Machine Learning EEG Biomarkers in SYNGAP1 Rodent Models

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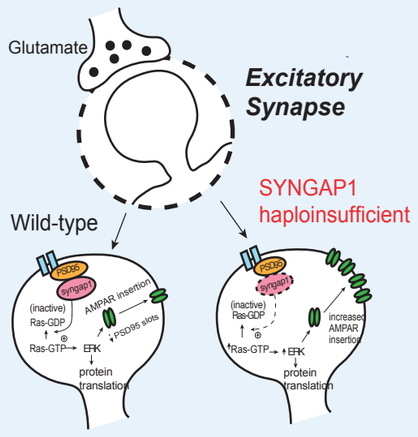
SIDB Simons Initiative for the Developing Brain

Linkedin

SYNGAP1

SYNGAP1 regulates excitatory synapse structure and function

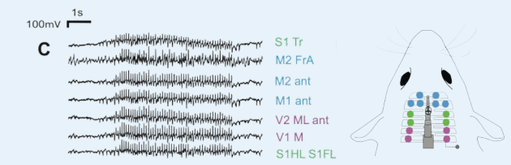


Syngap1-related disorder (SRD) is a rare disease where a mutation in the Syngap1 gene results in severe disruption of neurodevelopment, causing intellectual disability, autism and epilepsy[1]. Most SRD patients are non-verbal and requiring lifelong care.
There are currently no interventions to treat these symptoms effectively.

EEG

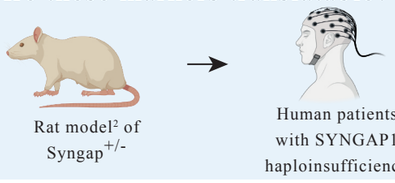
Multiple gene modification strategies are in development, but clinical trials require quantitative biomarkers to objectively measure effectiveness of intervention. Currently, no validated biomarkers exist for SRD. EEGs have great potential as biomarkers. ML technique offers a principled way to simultaneously analyse large numbers of EEG features.

1. Is it possible to identify synapse dysfunction caused by SYNGAP1 haploinsufficiency in EEG signals?



EEG recordings from a Rat model of Syngap$^{+/-}$

2. Are these markers translatable?



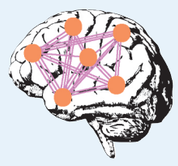
Rat model[2] of Syngap$^{+/-}$ → Human patients with SYNGAP1 haploinsufficiency

FEATURE EXTRACTION

Extracted features from 5-second non-seizure epochs

Connectivity Abnormalities

- Cross Correlation
- Phase Locking Value

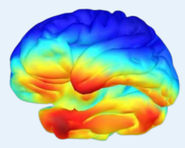


Complexity Abnormalities

- Dispersion Entropy
- Higuchi's Fractal Dimension

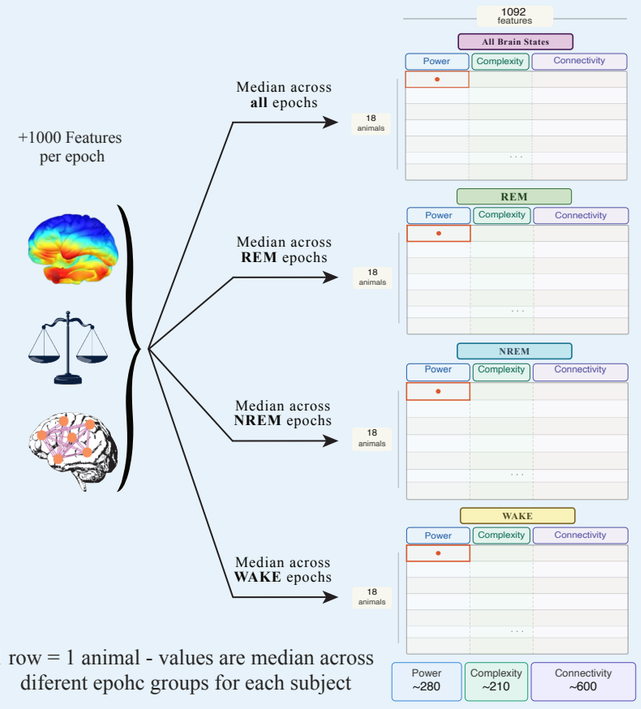
Power Spectra

- Average Band Power
- Spectral Slope and Intercept
- Band Power Ratios



Median Aggregation

4 experiments with Animal-level feature sets



MACHINE LEARNING

Input each median aggregated feature set into a classifier

LOOCV (N=18)
In every fold:

↓

Feature Selection with **BorutaSHAP**

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Baysian Hyperparameter Tunning

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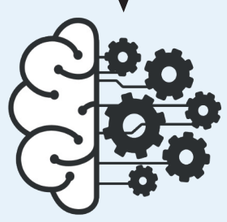
Model training



↙ Syngap$^{+/-}$ ↘ Wild-Type

Prediction and Evaluation (Permutation Test)

AIMS

1. Can a machine learning classifier distinguish SYNGAP1 haploinsufficient rats from wild-type controls using interictal EEG features?

