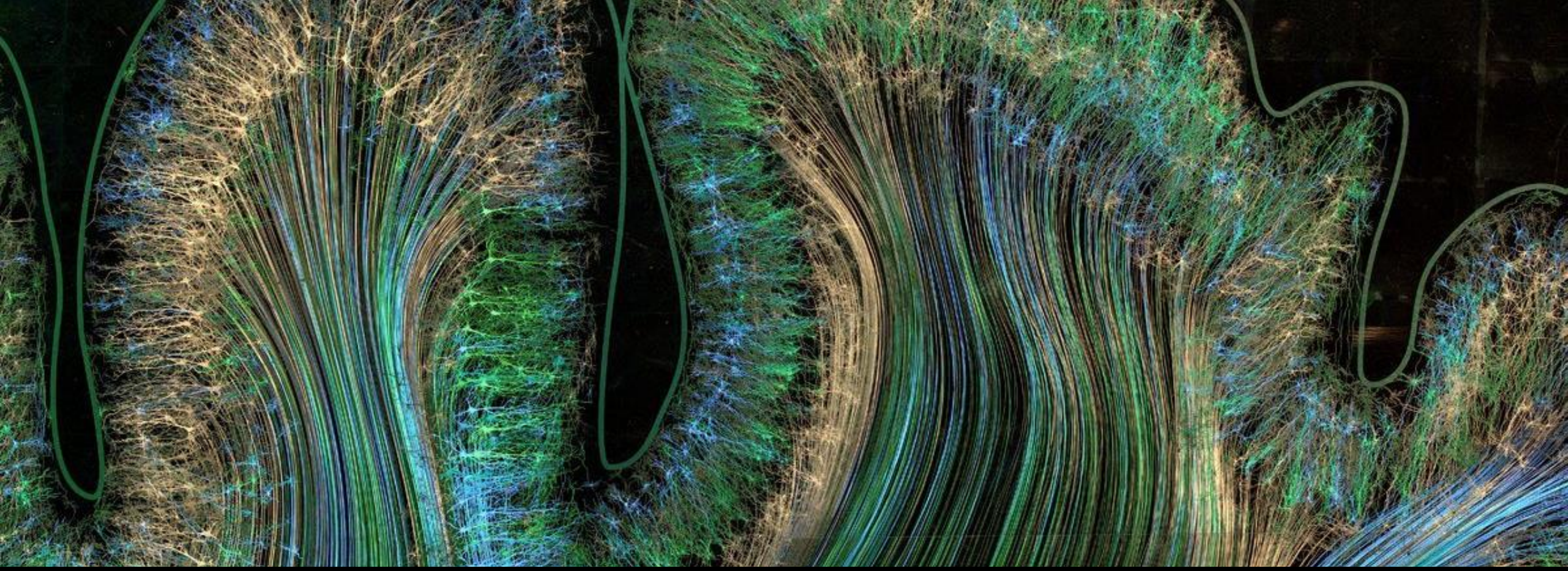

Cortical excitability in a conditional model of PCDH19 Epilepsy

Didi Lamers, PhD student biophysics
Scuola Normale Superiore
Roberta Mezzena, Dr. Silvia Landi, Dr. Gian Michele Ratto

Progress

Courses Scuola Normale Superiore
Introductory Quantum Physics
Fundamentals of Biophysics at the Nanoscale
Biophysical Principles of Neuroscience
Ciclo di Seminari - Scienze Biofisiche
Italian language courses A1 (intensive short course) and B1 at CLI

Conferences and Summer Schools
Neuroscience School of Advanced Studies: Sleep and Cognition
World Conference on PCDH19 - 4th edition
OIST Computational Neuroscience Course
Gordon Research Conference: Inhibition in the CNS

Paper
Perineuronal nets control visual input via thalamic recruitment of cortical PV interneurons *Faini G, Aguirre A, Landi S, Lamers D, Pizzorusso T, Ratto G M, Deleuze C, Bacci A.* eLife 2018;7:e41520

PCDH19 Epilepsy

- Second most clinically relevant genetic cause of epilepsy
- Seizure onset in early infancy
- Frequently associated with ID and ASD
- Caused by mutations in X-Chromosomal gene PCDH19
- Heterozygous females affected, or males with mosaic mutation

Dibbens et al. 2008
Marini et al. 2010

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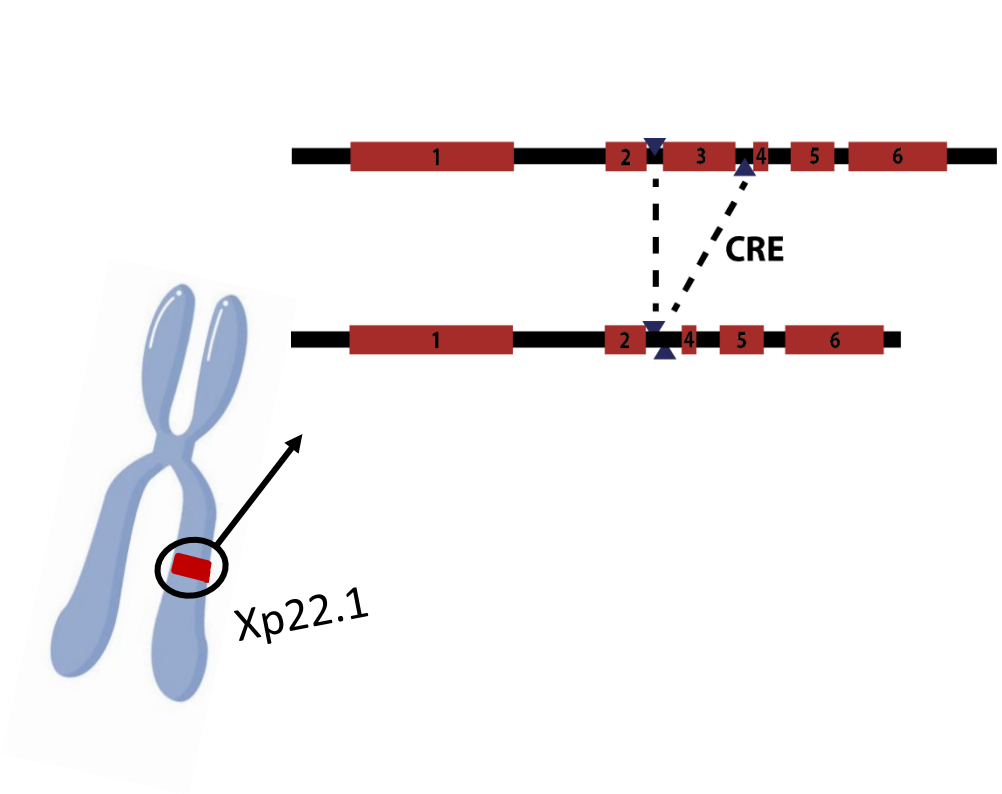
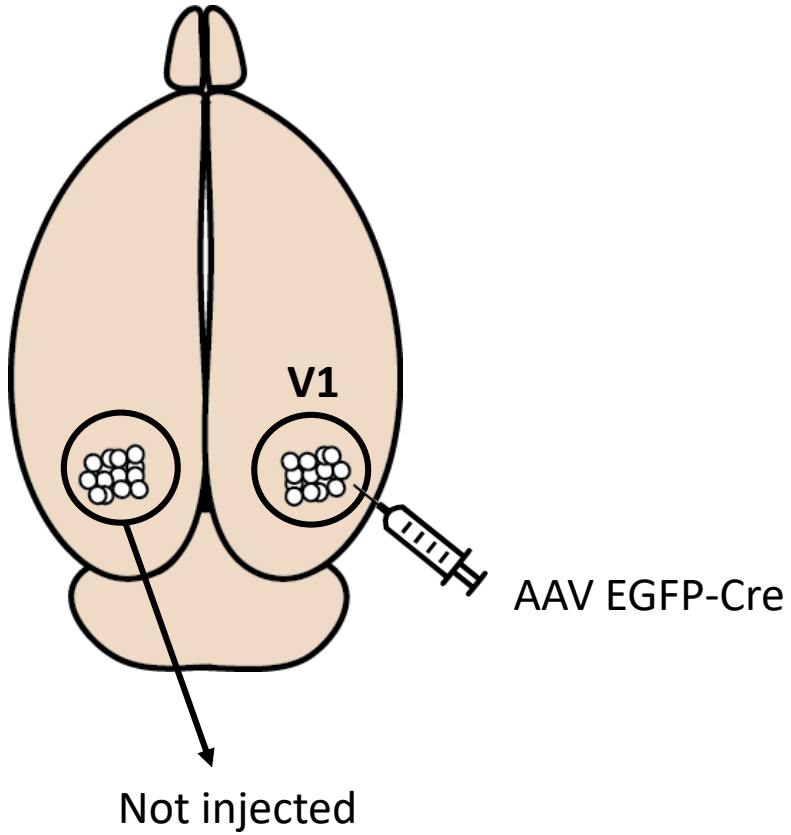
Dibbens et al. 2008
Marini et al. 2010

