Artificial Intelligence, EEG and Clinical Outcomes in Intensive Care Units

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Disclosures:

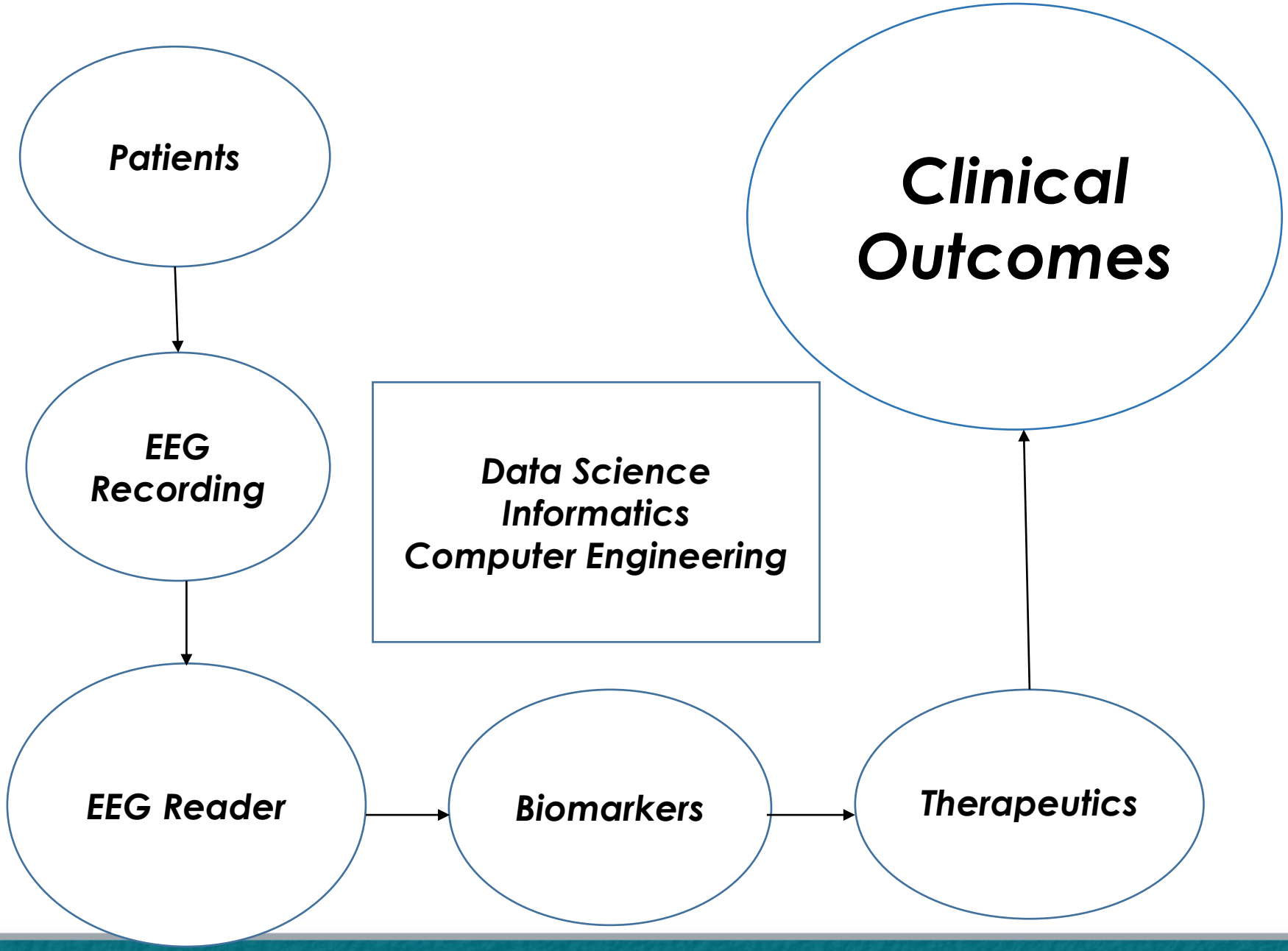
Site PI:

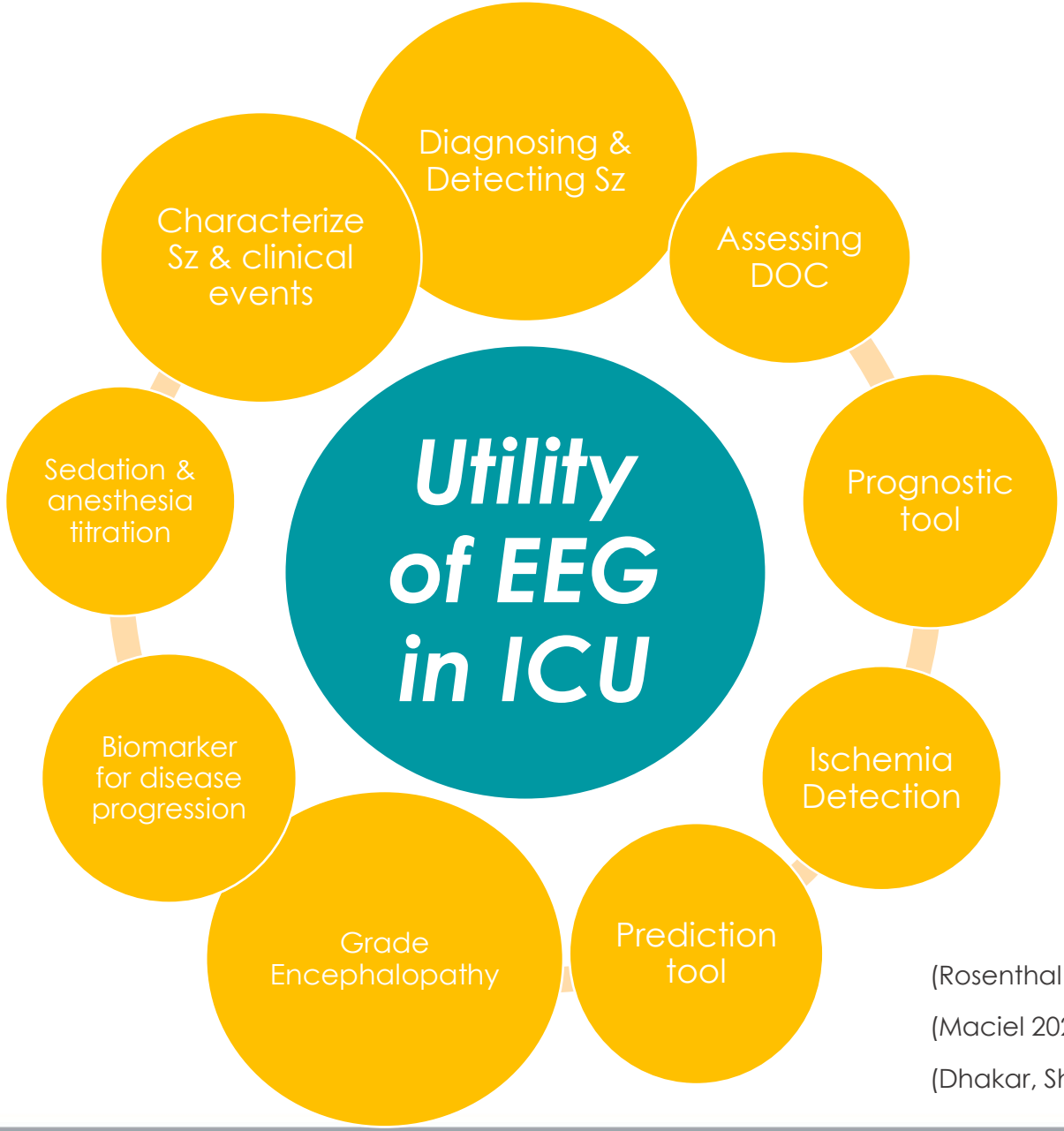
1. SAFER
2. RESET
3. RAISE
4. CHoRUS Bridge2AI
5. No financial disclosures—Work on Rapid-EEG clinical studies
6. Internal funding via CBRR

I am a clinician with interest in Data science

Objectives:

- Discuss utility of EEG in ICU
- Review EEG as a multi-dimensional biomarker
- Review applications of AI and ML for each type of biomarker
- Review cases highlighting biomarker usage in clinical management where available
- Summarize learnings for the session

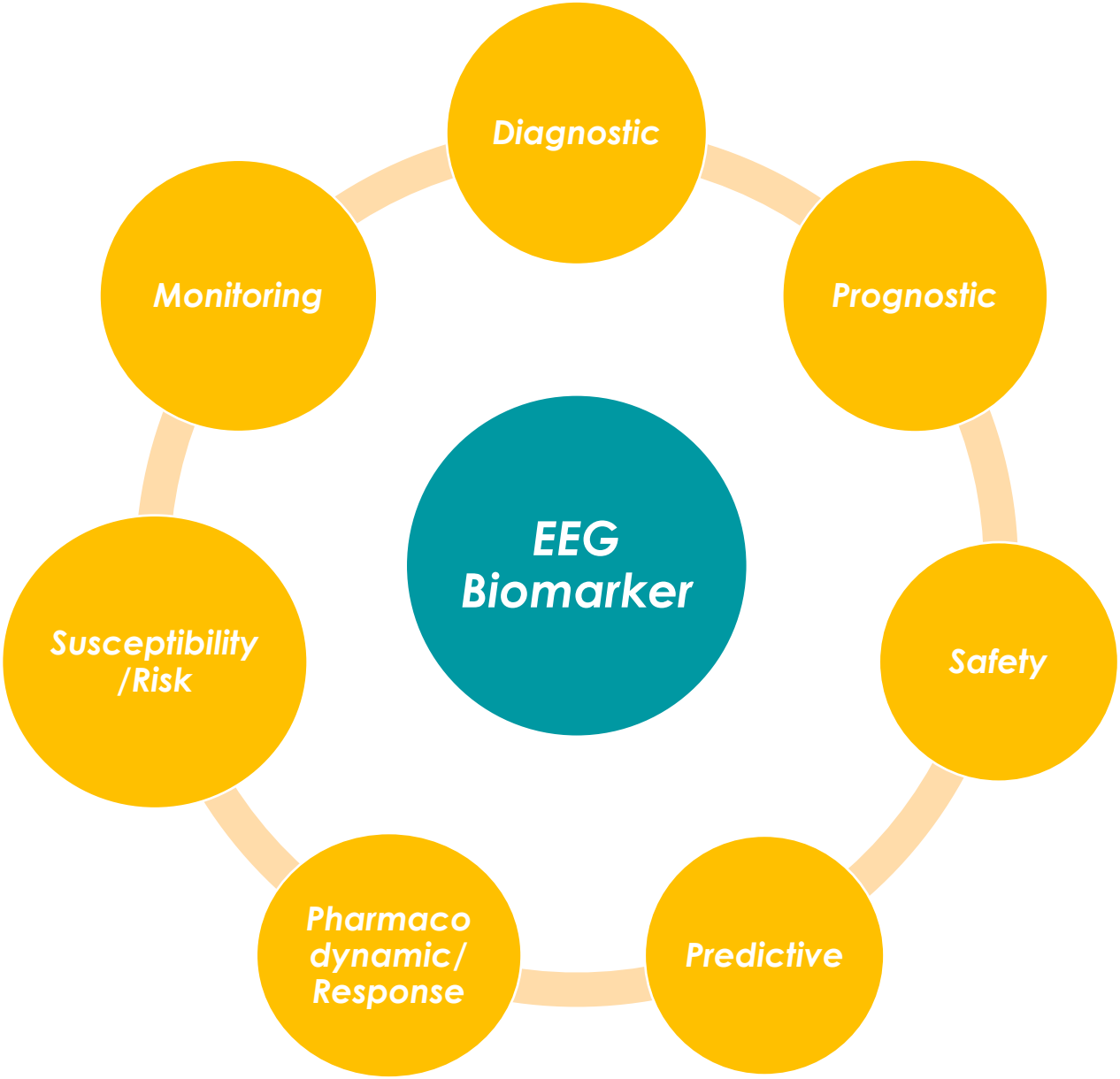

Patients
EEG Recording
EEG Reader
Biomarkers
Therapeutics
Clinical Outcomes
Data Science
Informatics
Computer Engineering



(Rosenthal 2021)

(Maciel 2021)

(Dhakar, Sheikh et al. 2022)



(Pitkänen, Ekolle Ndode-Ekane et al. 2019)

Seizure Forecasting:

Prediction of Sz:

- Critical Care EEG Monitoring Research Consortium (CCEMRC)
- Multi-Institutional Prospective Database
    - Yale, Brigham and Women's, Emory

- *Consecutive LTMs >6h*
- *ACNS Critical Care EEG terminology*
- *Large Dataset—5427 CEEGs*

(Struck, Ustun et al. 2017)

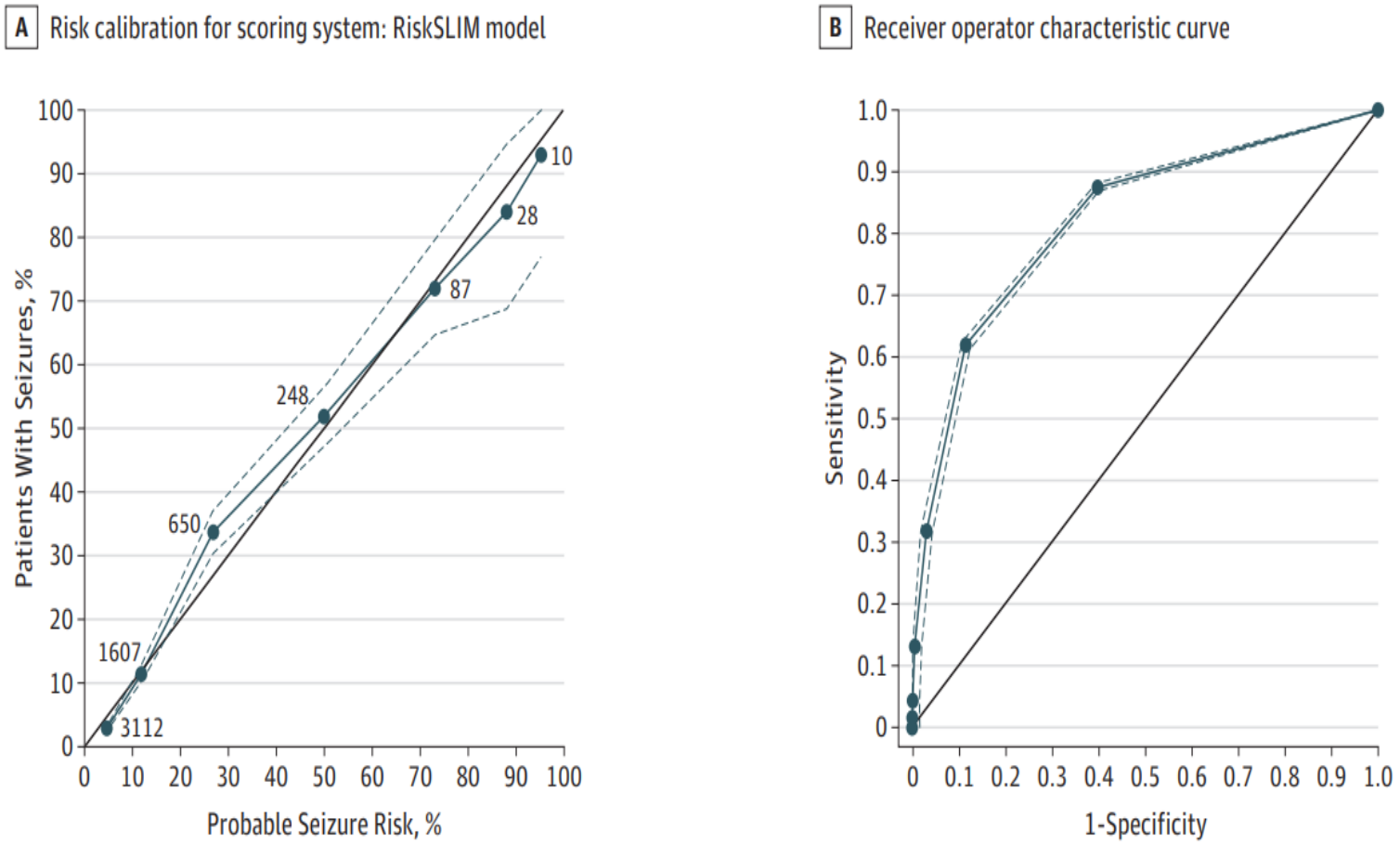
2HELPS2B:

		Score
1.	**Frequency > 2Hz**	1
2.	**Independent Sporadic Epileptiform Discharges**	1
3.	**LPD/BIPD/LRDA**	1
4.	**Plus Features (superimposed rhythmic, fast, sharp)**	1
5.	**Prior Seizure**	1
6.	**Brief Potentially Ictal Rhythmic Discharge (BIRD)**	2

Total Score	**0**	**1**	**2**	**3**	**4**	**5**	**6+**
Risk of Seizure	<5%	12%	27%	27%	73%	88%	>95%

(Struck, Ustun et al. 2017)

Figure. Risk Calibration and Receiver Operating Characteristics for Scoring System

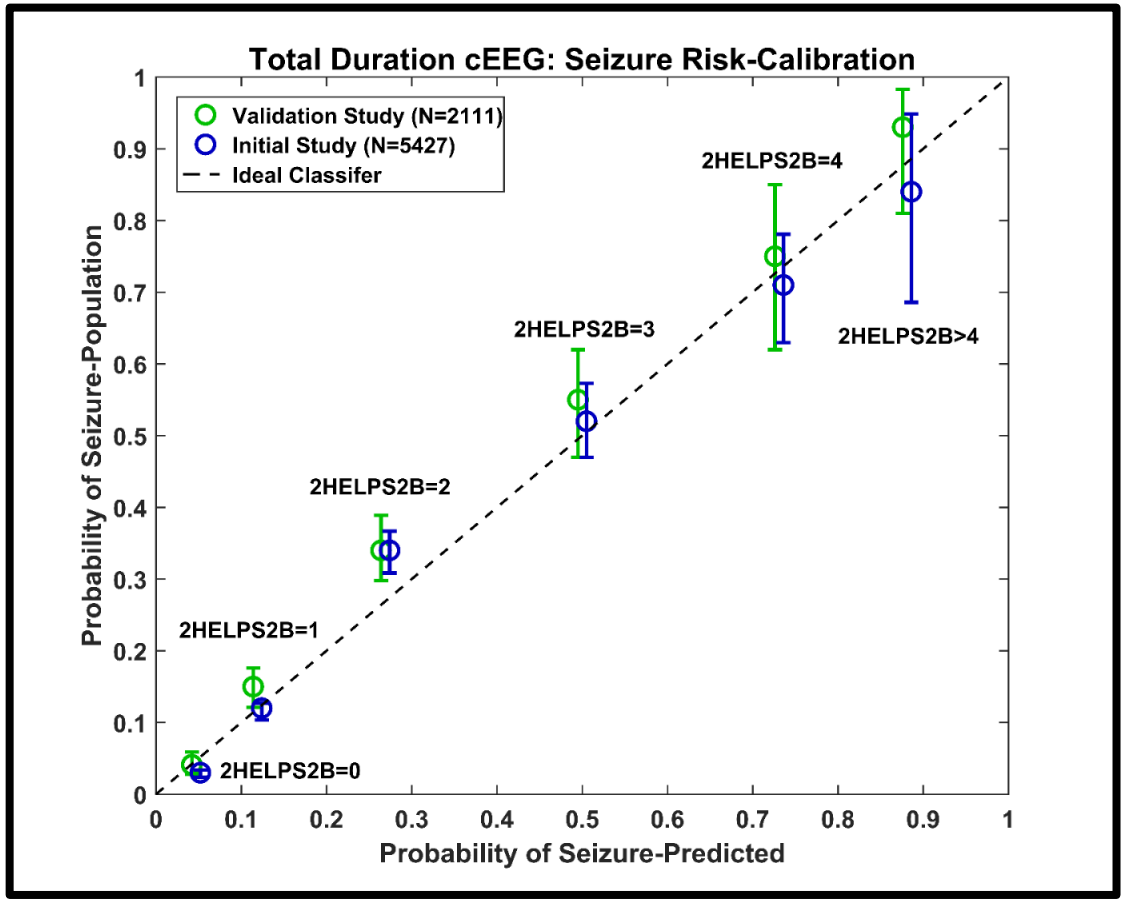


(Struck, Ustun et al. 2017)

