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TITLE: Deep Phenotyping for Physiologic Biomarkers for Posttraumatic Epilepsy in Children

PRINCIPAL INVESTIGATOR: Brian Appavu, MD

CONTRACTING ORGANIZATION: Barrow Neurological Institute at Phoenix Children's Hospital, Phoenix, AZ

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TYPE OF REPORT: Annual Report

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Brian Appavu, Stephen Foldes, Austin Jacobson, Hamy Temkit, P.

E-Mail: bappavu@phoenixchildrens.com**5d. PROJECT NUMBER****5e. TASK NUMBER****5f. WORK UNIT NUMBER****7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**Phoenix Children's Hospital
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13. SUPPLEMENTARY NOTES

14. ABSTRACT					
<p>PTE is a leading cause of acquired epilepsy, occurring in up to 20% of children following severe TBI and representing the leading cause of epilepsy in young adult adulthood. Increasing evidence suggests that the underlying physiologic environment immediately after TBI carries physiologic biomarkers for post-traumatic epileptogenesis. The goal of this project is to use advanced multivariate modeling to further our understanding of pediatric post-traumatic epileptogenesis. We proposed a statistical and data mining approach after pediatric severe TBI to identify physiologic biomarkers predictive of PTS and PTE. We will retrospectively explore our clinical database of high-frequency resolution multimodal neurologic monitoring data for predictive biomarkers of post-traumatic epilepsy, functional outcomes and post-traumatic seizures. We will also apply machine learning models towards predicting post-traumatic seizures.</p>					
15. SUBJECT TERMS:					
Post traumatic epilepsy, post-traumatic seizures.					
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1. INTRODUCTION:

PTE is a leading cause of acquired epilepsy, occurring in up to 20% of children following severe TBI. Increasing evidence suggests that the underlying physiologic environment immediately after TBI carries physiologic biomarkers for post-traumatic epileptogenesis. The goal of this project is to use advanced multivariate modeling to further our understanding of pediatric post-traumatic epileptogenesis. We proposed a statistical and data mining approach after pediatric severe TBI to identify physiologic biomarkers predictive of PTS and PTE.

2. KEYWORDS:

Traumatic brain injury, post-traumatic epilepsy,

3. ACCOMPLISHMENTS:

What were the major goals of the project?

1. Develop data transfer agreement with PCH and ASU – 100% Complete (07/01/2019)
2. Finalize eligibility criteria and screening protocol – 100% complete (04/2019)
3. Finalize eligibility consent and human subjects protocol – 100% complete (04/2019)
4. IRB protocol submission – 100% complete (04/2019; resubmission)
5. IRB Approval - 100% complete (initial completion 06/12/2019; resubmission completion 08/22/2019)
6. HRPO/ACURO Approval – 100% complete (09/30/2019)
7. Data extraction and file conversion - 95% complete
8. Check research files for completeness – 99% complete
9. Check database for entry errors – 99% complete
10. Data cleanup and artifact reduction – 99% complete
11. Statistical modeling – 80% complete
12. Machine learning modeling – 60% complete
13. Model development – 70% complete

What was accomplished under these goals?

Aim 1a: Identify a set of temporal features to predict post-traumatic seizures.

During this annual period, our primary major activities included developing a machine learning model for prediction of post-traumatic seizures. We applied a single-layer long short-term memory (LSTM) artificial neural network with a dual attentional model of EEG data to predict seizures, and among the initial four patients tested with 20 total seizures, we were able to predict $93 \pm 13\%$ seizures correctly with false prediction occurring during $0.03 \pm 0.05\%$ of non-seizure times (see below).

Forecasting of Pediatric Post-Traumatic Seizures from EEG

Manjusha Ravindranath, K.Selcuk Candan, Stephen Foldes, Brian Appavu

INTRO

- Post traumatic seizures are a common phenomena after traumatic brain injury and are known cause for secondary brain injury.
- Seizure detection and prediction requires modeling of complex non-linear spatio-temporal dynamics in electroencephalogram (EEG) signals.
- A particular challenge in detecting and predicting post-traumatic seizures is that they are very diverse.
- Multi-variate temporal features extracted by simultaneously considering, at multiple scales, temporal characteristics of the time series along with external knowledge, including variate relationships that are known a priori, can help accurately predict post-traumatic seizures.

