Decoding Dravet Syndrome: The Role of Advanced EEG Analytics in Phenotyping

Caroline Neuray[1]; Brecht Nerinckx[1]; Ekatherina Garzon[1]; Pieter van Mierlo[1]; M. Scott Perry[2]; Kelly G Knupp[3]; Joseph Sullivan[4]; Susana Boronat[5]; Matt Lallas[6]; Andreas Brunklaus[7]; Salvador Rico[8]; Jacqueline S Gofshteyn[8]

[1]Epilog, Clouds of Care NV, Ghent, Belgium; [2]Cook Children's Medical Center, Fort Worth, TX, USA; [3]Children's Hospital Colorado, Aurora, CO, USA; [4]University of California at San Francisco, San Francisco, CA, USA; [5]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [6]Nicklaus Children's Hospital, Miami, FL, USA; [7]School of Health & Wellbeing, University of Glasgow, Glasgow, UK; [8]Encoded Therapeutics, South San Francisco, CA, USA

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BACKGROUND

- Dravet syndrome (DS) is a severe, treatment-resistant developmental and epileptic encephalopathy[1]
- Development of novel disease-modifying therapies addressing seizure and non-seizure manifestations of DS underscores the need for objective non-seizure endpoints
- EEG interpretation is instrumental in diagnosis and management of DS, yet its utility as a biomarker is limited by:
  - Significant inter-individual variability
  - Potential absence of interictal epileptiform discharges (IED) and seizures
  - Variability in visual assessments among different raters
- The rise of advanced EEG-signal processing methods is essential to explore potential electrophysiologic diagnostic, prognostic, and predictive biomarkers

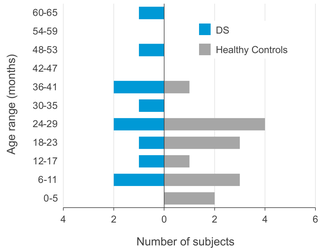
STUDY DESIGN

- ENVISION was an international, multicenter, longitudinal, prospective natural history study of children with *SCN1A*+ DS
- Participants aged 6 months to 5 years at study entry were assessed every 3 months (virtual assessments and clinic visits) using a combination of electronic and in-person assessments for neurodevelopment status and seizure characteristics

METHODS

- 30-minute EEG recordings during wakefulness were collected from ENVISION participants and age-matched healthy controls (provided by Epilog)
- EEGs were analyzed using a semi-automated approach by Epilog (Clouds of Care NV, Ghent, Belgium)
- Background activity was centrally assessed by an expert pediatric epileptologist
- IEDs were detected, automatically clustered, and verified by the same expert
- Spectral features were computed using Fast Fourier Transformation in the canonical frequency bands
- Functional connectomes between the atlas-based regions were calculated using the weighted phase-lag index. The degree and efficiency of connectomes were computed to characterize the network
- Correlation analyses (Pearson's) between EEG and the Bayley Scales of Infant and Toddler Development Version 3 (BSID-III) scores were performed

DEMOGRAPHICS



11 children with DS
- Median age at EEG recording 24 months (range 7 months to 5 years and 3 months)

14 healthy controls
- Median age of 18 months (range 3 months to 3 years and 2 months)

Figure 1. Comparative age distribution histogram for children with DS and healthy controls

RESULTS

EEG Background Activity

- **No significant differences in EEG background activity** were found in children with DS compared with age-matched healthy controls **(Figure 2)**

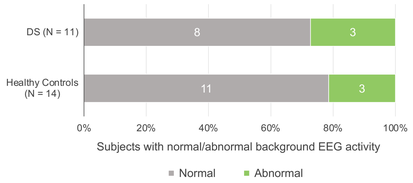


Figure 2. Background EEG activity classification (normal and abnormal) and frequency in children with DS and healthy controls

Spike Rate

- **Spikes were observed during wakefulness in 7/11 (64%) of children with DS**
- **Spike rate during wakefulness was significantly increased** in children with DS compared with healthy controls (**Figure 3**)
  - Median spike rate in healthy controls was 0
  - Median spike rate was 9.9 spikes/hour in all children with DS and 48.6 spikes/hour (range 9.8–1779.5 spikes/hour) in the subgroup of children with DS (N=7) where spikes were detected in the EEG
- The differences between DS and healthy controls were seen for both focal and generalized spikes

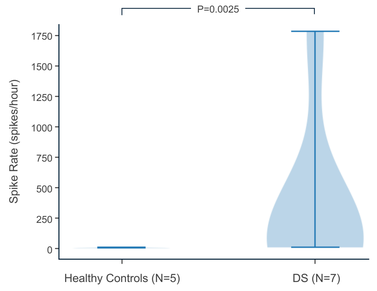


Figure 3. Violin plot showing spike rate distribution analysis of EEGs during wakefulness in 7 children with DS who had spikes and 5 age-matched healthy controls

Spectral Analysis During Wakefulness

- **A significant decrease in the gamma band power during wakefulness** was observed in children with DS compared with healthy controls **(Figure 4)**