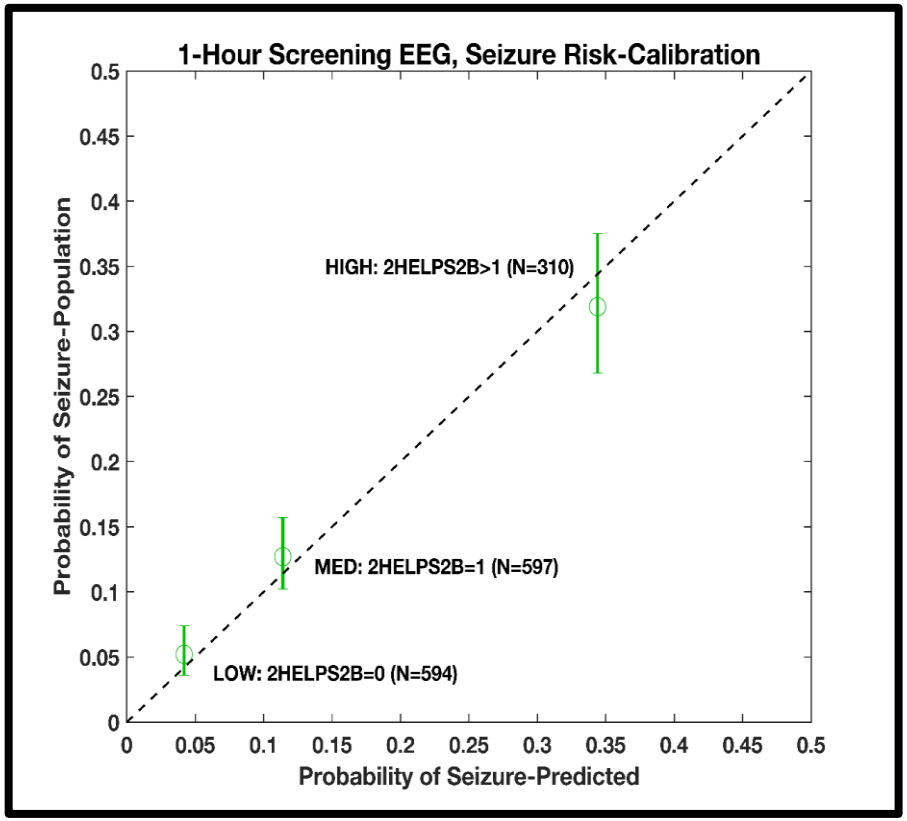
2HELPS2B: Validation

- To determine EEG duration needed to calculate 2HELPS2B
- To standardize forecast duration to 72Hours
- To validate on an independent cohort
  5 Centers (N=2111)
  - **One hour of screening EEG is sufficient to stratify continuous EEG (cEEG) seizure risk and recommend cEEG monitoring duration.**

(Struck, Tabaeizadeh et al. 2020)



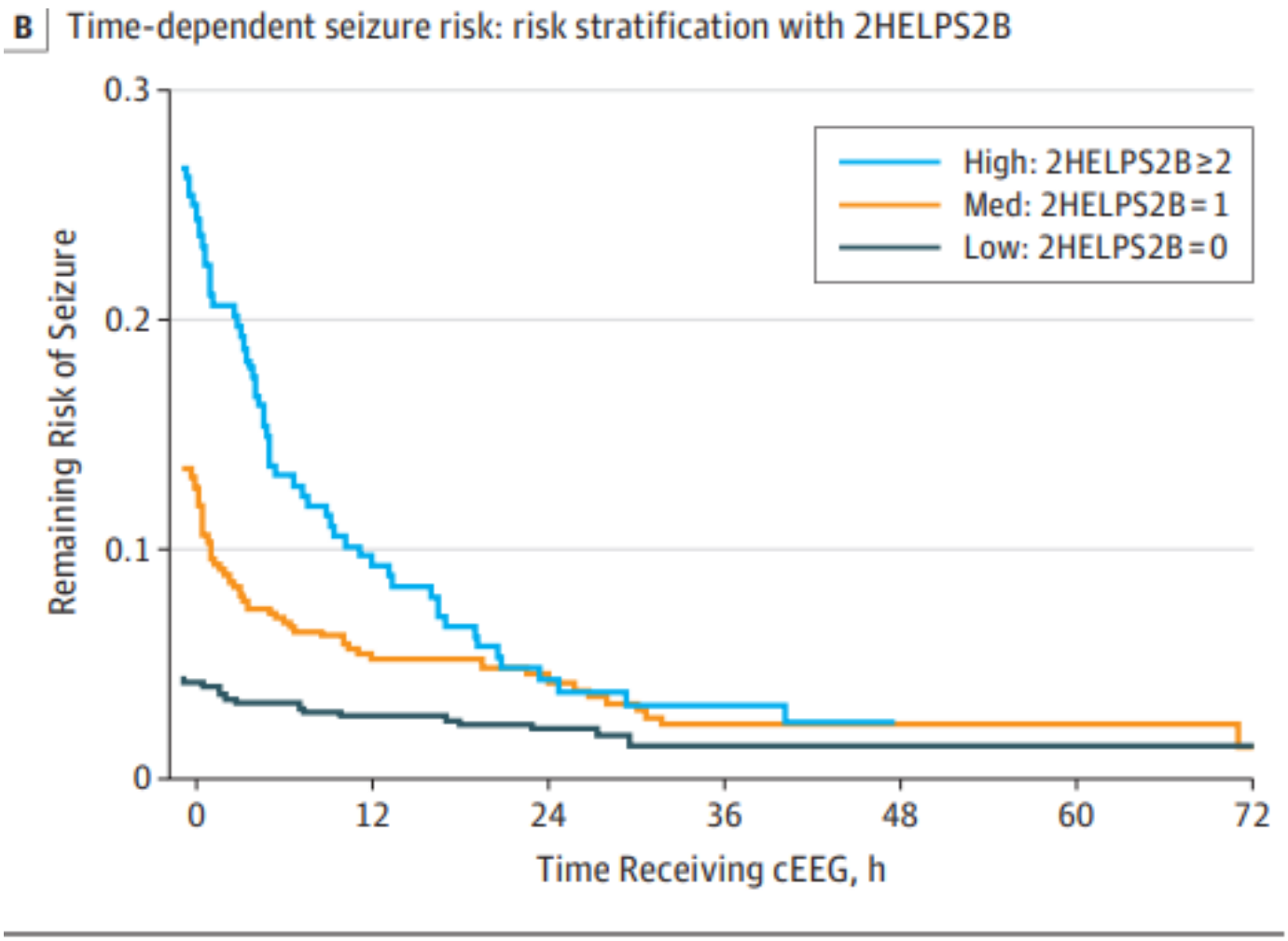
Risk-Calibration Graph of the Error for the 2HELPS2B Model in the Initial Study Cohort and the Validation Cohort



Risk-Calibration Graph of the Error for the 2HELPS2B Model Calculated Only During the 1st Hour of EEG in the Validation Cohort, Represented With 3 Risk Levels

(Struck, Tabaeizadeh et al. 2020)

Courtesy: Aaron Struck



(Struck, Tabaeizadeh et al. 2020)

Seizure Risk Group	% of Cohort	Overall Seizure Risk	False Negative Rate	Recommend Duration of EEG Monitoring
LOW RISK: 2HELPS2B=0	594 (40%)	3.1%	3.1%	**1 Hour (length of screening EEG)**
MED RISK: 2HELPS2B=1	597 (40%)	12.0%	4.0%	**12 Hours**
HIGH RISK: 2HELPS2B≥2	310 (21%)	26.6%	3.1%	**At least 24 Hours**

(Struck, Tabaeizadeh et al. 2020)

SAFER Trial

- Multi-center study
- **Main P.I.:** Aaron Struck, MD
- University of Wisconsin – Madison
- Retrospective comparative effectiveness analysis to determine the predictive value of seizure-risk forecasting with the **2HELPS2B scoring system in conventional and rapid EEGs**
- Goal: n=**500 patients Rapid-EEG**, & **500 patients who received conventional EEG**.
- To provide a roadmap for the use of **rEEG** in patients at risk for seizures.

Courtesy: Aaron STRUCK

Objectives:

- **Primary AIM -** Compare rEEG (Ceribell™ Devices) to cEEG for *seizure risk stratification*.
  - *1A Primary outcome*: AUC of ROC curve between rEEG and cEEG (**non-inferiority margin of 0.1**)
- **Secondary AIM -** Compare *sensitivity of rEEG and cEEG*
  - *2A Outcome*: Distribution of EEG patterns detected during first hour of monitoring
  - *2B Outcome*: Distribution of EEG patterns from first hour of EEG monitoring to follow-on prolonged continuous EEG
- **Secondary AIM -** Compare *outcomes at hospital discharge* between rEEG and cEEG
  - *3A Outcome*: Distribution of Hospital Discharges (Home, Rehab/skilled nursing, Death)

Courtesy: Aaron STRUCK

Results:

Utilization:

EEG use in Emergency Department: Rapid-EEG (27.1%) v. Conventional-EEG (3.7%)

-Decreased logistical constraints with rapid-EEG can improve utilization in ED

Primary Outcome: Rapid-EEG is *non-inferior* to Conventional-EEG for seizure risk stratification in hospitalized patients

-Rapid-EEG can be used to triage patients for seizure risk and determine need for follow-on Conventional-EEG

-2HELPS2B=0 on 1-hour screening rapid-EEG has <5% risk of seizure over the next 72 hours

Secondary Outcomes:

-There are ***no significant differences*** between ***rEEG and cEEG cohort*** in relevant **EEG patterns** (2HELPS2B) during **the 1st H of monitoring.**

-The **stability of EEG findings** observed from **1st H** to **rest of EEG** were ***not significantly different*** between rapid-EEG and conventional-EEG.

-Outcomes at hospital discharge was ***not significantly different*** between rapid-EEG and conventional-EEG.

Courtesy: Aaron STRUCK

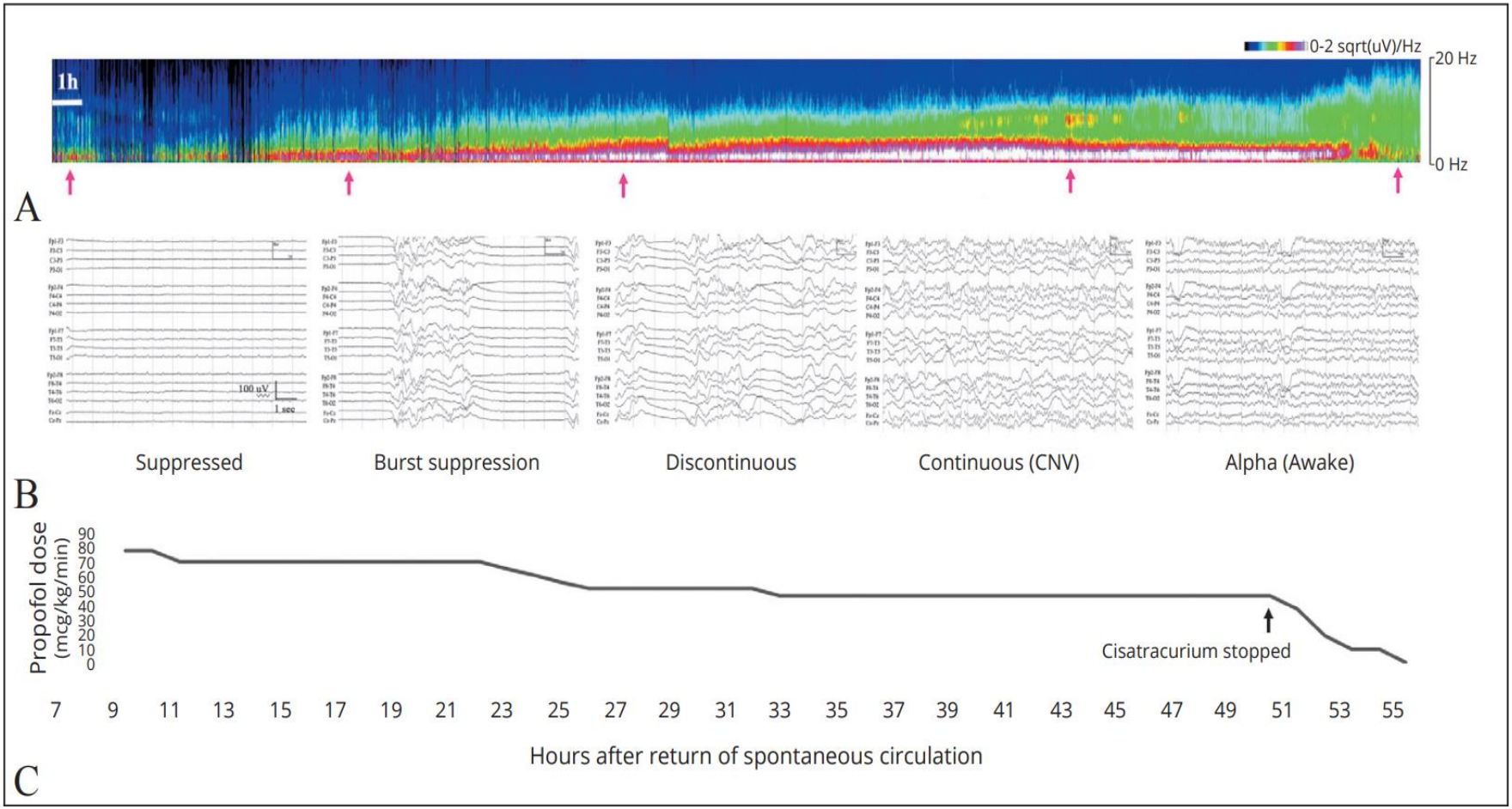
Future Direction:

- Establish biomarkers for seizure forecasting longitudinally after a single seizure and in patients with epilepsy

- Real time forecasting in both inpatient and outpatient clinical setting

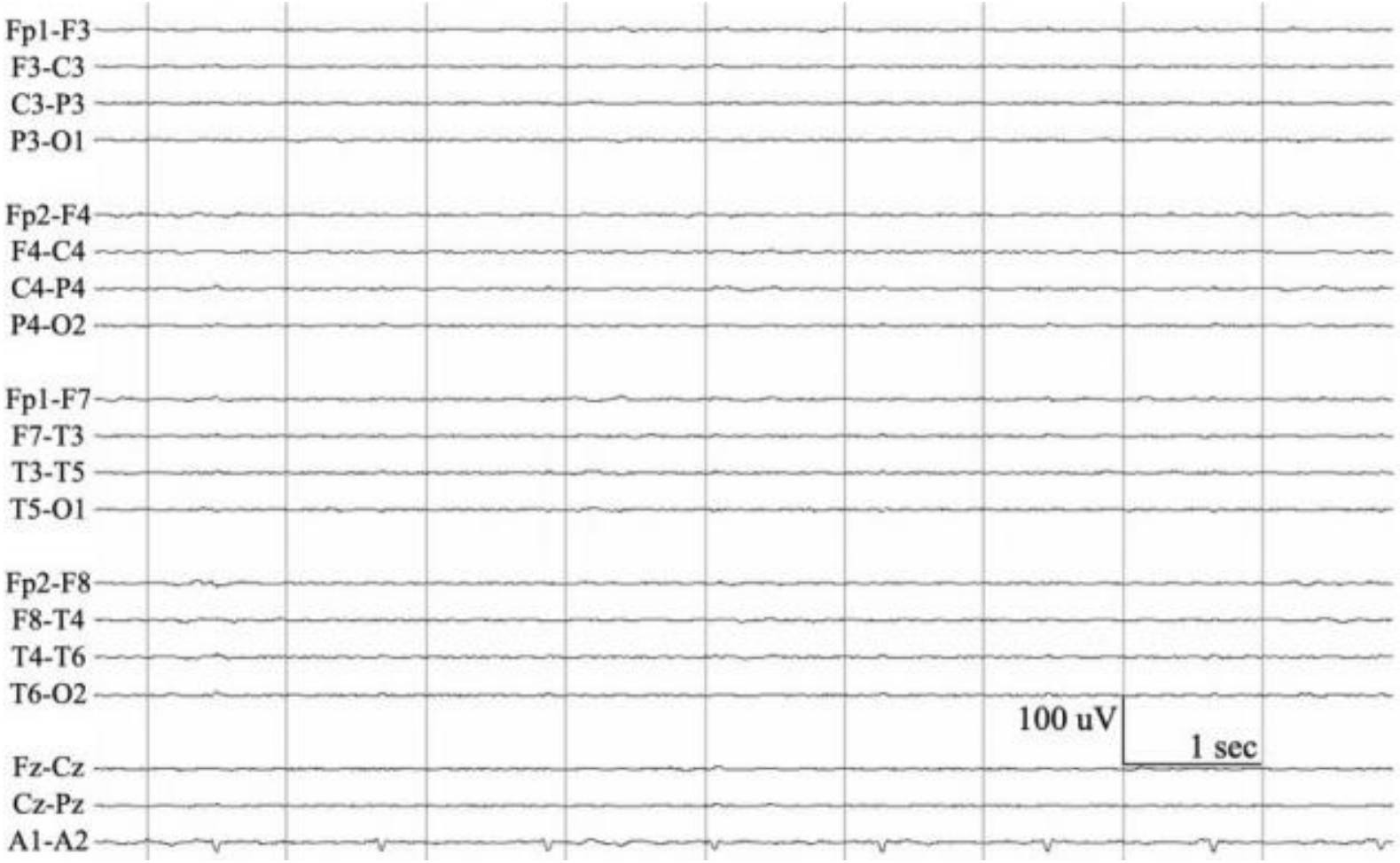
- Seizure forecasting – Could improve seizure control and clinician time for EEG review

Prognostication:



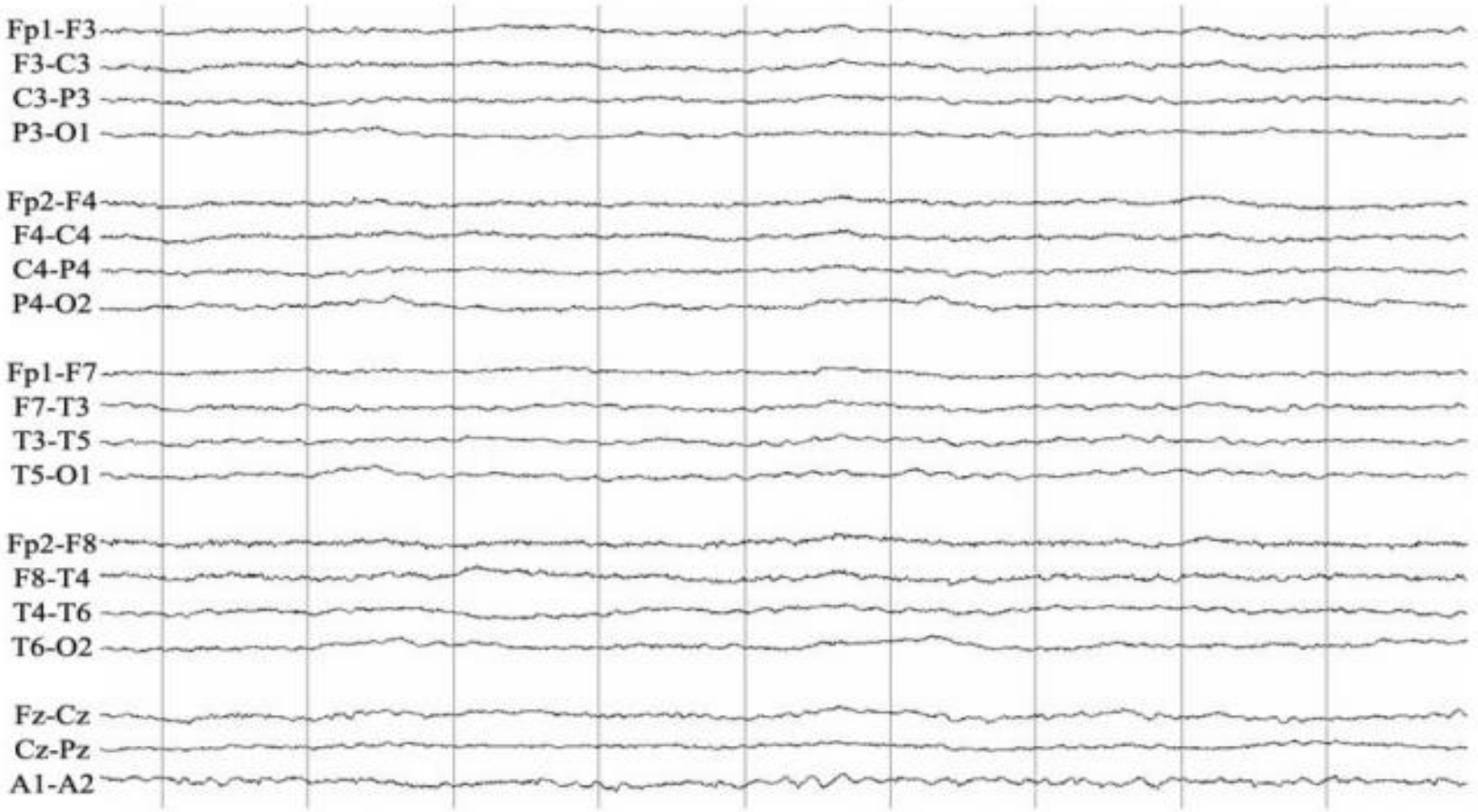
(Khazanova, Douglas et al. 2021)

Suppression:



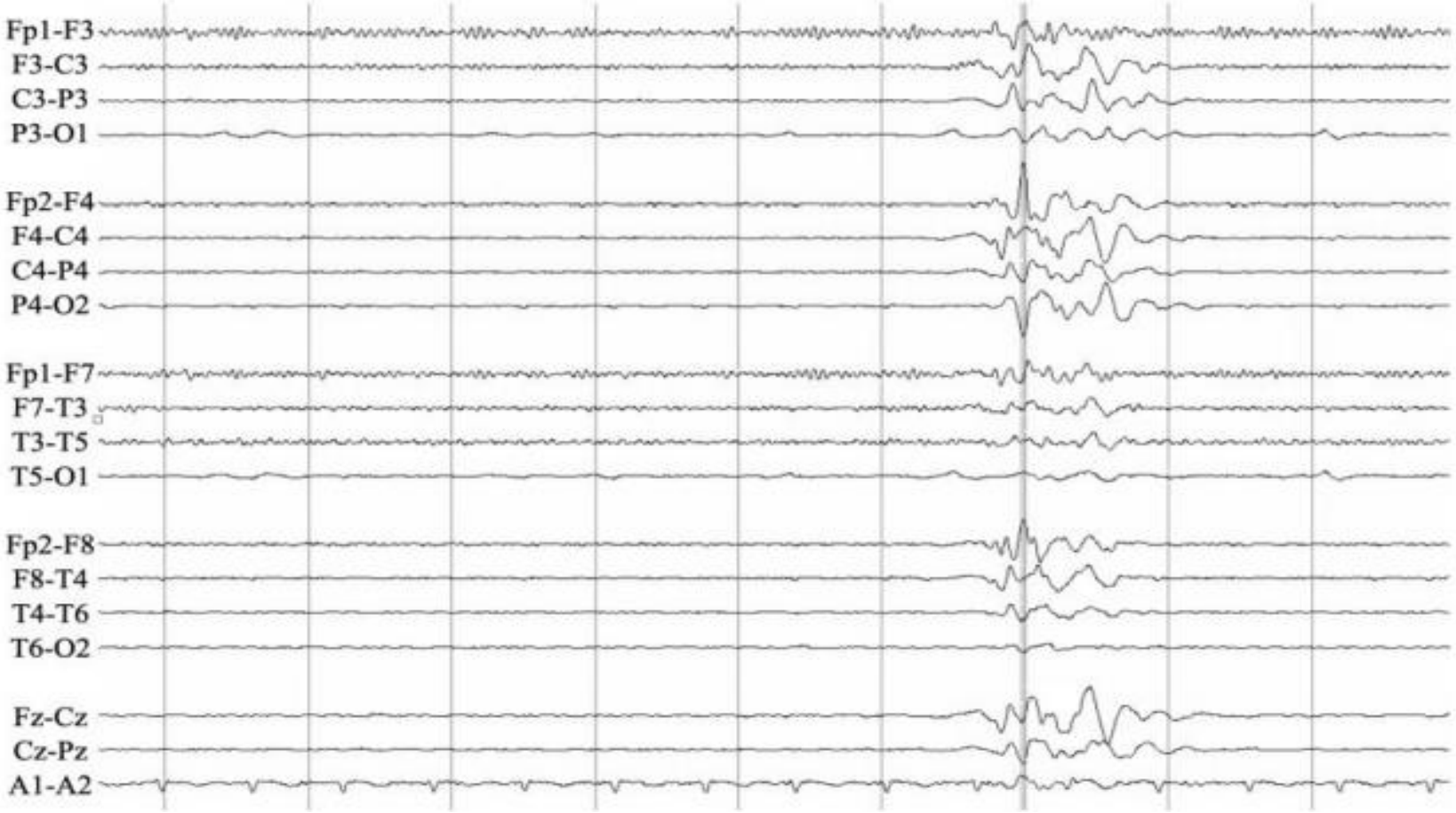
(Khazanova, Douglas et al. 2021)

Low Voltage:



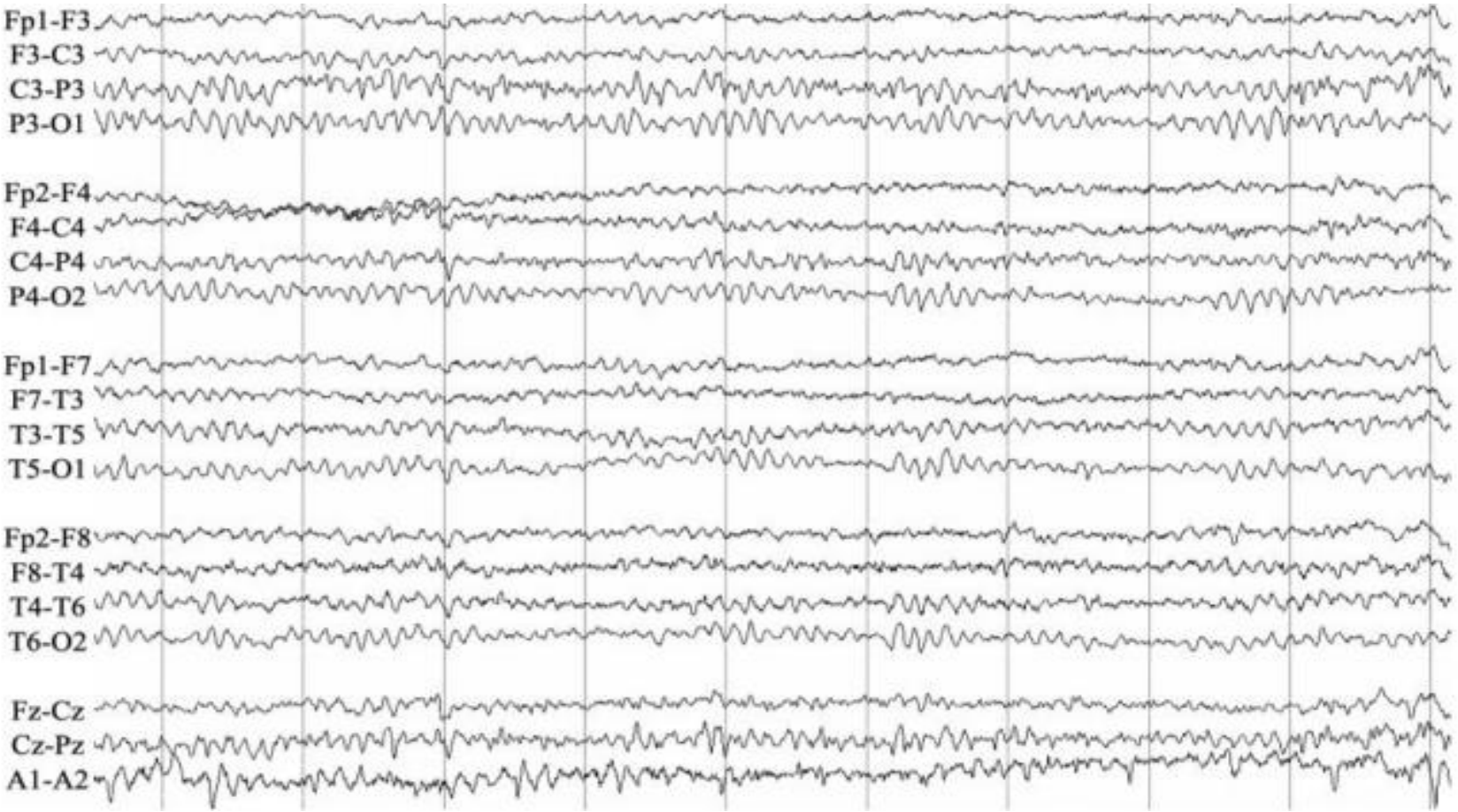
(Khazanova, Douglas et al. 2021)

Burst Suppression:



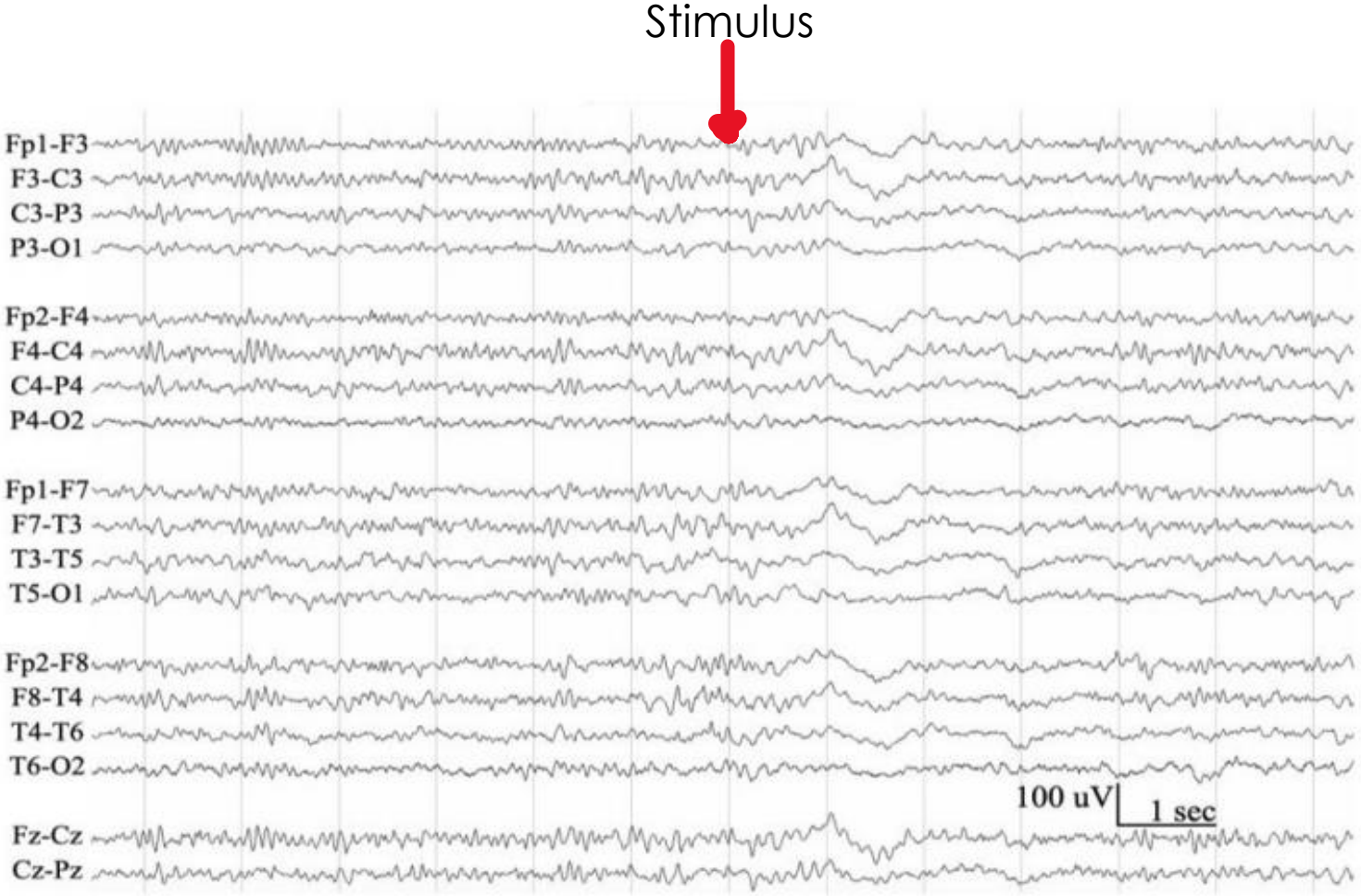
(Khazanova, Douglas et al. 2021)

Normal Continuous Background:



(Khazanova, Douglas et al. 2021)

Reactivity:



(Khazanova, Douglas et al. 2021)

Good Outcomes

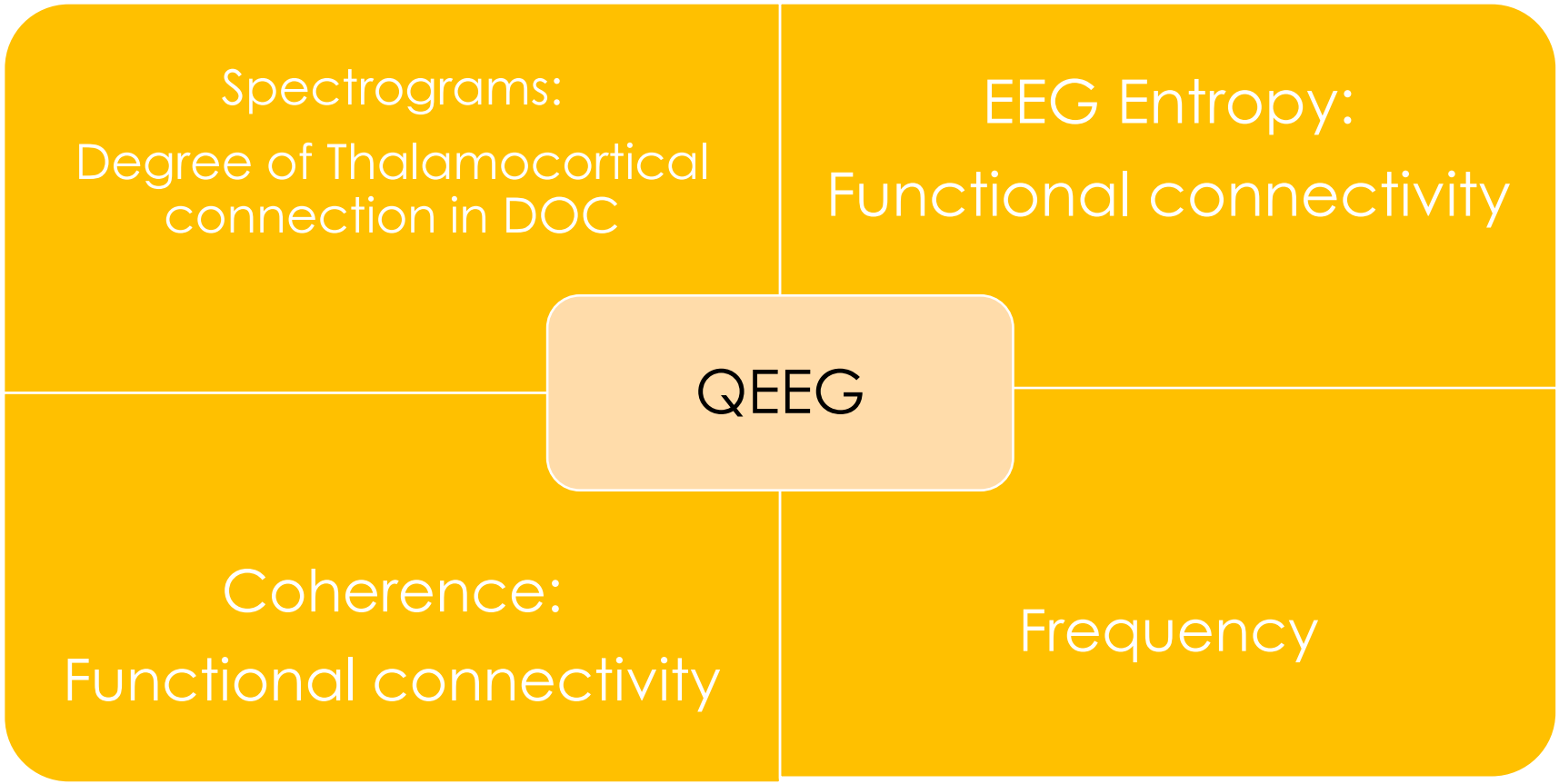
- Normal continuity
- Reactivity
- Preserved sleep-wake cycles

Poor Outcomes

- BS with identical bursts
- Suppression
- Low Voltage
- Myoclonic Status Epilepticus
- PD on a suppressed background

(Khazanova, Douglas et al. 2021)

QEEG Features:



(Edlow, Claassen et al. 2021)

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Quantitative EEG reactivity and machine learning for prognostication in hypoxic-ischemic brain injury ☆

Edilberto Amorim [a,b,*], Michelle van der Stoel [c], Sunil B. Nagaraj [d], Mohammad M. Ghassemi [e], Jin Jing [a], Una-May O'Reilly [b], Benjamin M. Scirica [f], Jong Woo Lee [g], Sydney S. Cash [a], M. Brandon Westover [a]

[a] Department of Neurology, Massachusetts General Hospital, Boston, MA, USA
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- 75 patients were analyzed for their EEG and clinical data.

Table 1
Summary of quantitative EEG features acquired for EEG reactivity assessment.

Feature domain	Quantitative EEG features
Complexity/ Entropy	Nonlinear Energy Operator (Mukhopadhyay and Ray, 1998); Hjorth Parameter (Activity; Mobility; Complexity) (Hjorth, 1970); Fractal Dimension (Lutzenberger et al., 1992); Singular Value Decomposition Entropy (Sabatini, 2000); Spectral Entropy (Zhang et al., 2001); State/Response Entropy (Lysakowski et al., 2009); Sample Entropy (Abasolo et al., 2006); Renyi Entropy (Kannathal et al., 2005); Shannon Entropy (Kannathal et al., 2005); Approximate Entropy (Liang et al., 2015); Permutation Entropy (Bandt and Pompe, 2002); Relative Entropy (Inouye et al., 1991); Kurtosis; Skewness
Amplitude	Root Mean Square Amplitude; Mean of Amplitude Modulation; Standard Deviation of Amplitude Modulation; Skewness of Amplitude Modulation; Kurtosis of Amplitude Modulation; Mean of Amplitude Modulation (Stevenson et al., 2013); Burst Suppression Ratio (Nagaraj et al., 2018)
Frequency	Band Power: Delta (0.5–4 Hz), Theta (4–8 Hz), Alpha (8–12 Hz), Spindle (12–16 Hz), and Beta (16–25 Hz) Band Power; Total Power (0.5–32 Hz) Band Power Normalized by Total Power: Delta (0.5–4 Hz), Theta (4–8 Hz), Alpha (8–12 Hz), Beta (16–25 Hz) Band Power Ratios: Theta/Delta, Alpha/Delta, Spindle/Delta, Beta/Delta, Alpha/Theta, Spindle/Theta, and Beta/Theta Brain Symmetry Index (BSI) (van Putten et al., 2004): BSI total; BSI alpha; BSI delta; BSI theta; BSI beta (12–17 Hz); BSI beta (18 Hz); BSI delta and alpha combined; BSI delta, theta, and alpha combined Two Group Test (TGT) (Bokil et al., 2007): TGT total; TGT alpha; TGT delta; TGT theta; TGT beta (12–17 Hz); TGT beta (18 Hz); TGT delta and alpha combined; TGT delta, theta, and alpha combined Standard Deviation of Frequency Modulation; Skewness of Frequency Modulation; Kurtosis of Frequency Modulation (Stevenson et al., 2013); Kolmogorov-Smirnov (spectral distribution) (McEwen and Anderson, 1975); Spectral Edge Frequency; Peak Frequency

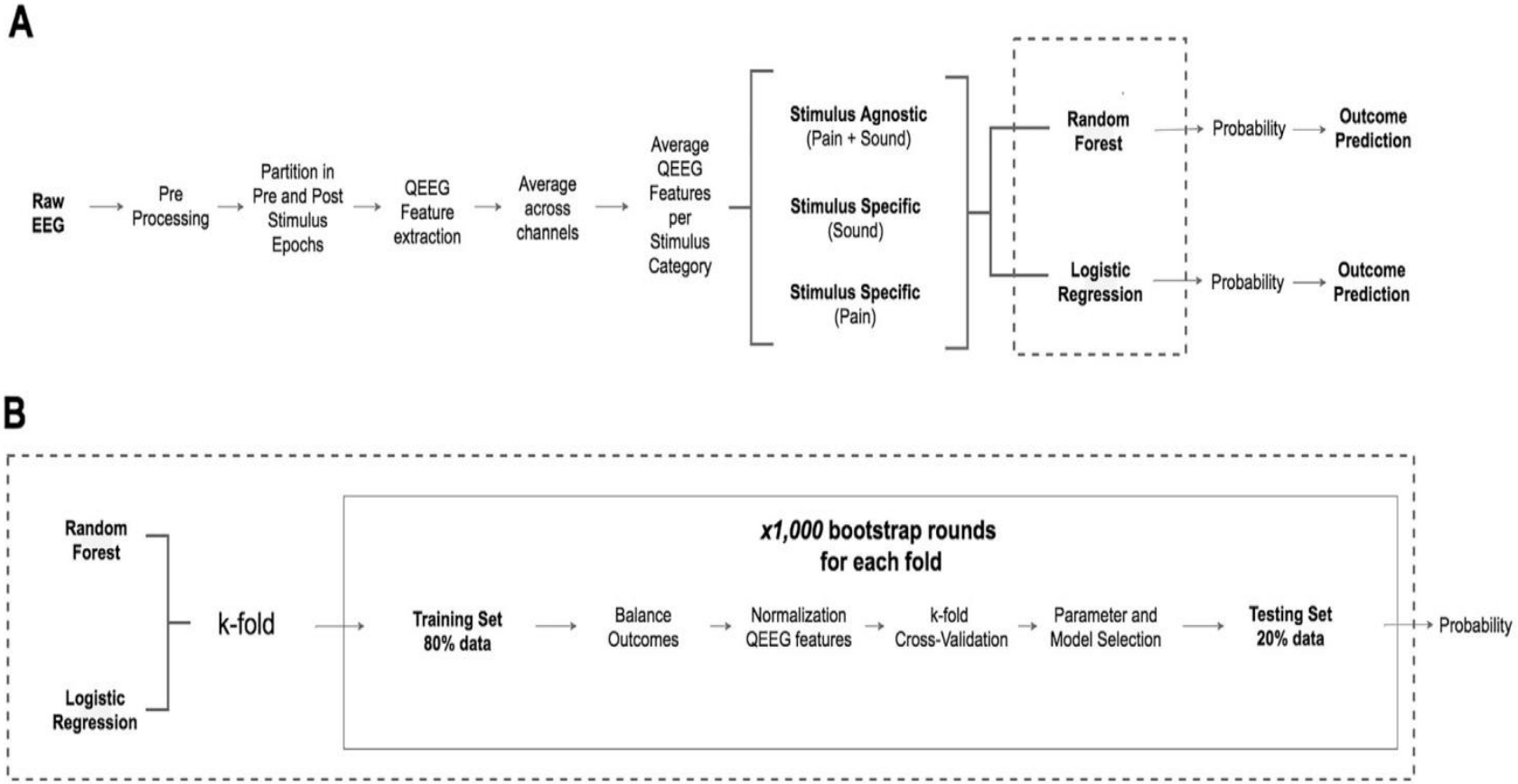


Fig. 1. A: Architecture data processing and evaluation: preprocessing, feature acquisition, separation by stimulus type; B: Classification steps for random forest model and penalized logistic regression.

