iStore : Key Findings from the Dravet Syndrome Registry

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Goals and Deliverables

Goals:

- A computationally efficient and stable modelling tool for incomplete multivariate longitudinal and heterogeneous data for small to ultra-small studies
- Developing and validating disease specific clinically meaningful outcomes with special interest in PCOMs, or composite endpoints

Deliverables:

- D1: Formulation of the statistical modelling framework:
  - Combined modelling framework compatible with missing data methods and adapted for small samples
  - Generalized Pairwise Comparison (GPC)
- D2: Development of open access software in R
- D3: Writing manuals and supporting materials (web lectures)

2. Statistical models (in R)

RANDOM EFFECTS MODELS

- Subject-specific random effect
- Fractional polynomials

Transition models

- Use history of the subject

Outcomes

01.

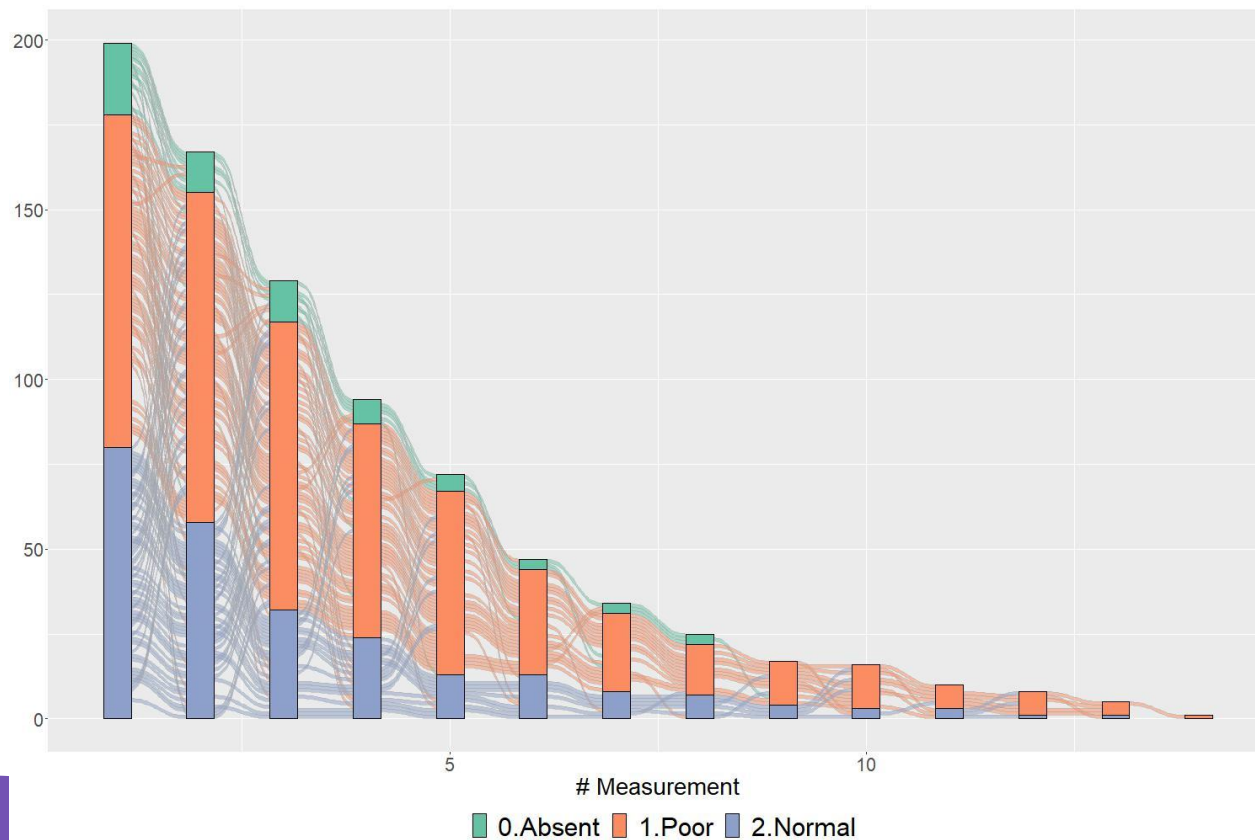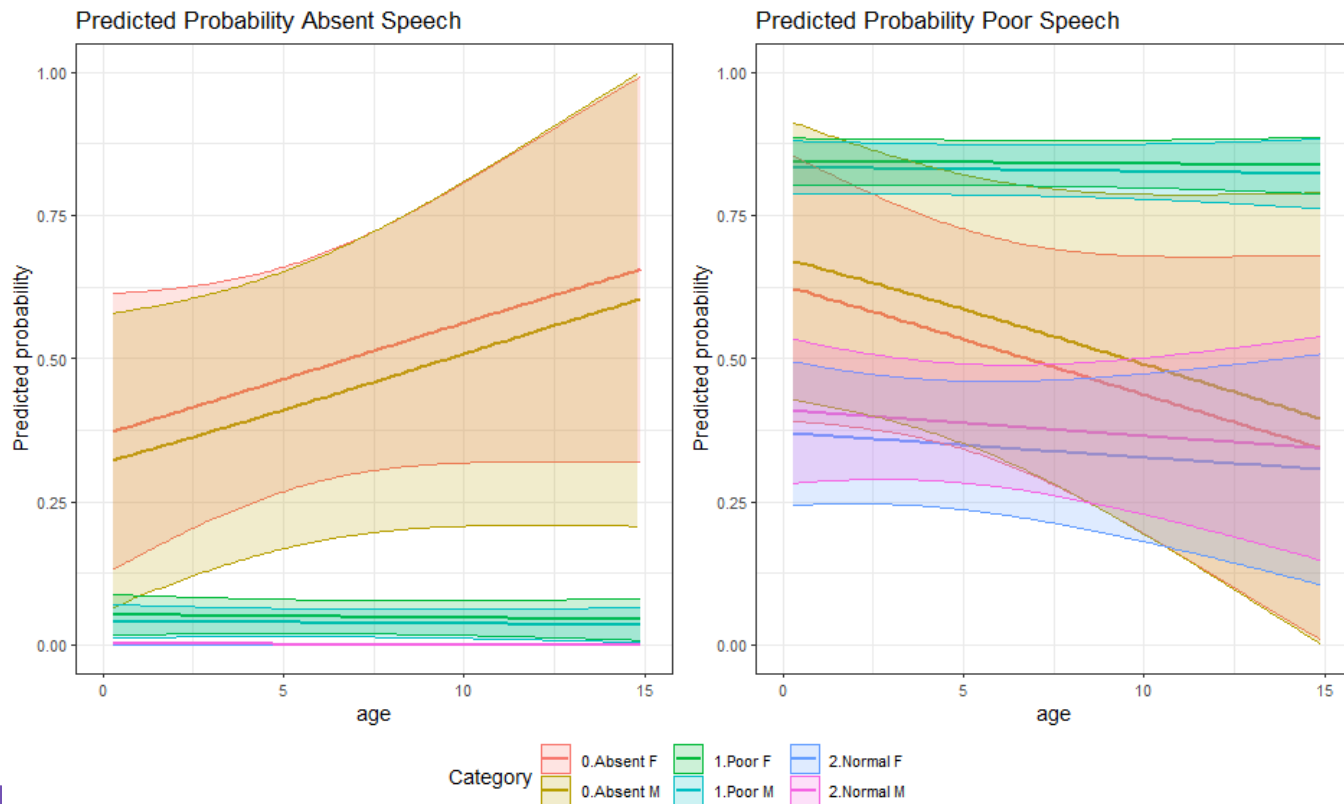## Speech analysis

Ordinal response

02.