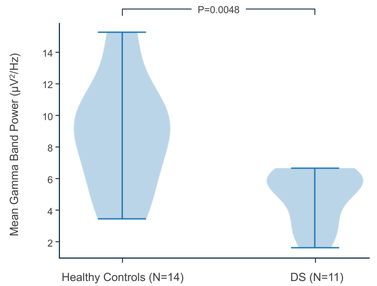


Figure 4. Violin plots showing distribution of EEGs by spectral power in the gamma band for children with DS and age-matched healthy controls

Functional Connectivity

- Distinct differences in connectivity were observed during wakefulness between children with DS and healthy controls using phase locking value **(Figure 6)**
- There was a global decrease in functional connectivity during wakefulness in children with DS, with statistical significance across the whole brain, except the frontal lobe
- Increased functional connectivity in the frontal lobe was observed in children with DS compared with healthy controls

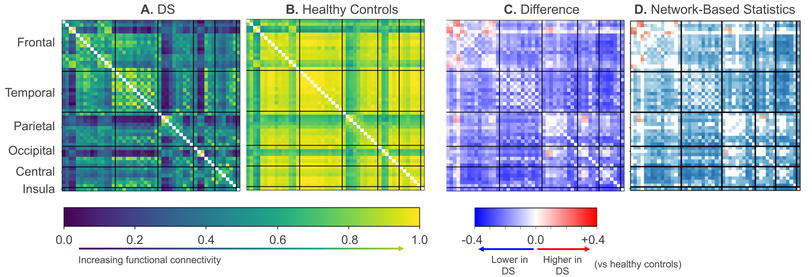


Figure 6. Connectivity matrix of children with DS and age-matched healthy controls. The left panels (**A,B**) indicate the connectivity during wakefulness. The right panels indicate the differences (**C**) and statistically significant nodes[2] (**D**) between DS and age-matched healthy controls

Spectral Analysis During Wakefulness *(continued)*

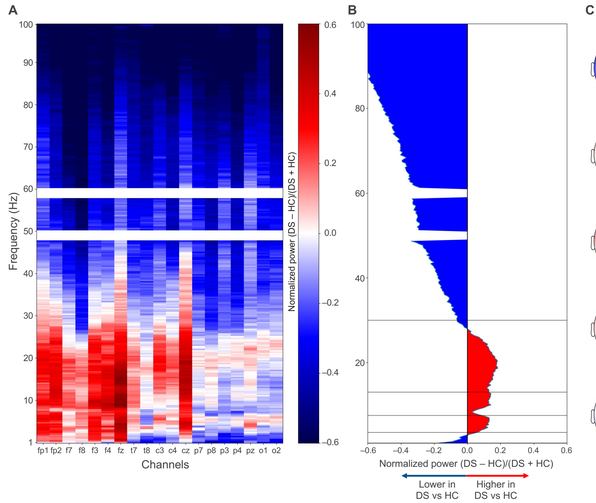


Figure 5. Differences in spectral power between children with DS and age-matched healthy controls (HC). The left panel (**A**) indicates the frequency and channel-specific differences. Normalization was done by dividing each individual power spectrum by the mean power over all channels and frequencies. Red indicates a higher power in children with DS compared with healthy controls, while blue indicates a lower power. The two white lines across all channels result from notch filters at 50 and 60 Hz. The middle panel (**B**) indicates global changes averaged over all channels. The right panel (**C**) depicts the change in topography for each canonical frequency band

- Relative to healthy controls, children with DS had (**Figure 5**):
  - **A decrease in gamma band power in all EEG channels, over the complete area of the head**
  - **A frontal lobe increase in delta, theta, alpha, and beta band power**
- In children with DS, gamma and theta mean power over time during wakefulness had a moderate positive correlation with BSID-III Cognitive raw scores (r^2 = 0.58 and 0.58, respectively, n=7) and BSID-III Fine Motor raw scores (r^2 = 0.54 and 0.69, respectively, n=6)

CONCLUSION

- Compared with healthy controls, children with DS showed:
  - No differences in EEG background activity
  - Significantly higher spike rate, even though only 60% of children with DS exhibited interictal spikes, with spike burden not associated with age
  - A marked decrease in gamma activity and an increase in theta activity in the frontal regions
  - Distinctive connectivity patterns over all brain regions, with a high degree of connections in the frontal lobe
- Cognitive and fine motor skills, as measured by BSID-III, had a moderate positive correlation with changes in spectral features in DS
  - Likely due to the topographic distribution of abnormal slow activity over the frontal lobe and its role in attention and executive functions
- Study limitations include a small sample size, retrospective EEGs, and potential outlier effects on correlation analyses
- Advanced EEG analyses reveal distinctive patterns in children with DS compared with healthy controls
  - Visual analysis limited to background activity and spikes may not show distinctive changes, especially in young patients
  - Additional research is required to establish the utility of advanced EEG biomarkers as diagnostic and prognostic tools

REFERENCES 1. Scheffer IE, Nabbout R. Epilepsia 2019;60(Suppl 3):S17–S24. 2. Zalesky A, et al. Neuroimage 2010;53:1197–1207. ABBREVIATIONS BSID-III, Bayley Scales of Infant and Toddler Development, 3rd edition; DS, Dravet syndrome; EEG, electroencephalogram; HC, healthy controls; IED, interictal epileptiform discharges.

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