpretation**: The results expand support for the hypothesis that alterations in pathways comprising the specific PNES network correspond to patient profiles. These findings implicate myelin-specific changes as possible contributors to PNES, thus introducing novel potential treatment targets.

Introduction

Psychogenic nonepileptic seizures (PNES), (also referred to as dissociative or functional seizures), are a functional neurological symptom (conversion) disorder (FNSD) characterized by episodes resembling epileptic seizures or convulsions (DSM-5 300.11; ICD-10 F44.5) not associated with ictal discharges.[1] While PNES are associated with underlying psychological conflicts or stressors and psychiatric comorbidities, many patients also report history of traumatic brain injury (TBI).[2] Patients with FNDs, including PNES, often report increased depression, anxiety, and posttraumatic stress symptom severity,[3] and their clinical outcomes are often linked to comorbid anxiety and mood disorders.[4,5] Current treatments for FNSDs include evidence-based psychotherapies[1,6] but the neurobiological mechanisms for symptom improvement with therapy are not well understood.

There is an emerging literature that patients with PNES exhibit alterations in brain structure and function observed in other FNSDs via disruption of normal emotion and motor function processes.[7] Recent studies of PNES and other FNSDs have begun to elucidate the neural basis for these disruptions by examining corresponding changes in volume and function of brain regions,[8] AUTHOR: Please check and confirm whether the funding information is correct[8–11] yet changes in the structural connections of these brain networks remains less well understood.[12] Determining network functionality and connectivity that underlies PNES may increase our ability to develop new therapies to target-specific parts of the network that yield greater treatment efficacy.

Structural imaging approaches, such as diffusion magnetic resonance imaging (dMRI), may be used to identify the implicated neural networks. DMRI is typically used to assess the integrity of the white matter (WM) pathways via diffusion metrics, including fractional anisotropy (FA), mean diffusivity (MD), and deterministic tractography metrics, including fiber bundle density and length. To our knowledge, only four preliminary PNES studies have demonstrated standard DTI measure alterations within sensorimotor, default-mode, attention, and emotion regulation functional networks.[13–16] More specifically, PNES have been linked to decreased FA and asymmetry of fiber bundle indices within the uncinate fasciculus pathway (i.e., emotion regulation),[13,14] widespread decreases in FA and increases in MD,[16] and reduced small-worldness (i.e., shortest mean path-length) among attention, sensorimotor, subcortical, and default-mode networks.[15] Likewise, other FNSD (i.e., functional dystonia), have been linked to global WM disconnection affecting main sensorimotor and emotional control circuits,[17] whereas FA decreases within stria terminalis/fornix, medial forebrain bundle, extreme capsule, uncinate fasciculus, cingulum bundle, corpus callosum, and striatal-postcentral gyrus projections have been linked to mixed FNSDs.[18]

Recently, specialized dMRI sequences known as high-angular resolution diffusion imaging (HARDI) have been made available to extend traditional assessment of WM integrity by further modeling distinct neuronal compartments, or neurites. Specifically, the neurite orientation dispersion and density indices (NODDI) toolbox[19] can be utilized to assess neurite dispersion [orientation dispersion index (ODI)] and density [intracellular volume fraction (ICVF), and isotropic-free water volume fraction (V-ISO)]. The statistical maps generated by the NODDI toolbox provide greater specificity for alterations and additional WM pathophysiologic information compared to traditional dMRI indices.

In this study, we utilized advanced NODDI analysis methods to evaluate the WM pathways within the PNES network model and to extend our understanding of PNES as a network disorder. Given that the majority of patients with PNES report one or more prior TBI,[2] comparing PNES to a control group without prior TBI would not adequately control for the likelihood of TBI in PNES and potentially produce collinearity among factors of TBI and PNES occurrence between groups. Furthermore, emotion networks are already inherently changed by the virtue of physical neurotrauma, and emotional processing is altered by the traumatic event (s).[20] Accordingly, TBI was selected as a model in the current investigation to better approximate the PNES population for studying networks involved in the development and maintenance of PNES. We hypothesized that WM integrity and neurite morphology assessments would demonstrate distinct alterations in the TBI with PNES group (TBI + PNES) compared to TBI without PNES group (TBI). Specifically, we assessed alterations in FA, MD, ODI, ICVF, and V-ISO indices between groups. Based on prior literature, we expected to find group differences within WM pathways that connect limbic and motor regions of the brain, and that differences in DTI and NODDI measures would correspond to distinct mental health profiles in PNES, including depressive, anxious, posttraumatic, psychoticism, and somatization symptoms. Based on prior literature, we hypothesized that increased depressive, anxious, posttraumatic and psychoticism symptoms of PNES would correspond to group differences within the uncinate fasciculus, fornix/stria terminalis, cingulum, whereas increased somatization symptoms would correspond to group differences within the corticospinal tract.[6,8–11,21–24]

Methods

Participants

Seventy-one participants were recruited prospectively from three sites [(1) Rhode Island Hospital, RIH; (2) Providence Veterans Affairs Medical Center, PVAMC; and (3) University of Alabama at Birmingham, UAB]. Participants were separated into two groups consisting of 37 TBI and 34 TBI + PNES participants. Diagnosis of PNES was established in all participants according to recommendations of the International League Against Epilepsy (e.g., video EEG confirmed PNES).[25] TBI was established by history and medical record review, along with the TBI-screening questionnaire.[26] History of TBI was reported by participants, including the number experienced, as well as the severity and duration since each TBI. The TBI + PNES participants also reported age of PNES onset. Participants were not excluded from the study based on visible lesions nor depending on whether consciousness was preserved in the temporal period surrounding the TBI. All protocols for this study received prior approval by the Institutional Review Boards of the participating institutions. All participants provided informed consent prior to participation in the study.

