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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

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6. AUTHOR(S):
Brian Appavu, Stephen Foldes, Austin Jacobson, Hamy Temkit, P.

E-Mail: bappavu@phoenixchildrens.com

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Phoenix Children's Hospital
1919 E. Thomas Rd.
Phoenix, AZ 85016-7710

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14. ABSTRACT

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.

15. SUBJECT TERMS:

Post traumatic epilepsy, post-traumatic seizures.

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

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

Traumatic brain injury, post-traumatic epilepsy,

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

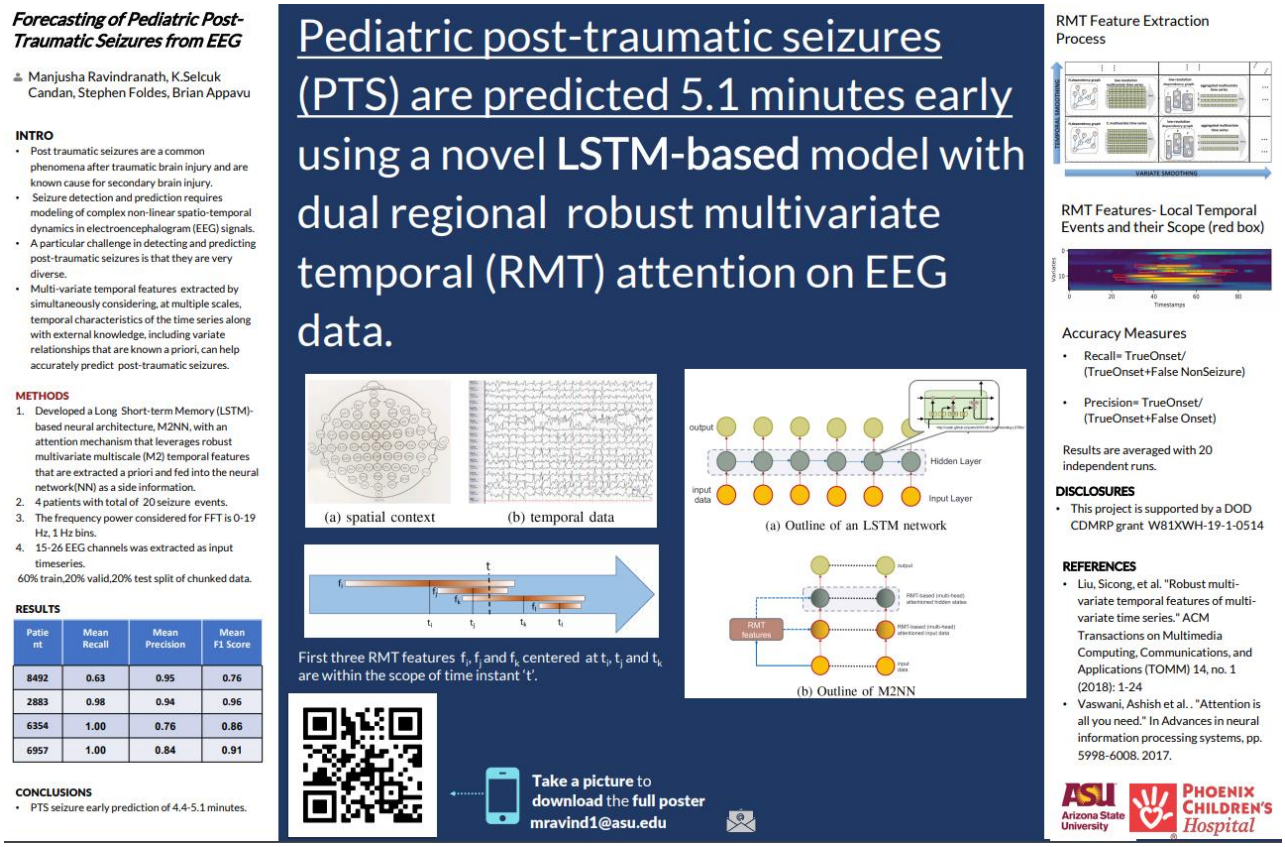
What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

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

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±13% seizures correctly with false prediction occurring during 0.03±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.