Virtually nothing known about PCDH19 or how its mosaic expression could cause epilepsy, ID, and ASD

Our aim: using in vivo electrophysiology and 2p-imaging in a novel PCDH19 mouse model to investigate how mosaic PCDH19 expression affects computation

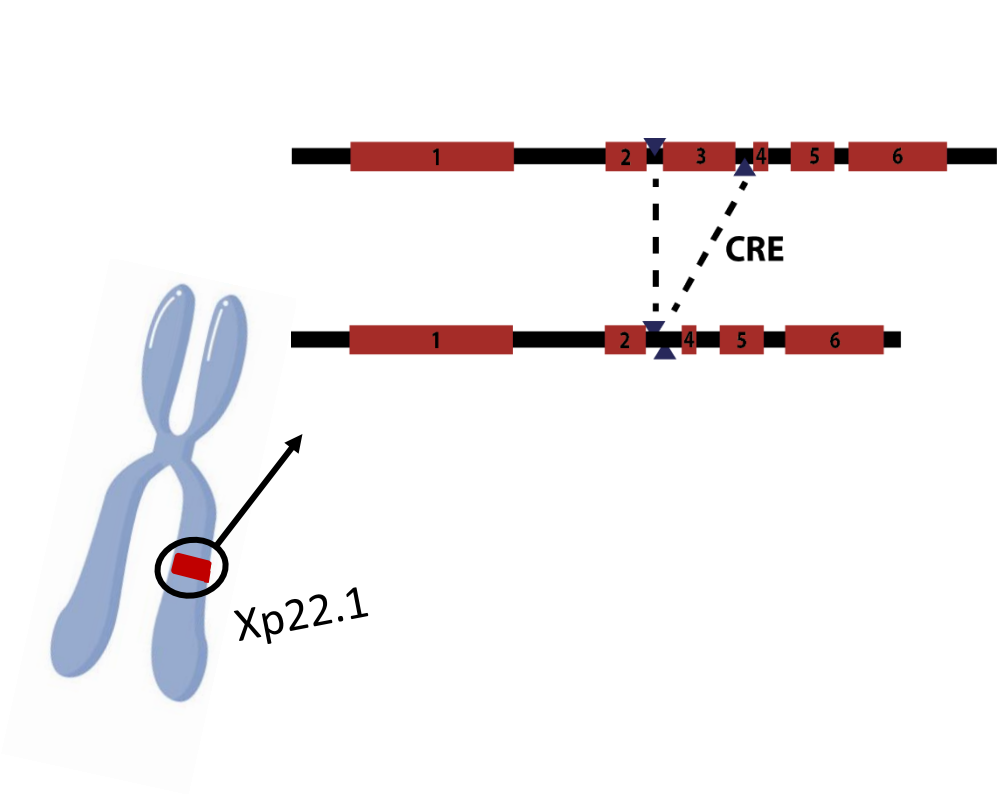
PCDH19 mosaicism in a conditional mouse model