Psychiatric and behavioral assessments

After consenting and prior to MRI scanning, all participants completed a series of clinical questionnaires assessing for commonly reported psychiatric and behavioral PNES and TBI comorbidities. Scales were selected based on prior literature on FNSDs demonstrating sensitivity to greater symptom severity compared to healthy controls, as well as relationships between limbic and motor brain regions structure and/or function.[3,8–11,21,27] Independent samples t-tests were used to compare TBI and TBI + PNES groups for depressive (Beck Depression Inventory-II, BDI-II),[28] anxious (Beck Anxiety Inventory, BAI),[29] posttraumatic stress (PTSD Checklist-Specific version, PCL-S),[30] psychoticism (Symptom Checklist-90, SCL-90 PSY), somatization (SCL-90 SOM)[31] symptoms, and symptom severity (Global Assessment of Functioning).[32] Corrected degrees of freedom were used for any comparison that violated assumptions for homogeneity of variance between groups.

MRI parameters and analysis

After prescreening, consenting, and initial assessments, participants completed HARDI protocols performed on two (RIH and UAB) 3 Tesla Prisma scanners (Siemens Healthcare, Erlangen, Germany) using a 64-channel head coil. Acquisition protocols were carefully harmonized *a priori* in this study. All scanner firmware, software, and hardware upgrades, if performed, were synchronized between sites. A multishell diffusion scheme (humanconnectome.org) with b-values of 1500 and 3000 s/mm^2 (47 and 46 directions, respectively) and 6 B0 images were acquired using a single-phase encoding direction (anterior-to-posterior) with the following protocol: TR = 3230 ms, TE = 89.2 ms, FOV = 21 × 21 cm, flip angle 78 degrees, multiband factor 4, 1.5 mm isotropic voxels. At both sites, auto-alignment localizers reduced variability in subject positioning using anatomical landmarks to direct placement of the FOV. Following data acquisition, a pipeline utilizing standard image processing software was used to preprocess, model, and compare the data (Figure 1). Each dataset was first corrected for motion, eddy currents and susceptibility artifacts, and rotation of gradient tables by selecting the standard option to include these adjustments in TORTOISE (v2.5.2b, nih.gov; DIFF_PREP). Briefly, diffusion tensor imaging (DTI) and NODDI metrics were estimated after preprocessing using TORTOISE (v2.5.2b, nih.gov; DIFF_CALC with linear fitting algorithm) and the NODDI toolbox (v1.01, nitrc.org)[19] in MATLAB R2018a (mathworks.com; MA, USA). Resulting statistical maps from this preprocessing pipeline produced five separate whole-brain maps for each subject, including FA, MD, ODI, ICVF, and V-ISO. To smooth and then spatially normalize diffusion images to the McConnell Brain Imaging Centre standard (ICBM 2009a Nonlinear Symmetric WM Template), AFNI (afni.nimh.nih.gov) algorithms were used to perform spatial smoothing (3dMedianFilter) to a 2 voxel (3mm) neighborhood radius on each participant's images before an optimized nonlinear image registration (3dQwarp) performed an iterative refinement on FA maps with a convergence criterion at each patch level to better resolve artifacts (final patch size of 3 mm isotropic). The resulting transformation matrix derived from warping the FA statistical map was then applied to warp the four remaining statistical maps for each subject (3dNwarpApply). For each subject, the five warped whole-brain statistical maps underwent visual inspection to ensure the validity of each statistical map and successful warping onto the MNI standard template (Figure 1). Specifically, each statistical map was inspected for spatial overlap between voxels with relatively high intensity that correspond to respective tissue regions of the MNI anatomical standard template. In other words, registration of V-ISO and MD were validated with high concordance to CSF in the ventricles/interhemispheric fissure, ODI was validated with high concordance to cortical gray matter regions, and ICVF and FA were validated with high concordance to white matter regions of the template.

Whole brain voxel-wise group differences (TBI vs TBI + PNES) were assessed using AFNI's 3dLME for each

