$Na_V1.1$ Potentiators Modulate Brain Rhythms Measured Through Quantitative Electrocorticography (qECoG) in a Dravet Mouse Model

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BACKGROUND

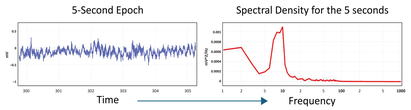
- Dravet syndrome is characterized by reduced expression of $Na_V1.1$ in inhibitory neurons that leads to hyperexcitability, resulting in epilepsy and multiple developmental, cognitive, and motor deficits. The nonseizure symptoms of the disorder emerge early in life and worsen over time
- There is a pressing need for new therapies. To address this need, we are developing $Na_V1.1$ isoform-selective potentiator small molecules
- Quantitative electrocorticography (qECoG) was used:
  - To test whether background brain activity is different in juvenile Dravet syndrome mice compared with their wild-type littermates
  - To assess whether **acute oral administration** of $Na_V1.1$ potentiator can alter brain rhythms in Dravet syndrome or wild-type mice
- Here, we evaluated pharmacokinetic (PK) and pharmacodynamic (PD) impacts on spectral qECoG power in wild-type mice after acute oral dosing, using XPC-418, a $Na_V1.1$ potentiator

METHODS

- **Electrode implantation:** On postnatal day 35, 4 surface screw electrodes (Plastics One) were implanted bilaterally in the cortex and a ground electrode over the cerebellar cortex. Cortical recordings were conducted in freely moving mice, and electrode placement was verified *post hoc*
- **Video qECoG monitoring:** Began 1 week after electrode implantation. qECoG recordings were synchronized to video, using software (LabChart Pro; ADInstruments)

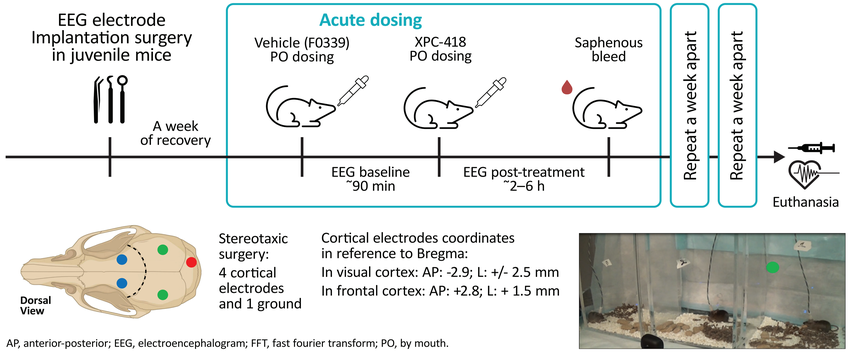
Data Analysis: Short Time Fast Fourier Transform (FFT) and Power Spectral Density (PSD)

- Neuronal activity between posterior and anterior electrodes for each hemisphere was recorded continuously for 4 to 8 hours
- The total recording was split into 20-minute time bins, followed by selection of 5-second epochs within each 20-minute bin
  A random set of 120 epochs in each 20-minute time bin was selected for frequency analysis
- Short time FFT and PSD was calculated for each epoch and averaged



Band	Frequency (Hz)
Delta (δ)	1–4
Theta (θ)	5–8
Alpha (α)	9–12
Beta (β)	13–29
Low Gamma (γ)	30–99
High Gamma (γ)	100–160

- FFT parameters: Sampling rate 2000 Hz, Hann window, 1 Hz resolution, 50% overlap

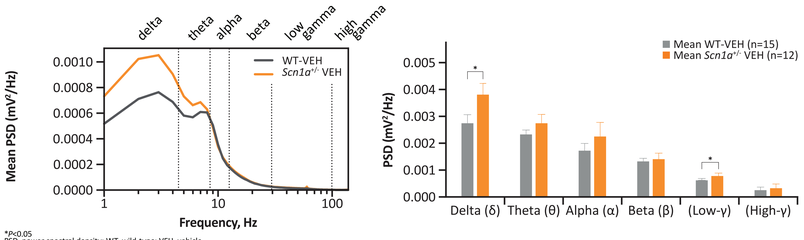


AP, anterior-posterior; EEG, electroencephalogram; FFT, fast fourier transform; PO, by mouth.