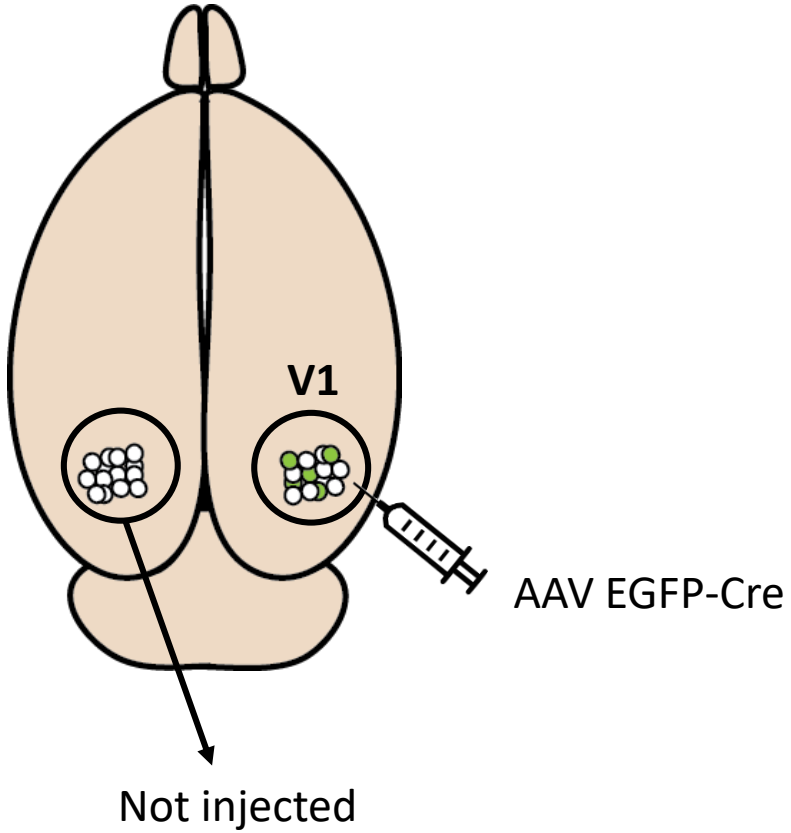




In collaboration with Maria Passafaro and Silvia Bassani, CNR Milan

PCDH19 mosaicism in a conditional mouse model





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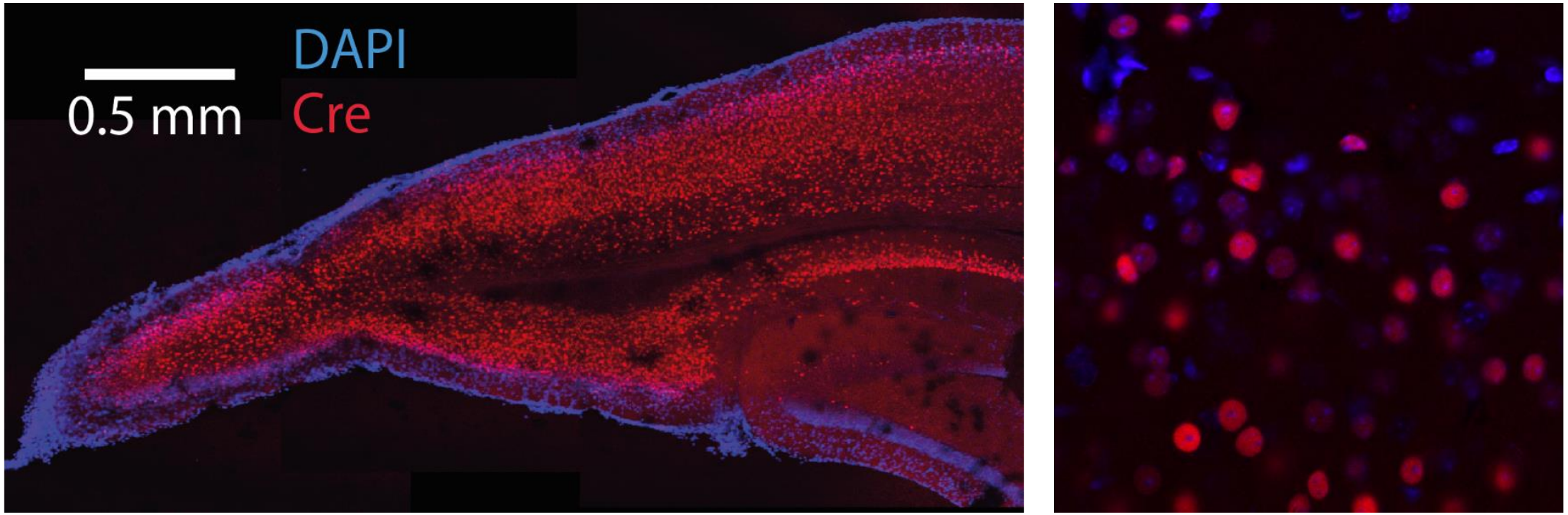
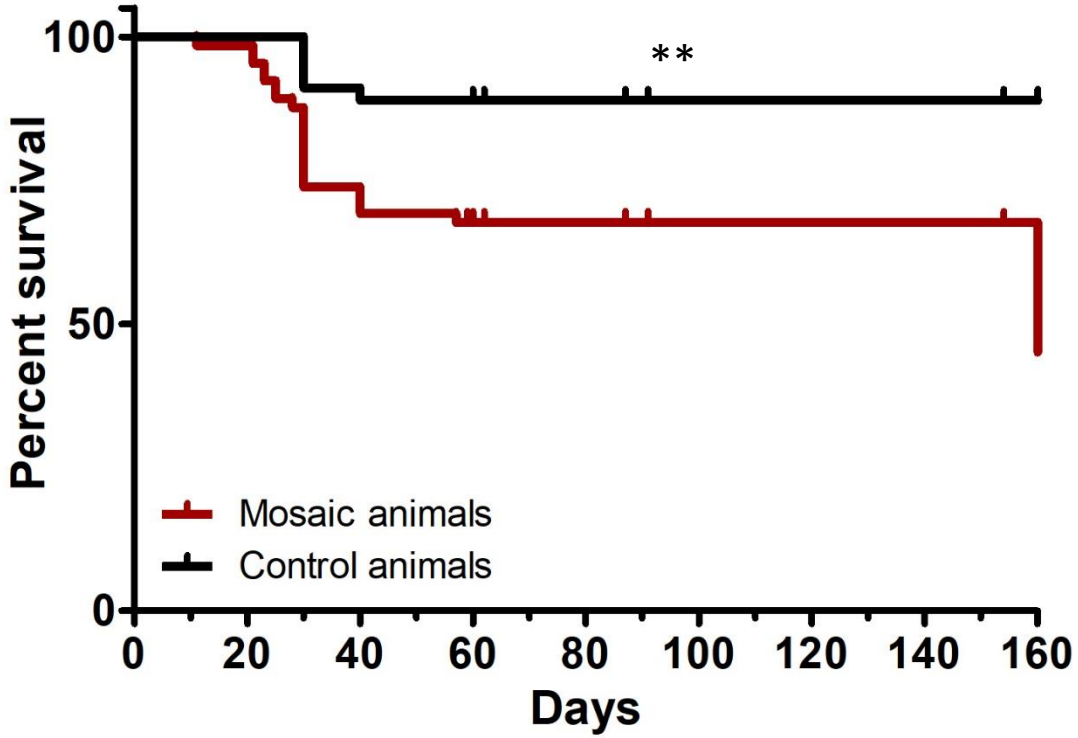
Mosaic PCDH19 expression