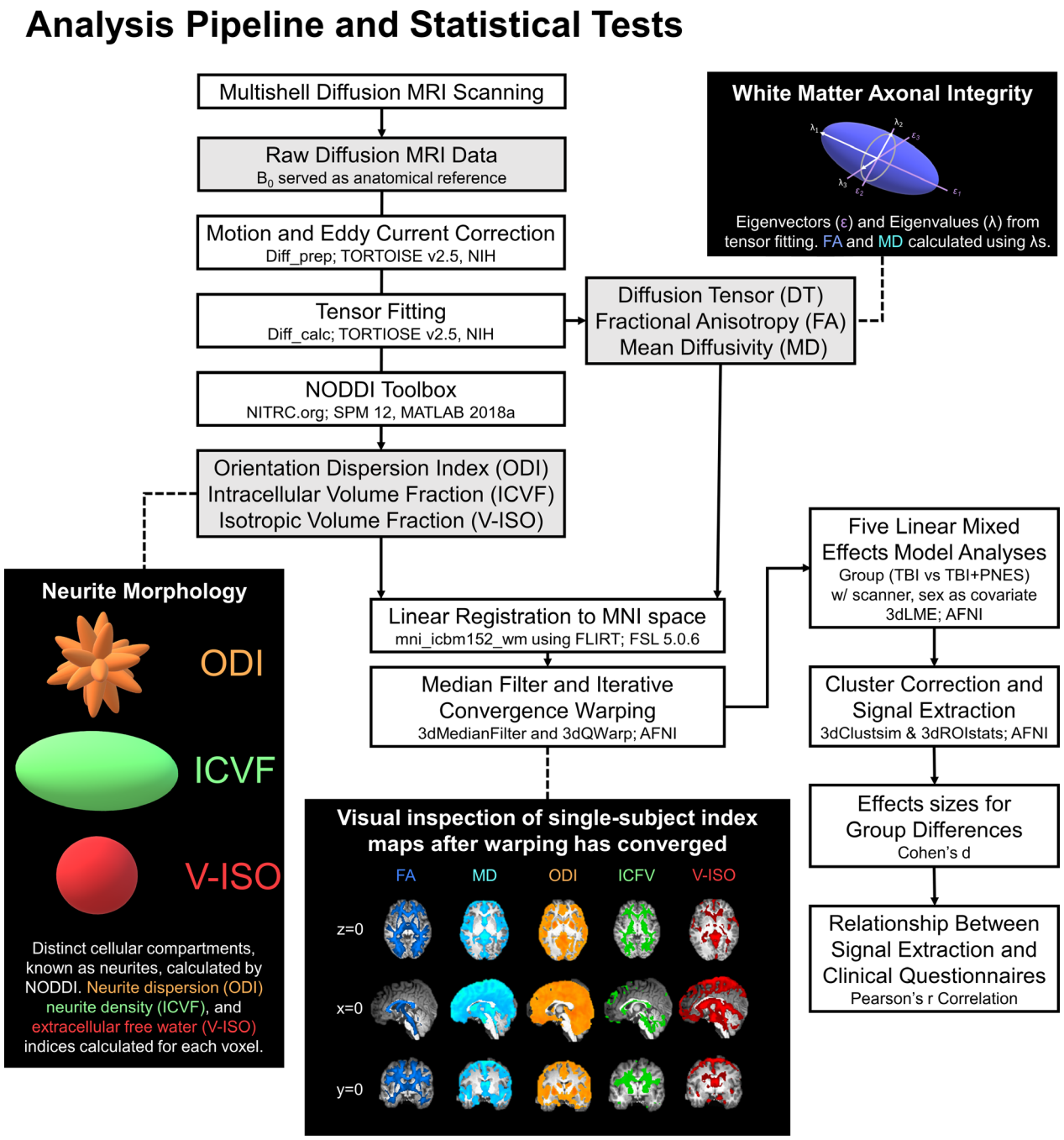

Figure 1. Schematic depicting the diffusion imaging analysis pipeline, modeling examples for DTI and NODDI indices, postwarping visual inspection example, and statistical tests performed.

of the five diffusion maps. Biweekly quality assurance was performed at both UAB and RIH scanners using the multicenter collaborative fMRI research project (FIRST-BIRN) quality assurance protocol[33] and confirmed that Signal-to-Noise Ratio (SNR), Signal-to-Fluctuation-Noise Ratio (SFNR), signal fluctuations, and signal drift were stable throughout the study. All 3dLMEs included an intercept to remove variability as a factor of scanner site (UAB, RIH) and sex (male, female). A WM mask derived from the ICBM 2009a WM Template, restricted 3dLME analyses to anatomically based WM boundaries in order to lower the overall number comparisons and reduce family wise error (FWE) rates. Specifically, based on prior literature, we hypothesized there would be group

differences within the uncinate fasciculus (UF; prefrontal cortex-hippocampus-amygdala), fornix/stria terminalis (FST; hippocampus-amygdala-hypothalamus), cingulum (cingulate cortex-dorsal/ventral prefrontal cortex), and corticospinal tract (pre/post central gyrus-spinal cord).[6,8–11,21–23] In order to further reduce the likelihood of type-I error, volume extent thresholds (mm^3) were calculated using AFNI's 3dClustSim based on an algorithm that uses randomization/permutation simulation to produce 10 000 iterations of noise only generated t-tests and to determine the global cluster-level threshold values for each of the five separate diffusion measures. Only clusters identified by 3dLMEs exceeding 443 mm^3 for FA, 460 mm^3 for MD, 437 mm^3 for ODI, 548 mm^3 for ICVF, and 612 mm^3 for V-ISO were considered statistically significant (uncorrected $P < 0.01$, cluster threshold $\alpha = 0.05$). Signal extractions (3dROIstats) were performed for clusters identified by the 3dLMEs that included *a priori* pathways of interest within UF, FST, cingulum (JHU-DTI WM labels),[34] and corticospinal tract (JHU-DTI tract probability map)[35] regions. To interpret any clusters of significant group differences identified by the 3dLMEs, mean signal and Cohen's d estimate of effect size determined the direction and strength of effects.