(Amorim, van der Stoel et al. 2019)

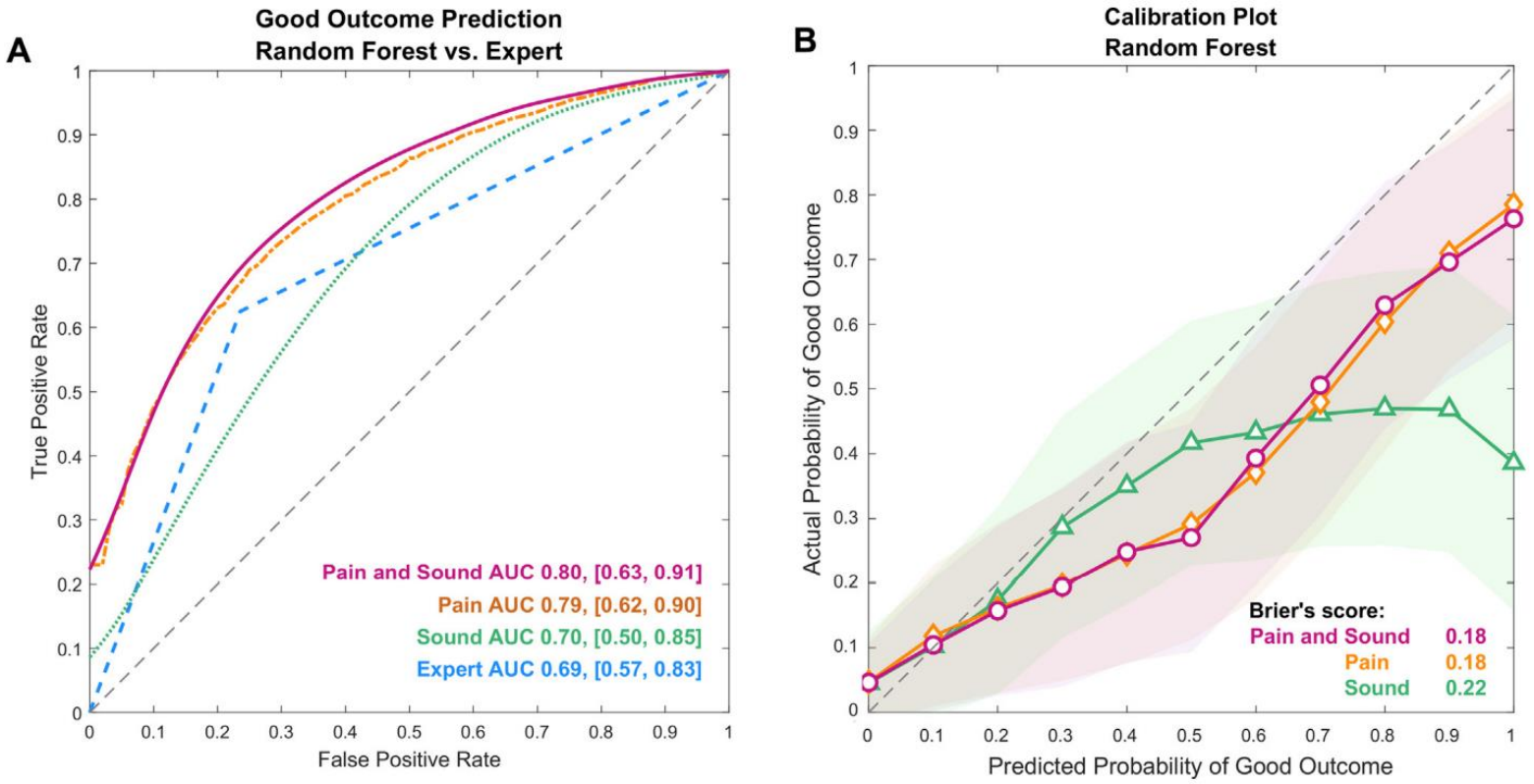
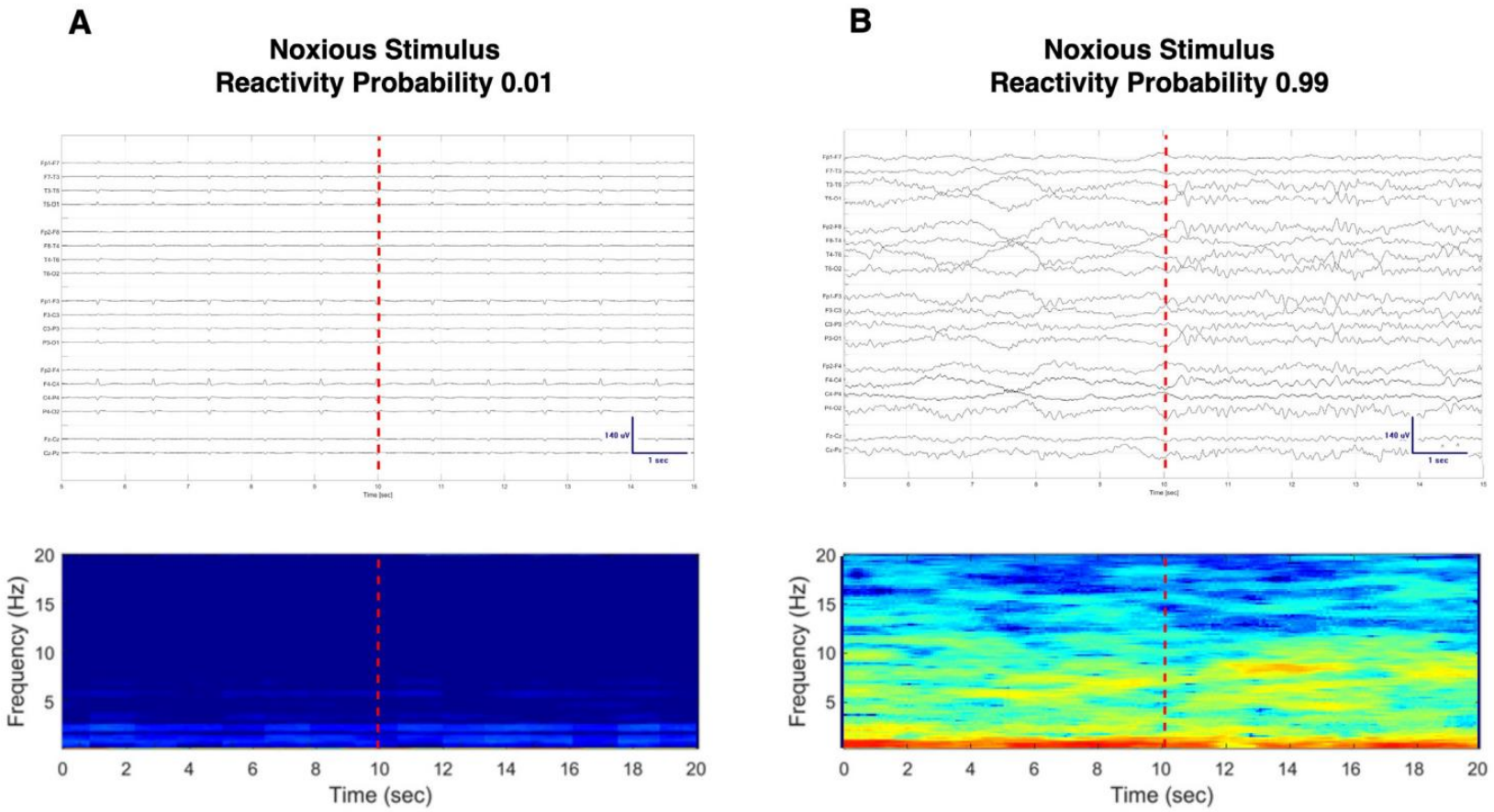
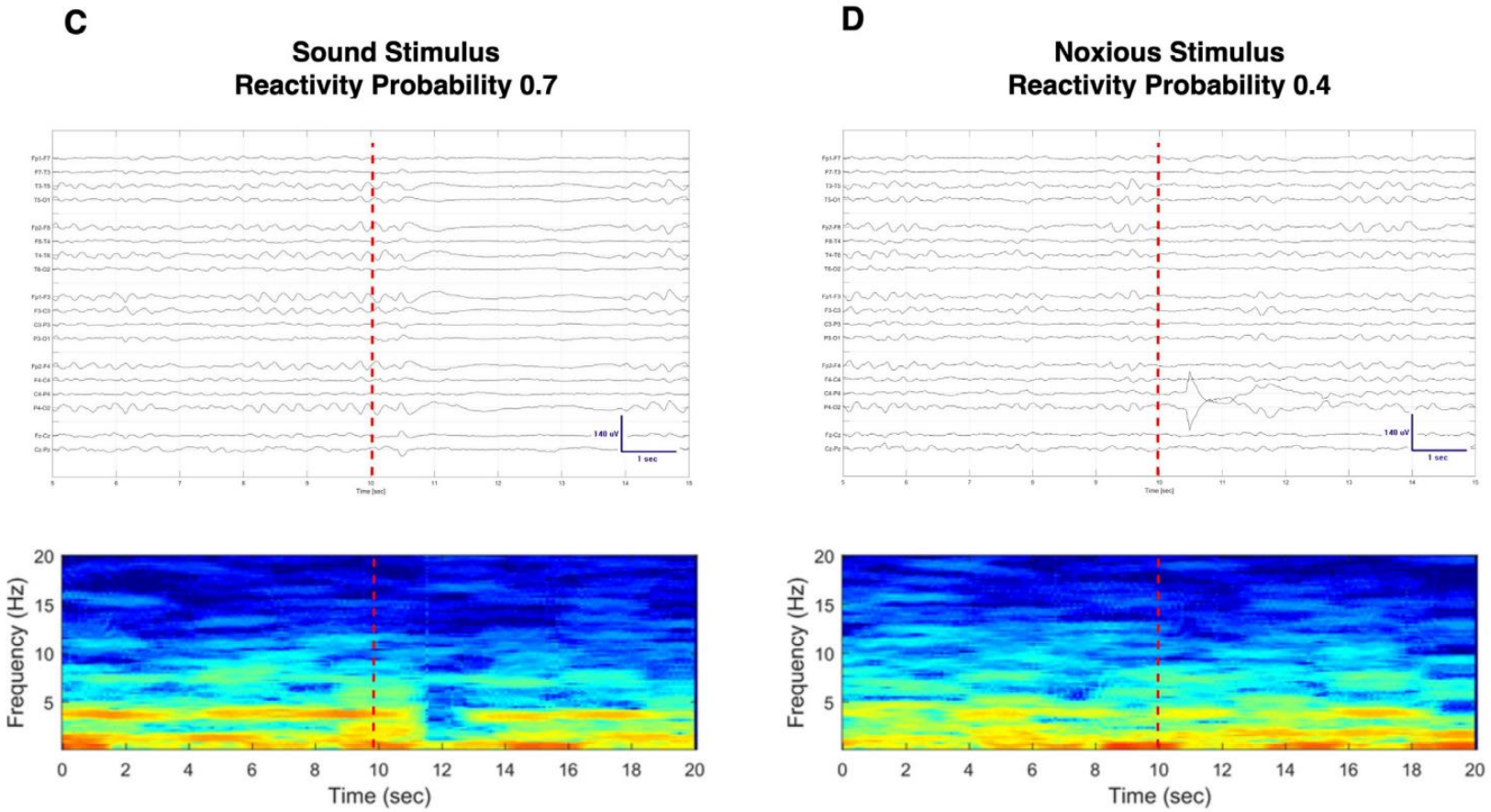


Fig. 2. A: Random forest model and expert visual review performance for good outcome prediction for different type of stimuli; B: Calibration plot of predicted vs. observed good outcome using a random forest model (mean score and standard deviation).

(Amorim, van der Stoel et al. 2019)



(Amorim, van der Stoel et al. 2019)



(Amorim, van der Stoel et al. 2019)

Future Directions:

- Inter-rater variability→ overcome by automated detectors—ML application
- Reduce time for review
- Longitudinal analysis of task-based EEG andspatial and temporal evolution of EEG markers imp→ ML based analysis
- Longitudinal multi-modal assessments → predictive models for outcome→ Novel computational techniques and ML applications

(Khazanova, Douglas et al. 2021)

Anesthesia titration and weaning:

- IV anesthetics 3rd line to Rx RSE

Duration of Rx

Success with weaning

Premature withdrawal Of anesthetics

Burst suppression vs Seizure suppression

Harm from Rx – LOS in ICU, infection, complications

(Rubin, Angelini et al. 2020)

Anesthesia titration and weaning:

- Varied indications for anesthesia including RSE

Raw EEG

- IIC pattern
- HEB
- IBI, Burst suppression ratio, length of bursts

QEEG

- Spectral components of EEG signal
- Spatial correlation-based measures of functional connectivity

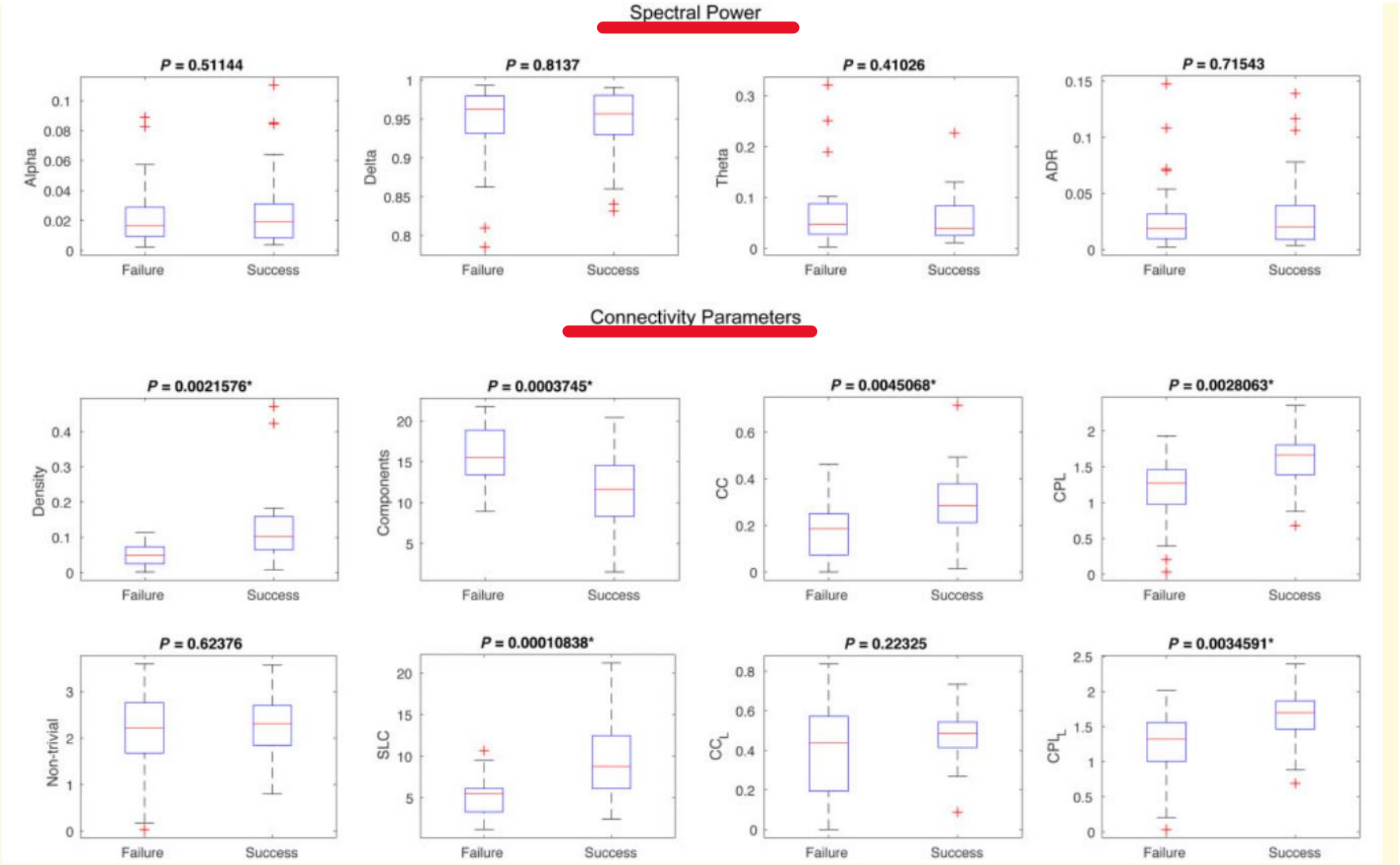
QEEG and ML in anesthetic wean:

- Study evaluated two types of features as predictors of successful weaning: spectral components of the EEG signal, and spatial-correlation-based measures of functional connectivity.

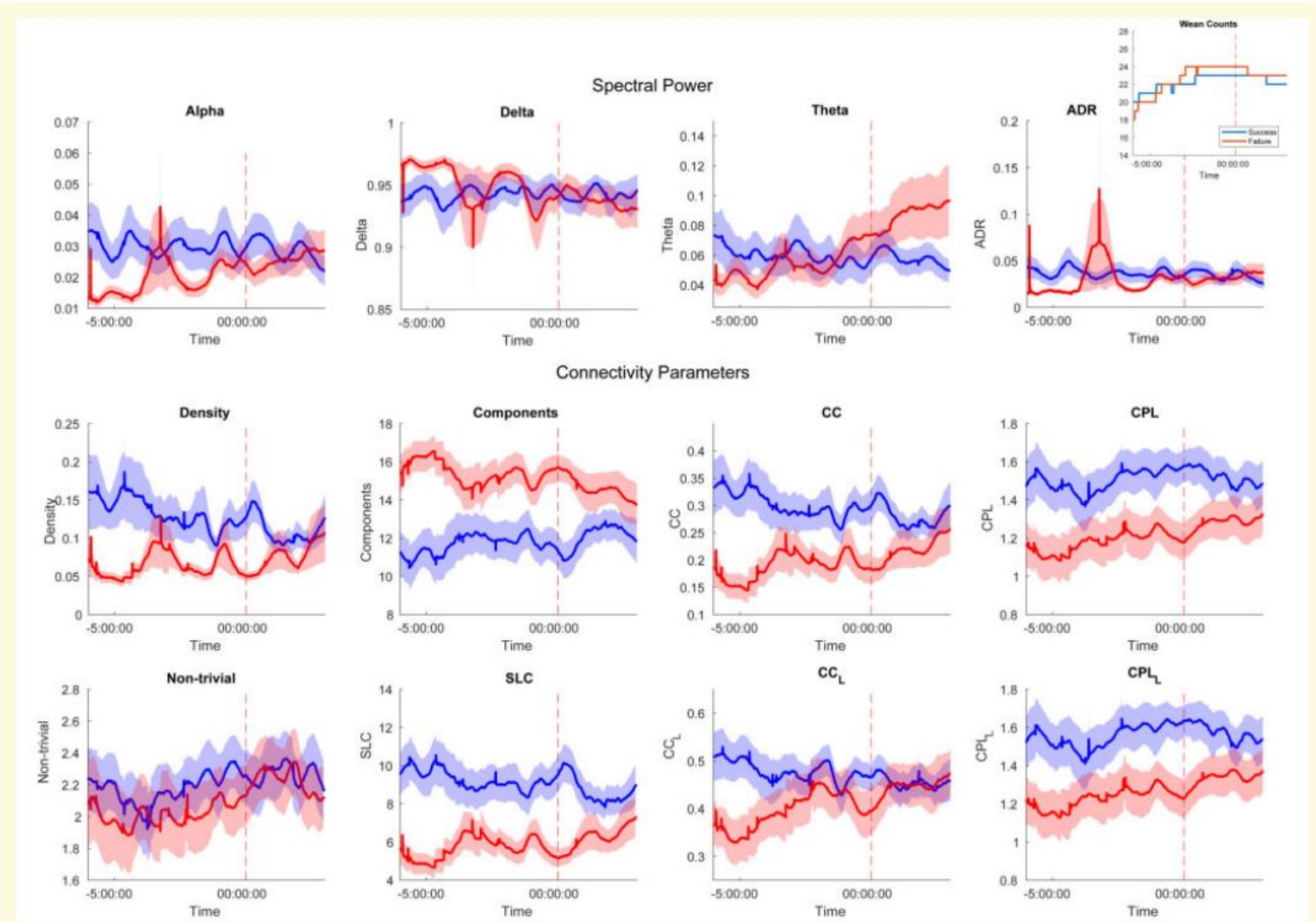
- 47 consecutive anesthetic weans (23 successes, 24 failures) from a single-center cohort of patients admitted with RSE from 2016-2019.

- The results of these analyses were used to train a classifier to predict wean outcome.