(a) spatial context (b) temporal data

First three RMT features f_i, f_j and f_k centered at t_i, t_j and t_k are within the scope of time instant 't'.

(a) Outline of an LSTM network

(b) Outline of M2NN

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.

Arizona State University

Phoenix Children's Hospital

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			
	0 (no) (N=40)	1 (yes) (N=10)	Total (N=50)	p value
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)	

[1]Wilcoxon Rank Sum [2]Fisher 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	

We submitted the above data for publication to Pediatric Critical Care Medicine, but our manuscript did not meet a high enough score to reach priority for publication. Based on feedback provided, we revised our analysis of GOSE-PEDs data to perform univariate and multiple linear regression to develop a best subset model for identification of the best predictive model for GOSE-PEDs scores. Best subset model selection identified that when accounting for GCS, increased tone of intracranial hypertension and percent time below the lower limit of autoregulation for wPRx are independently associated with higher GOSE-Peds scores.

	slope	95% Confidence Interval	p-value	R^2 (%)
Male	-0.18	(-1.26, 0.91)	0.7424	0.2
Age (years)	-0.01	(-0.10, 0.07)	0.7450	0.2
GCS, median	**-0.20**	**(-0.37, -0.03)**	**0.0247**	**7.2**
PRISM III	0.07	(-0.04, 0.18)	0.2311	2.1
Intracranial Hematoma Volume	-0.00	(-0.02, 0.02)	0.7374	0.2
Midline Shift	-0.09	(-0.22, 0.05)	0.2018	3.0
Basal Cistern Effacement	0.73	(-0.48, 1.93)	0.2318	2.1
CT Marshall	0.00	(-0.30, 0.30)	0.9995	0.0
Dichotomized dICH, mmHg/hour	**1.43**	**(0.47, 2.39)**	**0.0041**	**11.5**
CPP, median, mmHg	**-0.05**	**(-0.08, -0.02)**	**0.0039**	**11.6**
ABP, median, mmHg	-0.06	(-0.07, 0.04)	0.6066	0.3
HR, median, bpm	**0.03**	**(0.01, 0.05)**	**0.0084**	**9.8**
PRx, median	**3.04**	**(1.46, 4.62)**	**0.0003**	**17.8**
PAx, median	**2.89**	**(1.30, 4.48)**	**0.0006**	**16.2**
wPRx, median	**3.33**	**(1.65, 5.00)**	**0.0002**	**18.8**
RAC, median	**2.50**	**(1.01, 4.00)**	**0.0013**	**14.1**
% < LLA (PRx), median	**0.04**	**(0.02, 0.06)**	**0.0002**	**18.5**
% < LLA (PAx), median	**0.05**	**(0.03, 0.07)**	**< 0.0001**	**23.9**
% < LLA (wPRx), median	**0.04**	**(0.03, 0.06)**	**< 0.0001**	**32.2**
% < LLA (RAC), median	**0.05**	**(0.03, 0.07)**	**< 0.0001**	**25.1**
% > ULA (PRx), median	-0.05	(-0.11, 0.01)	0.0848	4.3
% > ULA (PAx), median	-0.15	(-0.31, 0.02)	0.0793	4.5
% > ULA (wPRx), median	-0.07	(-0.16, 0.02)	0.1111	3.7
% > ULA (RAC), median	-0.09	(-0.24, 0.05)	0.1960	2.5

	Slope	95% Confidence Interval	p-value
GCS, median	**-0.22**	**(-0.37, -0.06)**	**0.0068**
Dichotomized dICH, mmHg/hour	**1.40**	**(0.49, 2.31)**	**0.0031**
HR, median, bpm	**0.02**	**(0.00, 0.04)**	**0.0312**

	Slope	95% Confidence Interval	p-value	Standard Slope
GCS, median	-0.13	(-0.28, 0.02)	0.0896	-0.18
Dichotomized dICH, mmHg/hour	**1.05**	**(0.20, 1.90)**	**0.0166**	**0.25**
% time < LLA, wPRx	**0.04**	**(0.02, 0.05(**	**< 0.0001**	**0.46**

This latter data has been submitted to publication to the journal Neurocritical Care and is currently under review.