Brain and behavior comparisons

To better characterize the clinical implications of observed group differences in WM, Pearson's r correlations assessed the relationship between each cluster's mean signal with scores on BDI-II, BAI, PCL-S, SCL-90 PSY, and SCL-90 SOM scales across both the TBI and TBI + PNES groups. To reduce the type-I error rate from multiple comparisons, a false discovery rate corrected threshold (FDR threshold $\alpha = 0.05$, two-tailed) was used to determine any significant correlations. Additional follow-up Pearson's r correlation tests (FDR threshold $\alpha = 0.05$, two-tailed) assessed the relationship between each cluster's mean signal with scores on BDI-II, BAI, PCL-S, SCL-90 PSY, SCL-90 SOM, symptom severity (GAF[36]), and PNES duration (age of onset subtracted from current age) assessments for only the TBI + PNES group to contextualize potentially specific relevance of the psychiatric variables in PNES. To assess the potential role of age effects, all signal extractions were compared to age (years) using Pearson's r correlation tests (uncorrected $\alpha = 0.05$, two-tailed).

Results

Participant demographics and TBI history

Results for all statistical comparisons ($\alpha = 0.05$, two-tailed) of demographic factors and TBI history between TBI and TBI + PNES groups are reported in Table 1. There were no differences between the groups with respect to age, and as expected based on PNES epidemiology,[37] the proportion of female participants was greater in the TBI + PNES group. Likewise, the number of TBIs, time since TBI, TBI severity, TBI hemispheric laterality, and TBI lobe did not differ between groups (all $P > 0.05$; Table 1).

Psychiatric and behavioral assessments

Results for all statistical comparisons ($\alpha = 0.05$, two-tailed) of psychiatric and behavioral assessments between TBI and TBI + PNES groups are reported in Table 1. There were no differences between TBI and TBI + PNES groups with respect to prior psychiatric comorbidities or psychoticism scale symptoms, and as expected based on PNES epidemiology,[3,27] depressive, anxious, posttraumatic stress, and somatization symptoms were greater in the TBI + PNES group (Table 1).

MRI analysis

The results of the 3dLME analyses that compared DTI and NODDI indices between TBI and TBI + PNES groups, controlling for variability due to scanner site and sex, (corrected $\alpha = 0.05$, two-tailed) are reported in Figure 2. No clusters survived the correction for multiple comparisons in the 3dLME for group differences in ODI. Figure 2 (below each statistical map) shows the signal extraction means and Cohen's d estimates of effect size derived from clusters identified by 3dLMEs within the a priori pathways of interest (UF, FST, cingulum, and corticospinal tract). Mean FA values were higher in the TBI than TBI + PNES groups for clusters within bilateral corticospinal tract and FST. Mean ICVF values were higher in the TBI than TBI + PNES groups for clusters within the right FST, left UF, bilateral corticospinal tract, and right cingulum pathways. Mean V-ISO values were higher in the TBI than TBI + PNES groups for clusters within bilateral corticospinal tract pathways. Mean MD values were lower in the TBI than TBI + PNES groups for a cluster within bilateral corticospinal tract pathways.

Brain and behavior comparison results

Figure 3 reports the results of the Pearson's r (FDR corrected $\alpha = 0.05$, two-tailed) correlation tests that compared each of the five psychiatric assessments to mean signal values extracted from each of 12 clusters identified by the 3dLMEs that fell within the a priori pathways of interest (n = 60 comparisons). As bilateral FA signal decreased, there was a corresponding increase in values

Table 1. Demographics and TBI, Psychiatric, and Behavioral Assessments by Groups.

	Groups			
	TBI	TBI + PNES	Stat	*P*-value
Demographics and TBI history				
Total samples	n = 37	n = 34	-	-
Birmingham, AL enrollees	n = 9	n = 15	-	-
Providence, RI enrollees	n = 26	n = 19	-	-
Years of Age	39.7 [10.9]	36.7 [11.8]	$t = 1.2$	0.27
Sex (Female)	n = 16	n = 24	$\chi^2 = 4.8$	<0.05*
PNES duration (years)		5.73 [8.88]		
Number of TBIs	4.7 [4.7]	5.5 [8.6]	$t = -0.4$	0.66
Duration since TBI (months)	91.8 [103.8]	107.3 [130.7]	$t = -0.6$	0.58
TBI severity	mild; n = 31 moderate; n = 3 severe; n = 1 unknown; n = 2	mild; n = 28 moderate; n = 3 severe: n = 1 unknown; n = 2	$\chi^2 = 0.3$	0.87
TBI hemispheric laterality	left; n = 5 right; n = 8 bilateral; n = 16 unknown; n = 8	left; n = 3 right; n = 8 bilateral; n = 13 unknown; n = 10	$\chi^2 = 0.9$	0.82
TBI lobe(s)	frontal; n = 11 parietal; n = 4 occipital; n = 6 temporal; n = 2 multiple; n = 8 unknown; n = 6	frontal; n = 13 parietal; n = 2 occipital; n = 4 temporal; n = 0 multiple; n = 7 unknown; n = 8	$\chi^2 = 3.5$	0.63
Psychiatric and behavioral assessments				
Current Mood disorder (yes)	n = 14	n = 21	$\chi^2 = 1.3$	0.25
Current Anxiety disorder (yes)	n = 14	n = 19	$\chi^2 = 0.5$	0.49
GAF	76.24 [14.62]	53.52 [7.87]	$t = 8.2$	<0.001*
BDI-II	12.9 [13.5]	25.6 [13.1]	$t = -4.0$	<0.001*
BAI	12.3 [13.3]	27.8 [11.1]	$t = -5.3$	<0.001*
PCL-S	33.9 [17.0]	50.4]14.9]	$t = -4.2$	<0.001*
SCL-90 PSY	4.7 [6.1]	6.8 [6.8]	$t = -1.4$	0.18
SCL-90 SOM	8.8 [8.3]	18.2 [10.3]	$t = -4.2$	<0.001*