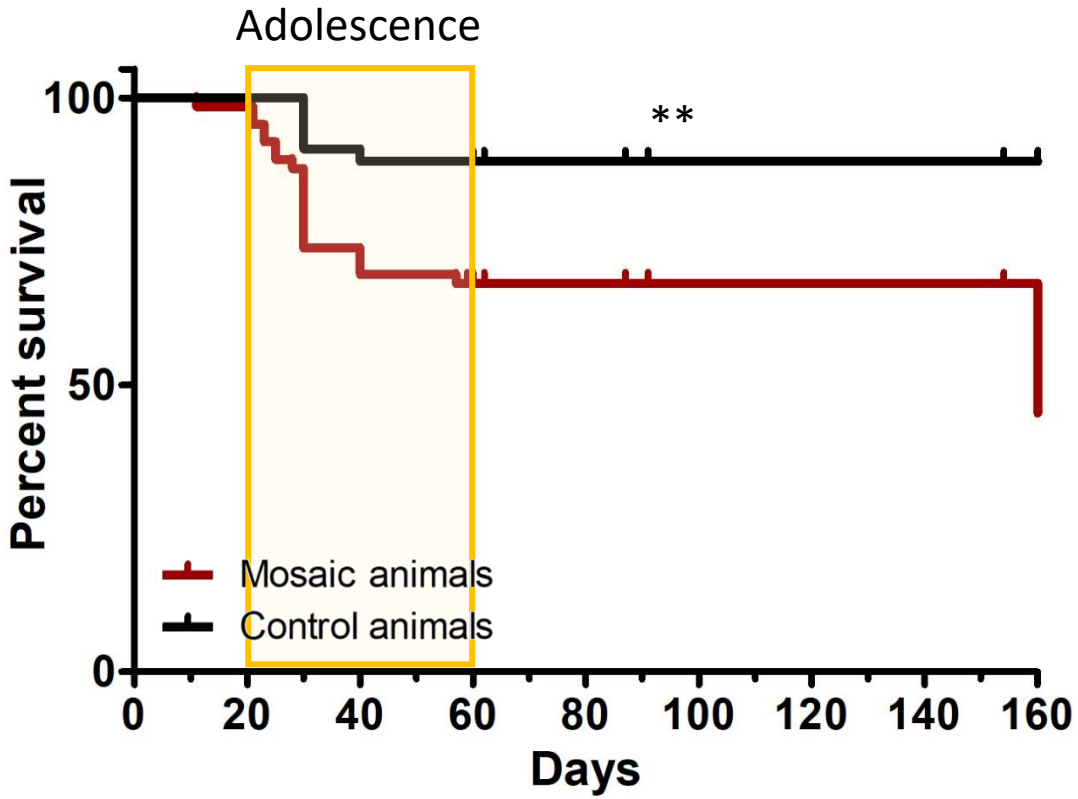


PCDH19 mosaicism increases mortality in adolescence



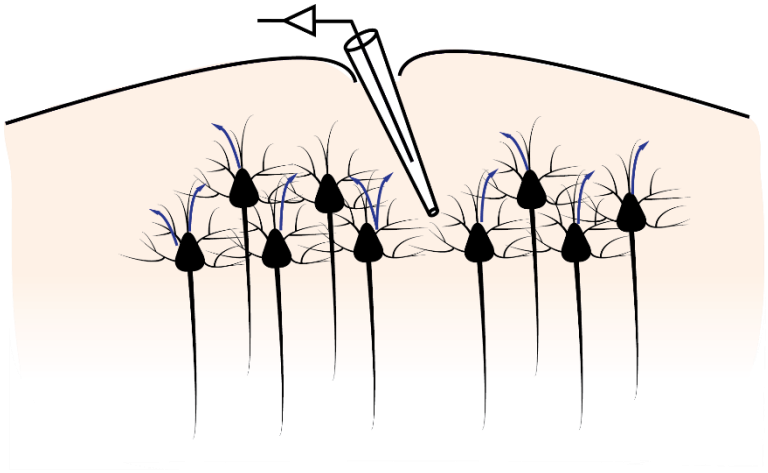
Mantel-Cox (Log-rank) test: P = 0.0062, N = 70 mosaics, N = 48 controls

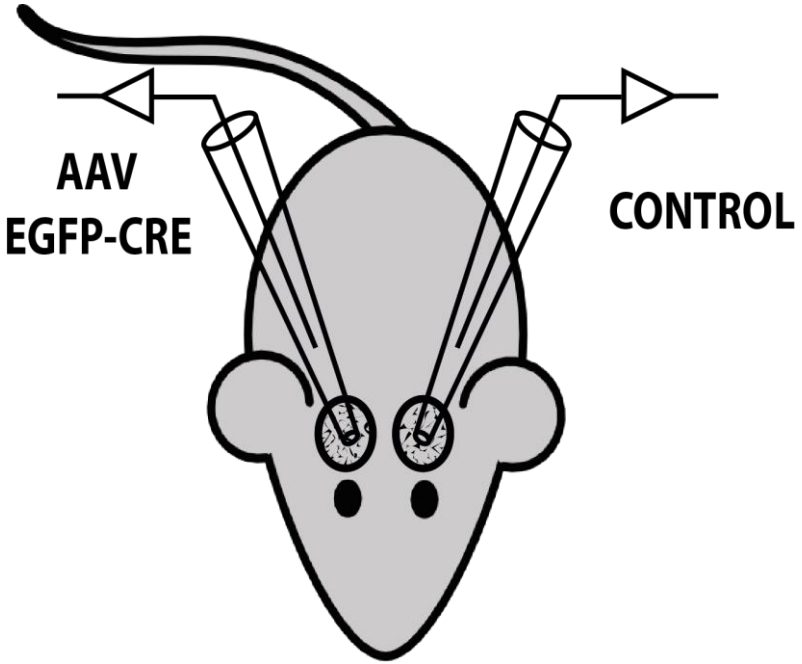
PCDH19 mosaicism increases mortality in adolescence



