Developing a Quantitative EEG-Based Biomarker for SLC6A1-Related Neurodevelopmental Disorder

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SLC6A1 Connect

1 Background

•SLC6A1 genetic variants have an estimated prevalence of 1/35,000. 85% of patients have epilepsy (Goodspeed et al., 2023)

•A clinical trial evaluating therapeutic efficacy of glycerol phenylbutyrate for children with SLC6A1 mutations (NCT04937062) demonstrated significant reduction of seizures

•People with SLC6A1 have a characteristic EEG finding of paroxysmal delta activity, which may have sinusoidal, notched, or spike-wave morphology. Automatically capturing these bursts has the potential to serve as a biomarker for treatment response.

2 Aim

•Developing signal processing pipelines to quantify EEG changes before and after glycerol phenylbutyrate therapy

3 Conceptualization

Review and Standards

- A pediatric epilepsy expert (ZG) marked paroxysmal delta bursts in 400 seconds of one pre-treatment EEG for use as a gold standard
- Reports from an ongoing clinical trial (NCT04937062) suggest these bursts decrease after treatment with glycerol phenylbutyrate
- This child was selected because they became seizure-free after treatment with glycerol phenylbutyrate.

Selection of Pipeline Parameters

- Existing literature was reviewed informally to develop knowledge of parameters utilized for other variants
- Expert clinician provided insight into EEG trends and related properties

Hypothesized Trends

- SLC6A1 seizure events tended to display (1) increased amplitude, (2) “slow waves” and (3) rhythmicity

4 Pipeline One

Methods-

- Three spectral features were calculated at one second intervals:
- Delta Power: total power in from 2.5 - 4 Hz, represented in μV^2
- Autocorrelation: the closeness of the wave to itself, one second intervals, lag times implemented
- Spectral Entropy: distribution of power across frequencies 1-30 Hz

Through trial and error, we selected thresholds and found when all three were met

PIPELINE 1 METRIC	THRESHOLD
POWER (FULL INTEGRAL)	*greater than* 105,000 μV^2
AUTOCORRELATION	*greater than* 0.41
SPECTRAL ENTROPY	*less than* 3.16

5 Pipeline One Results

Results-

- Pipeline 1 identified 24/25 bursts
- Second-by-second PPV 0.99; sensitivity 0.984
- “Hits” from when all 3 thresholds were met in a one second interval

Green- Expert Certain,
Yellow- Potential Activity

FIGURE 1. Pipeline 1. Channel (y-axis) by time (x-axis) for ~400 seconds of pre-treatment EEG. The green vertical bars represent the gold standard delta bursts. Blue triangles represent seconds in which all three thresholds were met by channel.

Pipeline Two

Methods-

- Generalizability: optimized selection of the thresholds via exhaustive search maximizing

- F1 = 2 * ((PPV x Sensitivity) / (PPV + Sensitivity))
  - Thresholds produced from this ultimate value utilizing an initial EEG for each patient
  - Sourced from existing literature

- The optimal solution was then applied to other EEGs for that patient to determine what percentage of seconds in each EEG met the three-part threshold

Delta Power Modification-

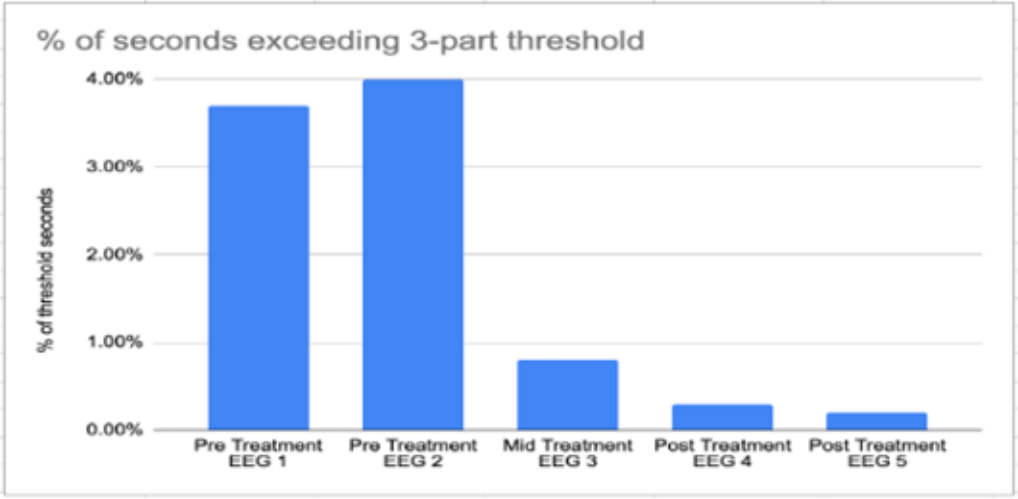
- Using a modified version of delta power where the amplitudes in the delta power range were squared to produce a vector, which we took the median of
  - Produces a different magnitude of value than Pipeline One's integration method