Occurrence of seizures
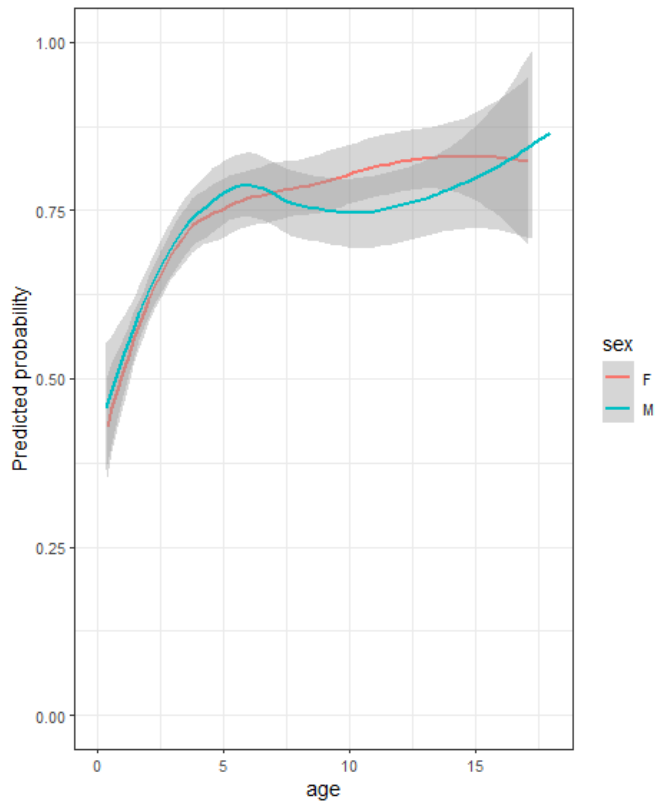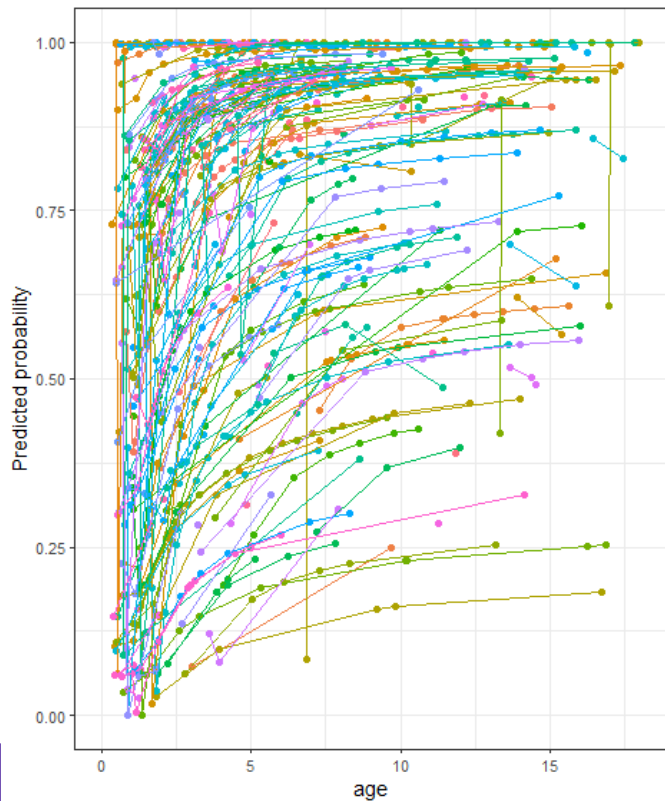
Binary response