Mantel-Cox (Log-rank) test: P = 0.0062, N = 70 mosaics, N = 48 controls

Local Field Potential Recordings

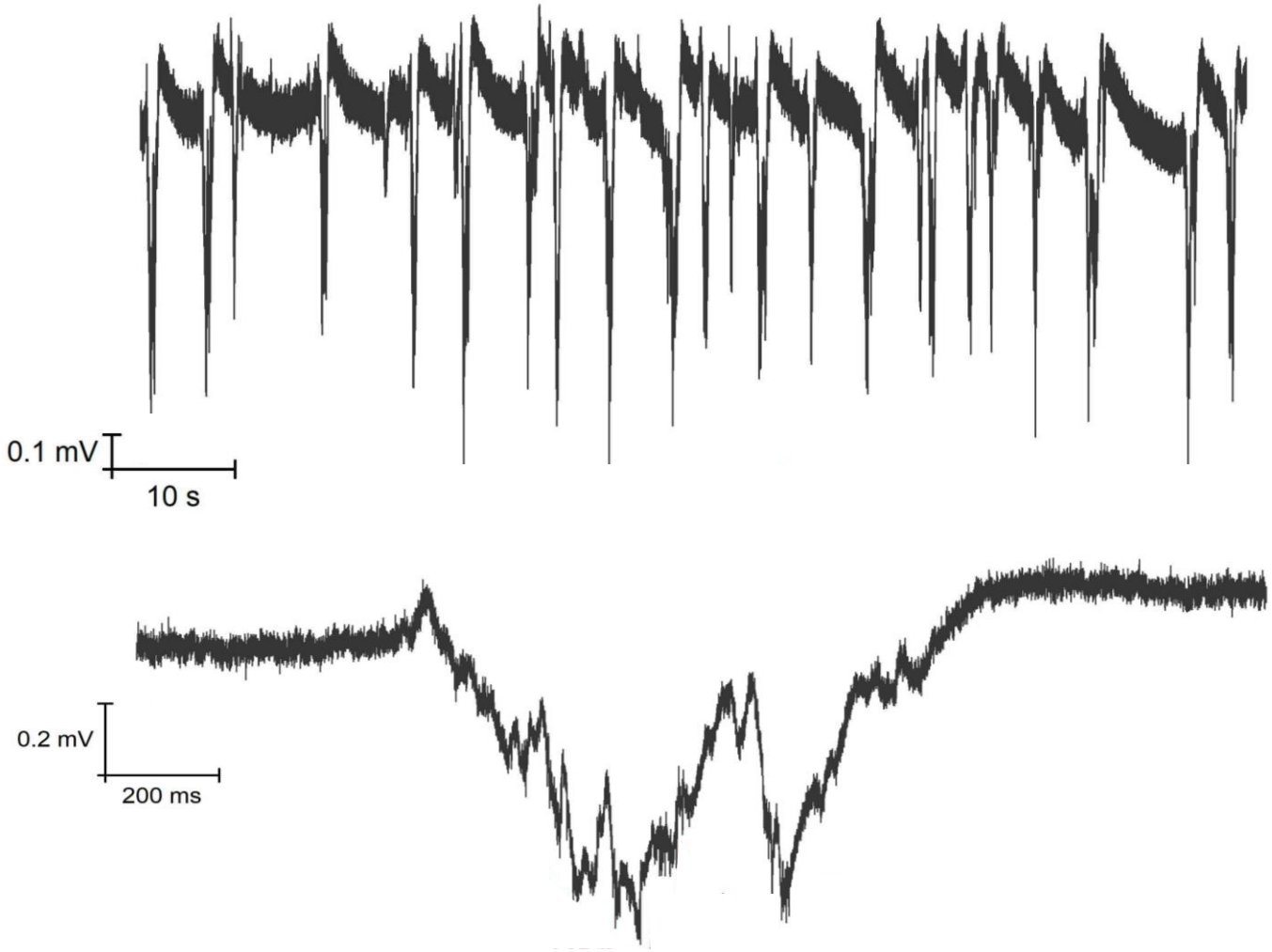




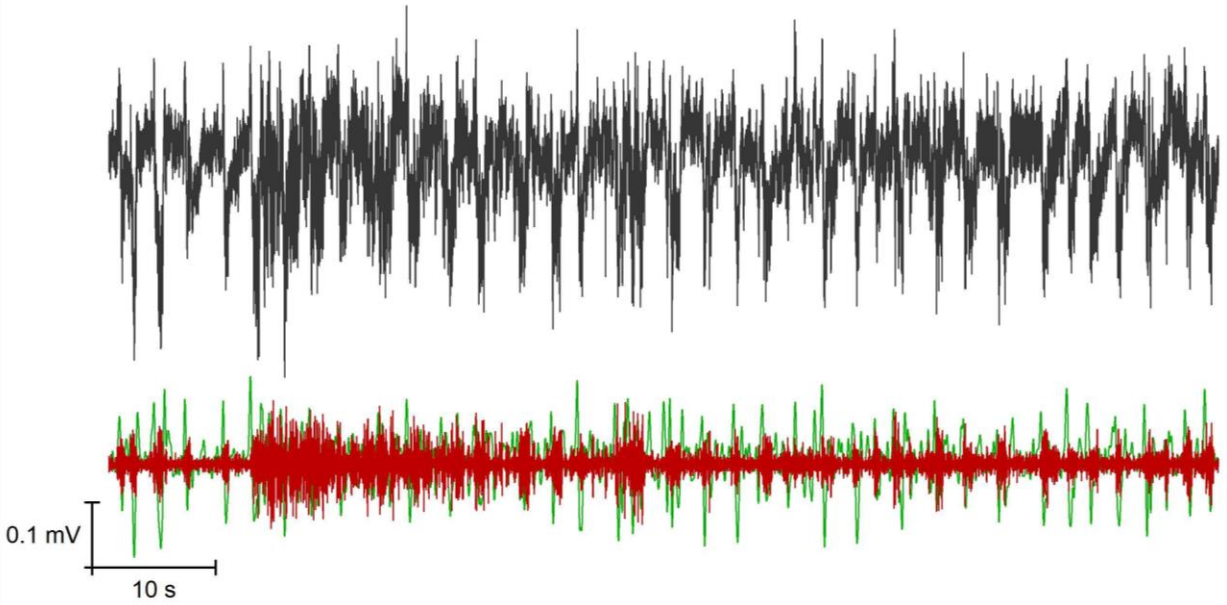
At least 30 days after injection

LFP recordings in anesthetized mice of baseline activity in layer 2/3 of the visual cortex in Cre-injected and control hemispheres

Slow Wave Activity in a control mouse



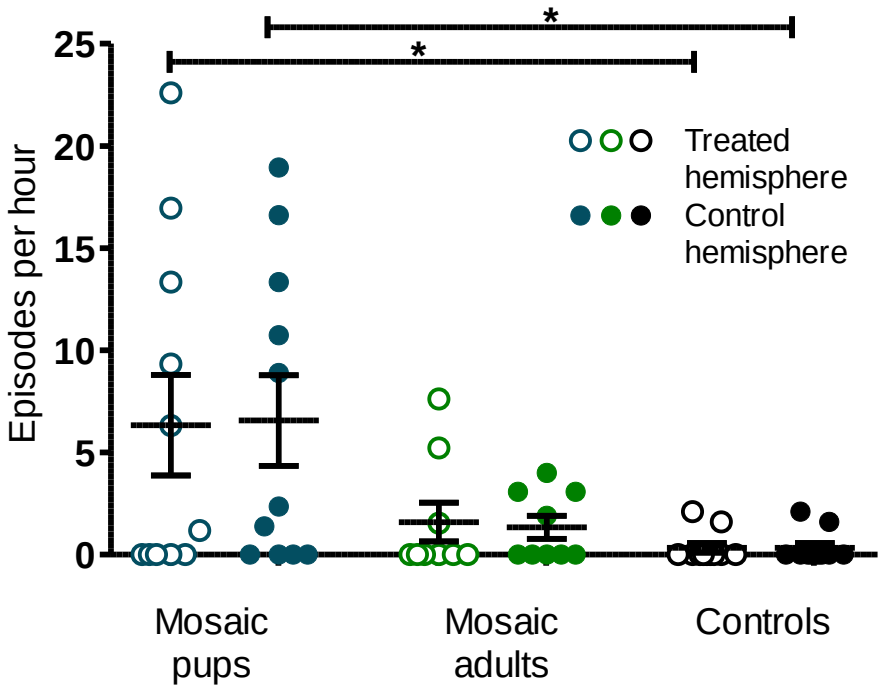
Signs of hyperexcitability: β oscillations