METHODS

1. Developed a Long Short-term Memory (LSTM)-based neural architecture, M2NN, with an attention mechanism that leverages robust multivariate multiscale (M2) temporal features that are extracted a priori and fed into the neural network (NN) as a side information.
 2. 4 patients with total of 20 seizure events.
 3. The frequency power considered for FFT is 0-19 Hz, 1 Hz bins.
 4. 15-26 EEG channels was extracted as input timeseries.
- 60% train, 20% valid, 20% test split of chunked data.

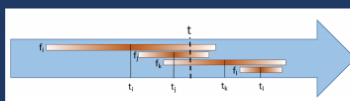
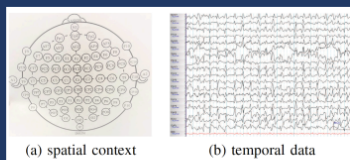
RESULTS

patient	Mean Recall	Mean Precision	Mean F1 Score
8492	0.63	0.95	0.76
2883	0.98	0.94	0.96
6354	1.00	0.76	0.86
6957	1.00	0.84	0.91

CONCLUSIONS

- PTS seizure early prediction of 4.4-5.1 minutes.

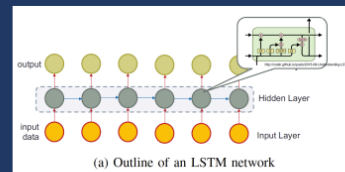
Pediatric post-traumatic seizures (PTS) are predicted 5.1 minutes early using a novel LSTM-based model with dual regional robust multivariate temporal (RMT) attention on EEG data.



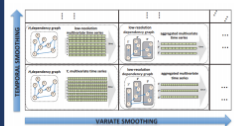
First three RMT features f_1 , f_2 and f_3 centered at t_1 , t_2 and t_3 are within the scope of time instant t' .



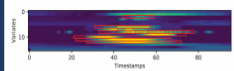
Take a picture to download the full poster
mravind1@asu.edu



RMT Feature Extraction Process



RMT Features- Local Temporal Events and their Scope (red box)



Accuracy Measures

- Recall = TrueOnset / (TrueOnset + False NonSeizure)
- Precision = TrueOnset / (TrueOnset + False Onset)

Results are averaged with 20 independent runs.

DISCLOSURES

- This project is supported by a DOD CDMRP grant W81XWH-19-1-0514

REFERENCES

- Liu, Sicong, et al. "Robust multivariate temporal features of multivariate time series." *ACM Transactions on Multimedia Computing, Communications, and Applications (TOMM)* 14, no. 1 (2018): 1-24
- Vaswani, Ashish et al. "Attention is all you need." In *Advances in neural information processing systems*, pp. 5998-6008. 2017.



Aim 1b: Separate patients who developed post-traumatic epilepsy from those who did not develop post-traumatic epilepsy.

We also implemented multivariate analysis to demonstrate that in 62 children with TBI, seizures between days 2-7 (OR=16.13, p=0.0006, C=0.81), epileptiform discharges (OR=7.94, p=0.0063, C=0.74), sleep spindle asymmetry (OR=11.34, p=0.0017, C=0.79), higher ICP (OR=1.26, p=0.0206, C=0.78) and lower HRsd (OR=0.53, p=0.0107, C=0.80) were associated with PTE, when adjusting for injury severity (as measured by Glasgow Coma Scale [GCS]).