Data for TBI versus TBI + PNES patients reported as mean [SD], except for Sample Size, Sex, Prior Mood, and Anxiety disorders, TBI severity, TBI hemispheric laterality, and TBI lobe, which are reported as counts (n). Chi-squared test (χ^2) tested the null hypothesis that the proportions for counts did not differ between groups. All other comparisons were tested using an independent samples *t*-test (t). The between group test statistic (Stat) and *P*-value (*P*) are presented.

*Indicates a comparison that reached statistical significance ($\alpha = 0.05$, two-tailed).

across all five measures (BDI-II, BAI, PCL-S, SCL-90 PSY, and SCL-90 SOM; Figure 3A-B). V-ISO values decreased within the right corticospinal tract with a corresponding increase in PCL-S values (Figure 3C). ICVF values decreased within the right FST/corticospinal tract (Figure 3D, left) and posterior cingulum (Figure 3D, right) with a corresponding increase in BDI-II values. All remaining Pearson's r correlations for relationships between cluster mean signal values and psychiatric and behavioral assessments failed to reach criteria for significance. Within group post hoc results of all follow-up Pearson's r correlation tests (FDR corrected $\alpha = 0.05$, two-tailed) that compared each of the five psychiatric assessments, GAF, and PNES duration to mean signal values extracted from each of 12 clusters identified by the 3dLMEs for the TBI + PNES only group failed to reach criterial for significance. Likewise, the results of all Pearson's r correlation tests (uncorrected $\alpha = 0.05$, two-tailed) that compared mean signal values extracted from each of 12 clusters identified by the 3dLMEs to age (years) failed to reach criteria for significance.

Discussion

This prospective study assessed the hypothesis that PNES in patients with TBI can be conceptualized as a brain network disorder in which mental health symptom expression varies according to alterations in specific motor and