(Rubin, Angelini et al. 2020)

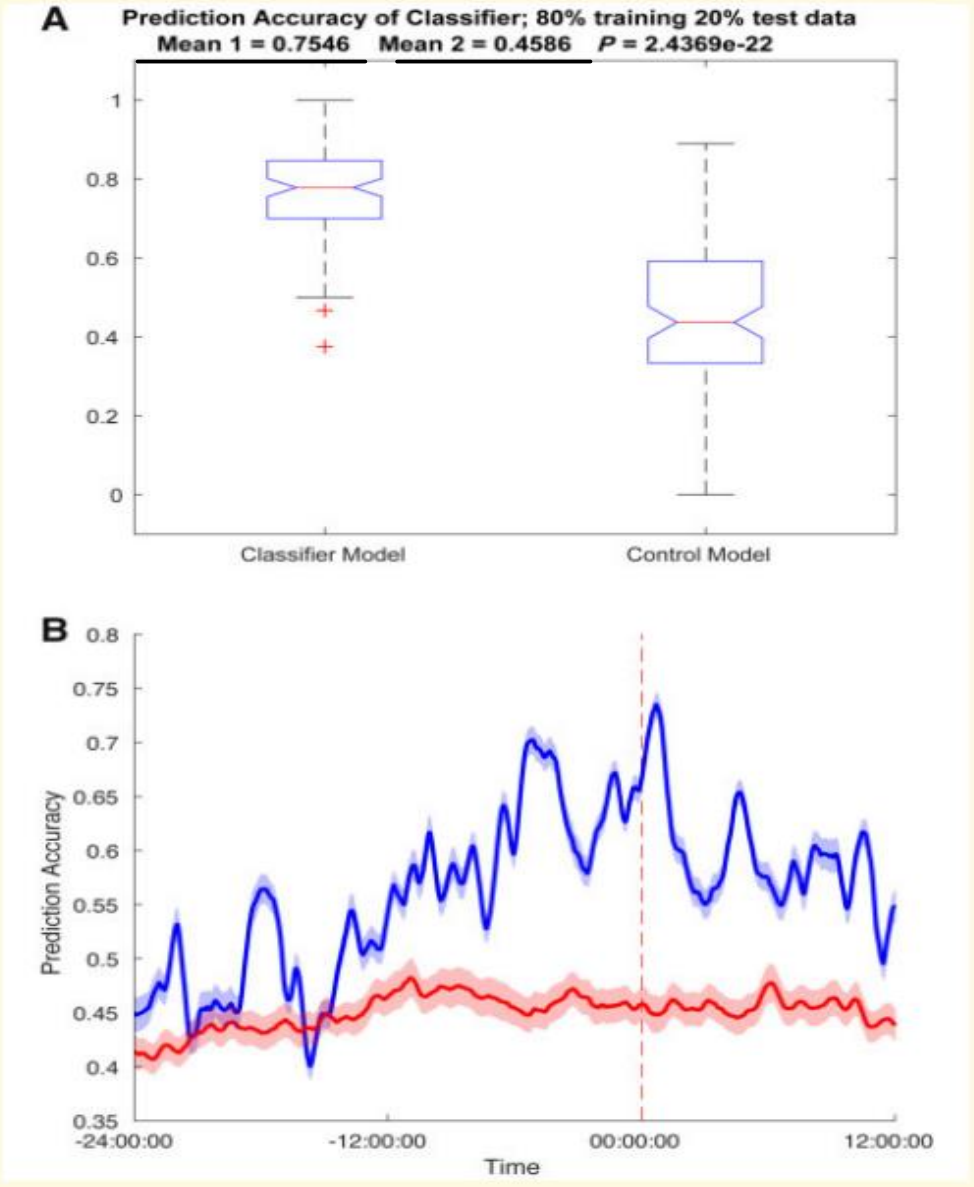


(Rubin, Angelini et al. 2020)



(Rubin, Angelini et al. 2020)

Prediction Model:



Accuracy of classifier

(Rubin, Angelini et al. 2020)

Future Directions:

- Prospective validation of sedation titration and successful weaning tools run in real-time.

(Rubin, Angelini et al. 2020)

Ischemia Detection:

Ischemia detection:

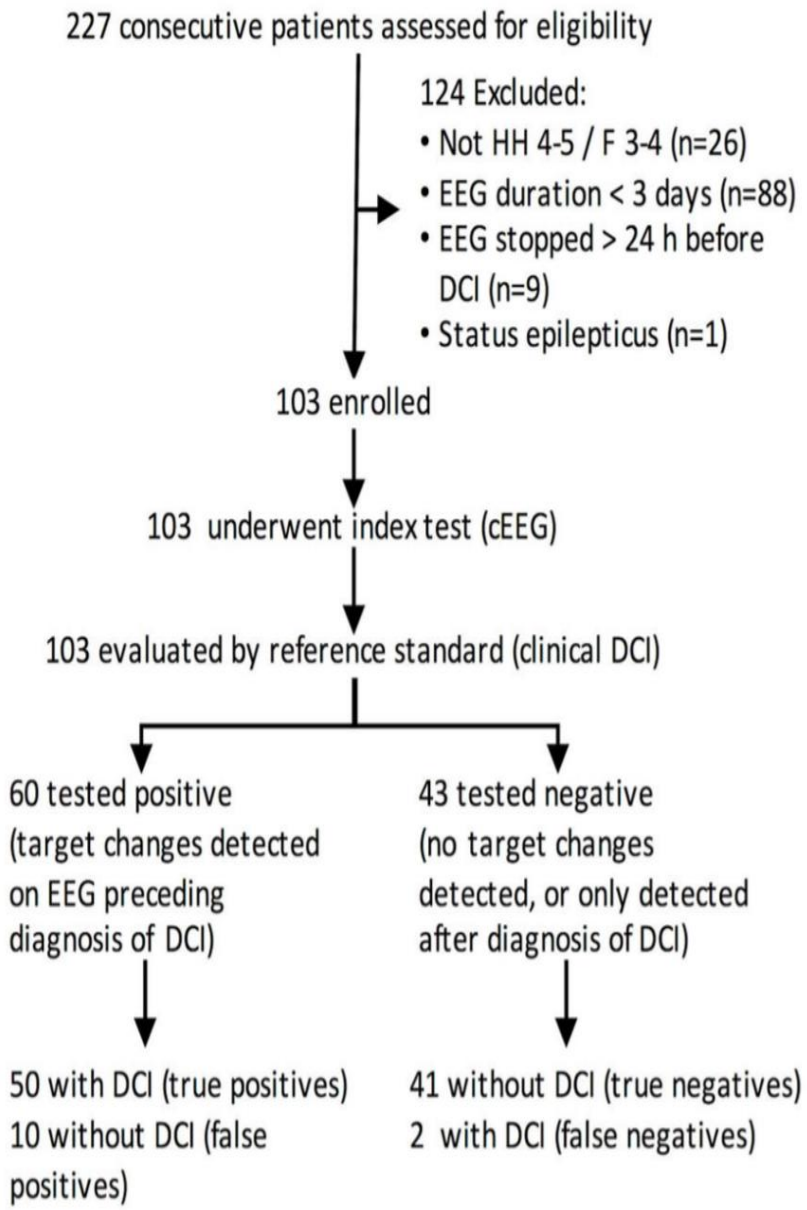
- Prospective single center study using Scalp EEG for ischemia detection
- The diagnostic reference standard was DCI determined by blinded, adjudicated review.
- Primary outcome measures were sensitivity and specificity of cEEG for subsequent DCI

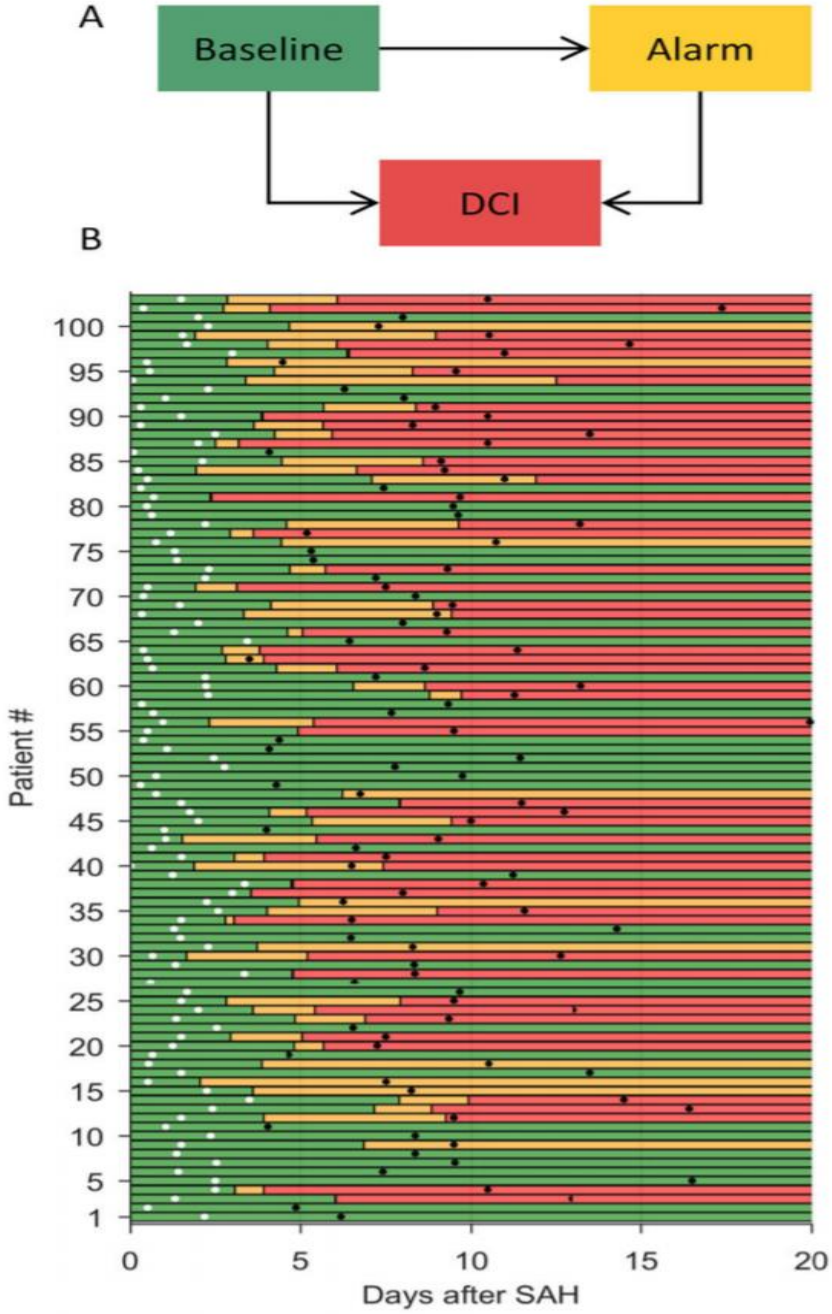
(Rosenthal, Biswal et al. 2018)

Ischemia detection:

- Decreasing RAV
- Decreasing alpha-delta ratio
- Worsening focal slowing
- Late-appearing epileptiform abnormalities (from "occasional" LPDs (1– 9% of an epoch) to "frequent" (10–49% of an epoch)

(Rosenthal, Biswal et al. 2018)





(Rosenthal, Biswal et al. 2018)

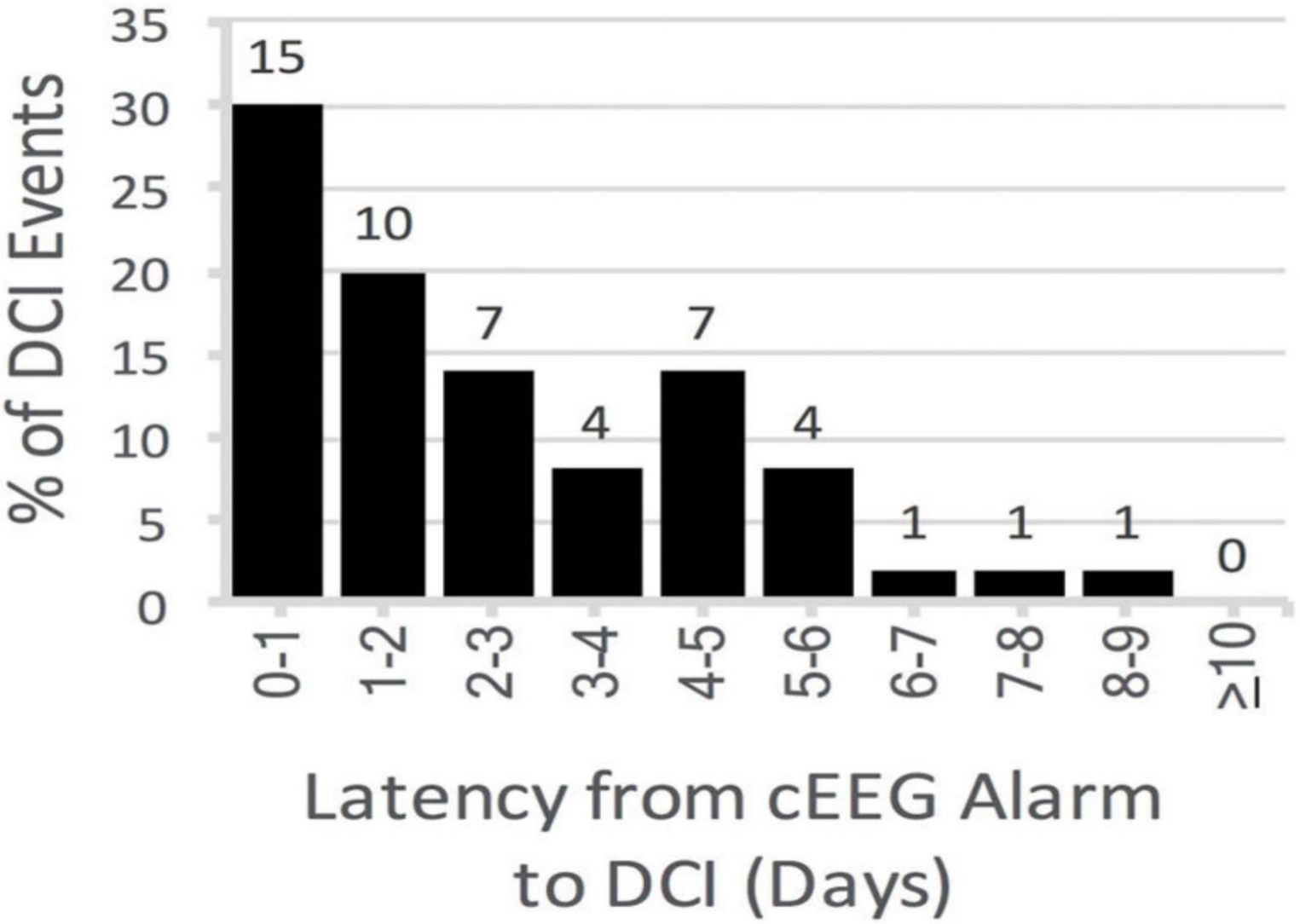
Univariate association between time-dependent predictors and subsequent DCI

	DCI (n=52)	No DCI (n=51)	OR [95% CI]	p-value
Any EEG alarm documented	96.2%	19.6%	102.5 [21.3, 494]	<0.01
Worsening slowing, ADR or RAV	63.5%	17.7%	8.11 [3.25, 20.2]	<0.01
Worsening focal slowing	15.4%	7.8%	2.14 [0.60, 7.60]	0.19
Worsening ADR	32.7%	9.8%	4.47 [1.50, 13.3]	<0.01
Worsening RAV	42.3%	2.0%	36.7 [4.70, 286.11]	<0.01
New epileptiform abnormality	63.5%	7.84%	20.4 [6.36, 65.5]	<0.01
Sonographic vasospasm				
Maximum PSV > 200 cm/sec	75.0%	45.1%	3.65 [1.58, 8.42]	<0.01
Maximum PSV > 250 cm/sec	57.7%	33.3%	2.73 [1.2, 6.1]	0.01
Maximum PSV > 300 cm/sec	30.8%	19.6%	1.80 [0.73, 4.52]	0.14

ARD = alpha-to-delta ratio; CI = confidence interval; DCI = delayed cerebral ischemia; EEG = electroencephalography; PSV = transcranial Doppler ultrasound peak systolic velocity; RAV = relative alpha variability.

(Rosenthal, Biswal et al. 2018)

Time to DCI Events from the cEEG Alarm:



(Rosenthal, Biswal et al. 2018)

Results:

- In high-risk patients, the high prevalence of DCI (79% [61–92]) and high PPV of EEG alarms (94% [79–100]) & nearly all patients with alarms subsequently transition to DCI.

- Conversely, for low-risk patients, the low DCI prevalence (37% [25–50]) and lower PPV (76% [58– 90]), some patients of low admission risk with EEG alarms never develop DCI

(Rosenthal, Biswal et al. 2018)

Results:

- Of 227 consecutive patients screened (2013 - 2015), 103 met criteria (75.7% women; mean age 57.7 years)
- Fifty-two [50.5%] developed DCI
- EEG predicts DCI with greater sensitivity and specificity than TCD criteria employing absolute velocities, which identify DCI with poor sensitivity, late detection and high false positive rates.
- The number needed to monitor to predict one additional case of DCI (NNM) ranged from 2.6 among patients with low admission risk, to 6.7 among those at high risk.
- The latency from an EEG alarm to DCI in true positive cases ranged from 30 minutes to 9.1 days (median 1.9 days [IQR 0.9–4.1] and exceeded 12-hours in 82% of cases (n=41).
- EEG changes predicted DCI despite pathology that was often severe at admission ("floor effect")

RESEARCH ARTICLE

Combining Transcranial Doppler and EEG Data to Predict Delayed Cerebral Ischemia After Subarachnoid Hemorrhage

Hsin Yi Chen, BS, Jonathan Elmer, MD, Sahar F. Zafar, MD, Manohar Ghanta, MS, Valdery Moura Junior, MS, Eric S. Rosenthal, MD, Emily J. Gilmore, MD, Lawrence J. Hirsch, MD, Hitten P. Zaveri, PhD, Kevin N. Sheth, MD, Nils H. Petersen, MD, PhD, M. Brandon Westover, MD, PhD,* and Jennifer A. Kim, MD, PhD*

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Neurology® 2022;98:e459-e469. doi:10.1212/WNL.0000000000013126

- EEG + TCD biomarkers combined provide the best prediction of DCI.
- The conjunction of clinical variables with the timing of EAs and high MCA velocities improved model performance.
- These results suggest that TCD and cEEG are promising complementary monitoring modalities for DCI prediction.
- This model has potential to serve as a decision support tool in SAH management.

J Neurosci Methods. 2021 March 01; 351: 108966. doi:10.1016/j.jneumeth.2020.108966.

Deep active learning for interictal ictal injury continuum EEG patterns

Wendong Ge[a,b,1], Jin Jing[a,b,1], Sungtae An[t,1], Aline Herlopian[d], Marcus Ng[e], Aaron F. Struck[f], Brian Appavu[g], Emily L. Johnson[h], Gamaleldin Osman[i], Hiba A. Haider[j], Ioannis Karakis[j], Jennifer A. Kim[d], Jonathan J. Halford[k], Monica B. Dhakar[j], Rani A. Sarkis[l], Christa B. Swisher[m], Sarah Schmitt[k], Jong Woo Lee[l], Mohammad Tabaeizadeh[n], Andres Rodriguez[j], Nicolas Gaspard[o], Emily Gilmore[p], Susan T. Herman[q], Peter W. Kaplan[r], Jay Pathmanathan[s], Shenda Hong[t], Eric S. Rosenthal[a,b], Sahar Zafar[a,b], Jimeng Sun[c], M. Brandon Westover[a,b,*]

In this study, authors were able to train models approaching expert-level performance across all pattern categories after obtaining ~7000 expert labels.

Future Directions:

- Issues with prior ischemia detection studies via EEG tools→ cumbersome
- Real time annotation to detect ischemia and gauge therapeutic response→ guide optimal perfusion and prevent SBI

Therapeutic Biomarker:

Automated Annotation of Epileptiform Burden and Its Association with Outcomes

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Objective: This study was undertaken to determine the dose–response relation between epileptiform activity burden and outcomes in acutely ill patients.

Methods: A single center retrospective analysis was made of 1,967 neurologic, medical, and surgical patients who underwent >16 hours of continuous electroencephalography (EEG) between 2011 and 2017. We developed an artificial intelligence algorithm to annotate 11.02 terabytes of EEG and quantify epileptiform activity burden within 72 hours of recording. We evaluated burden (1) in the first 24 hours of recording, (2) in the 12-hours epoch with highest burden (peak burden), and (3) cumulatively through the first 72 hours of monitoring. Machine learning was applied to estimate the effect of epileptiform burden on outcome. Outcome measure was discharge modified Rankin Scale, dichotomized as good (0–4) versus poor (5–6).

Results: Peak epileptiform burden was independently associated with poor outcomes ($p < 0.0001$). Other independent associations included age, Acute Physiology and Chronic Health Evaluation II score, seizure on presentation, and diagnosis of hypoxic–ischemic encephalopathy. Model calibration error was calculated across 3 strata based on the time interval between last EEG measurement (up to 72 hours of monitoring) and discharge: (1) <5 days between last measurement and discharge, 0.0941 (95% confidence interval [CI] = 0.0706–0.1191); 5 to 10 days between last measurement and discharge, 0.0946 (95% CI = 0.0631–0.1290); >10 days between last measurement and discharge, 0.0998 (95% CI = 0.0698–0.1335). After adjusting for covariates, increase in peak epileptiform activity burden from 0 to 100% increased the probability of poor outcome by 35%.

Interpretation: Automated measurement of peak epileptiform activity burden affords a convenient, consistent, and quantifiable target for future multicenter randomized trials investigating whether suppressing epileptiform activity improves outcomes.

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Encephalopathy Grading/ Disease progression

Developing a Standardized Approach to Grading the Level of Brain Dysfunction on EEG

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Purpose: To assess variability in interpretation of electroencephalogram (EEG) background activity and qualitative grading of cerebral dysfunction based on EEG findings, including which EEG features are deemed most important in this determination.

Methods: A web-based survey (Qualtrics) was disseminated to electroencephalographers practicing in institutions participating in the Critical Care EEG Monitoring Research Consortium between May 2017 and August 2018. Respondents answered 12 questions pertaining to their training and EEG interpretation practices and graded 40 EEG segments (15-second epochs depicting patients' most stimulated state) using a 6-grade scale. Fleiss' Kappa statistic evaluated interrater agreement.

Results: Of 110 respondents, 78.2% were attending electroencephalographers with a mean of 8.3 years of experience beyond training. Despite 83% supporting the need for a standardized approach to interpreting the degree of dysfunction on EEG, only 13.6% used a previously published or an institutional grading scale. The overall interrater agreement was fair ($k = 0.35$). Having Critical Care EEG Monitoring Research Consortium nomenclature certification (40.9%) or EEG board certification (70%) did not improve interrater agreement ($k = 0.26$). Predominant awake frequencies and posterior dominant rhythm were ranked as the most important variables in grading background dysfunction, followed by continuity and reactivity.