Raw LFP trace

Band-pass filtered signal at 0.5-4 Hz

Band-pass filtered signal at 9-25 Hz

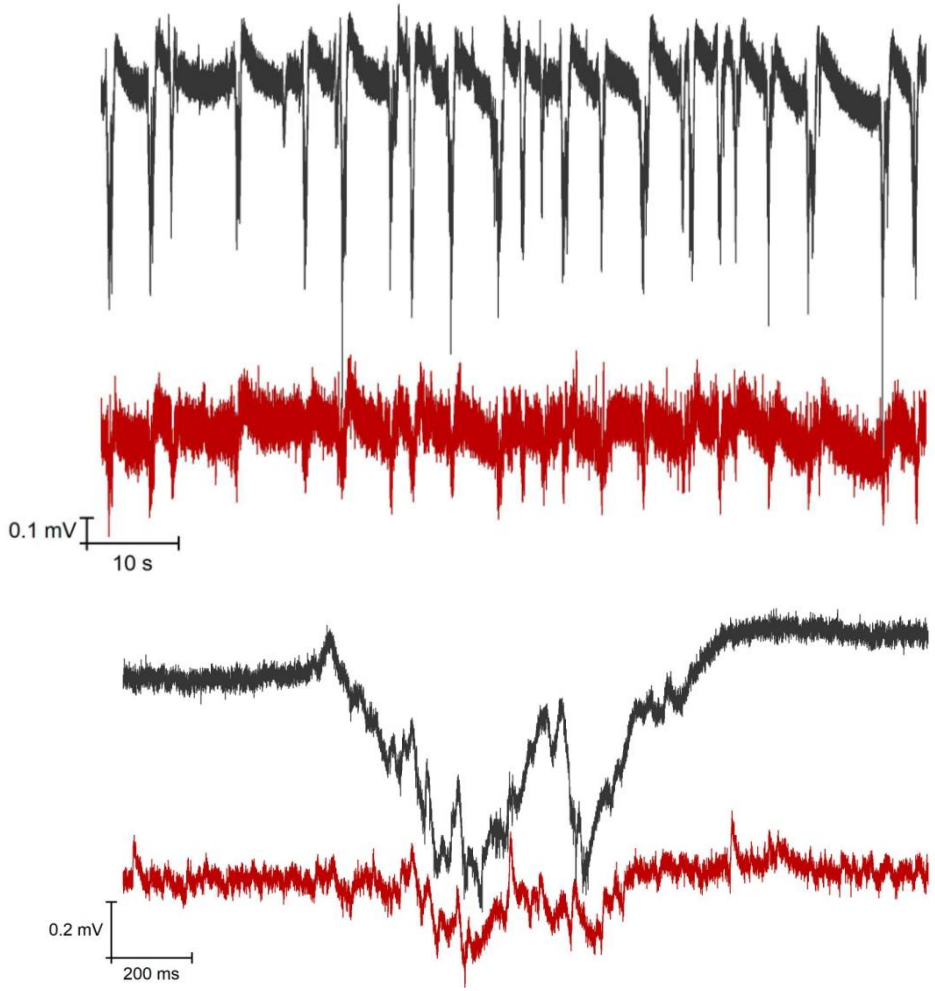


Signs of hyperexcitability: β oscillations

- Epileptiform activity spreads from the mosaic patch (the likely induction site) to the opposite hemisphere

- Our mouse model can be useful to study aberrant network activity in PCDH19 Epilepsy