3. Analysis of the speech variable
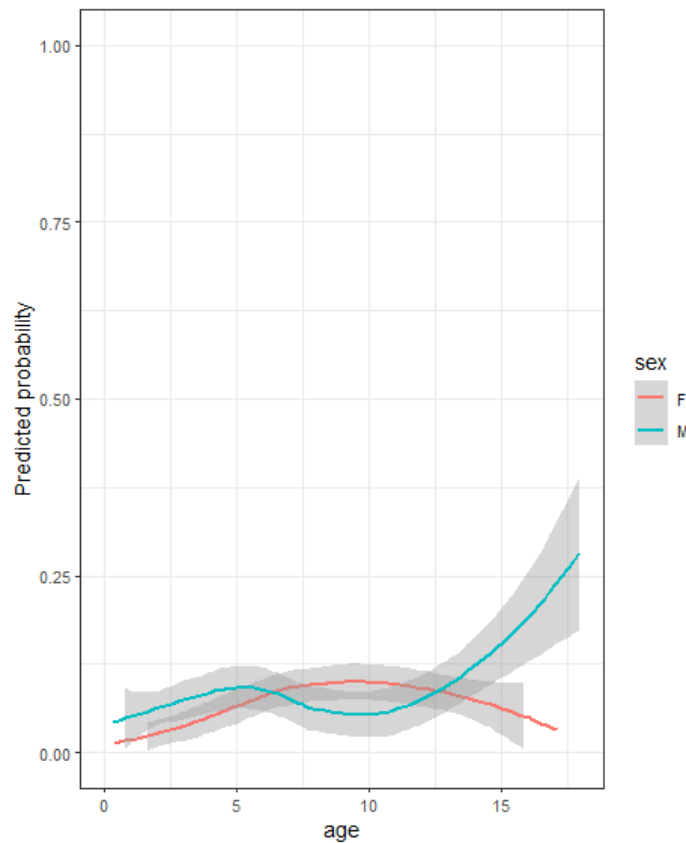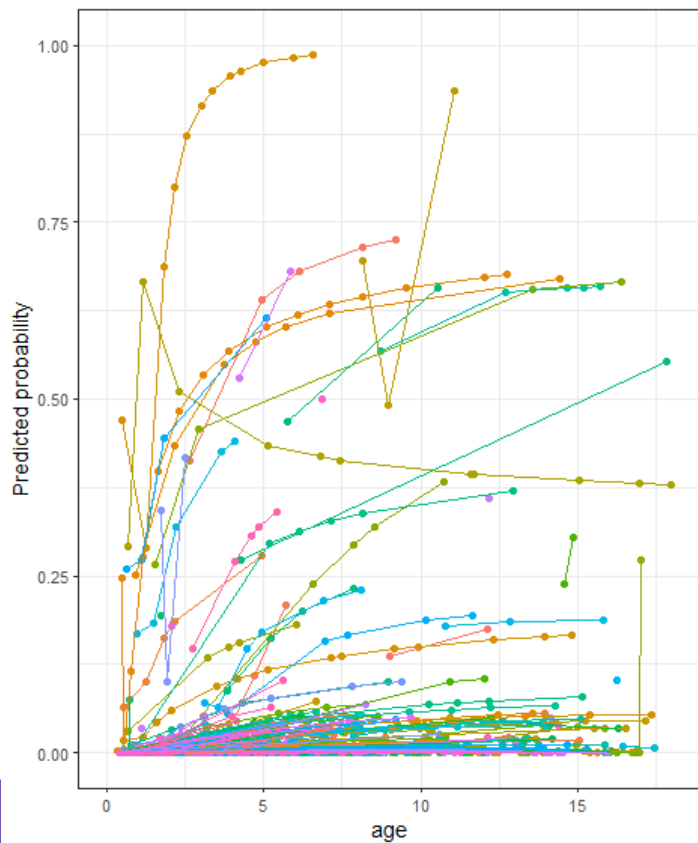
Transition Model