Conclusions: Despite the preference for a standardized grading scale for background EEG interpretation, the lack of interrater agreement on levels of dysfunction even among experienced academic electroencephalographers unveils a barrier to the widespread use of EEG as a clinical and research neuromonitoring tool. There was reasonable agreement on the features that are most important in this determination. A standardized approach to grading cerebral dysfunction, currently used by the authors, and based on this work, is proposed.

Key Words: Electroencephalography, Long-term monitoring, Encephalopathy, Brain telemetry, Neuromonitoring, Neurophysiology, Neurocritical care, ICU EEG, Continuous EEG.

(J Clin Neurophysiol 2022;00: 1–9)

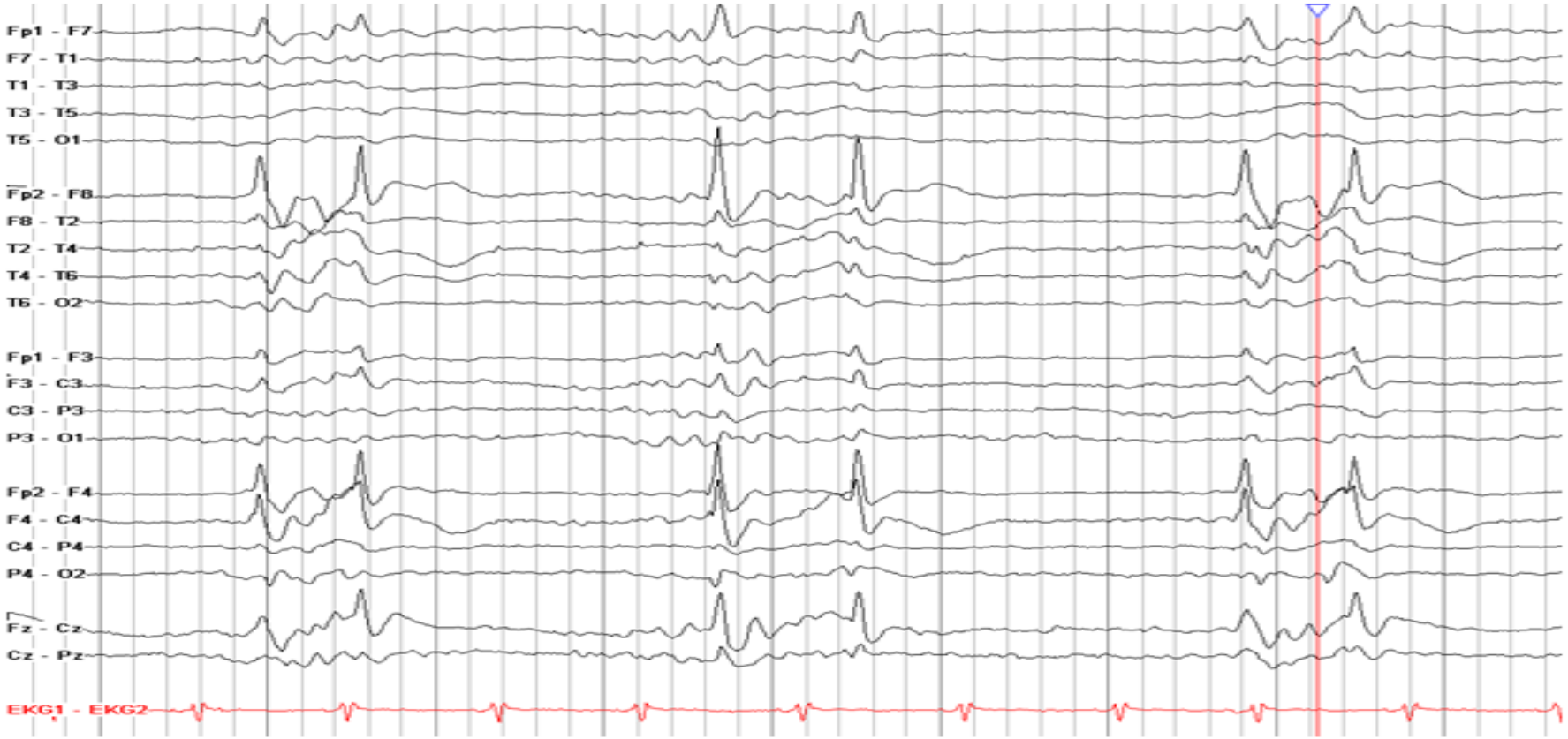
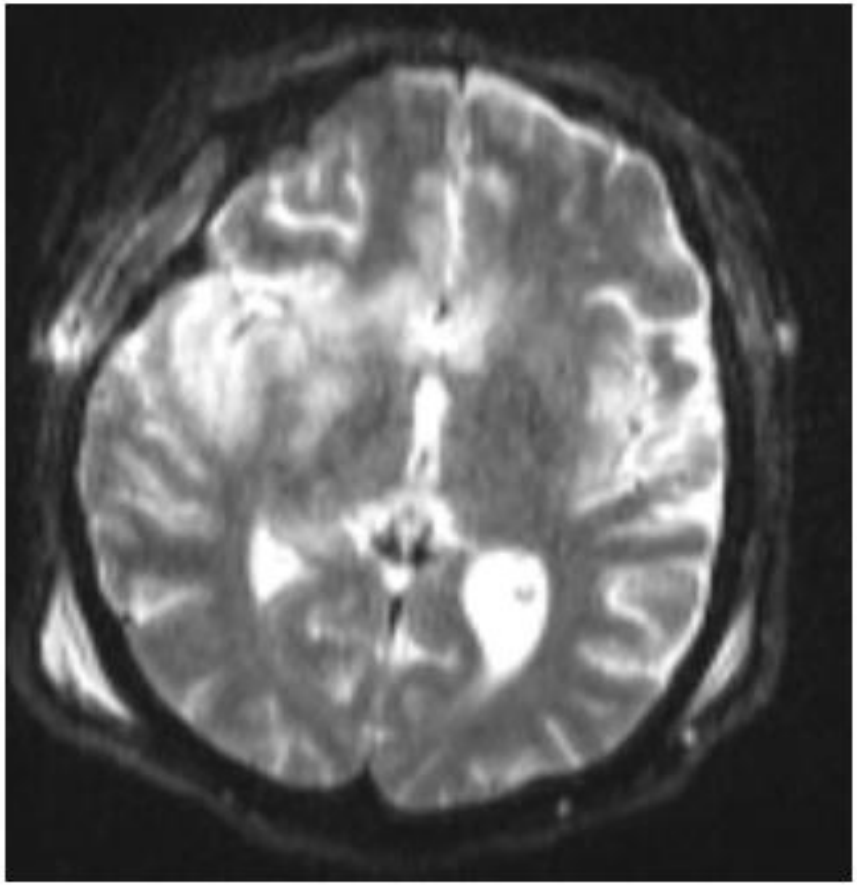


Figure 1: Right frontopolar (Fp2) LPD's.

Day 2 EEG: right fronto-central LPDs 2 HZ with background suppression

Baten; Desai, 2019



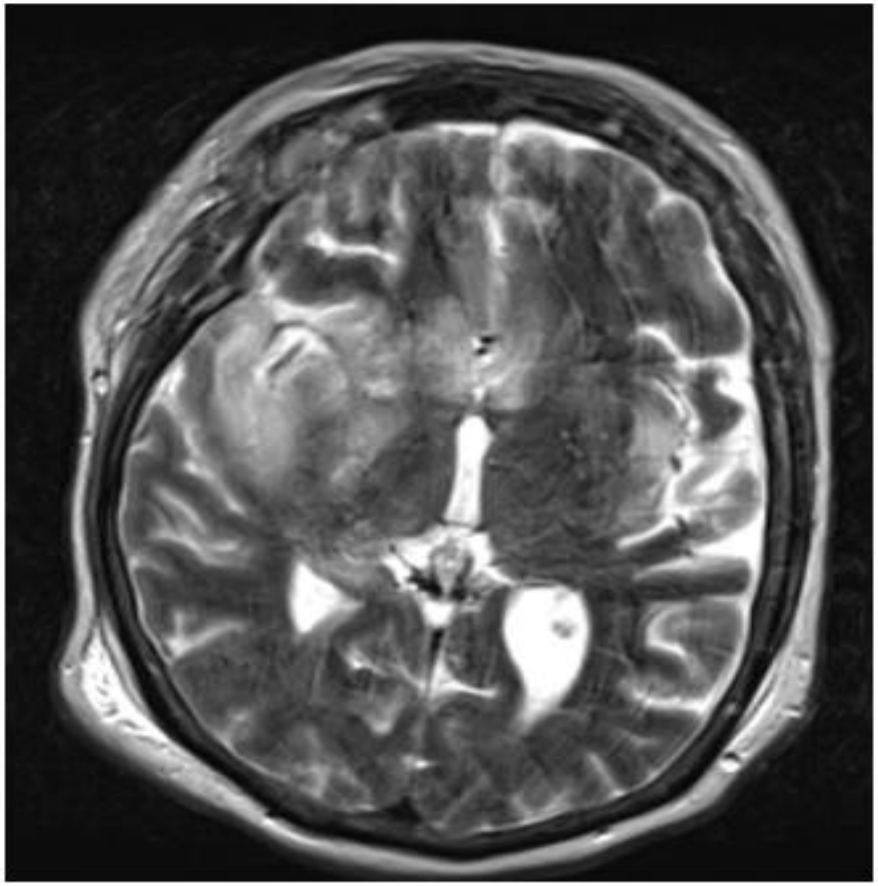


Figure 7a and 7b: Initial MRI with diffusion restriction & T2 hyperintensity of the bilateral (right>left) insular cortices, right hippocampus/amygdala, olfactory gyri

Day 3 MRI

Baten; Desai, 2019

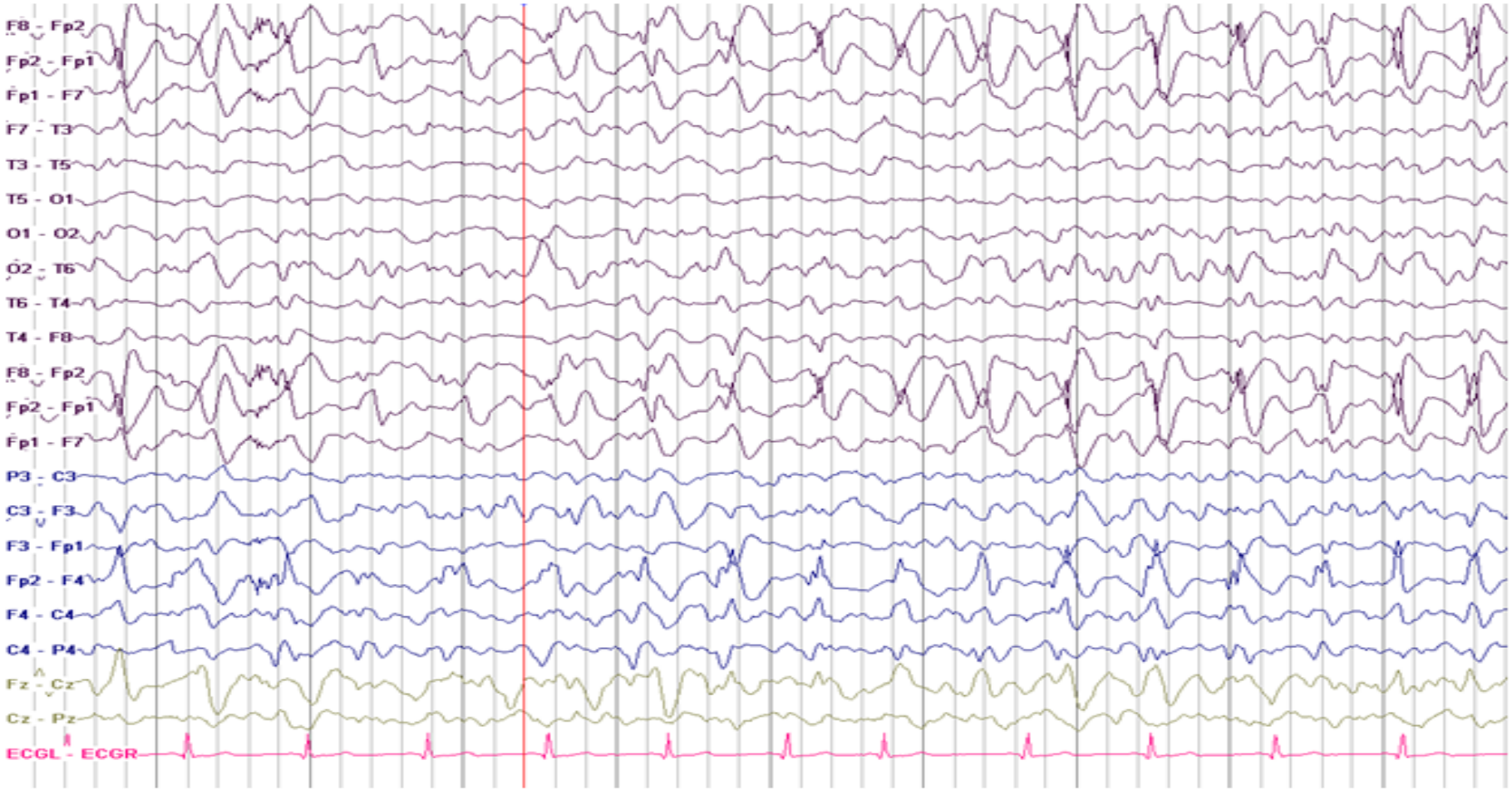


Figure 2. Fp2 maximal focal seizures, seen in circular montage.

Day 4 EEG: Right frontal status / Patient still comatose

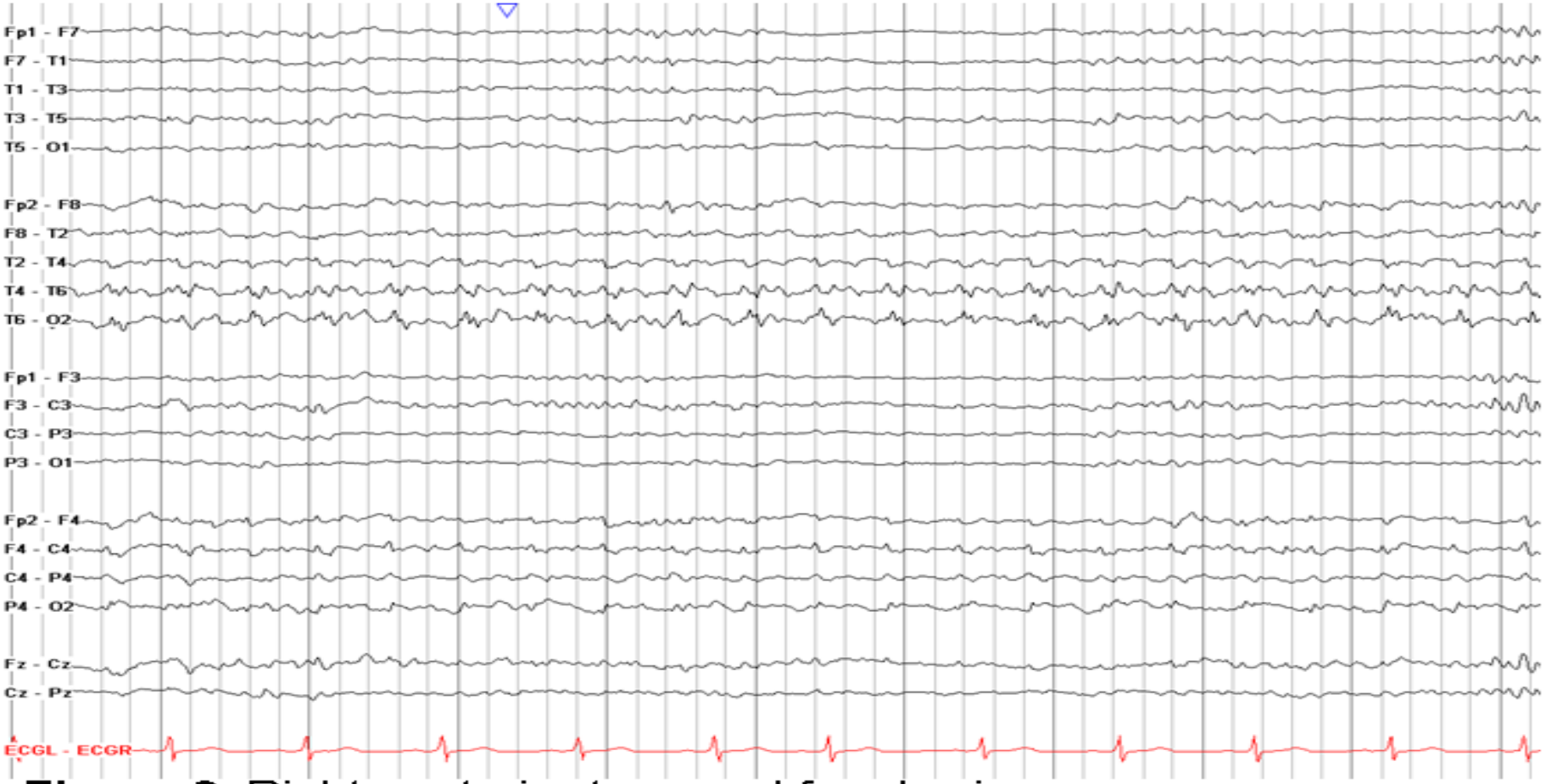
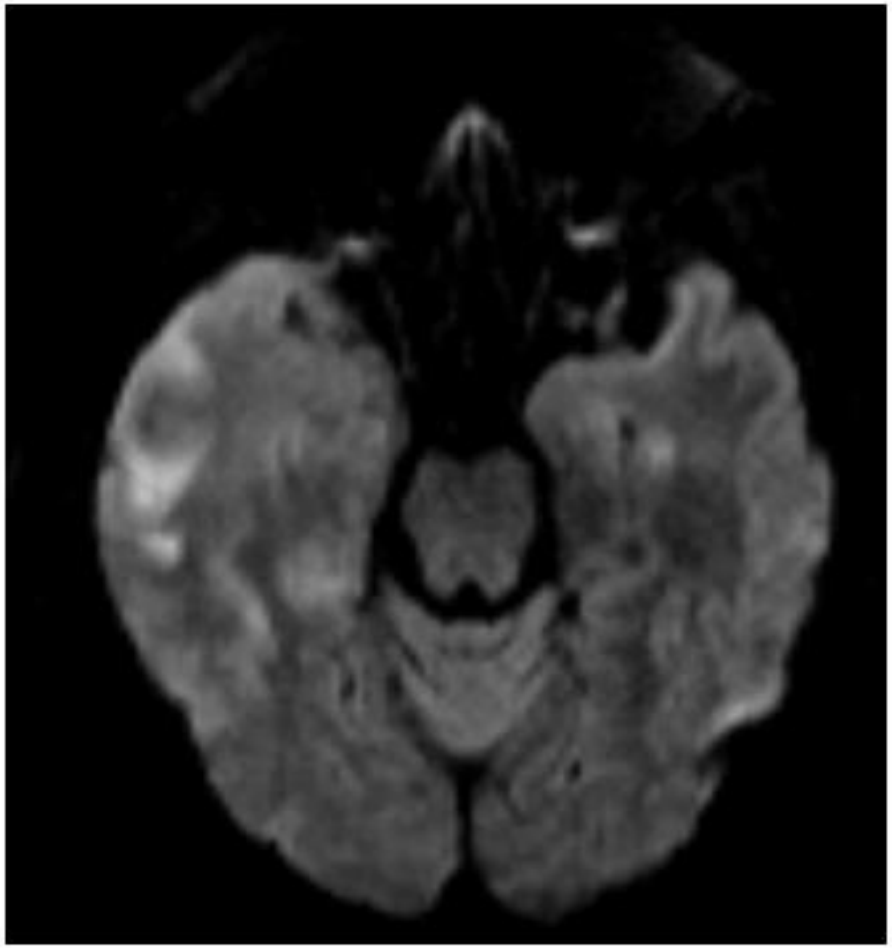


Figure 3. Right posterior temporal focal seizures.