2. Which feature domains contribute most to the classification?

3. Does the classifier generalise across individual animals, and is the performance above chance as assessed by permutation testing?

MAIN FINDINGS

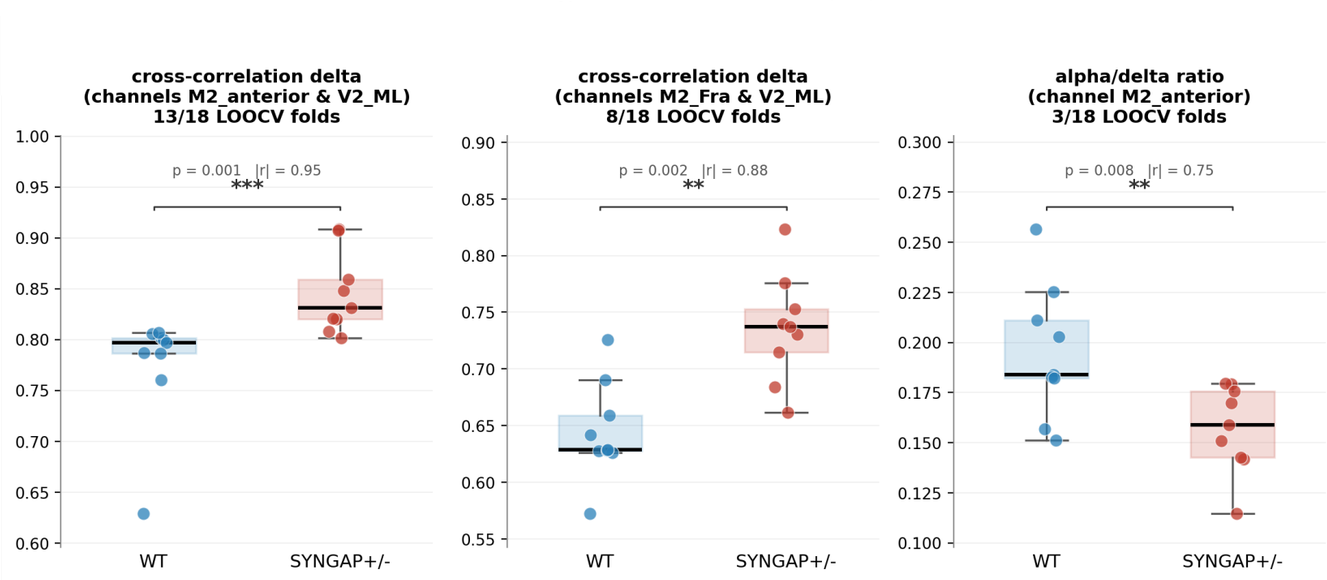
- XGBoost outperforms CatBoost in every brain state, with the strongest result on the full (all brain states) feature set (AUC = 0.9630, $p < 0.0001$).
- XGBoost is significant above chance (confirmed by permutation test) in all 4 brain states ($p \leq 0.004$); CatBoost only in Wake and NREM.
- Top features: **reduced alpha/delta ratio** in Motor Cortex and **stronger cross-correlation in the delta band** between Motor and Visual cortex. Align with SYNGAP1 EEG signatures: elevated delta/hyperexcitability in rodents[3], and a significantly lower alpha/delta ratio in SYNGAP1 children vs. controls ($p = 0.043$)[4].

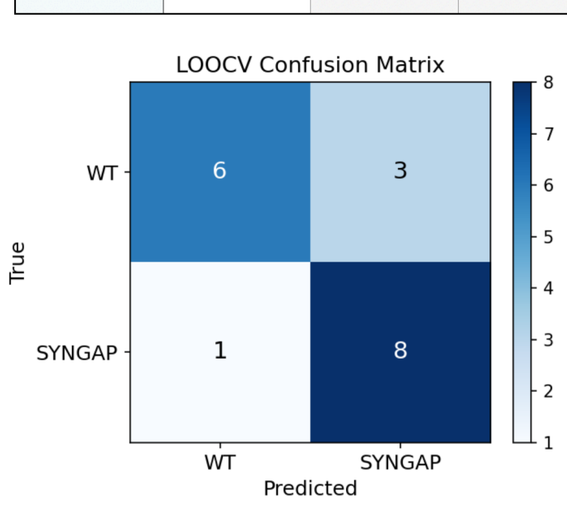
RESULTS:

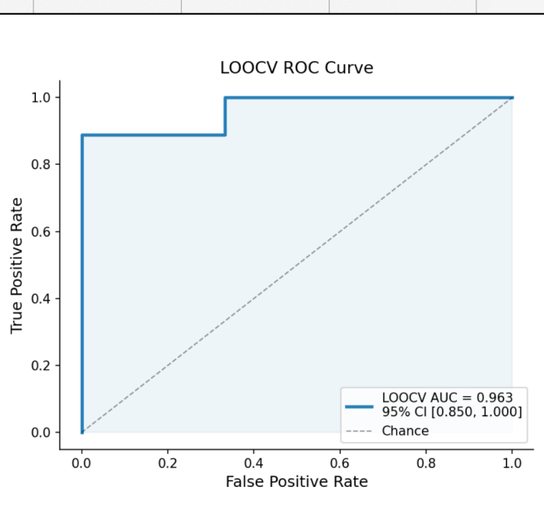
Table 1 _ Classification performance (global)

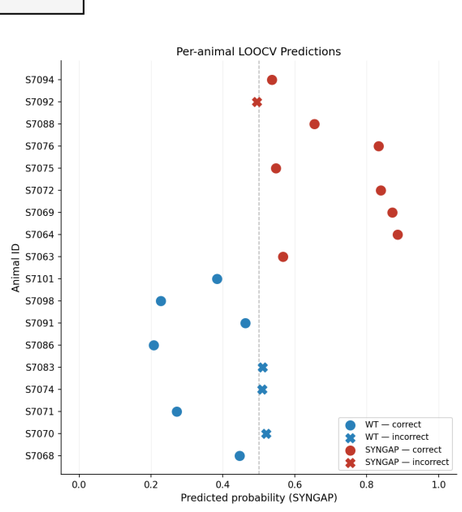
LOOCV results for all model configurations, N = 18 animals (9 SYNGAP1, 9 wilt-type), 1000 label permutations per model:

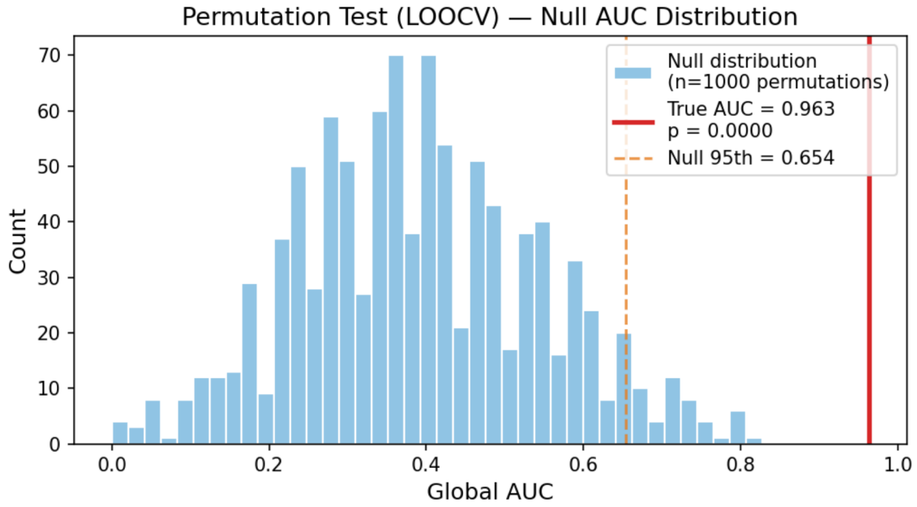
Model	Brain state	AUC	Accuracy	F1	Precision	Recall	Perm.p
XGBoost	All	**0.9630**	**0.7778**	**0.8000**	**0.7273**	**0.8889**	**<0.0001**
CatBoost		0.6790	0.6667	0.7000	0.6364	0.7778	0.0770 (ns)
XGBoost	Wake	0.8272	0.6111	0.6316	0.6000	0.6667	0.0020
CatBoost		0.7037	0.6667	0.7000	0.6364	0.7778	0.0460
XGBoost	REM	0.8642	0.6667	0.7000	0.6364	0.7778	0.0010
CatBoost		0.6296	0.6667	0.7000	0.6364	0.7778	0.1112 (ns)
XGBoost	NREM	0.8272	0.6667	0.6250	0.7143	0.5556	0.0040
CatBoost		0.7160	0.7778	0.8000	0.7273	0.8889	0.0320











Acknowledgement and References:

UK Research and Innovation

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3. T. A. Fenton et al., "Hyperexcitability and translational phenotypes in a preclinical mouse model of SYNGAP1-related intellectual disability," Translational Psychiatry, 2024.
4. P. D. Galer et al., "Quantitative EEG biomarkers in the genetic epilepsies and associations with neurologic outcomes," Neurology, 2025.

Future Work:

- Translate to human SRD patients: Apply the pipeline to human SYNGAP1 EEG recordings to validate biomarker translatability