Based upon scoring of GOSE-PEDs scores performed as part of our project, we did an ancillary quality improvement study in which we investigated our use of multimodal neurologic monitoring reporting on GOSE-PEDs scores. We did not observe that GOSE-PEDs scores were associated with changes in the implementation of multimodal neurologic monitoring reporting.

	Before MMM Reporting		After MMM Reporting		p-value
	N = 67		N = 18		
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Initial GCS	6.0 (2.9)	6.0 (4.0)	6.6 (3.4)	6.5 (5.5)	0.4972
PRISM III	16.2 (4.3)	16.0 (14.5)	17.9 (8.0)	16.0 (12.0)	0.5837
Length of hospitalization (days)	24.1 (16.7)	21 (17.7)	21.6 (17.2)	17.5 (15.3)	0.4074
PICU Length (days)	17.3 (11.9)	14.0 (12.0)	12.3 (9.0)	10.0 (9.3)	0.0546
Ventilator days	11.1 (8.3)	9.0 (7.0)	6.6 (3.9)	5.5 (6.8)	**0.0118**
ICP monitoring days	7.8 (4.2)	7.0 (5.0)	4.6 (2.7)	3.5 (4.0)	**0.0017**
Total complications (per patient)	0.4 (0.7)	0.0 (1.0)	0.1 (0.3)	0.0 (0.0)	0.0672
	N = 62		N = 18		
% time ICP > 20 mmHg	15.7 (27.5)	4.7 (10.9)	20.3 (30.6)	8.0 (24.1)	0.2943
% time CPP < 40 mmHg	9.1 (25.2)	0.2 (0.7)	8.1 (23.5)	0.3 (1.4)	0.5310
	N = 67		N = 9		
GOSE-PEDs, 12 months	4.4 (2.2)	5.0 (3.0)	4.0 (1.7)	3.0 (1.0)	0.5639

This quality improvement work has been accepted for publication to the journal Neurocritical Care and is awaitiing final proofs before print and release.

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

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

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".

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

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.

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

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

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

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

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

Nothing to report

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

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report

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

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

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

Nothing to report

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

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report

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

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

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

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

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

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.
2. Appavu B, Burrows BT, Nickoles T, Boerwinkle V, Willyerd A, Gunnala V, et al. Implementation of Multimodal Neurologic Monitoring Reporting in Pediatric Traumatic Brain Injury Management. Neurocritical Care 2020. [Accepted for publication, awaiting for publication].

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

Nothing to report.

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

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

  Nothing to Report.

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

  Nothing to report

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

  Nothing to report

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

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?

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

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Brian Appavu
Project Role: Principal Investigator
Research Identifier: ORCID ID: https://orcid.org/0000-0002-5396-2559
Nearest person month worked: 1.2
Contribution to Project: Dr. Appavu has coordinated all efforts related to regulatory approvals and research data analysis.

Name: Stephen Foldes
Project Role: Scientist
Research Identifier: ORCID ID: https://orcid.org/0000-0002-2061-3790
Nearest person month worked: .9
Contribution to the Project: Dr. Foldes is involved in data analysis, data cleaning, and data artifact reduction. He is particularly putting effort towards EEG analysis.

Name: Austin Jacobson
Project Role: Scientist
Research Identifier: None
Nearest person month worked: 1.9
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: 1.2
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: 2
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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

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

Nothing to Report

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

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

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

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

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.*