Day 10 EEG



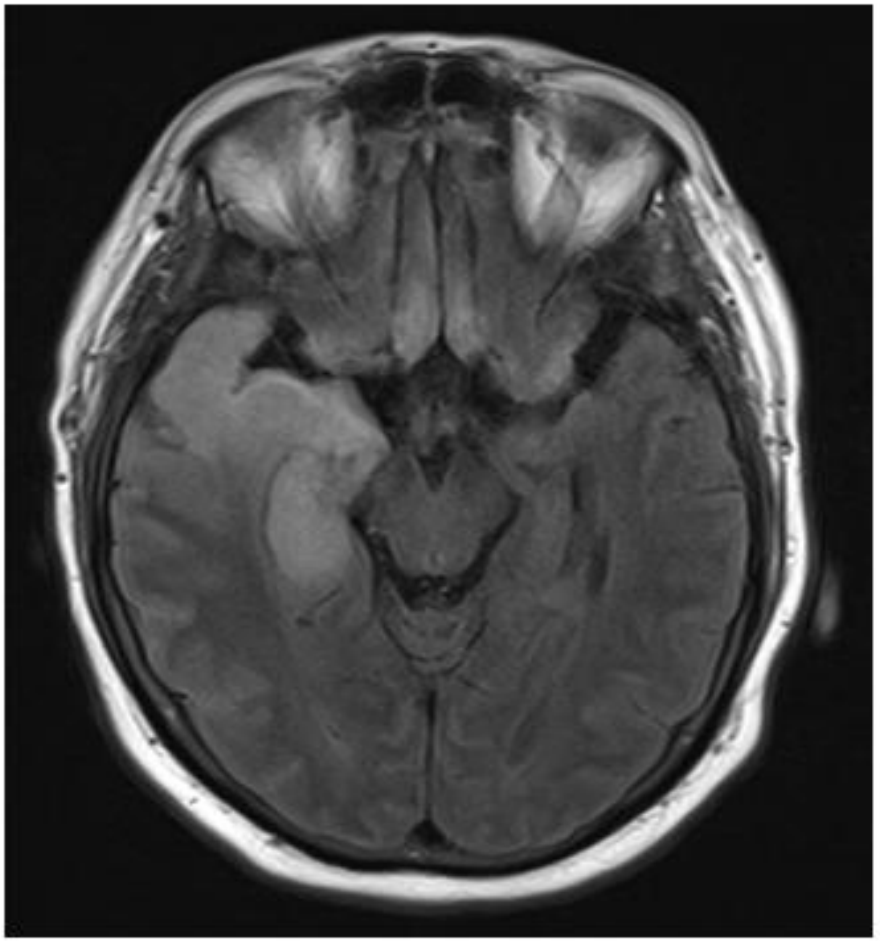


Figure 8a and 8b: Repeat MRI showed diffusion normalization with T2-weighted and FLAIR hyperintensity in the right > left insula and new involvement of the right temporal lobe

Day 12 MRI

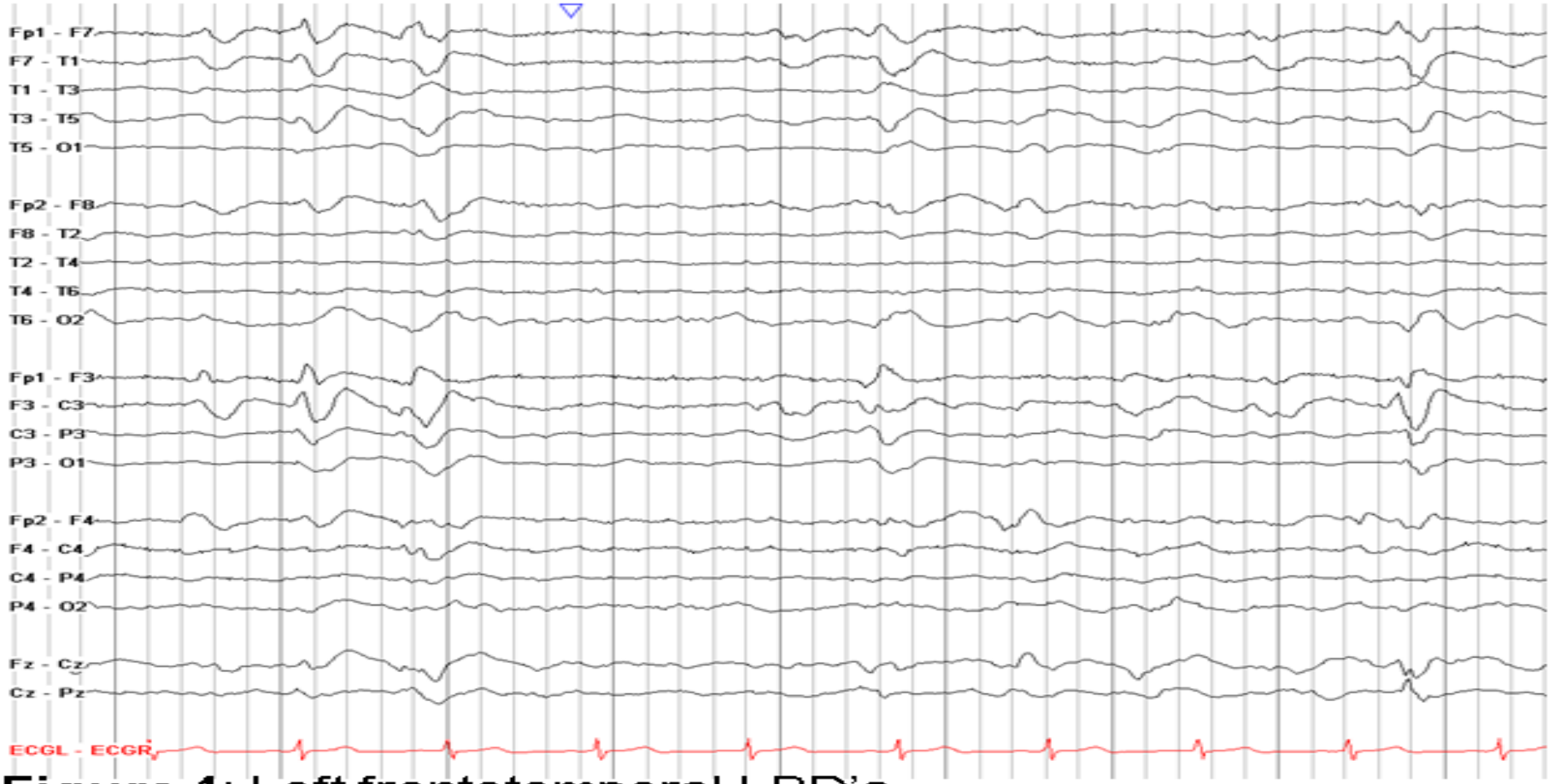


Figure 4: Left frontotemporal LPD's.

Day 14 EEG: Now new left frontotemporal LPD

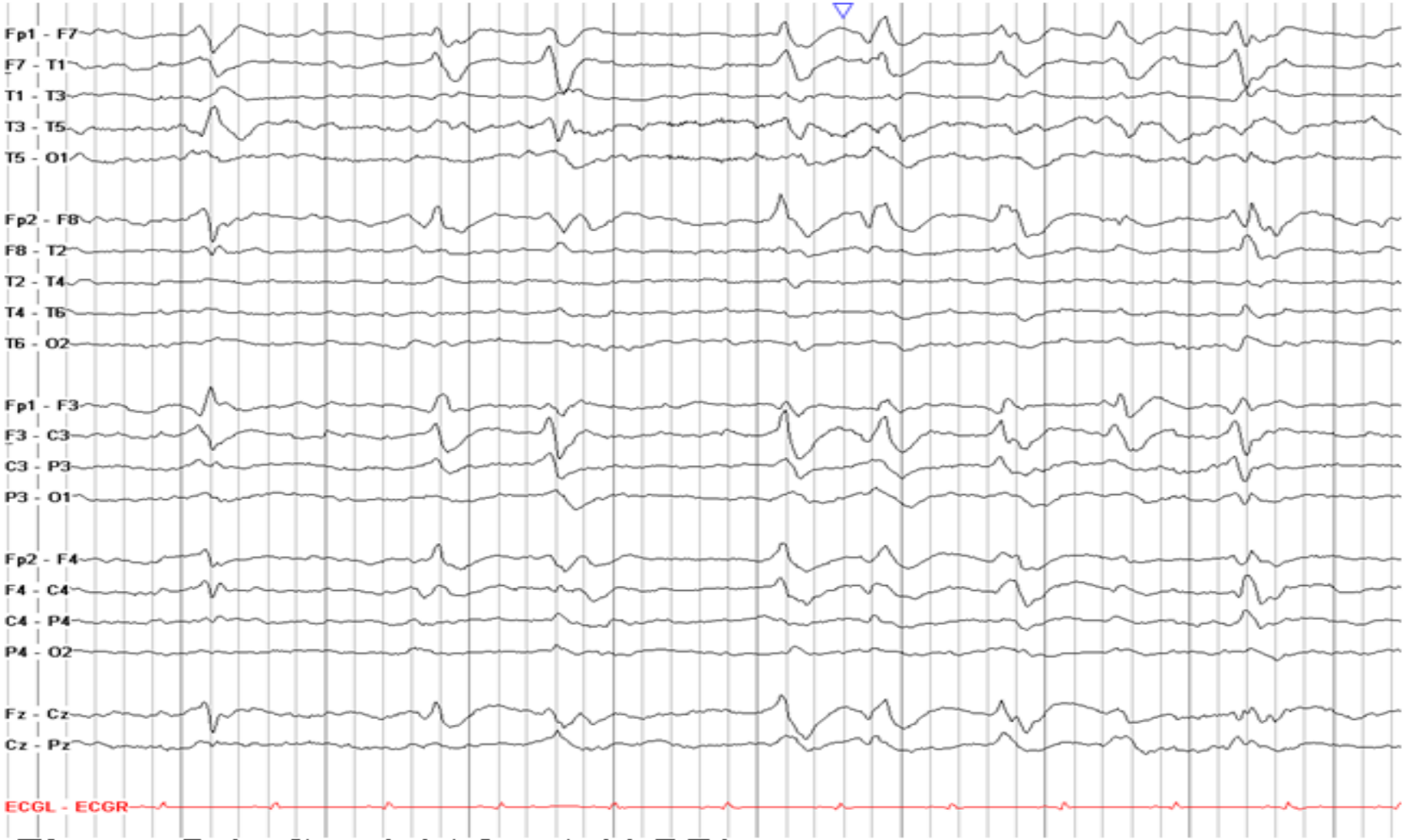


Figure 5: Left > right frontal LPD's.

Day 16 EEG

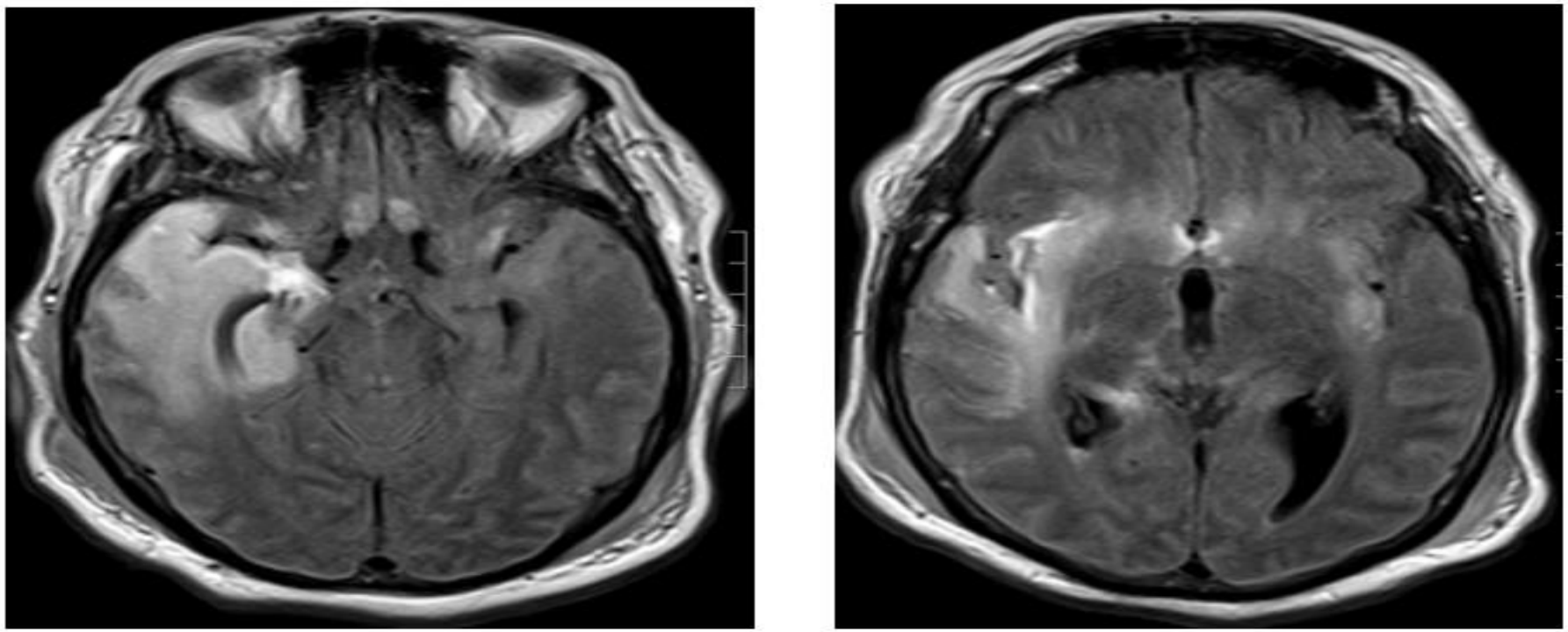


Figure 9a and 9b: Final MRI demonstrated FLAIR hyperintensity with involvement of the bilateral inferior frontal regions and left temporal lobe.

Day 16: Figure: Last MRI with left temporal lobe and insular involvement

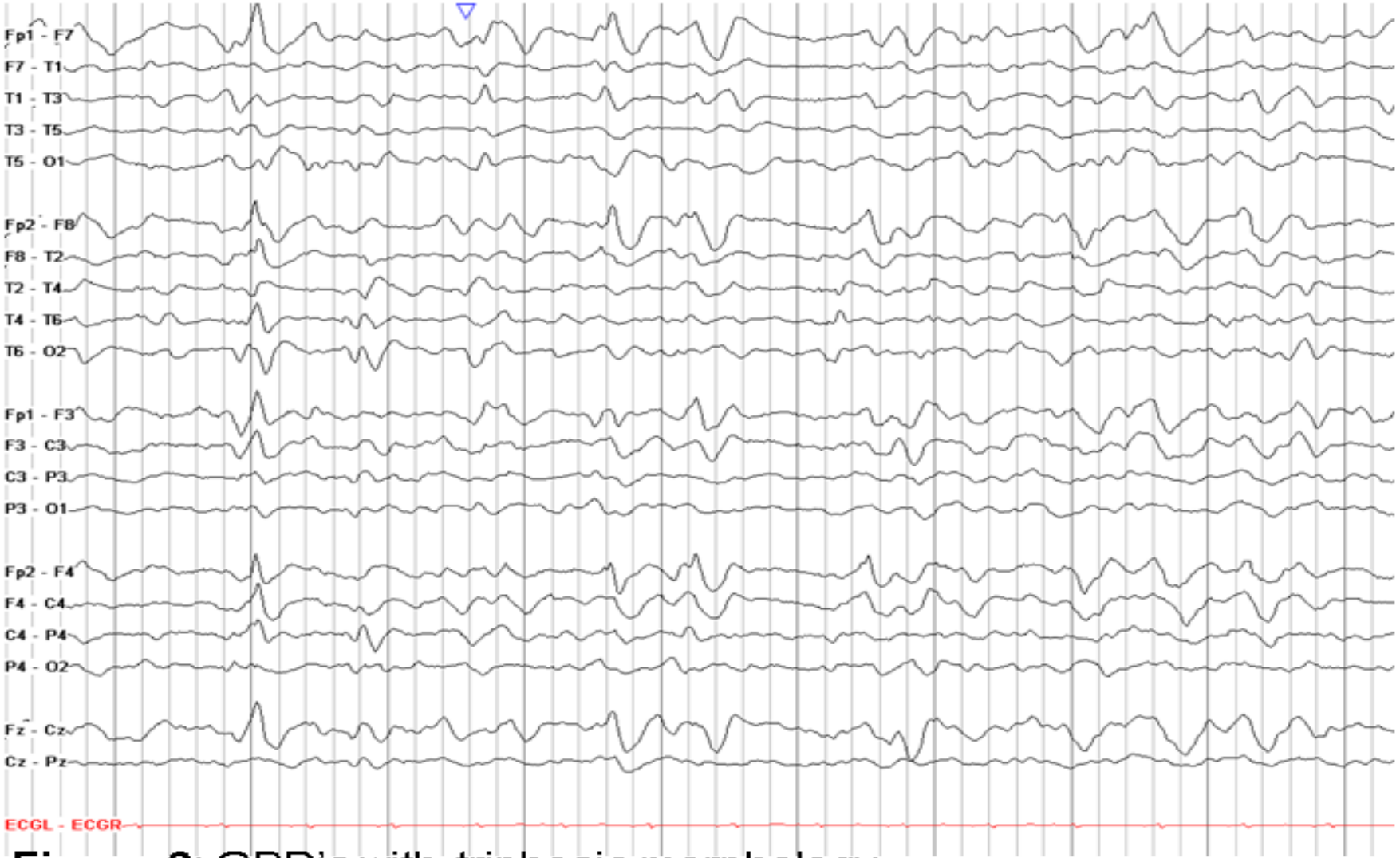
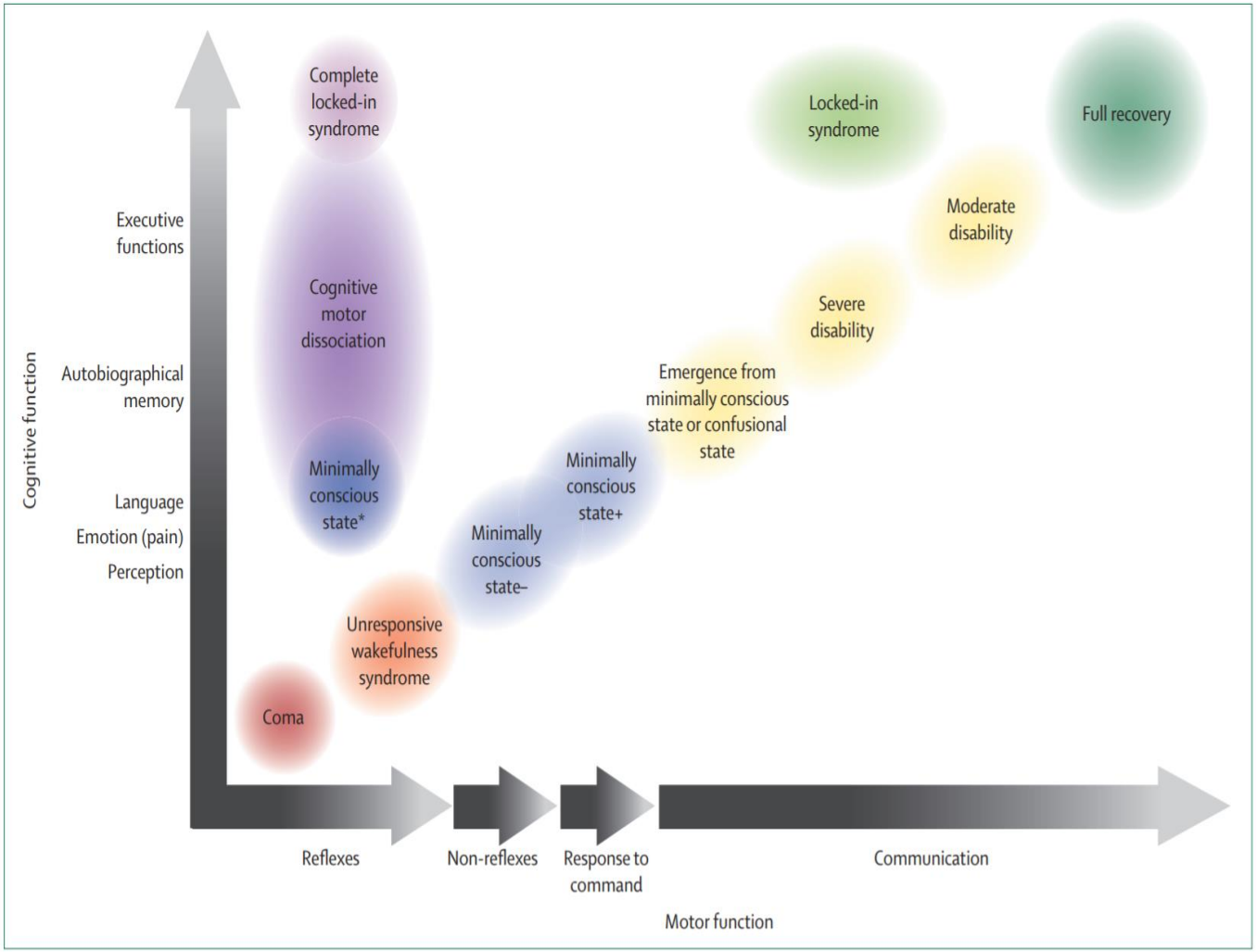


Figure 6: GPD's with triphasic morphology.