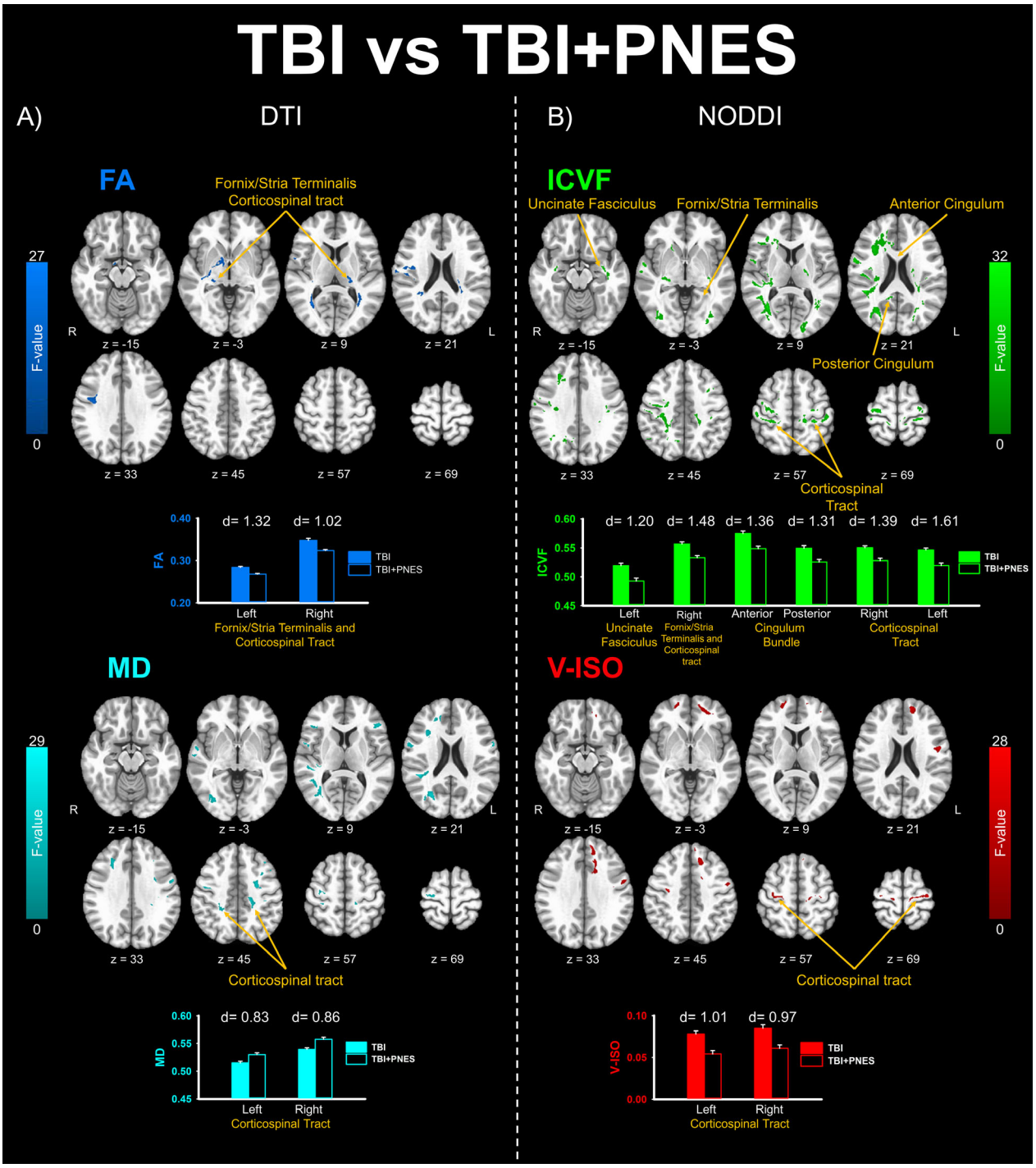

Figure 2. Results from the five linear mixed effects analysis comparing TBI versus TBI + PNES that survived the cluster correction volume threshold (uncorrected $P < 0.01$, cluster threshold $\alpha = 0.05$). Clusters that survived group-level analysis for dMRI-based statistical maps (FA, Fractional Anisotropy; MD, Mean Diffusivity) appear in the left panel (A) and for NODDI-based statistical maps (ICVF, Intracellular Volume Fraction, V-ISO, Isotropic Volume Fraction) appear in the right panel (B). No clusters survived group-level analysis for ODI measures. Volume extent thresholds (Monte Carlo simulation) were determined separately for FA (443mm^3); MD (460mm^3); ODI (437mm^3); ICVF (548mm^3); and V-ISO (612 mm^3) based on whole-brain spatial noise distributions for each index. Clusters that included pathways identified as a priori tracts of interest are identified with yellow arrows and labels. Images appear in radiological view (R->L). In order to interpret the direction of statistically significant group differences identified by the 3dLMEs, cluster means are plotted for each group below statistical maps. The strength of these group differences was determined by comparing cluster-wise signal mean compared between groups (TBI vs. TBI + PNES) using Cohen's d estimate of effects size.

limbic regional PNES networks.[7] This hypothesis was formulated based on prior literature demonstrating that changes in structure and function of motor and limbic regions are associated with symptom expression in PNES[8–11,21] and that PNES are associated with decreased WM integrity within neural projections that connect these brain regions.[13–15] To this end, FNSDs including PNES have been conceptualized as a network brain disorder, rather than a focal deficit, in which patient profiles vary, depending on how limbic and motor regions that comprise the specific FNSD network are altered.[7] While these recent volumetric and functional activation studies provide an important foundation for identifying the specific brain regions and networks involved in FNSDs including PNES, yet changes in the structural connections of these brain networks remain less well understood.

Preliminary studies have linked standard DTI measure (FA and fiber bundle) alterations to PNES within sensorimotor, default-mode, attention, and emotion regulation functional networks[13–15] and are consistent with findings that WM integrity is decreased within limbic and motor functional networks and associated with worsened psychiatric symptoms in mixed FNSDs.[18] However, NODDI analysis further extends the PNES network model by providing a more specific assessment of tissue. Specifically, DTI analysis provides FA and MD statistical maps that serve as indices of WM integrity. As FA decreases and MD increases, there are corresponding decreases in nonspecific WM integrity and microstructure that may be affected by one or more tissue alterations that include, for example, axonal dispersion, density, or injury.[38] Alternatively, NODDI analysis relates diffusion data to geometric models (Figure 1) providing a more targeted and specific assessment of tissue microstructure. Specifically, NODDI statistical maps separately index: 1) dispersion of crossing fiber orientations with increasing ODI values; 2) dense fiber bundling and myelination with increasing ICVF values; and 3) demyelination and/or edema with increasing V-ISO values.[19,39–41] Unlike ODI and ICVF measures that have been histologically confirmed as a proxy of neurite dispersion and myelination,[39] ex vivo histological validation of V-ISO as a proxy of edema is not currently feasible due to the active physiological nature of this process[42] or dehydration during sample preparation.[40] Thus, microstructure changes that lead to fluctuation in V-ISO measures within white matter regions may more broadly include neurodegenerative progression, including edema and/or axonal degeneration related to the myelin sheath.[43]

Despite similar severity of the TBI between groups, the TBI + PNES group had greater depressive, anxious, posttraumatic stress, psychoticism, and somatization symptoms compared to the TBI without PNES group. Furthermore, we observed an association between increasing symptoms of depression, anxiety, PTSD, psychoticism, and somatization symptom severity and decreasing WM integrity (i.e., FA), myelination (i.e., ICVF), and free water (i.e., V-ISO) within pathways connecting motor