7 Pipeline Two Results

Results-

- Example Values Optimized for in Initial EEG:

PIPELINE 2 METRIC	THRESHOLD
MEDIAN POWER	*greater than* 50 μV^2
AUTOCORRELATION	*greater than* 0.41
NORMALIZED ENTROPY	*less than 0.3*



Fewer % seconds exceeding tri-threshold values post treatment

FIGURE 2. Pipeline 2. Comparing pre- and post- treatment EEGs, there was a substantial reduction in the percentage of seconds meeting the three metric thresholds.

Pipeline Three

Methods-

- Cross-correlation: the fit of the waveform across the eighteen channel pairs in each second-long time span (median value used)
  - Added to original 3 parameter model (delta power, autocorrelation, spectral entropy)

- Across the EEG, 25%ile, 50%ile, and 75%ile were calculated for each one second interval
  - 12 predictors total: 3 percentile levels * 4 variables

Model Comparisons-

- Logistic regression models were fitted to the data
  - Best Subset Model: Bayesian Information Criterion, weighting both fit and simplicity through number of variables (chosen from the 12 predictors)
  - Compared the median values of all 4 original parameters

9 Pipeline One Results

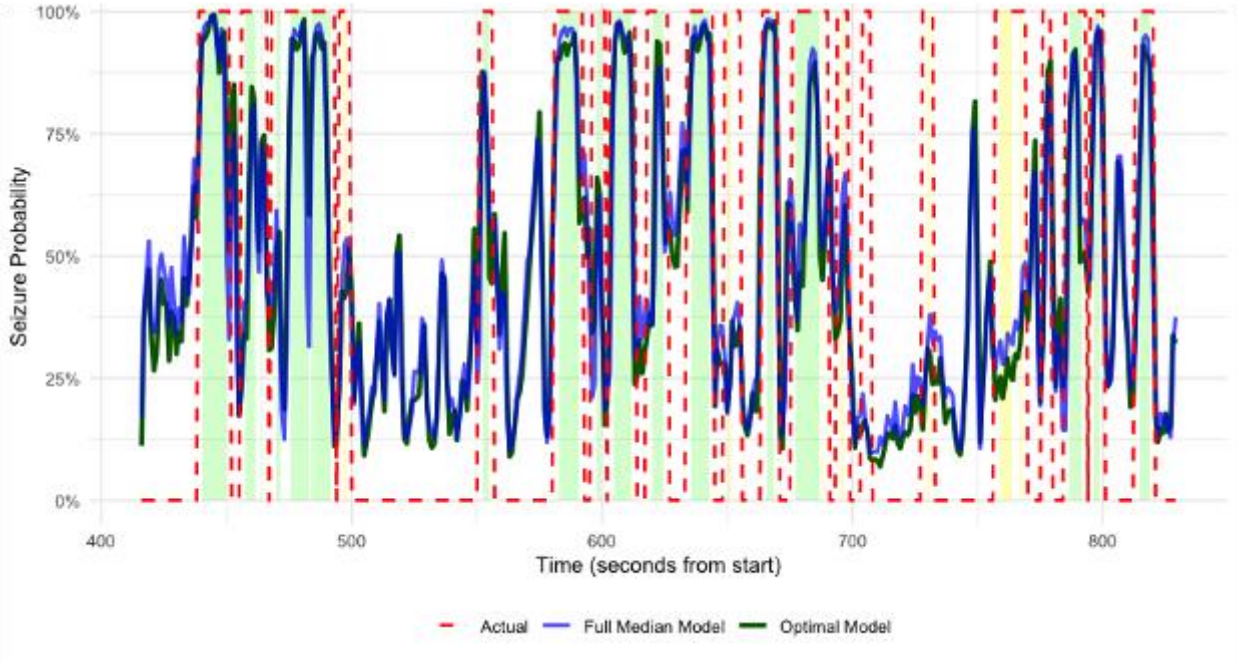


FIGURE 3. Pipeline 3. The full model (blue) and optimal model (green) generated probabilities that mirrored timing of events

Conclusion/Discussion

- We have developed a measure to detect SLC6A1-related EEG abnormalities and used this to discriminate pre-treatment from post-medication EEGs.
- Ongoing work is exploring additional features and generalizability across the full set of 10 patients from the glycerol phenylbutyrate clinical trial (NCT04937062).
- We will continue to refine our predictive models to improve individual EEG statistics such as PPV & Sensitivity, along with applicability to large samples of EEGs
- Further properties, such as wavelet forms, will be used to simplify correlation measures and improve generalizability.

Acknowledgements & Thanks

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