RESULTS

Brain Rhythms Distinguish Wild-Type and *Scn1a*$^{+/-}$ Mice

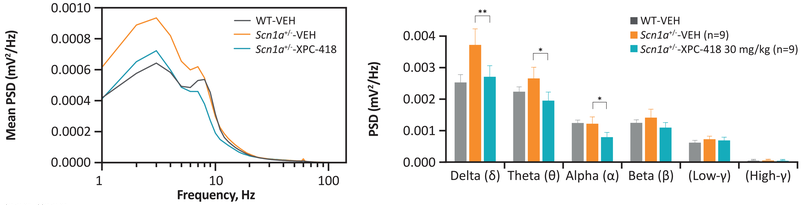
- Vehicle-dosed *Scn1a*$^{+/-}$ mice had significantly higher delta and low gamma PSD vs wild-type mice. There was a trend towards increased theta and beta frequency bands power



*P<0.05
PSD, power spectral density; WT, wild-type; VEH, vehicle.

$Na_V1.1$ Potentiator Compound XPC-418 Shifts *Scn1a*$^{+/-}$ Power Spectral Density Towards Wild-Type Phenotype

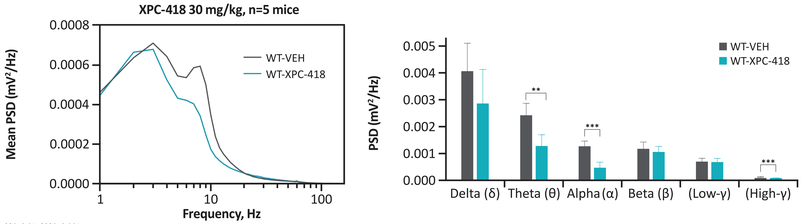
- Acute dosing of XPC-418 at 30 mg/kg significantly decreased PSD compared with vehicle treatment of *Scn1a*$^{+/-}$ mice
- PSD of *Scn1a*$^{+/-}$ mice dosed with XPC-418 was similar to the vehicle-dosed wild-type mice



*P<0.05. **P<0.01.
PSD, power spectral density; WT, wild-type; VEH, vehicle.

qECoG Can Be Used to Monitor CNS Penetration in Wild-Type Mice

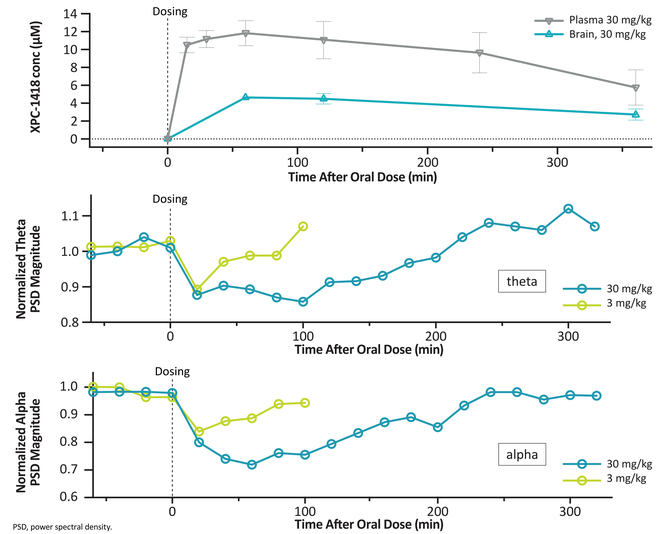
- XPC-418 significantly changed the PSD for several frequency bands after acute oral dosing



**P<0.01. ***P<0.001.
PSD, power spectral density; WT, wild-type; VEH, vehicle.

qECoG as a Tool to Monitor Target Engagement: Dose- and Time-Dependent PSD Alterations After XPC-418 Acute Oral Dosing in Wild-Type Mice

- **Time-dependence effects:** As the concentration in the brain decreased over time, the effect of XPC-418 on the brain rhythms was attenuated
  - XPC-418 was dosed at 30 mg/kg in wild-type mice (n=9): ECoG recorded up to 6 hours
  - XPC-418 was dosed at 3 mg/kg in wild-type mice (n=8): ECoG recorded up to 2 hours
  - Satellite PK was performed in parallel (0.25-, 0.5-, 1-, 2-, 4-, and 6-hour time points, brain and plasma samples).



PSD, power spectral density.

CONCLUSIONS

- *Scn1a*$^{+/-}$ mouse brain activity is differentiated from that in wild-type littermates
- XPC-418 altered brain activity in *Scn1a*$^{+/-}$ mice, making the phenotype more similar to that of wild-type animals
- XPC-418 also changes brain activity in wild-type mice in a dose- and time-dependent manner
- These data suggest that $Na_V1.1$ potentiation could normalize the power spectrum phenotype of Dravet syndrome mice to the wild-type phenotype

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DISCLOSURES All authors are employees of and own stock or stock options in Xenon Pharmaceuticals Inc.

REFERENCE Höller Y, et al. *CNS Drugs*. 2018;32(9):839–848.

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