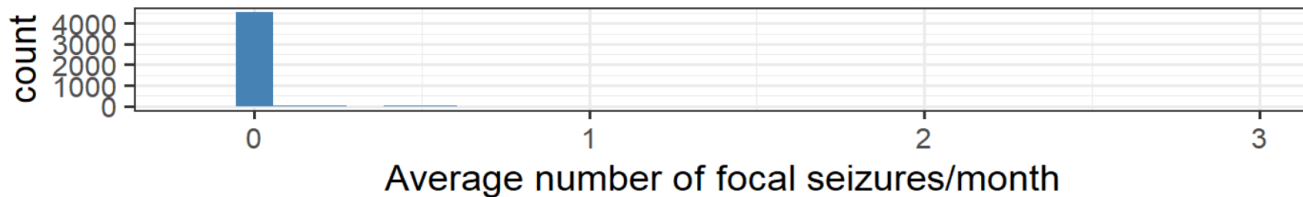Predicted Probability Absent Speech | Predicted Probability Poor Speech
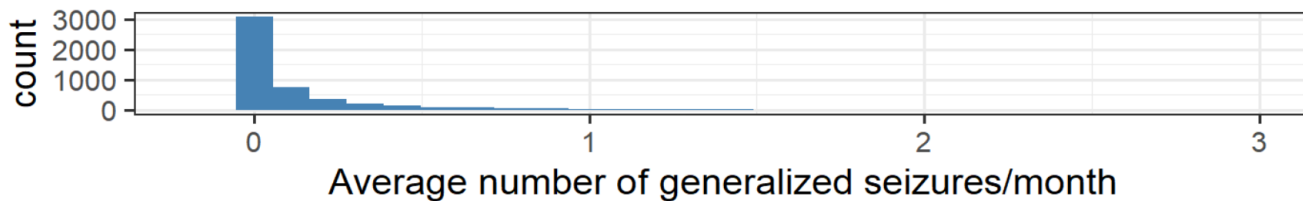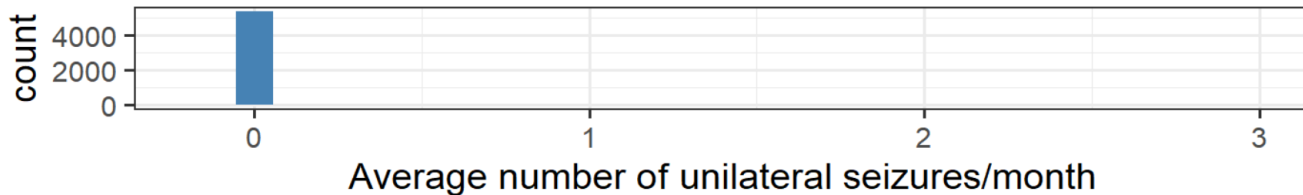
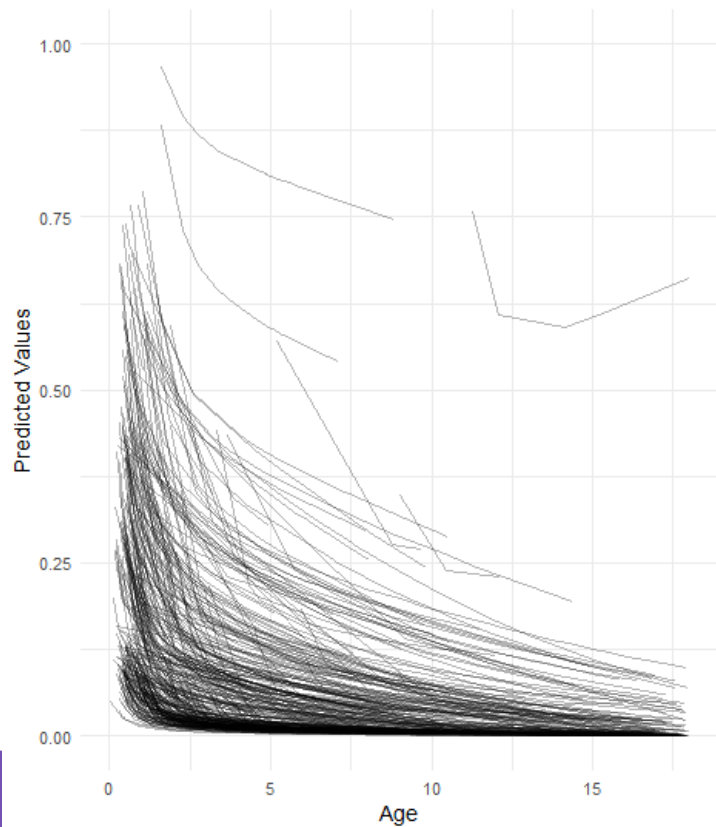# Probability poor/absent speech