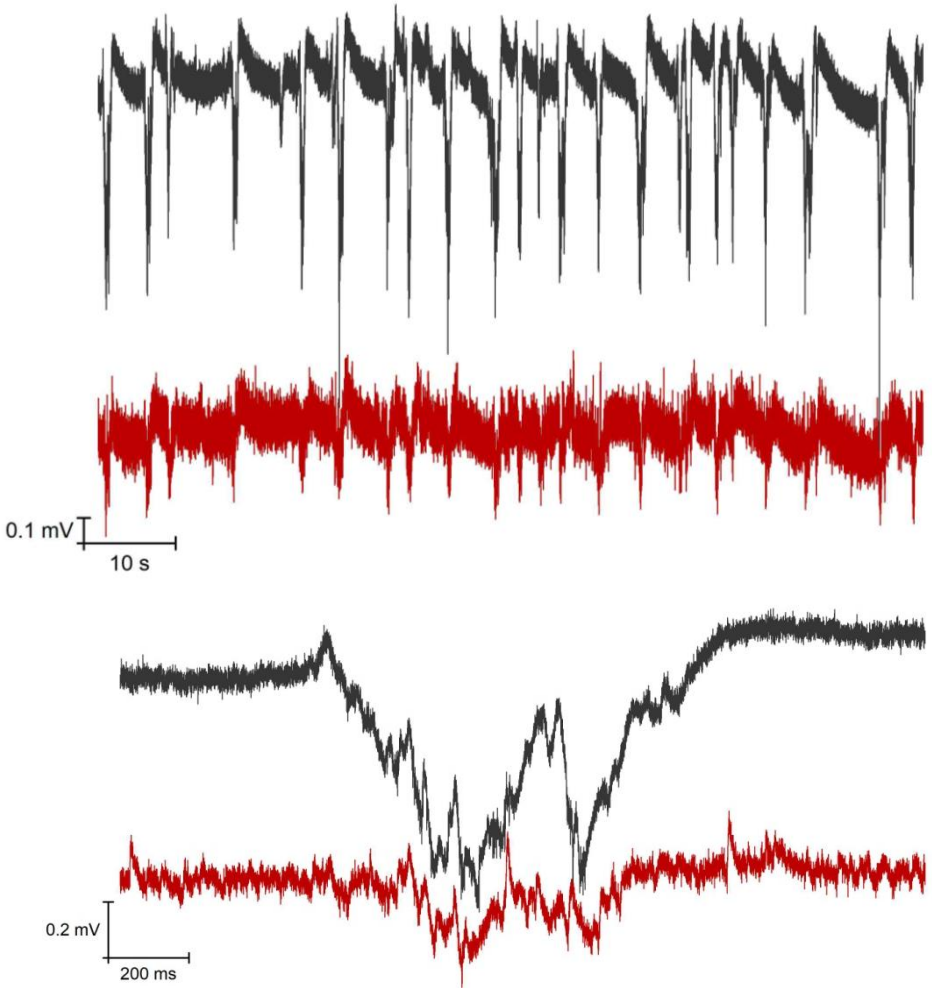
Disrupted Slow Wave Activity



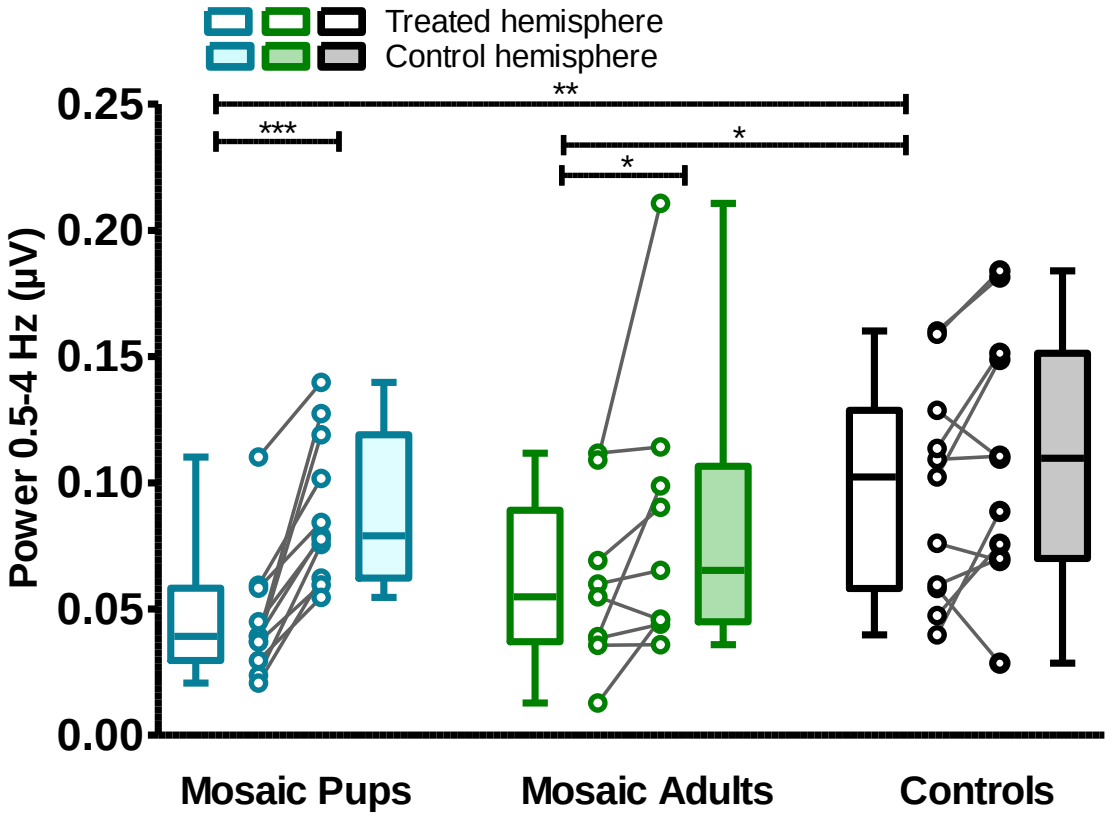
Control hemisphere

Treated hemisphere

Disrupted Slow Wave Activity

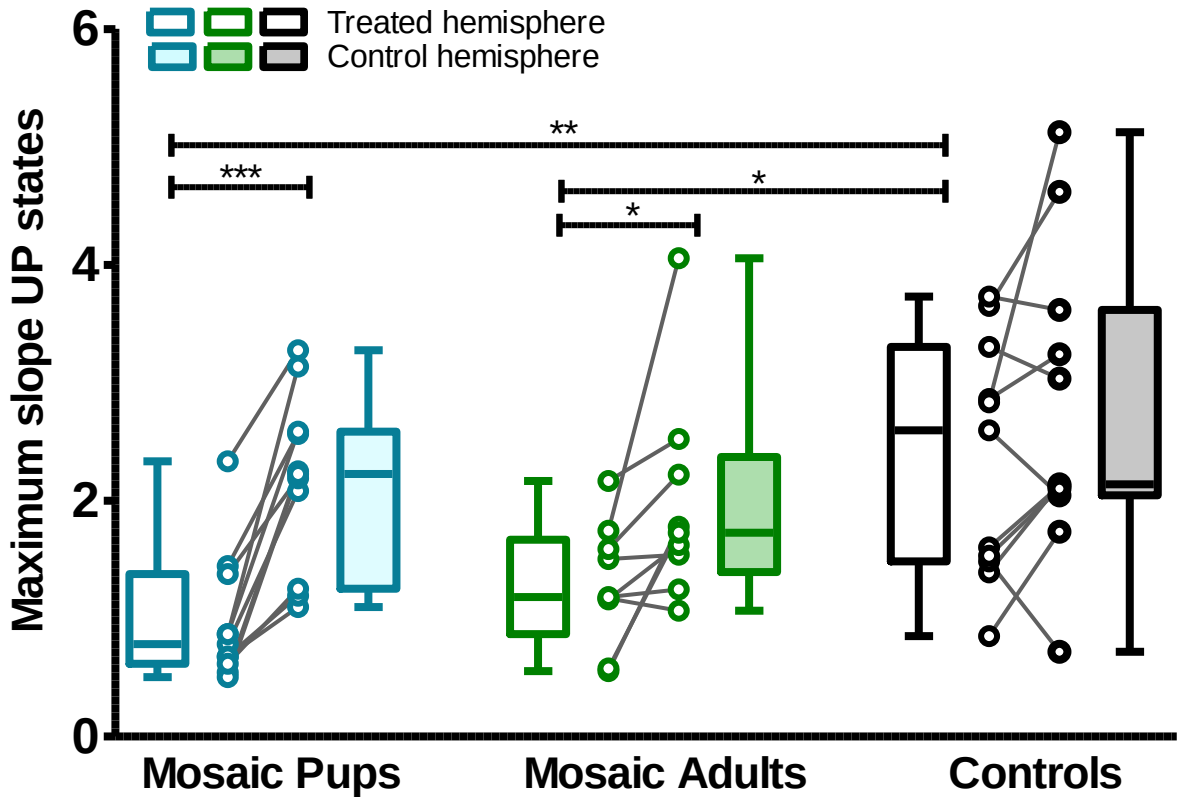


Control hemisphere
Treated hemisphere



How to explain disrupted SWA?

Reduction in slope hints at less connected network



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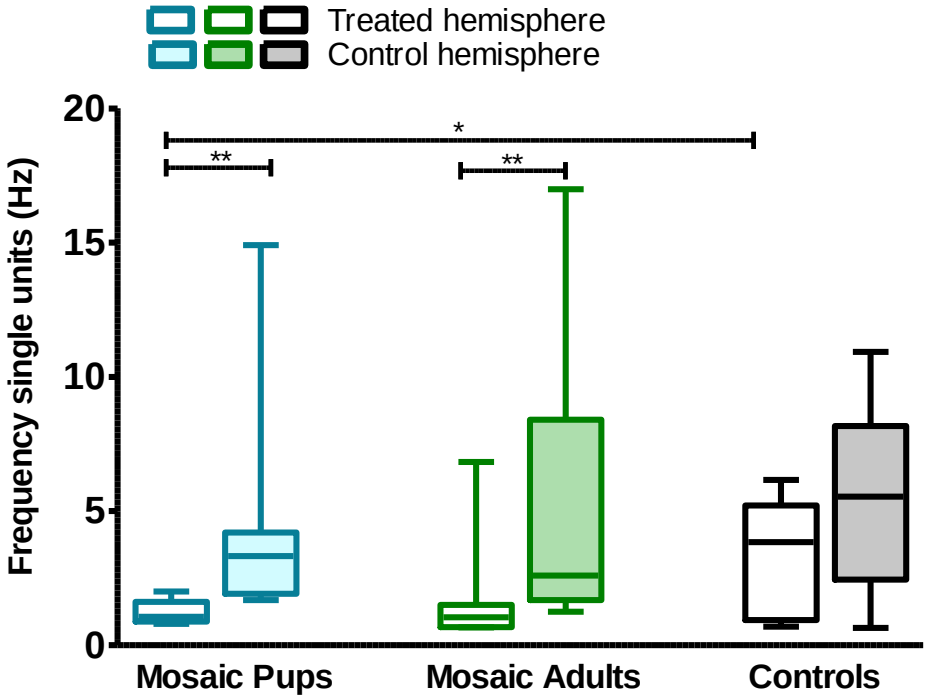