	PTE (n=62)		Odds Ratio [95% Confidence Interval]	p-value	C-Statistic
	N (n=51)	Y (n=11)			
Univariate Analysis					
Gender					
Female	18 (35.3%)	2 (18.2%)	0.41 [0.08, 2.09]	0.2821	0.59
Male	33 (64.7%)	9 (81.8%)			
Age in years, median	7.0	12.0	1.03 [0.92, 1.15]	0.6539	0.53
GCS, median [SD]	7.0 [2.9]	5.0 [2.3]	0.80 [0.60, 1.07]	0.1302	0.65
Seizures < 24 hours	8 (15.7%)	1 (9.1%)	1.86 [0.06, 4.80]	0.5784	0.53
Seizures on days 2-7	5 (9.8%)	7 (63.6%)	16.13 [3.46, 74.84]	0.0004	0.77
Sleep spindle asymmetry	6 (11.8%)	7 (63.6%)	13.12 [2.94, 58.52]	0.0007	0.76
Epileptiform discharges	7 (13.7%)	6 (54.5%)	7.52 [1.81, 31.52]	0.0056	0.70
ICP, median [SD], mmHg	9.7 [3.3]	12.9 [5.9]	1.24 [1.03, 1.50]	0.0232	0.73
CPP, median [SD], mmHg	69.1 [7.3]	67.3 [13.7]	0.99 [0.92, 1.06]	0.7386	0.50
ABP, median [SD], mmHg	80.1 [7.2]	82.8 [8.7]	1.05 [0.96, 1.15]	0.2850	0.59
HR, median [SD], bpm	97.7 [21.8]	92.2 [19.6]	0.990 [0.96, 1.02]	0.5508	0.56
HRsd, median	4.1 [1.9]	1.8 [1.4]	0.513 [0.32, 0.83]	0.0061	0.81
BRs, median	5.2 [5.2]	5.5 [3.0]	0.851 [0.70, 1.04]	0.1118	0.68
PRx, median	0.1 [0.2]	0.2 [0.3]	23.22 [1.09, 495.79]	0.0441	0.64
wPRx, median	0.1 [0.2]	0.2 [0.3]	28.95 [1.09, 769.55]	0.0443	0.65
Multivariate Analysis					
Seizures on days 2-7 adjusted for GCS			16.13 [3.26, 79.01]	0.0004	0.77
Sleep spindle asymmetry, adjusted for GCS			11.34 [2.50, 51.47]	0.0017	0.79
Epileptiform discharges, adjusted for GCS			7.52 [1.80, 35.17]	0.0056	0.70
ICP, adjusted for GCS			1.26 [1.04, 1.52]	0.0206	0.78
HRsd, adjusted for GCS			0.53 [0.33, 0.86]	0.0107	0.80
PRx, adjusted for GCS			20.47 [0.99, 424.51]	0.0510	0.75
wPRx, adjusted for GCS			23.71 [0.92, 613.35]	0.0565	0.74

During quarter 4, we recruited a neuroradiologist, Dr. Michael Kuwabara, to independently calculate hematoma volume, midline shift, basal cistern hemorrhage, and CT Marshall scores on initial CT scans of our subject cohort. We performed univariate logistic regression on these predictor variables to demonstrate that PTE was associated with hematoma volume (OR=1.026, p=0.0338) and CT Marshall Scores (OR=1.559, p=0.0264).

	PTE			p value
	0 (no) (N=40)	1 (yes) (N=10)	Total (N=50)	
HematomaVolume				0.0569 ¹
N	40	10	50	
Mean (SD)	20.0 (23.5)	45.4 (43.2)	25.1 (29.8)	
Median	10.5	39.0	13.0	
Q1, Q3	1.6, 28.4	12.3, 58.8	1.7, 36.3	
Range	(0.0-97.3)	(0.5-143.7)	(0.0-143.7)	
MidlineShift				0.4897 ¹
N	40	10	50	
Mean (SD)	3.0 (3.4)	5.5 (7.0)	3.5 (4.4)	
Median	2.0	2.5	2.0	
Q1, Q3	0.0, 5.0	0.0, 9.0	0.0, 6.0	
Range	(0.0-12.0)	(0.0-21.0)	(0.0-21.0)	
BasalCisternEffacement				0.2251 ²
no	32 (80.0%)	6 (60.0%)	38 (76.0%)	
yes	8 (20.0%)	4 (40.0%)	12 (24.0%)	
CTMarshall				0.0347 ¹
N	40	10	50	
Mean (SD)	3.2 (1.8)	4.8 (1.9)	3.5 (1.9)	
Median	2.0	6.0	2.0	
Q1, Q3	2.0, 6.0	2.0, 6.0	2.0, 6.0	
Range	(1.0-6.0)	(2.0-6.0)	(1.0-6.0)	

¹Wilcoxon Rank Sum ²Fisher Exact

outcome	Effect	OddsRatioEst	LowerCL	UpperCL	pval
PTE (yes vs no)	HematomaVolume	1.026	1.002	1.050	0.0338
	MidlineShift	1.122	0.968	1.299	0.1255
	BasalCistern (y vs n)	0.375	0.085	1.653	0.1950
	CTMarshall	1.559	1.053	2.307	0.0264

We also reviewed global functional outcomes as related to GOSE-PEDs scores at 12 months. A team member blinded to physiologic data (Brian Burrows) independently assessed patients for GOSE_PEDs scores at 12 months post-injury, dichotomizing outcomes to favorable (scores 1-3) or unfavorable (scores 4-8). Using multivariate logistic regression, we were able to demonstrate that after adjusting for initial CT Marshall scores and GCS at presentation, median ICP, PRx, PAX and wPRx values were associated with unfavorable outcomes. Furthermore, when reviewing CPPOpt curves of each of the four model-based indices of cerebral autoregulation, percent time with CPP values below the lower limit of autoregulation for PAX, wPRx and RAC were associated with unfavorable outcomes.