Probability absent speech

3. Analyis of the seizures
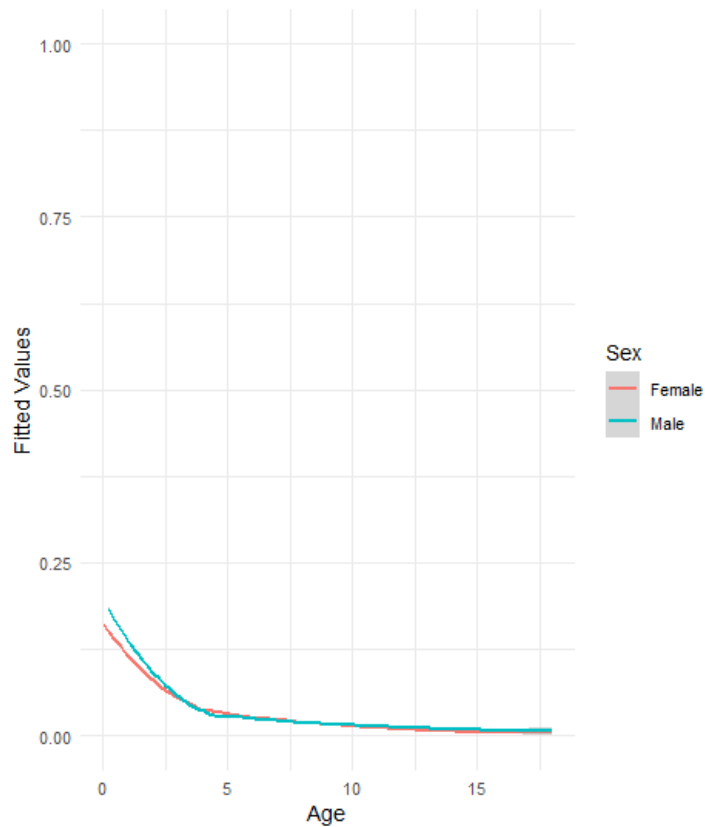
Probability unilateral seizures

Spaghetti Plot of Fitted Values

Loess Curve of Fitted Values by Gender

Probability generalized seizures
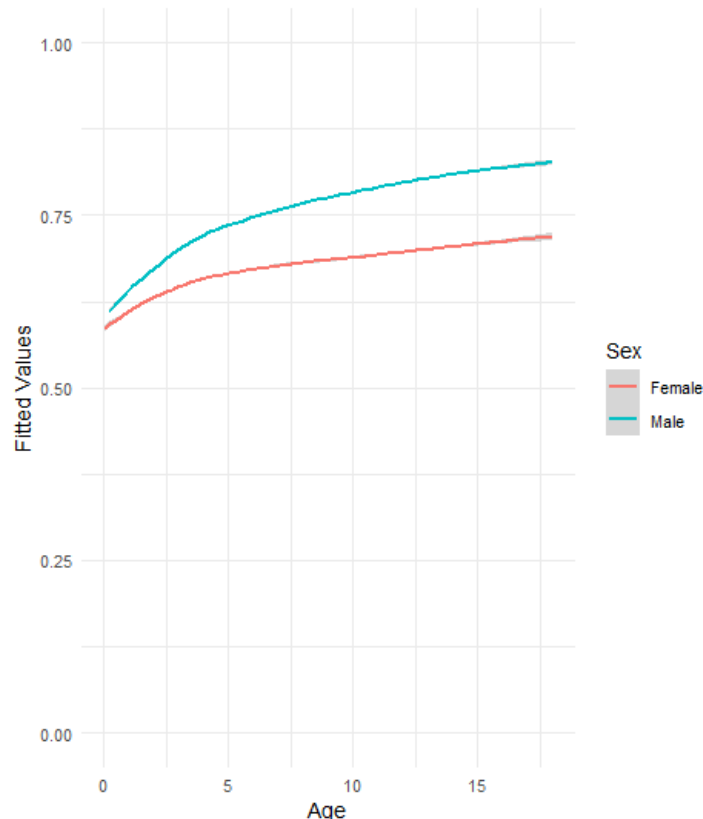
Probability focal seizures