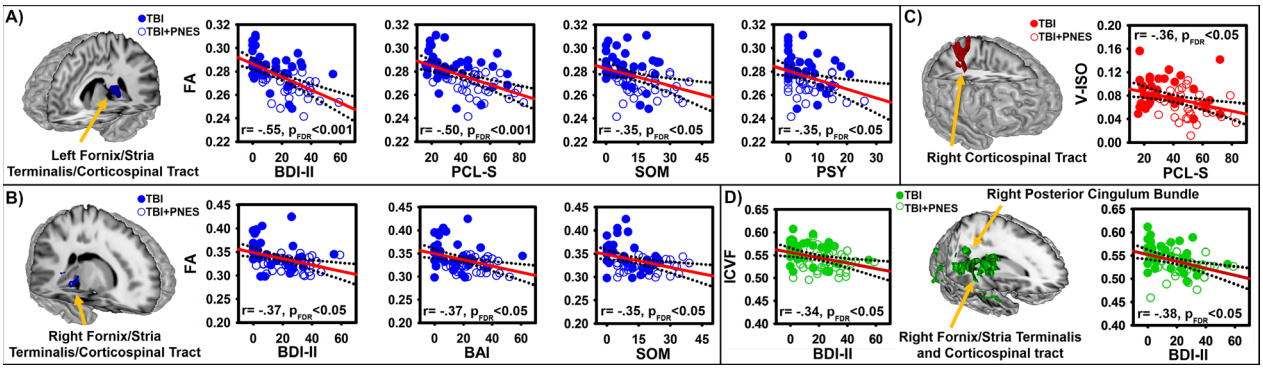

Figure 3. Depiction of significant linear relationships between mean signal comparisons within each of the 12 clusters (Figure 2), identified by tract and area within tracts, compared (Pearson's r) against mood (BDI-II,), anxiety (BAI), PTSD (PCL-S), psychoticism (SCL-90 PSY), and somatization (SCL-90 SOM) symptom severity. Correlations were considered significant based on a false discovery rate (FDR) corrected threshold (FDR adjusted $P < 0.05$, two-tailed). Strength and direction of correlations are indicated by r-value and corresponding FDR adjusted *P*-value (p_{FDR}) within each scatterplot. Significant correlations with symptom severity were found for FA within the left (A) and right (B) fornix/stria terminalis/corticospinal tract pathways, for V-ISO within the right corticospinal tract pathway (C), and for ICVF within the right fornix/stria terminalis/corticospinal tract pathways (D; left) and right posterior cingulum bundle pathway (D; right). All remaining correlations failed to reach the criteria for significance. Least squares regression lines (red line) and 95% confidence interval bands (dotted lines) were fitted to visually depict trend directions and variability across comparisons. Correlations, least-squares regression lines, and confidence interval bands were calculated by collapsing TBI (closed circles) and TBI + PNES (open circles) groups. Follow-up within-group analyses revealed that these correlations failed to reach the criteria for significance among TBI or TBI + PNES group alone.

and limbic networks. Although similar WM changes within limbic and motor networks have been previously identified in patients with TBI and psychiatric conditions[41,44,45], this study extends these changes to PNES and highlights several key differences that are discussed below. By comparing individual differences in mental health symptom severity to differences in NODDI indices in TBI + PNES compared to TBI, we provide new evidence that suggests specific tissue microstructure alterations within motor and limbic WM pathways in TBI can be associated with the occurrence of mental health symptom expression in PNES.

In this study, PNES are associated with decreases in WM integrity within pathways connecting motor and emotion networks. Specifically, we found decreased FA values in TBI + PNES compared to TBI within bilateral FST and corticospinal tract. Amygdala and hippocampal regulation of the autonomic and endocrine response to stress[46] critically involves projections through FST on to the hypothalamus.[34] During processing of stressful information, hippocampal disinhibition serves as a release mechanism triggering the hypothalamic pituitary adrenal (HPA) axis and release of glucocorticoids in response to stress.[47] Thus, decreased WM integrity within the fornix may be related to hippocampal hyporeactivty to stress in PNES.[24] In general, increased glucocorticoid reactivity to stressors is associated with psychological vulnerability and psychosocial stress.[48] The association between decreased FA within these clusters and increased mood, anxiety, PTSD, psychoticism, and somatization symptoms suggests that overlapping disruption of the corticospinal tract and FST may be associated with the diversity of comorbid mental health symptoms in PNES.

In this study, we observed reduced free water (i.e., V-ISO) measures within corticospinal tract pathways among the PNES group that related to PTSD symptom severity. Although the biological specificity of increased free water remains unclear[40,42,43], other studies report V-ISO changes related to vasogenic edema[49] or mylenation,[50] which could be associated with chronic phase TBI. Given the lack of prior validation for neurobiological specificity for V-ISO measures and that this study did not assess additional markers edema within WM pathways, future studies are needed to directly investigate any potential dynamic relationships between free-water and posttraumatic stress symptoms in PNES.

Compared to TBI, TBI + PNES were associated with decreased ICVF within FST, UF, cingulum, and corticospinal tract WM pathways. These results extend prior studies on alterations in WM integrity within these networks for PNES,[13–15] by implicating specific WM tissue microstructure (i.e., myelin). Additionally, decreases in ICVF within FST, corticospinal tract, and cingulum pathways were correlated with increased depressive symptom expression. Prior studies have reported that hyperfunctional connectivity between medial prefrontal cortex-hippocampus-posterior cingulate is linked to depressive mood symptoms.[51,52] Furthermore, another recent study found that changes in task-elicited anterior cingulate/paracingulate activation was associated with improvement in functional tremor severity and depressive symptoms after cognitive behavioral therapy (CBT).[6] Accordingly, myelination differences within cingulum and FST pathways may play an important role in the expression of depressive symptoms associated with PNES.