Future Direction:

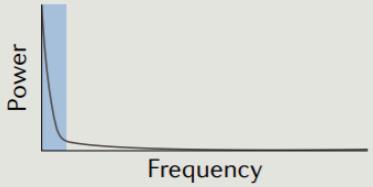
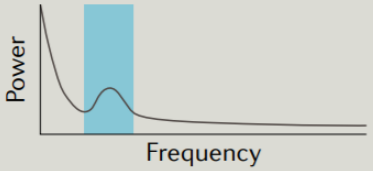
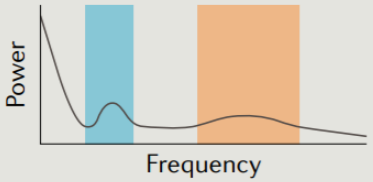
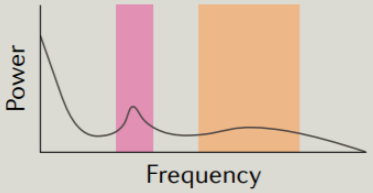
- Real-time detection of disease progression
- CEEG utilized for brain telemetry

DOC:



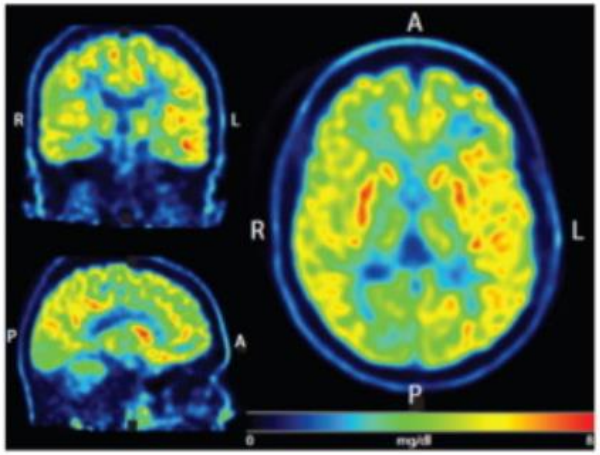
(Thibaut, Schiff et al. 2019)

Table 1 | **The 'ABCD' model of corticothalamic dynamics**

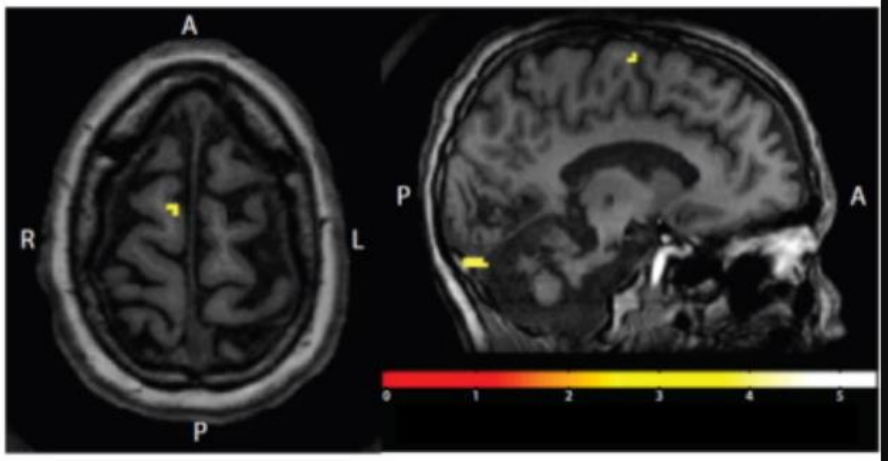
Category	EEG power spectrum[a]	Dominant frequency (Hz)	Thalamocortical connectivity	Central thalamic activity	Neocortical activity	Behavioural diagnoses
A		<1 (blue)	Complete deafferentation	Quiescent	'Slab-like' dynamics	VS/UWS
B		~5–9 (turquoise)	Severe deafferentation	Quiescent	Intrinsic oscillations	VS/UWS, MCS
C		~5–9 (turquoise); ~20–35 (orange)	Moderate deafferentation	Bursting	High-frequency activity driven by thalamic bursting	MCS, CS
D		~8–13 (red); ~20–35 (orange)	Healthy	Tonic	Varying motifs elicited by depolarization of specific neocortical cell types (for example, fast rhythmic bursting)	CS, healthy

(Edlow, Claassen et al. 2021)

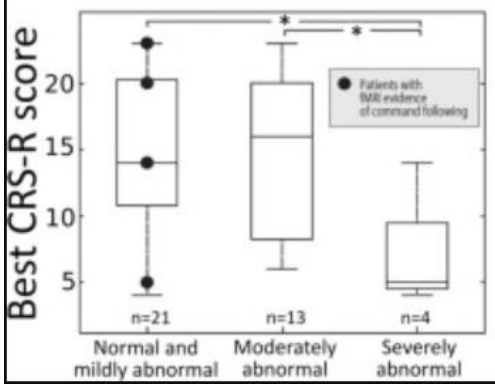
^{18}FDG-PET
(resting state metabolic activity)

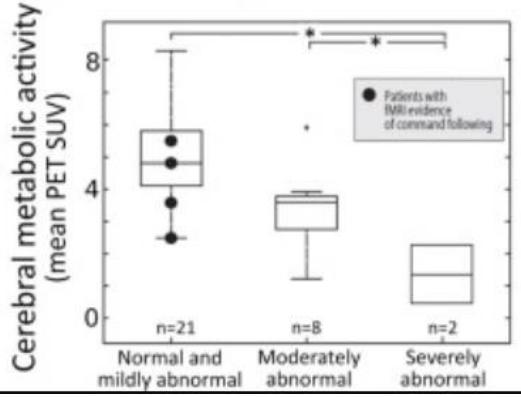


fMRI Command Following
("Imagine yourself swimming" vs "Stop imagining swimming")

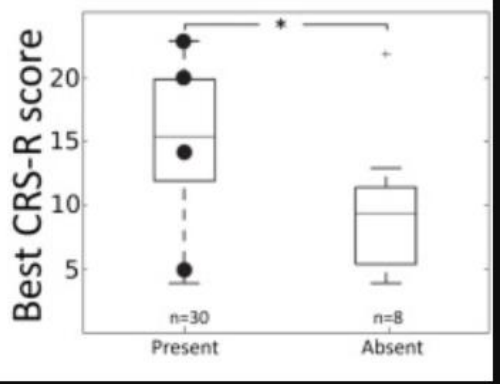


Best awake EEG background organization





Sleep spindles



(Comanducci, Boly et al. 2020)
(Forgacs, Conte et al. 2014)

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Multicenter prospective study on predictors of short-term outcome in disorders of consciousness

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Results

We enrolled 147 patients (44 women; mean age 49.4 [95% confidence interval 46.1–52.6] years; VS/UWS 71, MCS 76; traumatic 55, vascular 56, anoxic 36; mean time postinjury 59.6 [55.4–63.6] days). The 6-month follow-up was complete for 143 patients (VS/UWS 70; MCS 73). With respect to study entry, the clinical diagnosis improved in 72 patients (VS/UWS 27; MCS 45). Younger age, shorter time postinjury, higher Coma Recovery Scale–Revised total score, and presence of EEG reactivity to eye opening at study entry predicted better outcome, whereas etiology, clinical diagnosis, Disability Rating Scale score, EEG background activity, acoustic reactivity, and P300 on event-related potentials were not associated with outcome.

Conclusions

Multimodal assessment could identify patients with higher likelihood of clinical improvement in order to help clinicians, families, and funding sources with various aspects of decision-making. This

Merging Clinical and EEG Biomarkers in an Elastic-Net Regression for Disorder of Consciousness Prognosis Prediction

Piergiuseppe Liuzzi, Antonello Grippo, Silvia Campagnini, Maenia Scarpino, Francesca Draghi, Annamaria Romoli, Bahia Hakiki, Raisa Sterpu, Antonio Maiorelli, Claudio Macchi, Francesca Cecchi, Maria Chiara Carrozza, *Senior Member, IEEE*, and Andrea Mannini

- 3 different ML models internally cross-validated & tested using data from 271 sABI patients entering the intensive rehab with a DoC

- Estimation of the CRS-R total score at discharge via an Elastic Net regressor with three different input datasets (one based only on EEG, one based only on clinical evaluation, and one based on the union of the two, namely "hybrid")

- The study evaluated classification accuracies of overcoming boundary values in the CRS-R at discharge→ indicating a significant change of consciousness state.

TABLE I

DESCRIPTIVE STATISTICS AND PREDICTORS UNIVARIATE ANALYSIS

	Median [IQR], (% of occurrences)	Test Statistics	p-value
Age	55 [65]	-0.054	0.382
Gender	Female: 33.1, Male: 66.9	1.088(1)	0.297
Clinical parameters			
Etiology	Traumatic: 30.9, Anoxic: 20.8, Ischemic: 17.8, Hemorrhagic 26.4, Other: 4.1	27.818(4)	**< 0.001**
TPO	45 [37]	-0.152	**0.015**
CRS-R adm.	11 [16]	0.651	**< 0.001**
Consciousness state at adm.	UWS: 30.4, MCS: 44.1, EMCS: 25.6	112.498(2)	**< 0.001**
GCS adm.	9 [4]	0.533	**< 0.001**
FOIS adm.	1 [0]	0.237	**< 0.001**
LCF adm.	3 [1]	0.577	**< 0.001**
FIM adm.	18 [10]	0.427	**< 0.001**
EEG parameters			
Seizures in the acute phase	Present: 19, Absent: 81	2.409(1)	0.121
AP gradient	Present: 73.2, Absent: 27.8	51.822(1)	**< 0.001**
Frequency	Delta: 2.6, Theta: 74.0, Alpha: 23.4	21.735(2)	**< 0.001**
Reactivity	Absent: 27.2, Unclear: 18.3, Present: 54.5		
Epileptic activity	No: 74.9, Rare: 19.1, Abundant 1.7, Frequent 4.3	15.409(3)	**0.001**
Sleep spindles	Absent: 85.5, Present & abnormal: 9.8, Present & normal: 4.7	5.409(2)	0.067
Symmetry	Symmetric: 60, Moderately Asymm.: 18.7, Sever. Asymm.: 21.3	0.876(2)	0.645
Variability	Absent: 21.4, Unclear: 9.8, Present: 68.8	77.484(3)	**< 0.001**
Voltage	Suppressed: 11.5, Normal: 86.8, Low voltage: 1.7	32.177(2)	**< 0.001**
Estraneo's score	Norm.: 4.3, Mildly abn.: 47.9, Moderately. abn. 18.4, Diffuse Slowing: 17.9, Suppr. 11.5	65.947(4)	**< 0.001**
Bagnato's score	3: 1.7, 4: 10.3, 5: 33.8, 6: 33.8, 7: 20.5	71.951(4)	**< 0.001**

For continuous variables median and IQR were presented in brackets whilst for categorical independent variables the percentage of occurrence of each label is indicated. The column test statistics indicates the R^2 value of spearman correlations for continuous independent variables and the χ value (degrees of freedom) of the KW test between the variables and the CRS-R continuous value.

TPO: time-post onset; CRS-R: Coma Recovery Scale-Revised, GCS: Glasgow Coma Scale; FOIS: Functional Oral Intake Scale; LCF: Level of Cognitive Functioning; FIM: Functional Independence Measure; UWS: Unresponsive Wakefulness State; MCS: Minimally Conscious State; EMCS: Emergence from MCS.

(Liuzzi, Grippo et al. 2022)

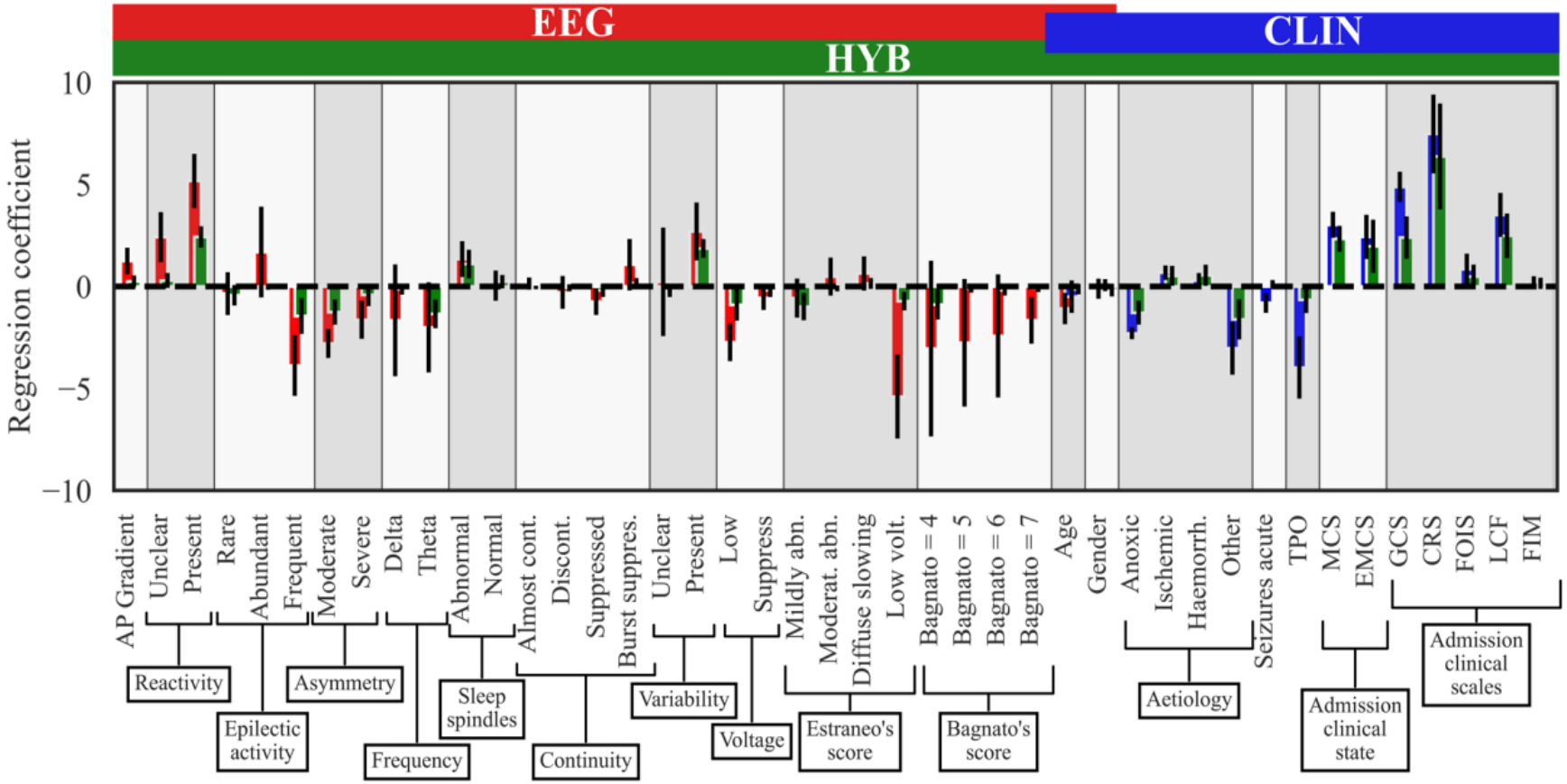

Fig. 4. Elastic-Net regression coefficients for the EEG (red), the CLIN (blue) and the HYB (green) models. The height of each colored bar is the average value of the regression coefficients of the models trained in the outer folds. The black bar indicates the standard deviation of the regression coefficients of the outer folds.

(Liuzzi, Grippo et al. 2022)

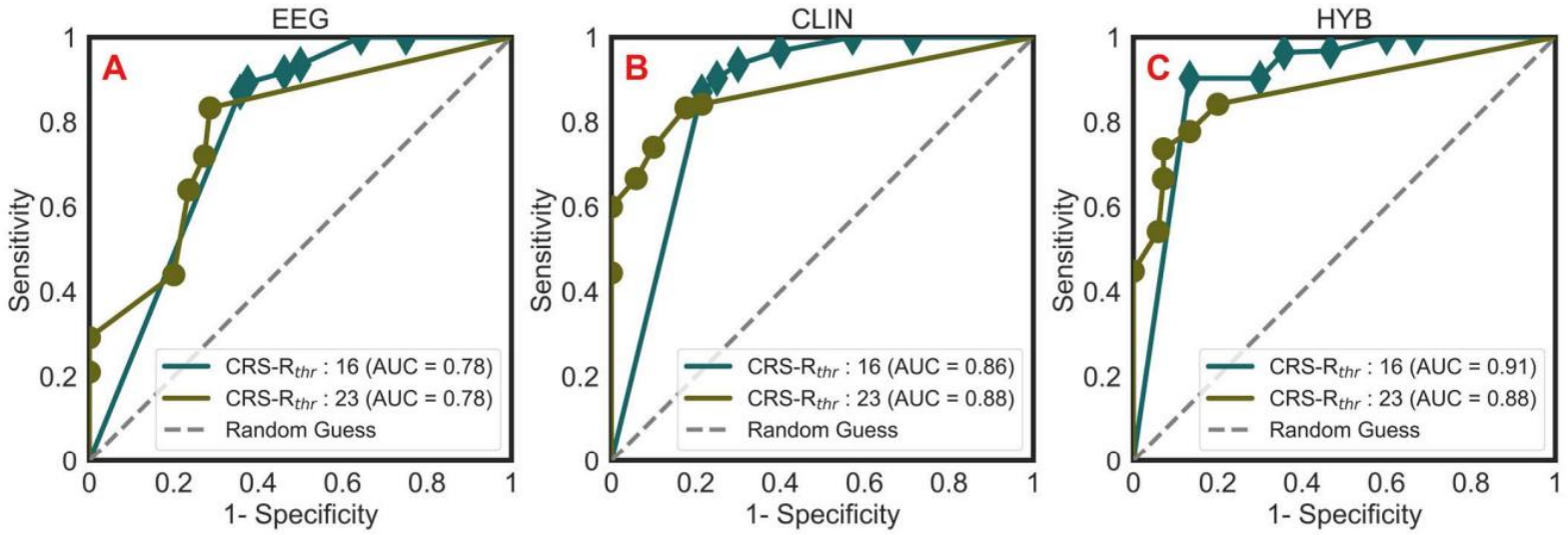

Fig. 5. Receiver-Operating Curve (ROC) of the three models with outcome: overcoming the CRS-R threshold (equal or bigger than 16 or 23). Respectively, the EEG, CLIN and HYB model are represented in panel A,B,C.

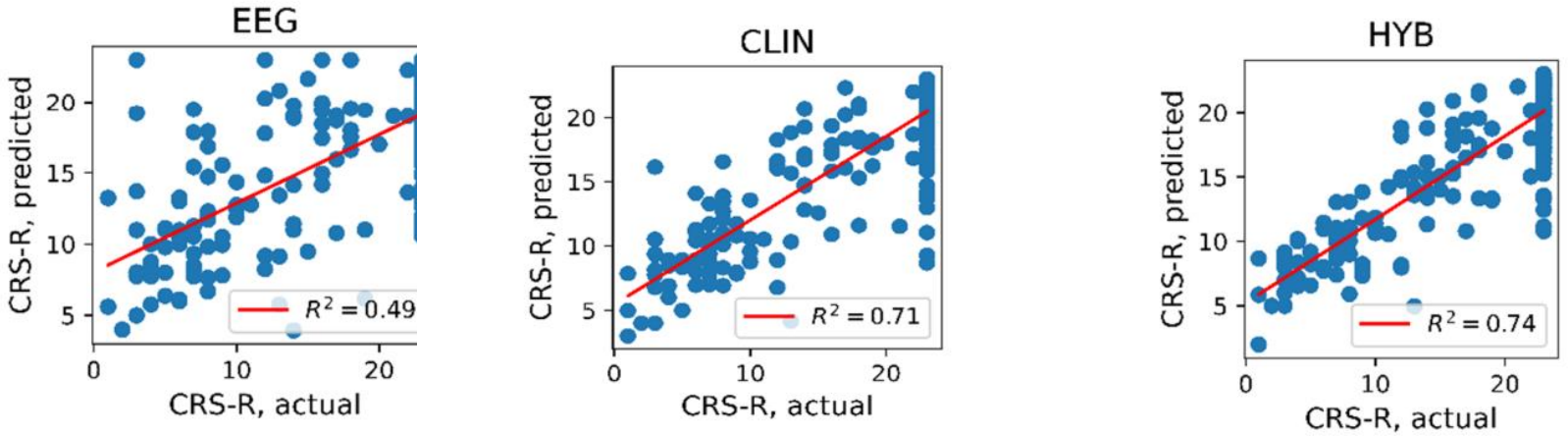

Fig. 6. Scatter-plot of actual (x-axis) versus predicted (y-axis) CRS-R values for the three models.

Results:

- Small & useful but improvements are added by the EEG dataset to the clinical model for what concerns overcoming an unresponsive wakefulness state.

- Data-driven techniques and namely, machine learning models are hereby shown to be capable of supporting the complex decision-making process the practitioners must face

(Liuzzi, Grippo et al. 2022)

Biomarkers for Therapeutic response

- Biomarkers for cure
- Biomarkers for therapeutic response

Summary:

- CEEG is an invaluable tool in ICU
- CEEG yields multi-dimensional biomarkers
- AI can overcome or ameliorate limitations of CEEG applications in ICU
- Real-time analysis and interpretation of CEEG data is essential to influence clinical decision making and clinical outcomes
- ML models and AI integration into decision making process provides standardization and automation

Acknowledgements:

- Aaron Struck, MD
- Elizabeth Gerard, MD
- Joseph Picone, PhD

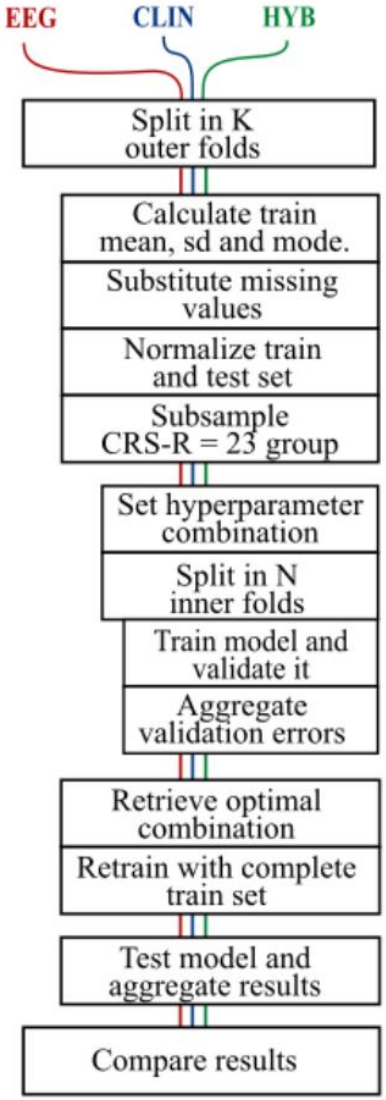

Fig. 1. Nested cross-validation approach used embedding hyperparameters optimization. A subsampling is performed in each outer training set, reducing the instances having discharge CRS-R = 23 to 1/23 and consequently balancing the regression problem. Each indentation corresponds to a for loop in the code.

(Liuzzi, Grippo et al. 2022)