	Outcomes (n=72)	Odds Ratio of Unfavorable Outcome [95% Confidence Interval]	p-value	C-Statistic
Multivariate Analysis				
ICP, median		1.17 [1.00, 1.37]	0.0452	0.71
GCS		0.96 [0.78, 1.18]	0.6847	
CT Marshall Score		0.95 [0.70, 1.30]	0.7574	
CPP, median		0.97 [0.93, 1.01]	0.1433	0.58
GCS		0.93 [0.76, 1.15]	0.5185	
CT Marshall Score		1.00 [0.75, 1.35]	0.9763	
PRx, median		12.66 [1.21, 125.00]	0.0339	0.65
GCS		0.99 [0.80, 1.22]	0.9111	
CT Marshall Score		0.98 [0.73, 1.33]	0.9155	
PAX, median		19.61 [1.35, 250.00]	0.0291	0.66
GCS		0.98 [0.80, 1.21]	0.8707	
CT Marshall Score		1.03 [0.77, 1.39]	0.8339	
wPRx, median		14.71 [1.09, 200.00]	0.0432	0.64
GCS		0.99 [0.80, 1.23]	0.9512	
CT Marshall Score		0.96 [0.71, 1.31]	0.8006	
RAC, median		7.41 [0.96, 58.82]	0.0548	0.64
GCS		0.99 [0.80, 1.22]	0.9071	
CT Marshall Score		1.05 [0.78, 1.41]	0.7423	
% < LLA, PRx		1.03 [1.00, 1.05]	0.0690	0.60
GCS		1.00 [0.81, 1.23]	0.9693	
CT Marshall Score		1.00 [0.75, 1.35]	0.8669	
% < LLA, PAX		1.04 [1.00, 1.09]	0.0328	0.66
GCS		1.01 [0.81, 1.25]	0.9493	
CT Marshall Score		0.94 [0.72, 1.32]	0.8669	
% < LLA, wPRx		1.04 [1.01, 1.08]	0.0100	0.76
GCS		0.99 [0.79, 1.23]	0.9136	
CT Marshall Score		0.90 [0.65, 1.25]	0.5454	
% < LLA, RAC		1.05 [1.01, 1.09]	0.0269	0.68
GCS		1.01 [0.81, 1.25]	0.9549	
CT Marshall Score		0.97 [0.71, 1.32]	0.8403	

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

Professional development: Dr. Brian Appavu and graduate student, Manjusha Ravindranath, were able to participate in the 2020 Neurocritical Care Society Annual Meeting. This afforded an opportunity to learn more about multimodality monitoring in traumatic brain injury and neurocritical care and gain greater knowledge to aid in fostering new research questions regarding management of traumatic brain injury.

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

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

We have submitted an abstract, “Acute Neurophysiologic Biomarkers Predicting Pediatric Post-Traumatic Epilepsy” to the 2020 American Epilepsy Society Virtual Meeting, which has been accepted for a poster presentation. We also submitted an abstract, “Association of Outcomes with Cerebral Autoregulation after Pediatric Traumatic Brain Injury” to the 2020 Neurocritical Care Society Virtual meeting, which was accepted as a platform presentation on September 24th, 2020 and presented on that date. We also submitted an abstract entitled, “Forecasting of Pediatric Post-Traumatic Seizures from EEG” to the 2020 Neurocritical Care Society Virtual meeting, which was accepted as a poster presentation (Poster available under “Accomplishments” section above). Dr. Selcuk Candan and our graduate student, Manjusha Ravindranath, had a manuscript accepted entitled, “M2NN: Rare Event Inference through Multi-variate Multi-scale Attention” to IEEE Smart Data Services 2020, with a conference paper presentation to be presented October 18-23rd. This manuscript describes the methodology by which we applied LSTM with dual, multivariate multiscale attention to predict post-traumatic seizures, as described in the poster, “Forecasting of Pediatric Post-Traumatic Seizures from EEG”.

We will expand our LSTM model to all subjects in our cohort, and include waveforms of ABP, ICP and EKG to determine what factors lead to optimization in this prediction model.