Spaghetti Plot of Fitted Values

Loess Curve of Fitted Values by Gender

Data issues

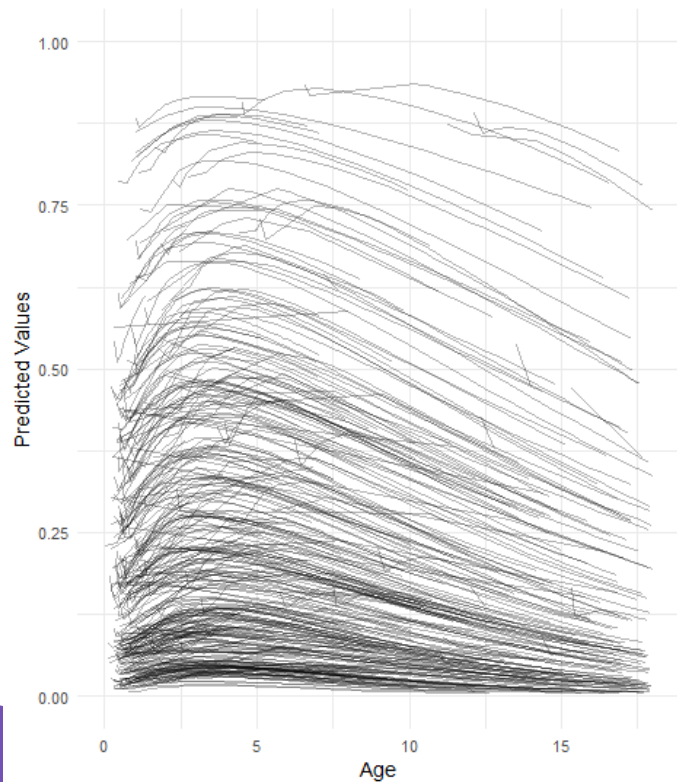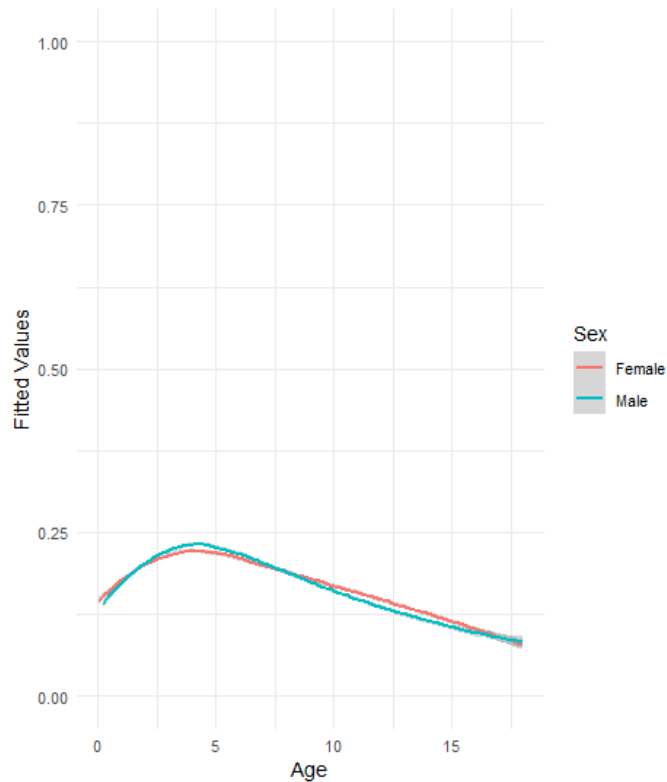- Complexity: many different medications (n=90)

- Cumbersome data manipulation

- Missing data and variables

Next steps

- Joint modelling to study the effect of medication
- Investigate psychological scales (e.g. WISC)

Cognitive / behavioral development variables

Goal: Studying associations between these variables (and with seizure frequency)

Which variables? – Nabbout et al., Epilepsy Behav 2018, DOI: 10.1016/j.yebeh.2017.08.029

Statistical methods

- Simple pairwise correlations
- Exploratory analyses (e.g., PCA / clustering?)
- For associations with seizure frequency: (ordinal) linear modeling (e.g., PIM)?

Cognitive / behavioral development variables

Goal: Studying longitudinal trajectories and the potential impact of predictors / covariates

Which variables? – 2 specific scales (with a reasonable amount of missing data) as outcome, mutation and / or number of ASMs as predictors

Statistical methods

- Generalized pairwise comparisons
- nparLD (potentially allowing also for missing data)
- If scales are measured at fixed time points, and if a time-point-specific analysis is of interest (instead of the trajectories): also, for example, MANOVA.RM, or nonparametric multivariate MCTPs (advantage: consider scales simultaneously, potentially also together with seizure counts, thereby taking the correlations implicitly into account)