We hypothesized that the degree of changes in psychiatric symptoms and the degree of changes in white matter associated with PNES are related. This combination of groups in the analysis allows for modeling brain and behavior relationships to assess potential pathophysiological mechanisms that exist on a continuum and at both the clinical and subclinical level. Alternatively, post hoc follow-up analysis that assessed only the TBI + PNES group was designed to contextualize the specificity of these relationships to PNES. The results of this follow-up analysis failed to yield any significant relationships for symptom specificity. It is likely that the reason significant correlations were not observed for only TBI + PNES comparisons is that this restriction did not capture the full gamut of these relationships, given the relatively high and truncated psychiatric symptom severity in the PNES group. The results from including both groups in the correlation tests, in contrast, suggest that both mental health symptom severity and white matter differences for TBI + PNES vary from TBI in degrees, rather than in kind. We take the brain and behavior comparisons and post hoc comparisons results in this study to suggest that the increased expression of psychiatric symptoms is linked to more severe changes in white matter pathophysiology, rather than distinct relationships between these factors in PNES. Future studies may increase the understanding of such relationships by utilizing an independent within-group analysis to assess white matter changes that vary with PNES symptom expression.

Several limitations should be considered when interpreting our findings. Our diffusion MR data acquisition was acquired using a single-anterior-to-posterior phase encoding direction sequence; however, implementation of a complimentary reverse encoding direction sequence may improve susceptibility distortions that can degrade diffusion MRI data quality. Unlike tractography analysis, our voxel wise approach and hypotheses assessed white matter changes within dorsal and subcortical JHU white matter atlas regions. Although we did not assess areas that are highly susceptible to distortion when acquired in the anterior-to-posterior direction, such as cerebral cortex

within anterior frontal and posterior occipital lobes, it is important to note that different phase encoding directions may still produce slightly different results[53] when interpreting the results of this study in the context of the literature. Tractography analysis (i.e., changes in fiber bundle density and length) of NODDI metrics was not conducted in this study but may provide additional knowledge in future investigations of white matter differences in PNES and their role in symptom expression. While our sample size is moderate, this issue is mitigated by multisite recruitment and robust sample size compared to prior neuroimaging studies of PNES.[13–15]

Another limitation involves comparison group(s). Future studies may consider including a sample with epileptic seizures or mixed PNES and epilepsy comparison group in order to assess potential additive effects of epilepsy on white matter changes. Minimal prior investigation on white matter changes linked to TBI with epileptic seizures are a limitation for establishing the specificity of our findings in PNES compared to epilepsy. One human DTI study reported the ratio of FA values within TBI lesions compared to the corresponding contralateral MRI-normal region and found significantly lower FA ratios in patients with epilepsy compared with those without epilepsy, but no significant difference in MD ratio for these same regions between groups.[54] Thus, the lack of a comparison group in this study or prior literature investigating TBI and epileptic seizures limits our understanding of the specificity of white matter changes in PNES compared to epileptic seizures in chronic phase TBI. The absence of a healthy control group [i.e., without history of (non) epileptic seizures or TBI] comparison to contextualize the findings of this study; however, limits our understanding of how these white matter changes compare to a typical range for measures within these pathways. Furthermore, while this study was open to all severities of TBI, the majority of our sample is mild TBI; thus, how the findings generalize to moderate and severe TBI remains to be addressed in future studies. There was also an absence of a PNES group without TBI, other FNSDs, or related psychiatric diagnoses which may limit the generalizability of the findings. However, in agreement with the notion that PNES are part of the FNSD spectrum and an expression of the disruption in the different part of the FNSD network,[7] we expect these findings to provide excellent springboard for further studies in FNSDs.

Lastly, this study utilized a limited subset of psychiatric comorbidity assessments, rather than implementing a broad exploratory evaluation that might include more targeted scales (e.g., Dissociative Experiences Scale)[55,56] or additional comorbidities (e.g., alexithymia)[57] in PNES. The assessment scales utilized in this study were chosen *a priori* based on prior literature linking the specific comorbidities mental health states to neural function and structure, effectively reducing the potential for type-I error rates inherent in exploratory studies. Future exploratory or targeted studies might implement such additional assessments to extend our assessment of relationships between alterations in WM tissue microstructure and psychopathology in PNES.

Conclusions

By utilizing NODDI analysis to assess WM tissue microstructure in greater detail, this study provides evidence that PNES involves aberrant structural connectivity of brain networks. The current findings suggest pathophysiological relationships may exist between PNES symptoms and WM integrity and myelination, within cingulum, FST, UF, and corticospinal tract pathways. Future studies that utilize controlled clinical trials to assess changes in WM tissue microstructure that correspond to FNSD symptom improvement after psychotherapy[1,6] may increase our ability to develop therapies that target-specific networks and nodes. Additionally, WM changes within motor and limbic networks that correspond with symptom improvement may lend support to the hypothesis that WM integrity and tissue microstructure may play a role in symptom profiles of patients with PNES.

Author Contributions

WCL and JPS contributed conception and design of the study; AMG, JBA, MSB, ANM, VV, KT, and WSM contributed to acquisition and analysis of data; and AMG, JPS, JBA, ASB, SC, LWH, TEG, LRG, NVK, ACL, NSP, and WCL contributed to drafting of the manuscript.

Role of the Sponsor

The Department of Defense had no role in the conduct of the study, manuscript preparation, or the decision to submit for publication. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs, Department of Defense, or the United States government.

Additional Contributions

Frank Skidmore, MD, and Grayson Baird, PhD, provided consultation on study design and interpretation. Valencia Williams and Katlyn Jackson assisted with recruitment and data collections. Ravi Tripathi and Thomas Anthony provided technical support.

Conflict of Interest

The authors do not report any disclosures of conflict of interest.

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