We will perform multivariate modeling including CT Marshall and Hematoma Volume that includes significant variables from univariate modeling in relation to PTE development. We will draft manuscripts to describe these models, either in relation to PTE or to GOSE-Peds at 12 months.

We will also perform DSEM on post-traumatic seizures in relation to ABP, ICP, EKG and EtCO₂, and describe is specific elements of seizures on EEG or their relationship to those parameters are predictive of development of PTE.

We are actively drafting a manuscript describing our investigation of the association of biomarkers of cerebral autoregulation with 12-month functional outcomes after pediatric TBI. Once we complete multivariate modeling of CT Marshall and Hematoma volumes in relation to PTE development, we will develop a manuscript describing that investigation.

4. IMPACT:

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

We anticipate that findings within this proposal will support multicenter prospective observational trials to investigate model-based indices of cerebral autoregulation in pediatric traumatic brain injury, as well as multicenter observational trials to investigate for physiologic biomarkers of post-traumatic epilepsy. We also anticipate these findings will allow for patient selection for clinical trials of anti-epileptogenic therapies in patients with TBI.

We are using statistical modeling results for prediction of PTE to apply for the 2020 CDRMP ERP Research Partnership Award for the proposal to investigate early and latent biomarkers of PTE in adult patients with traumatic brain injury.

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

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

We are delayed in providing a machine learning model, based on RMTS for PTE, and the focus has been on PTS. We will work towards this in the next quarter, and potentially apply a no-cost extension to focus on this work.

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

Nothing to report.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

1. Ravindranath M, Candan KS, Sapino ML. M2NN: Rare Event Inference through Multi-variate Multi-scale Attention. IEEE Smart Data Services 2020. [Accepted for publication, awaiting publication]. Acknowledgment of federal support (yes). See appendix for accepted draft.

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

Nothing to report.

Other publications, conference papers and presentations.

1. “Forecasting of Pediatric Post-Traumatic Seizures from EEG” – Accepted to be presented at the 2020 Neurocritical Care Society Annual Meeting
2. “Acute Neurophysiologic Biomarkers Predicting Pediatric Post-Traumatic Epilepsy” – Accepted for Presentation at the 2020 American Epilepsy Society Annual Meeting
3. “Association of Outcomes with Cerebral Autoregulation after Pediatric Traumatic Brain Injury” – Accepted for Platform Presentation at the 2020 Neurocritical Care Annual Meeting

- **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**

We have developed multivariate logistic regression models for post-traumatic epilepsy and 12-month GOSE-Peds scores after pediatric TBI. We have developed a machine learning model using LSTM with robust multivariate temporal scaling for prediction of post-traumatic seizures from EEG.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Brian Appavu

Project Role: Principal Investigator

Research Identifier: ORCID ID: <https://orcid.org/0000-0002-5396-2559>

Nearest person month worked: 1.07

Contribution to Project: Dr. Appavu has coordinated all efforts related to regulatory approvals and research data analysis.

Name: Austin Jacobson

Project Role: Scientist

Research Identifier: None

Nearest person month worked: 1.75

Contribution to the Project: Mr. Jacobson is involved in data analysis, data cleaning, and data artifact reduction. He is involved in data management between Phoenix Children's Hospital and Arizona State University.

Name: Brian Burrows

Project Role: Research Coordinator

Research Identifier: None

Nearest person month worked: 1.93

Contribution to the Project: Mr. Burrows is involved in research coordination, data analysis, data cleaning, and data artifact reduction. Mr. Burrows is gathering and accumulating information regarding functional outcome scores and epilepsy categorization for research subjects.

Name: Kasim Selcuk Candan

Project Role: Clinical Scientist

Nearest person month worked: 0.5

Contribution to the Project: Dr. Candan is involved in machine learning analysis

Name: Manjusha Ravindranath

Project Role: Clinical Scientist

Nearest person month worked: 3

Contribution to the Project: Dr. Candan is involved in machine learning analysis

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

Nothing to Report

What other organizations were involved as partners?

Organization: Arizona State University

Location of Organization: Tempe, Arizona, USA

Facilities: ASU Center for Assured and SCALable Data Engineering

Support: Funding

Personnel: Dr. Selcuk Candan provides leadership and direction in the aspect of machine learning of pediatric post-traumatic seizures. His graduate student, Manjusha Ravindranath, utilizes resources at ASU, in collaboration with personnel at PCH, to help develop machine learning models to predict post-traumatic seizures.

8. SPECIAL REPORTING REQUIREMENTS

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

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

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