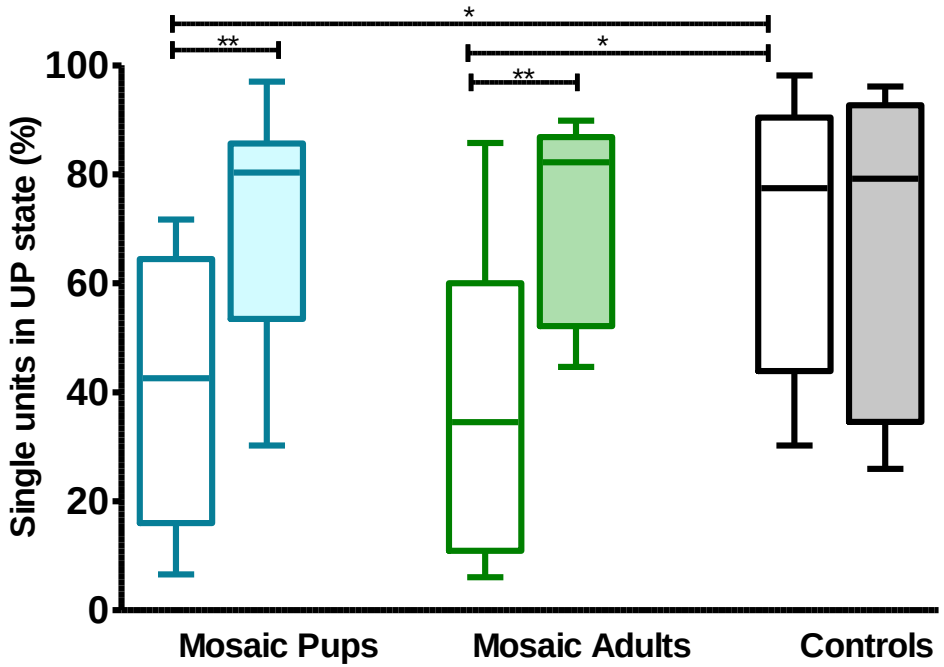

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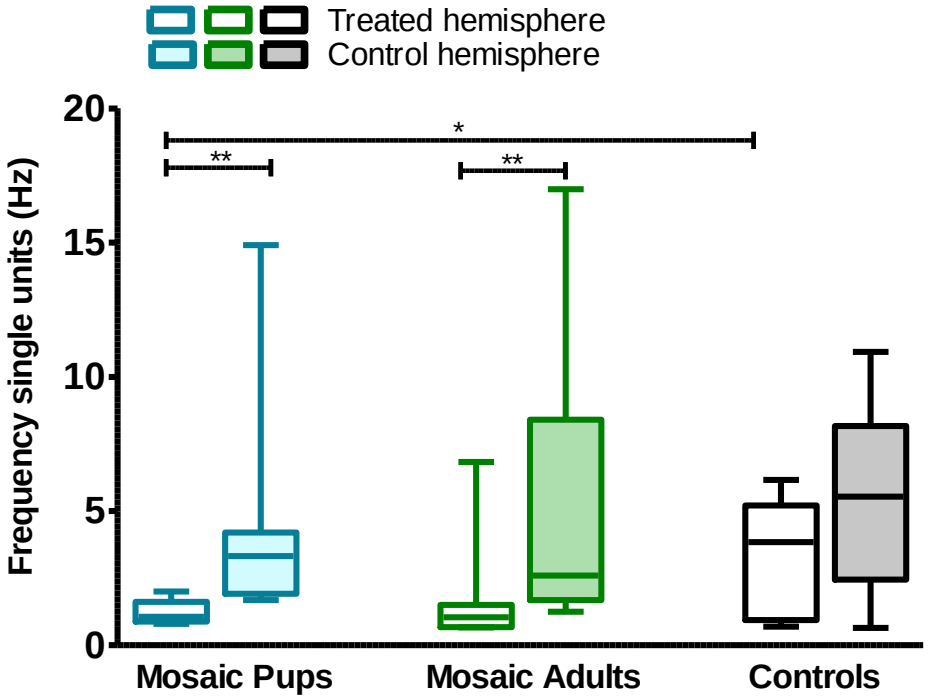
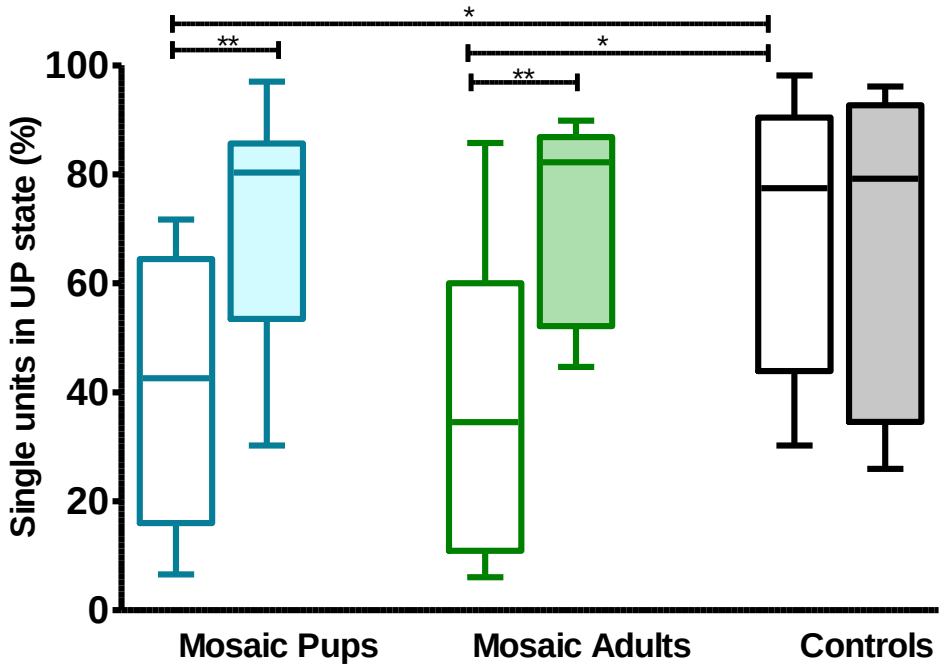
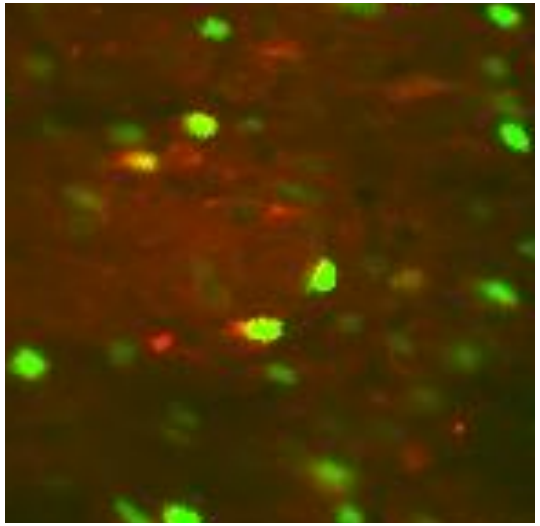




In agreement with a reduced network strength: reduced firing and network synchronization

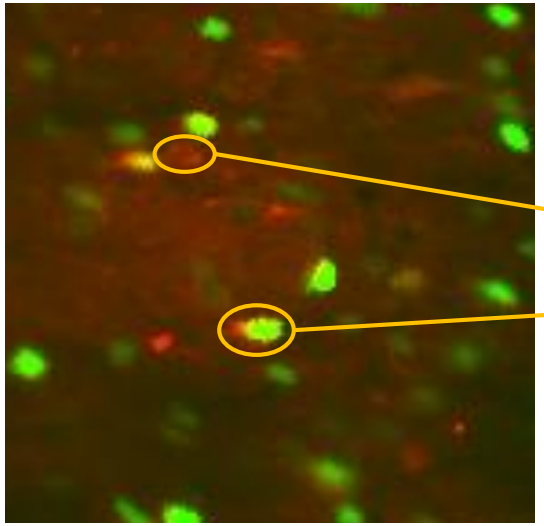
But: what about the transient episodes of hyperexcitability?

Combined calcium imaging and LFP recordings in vivo

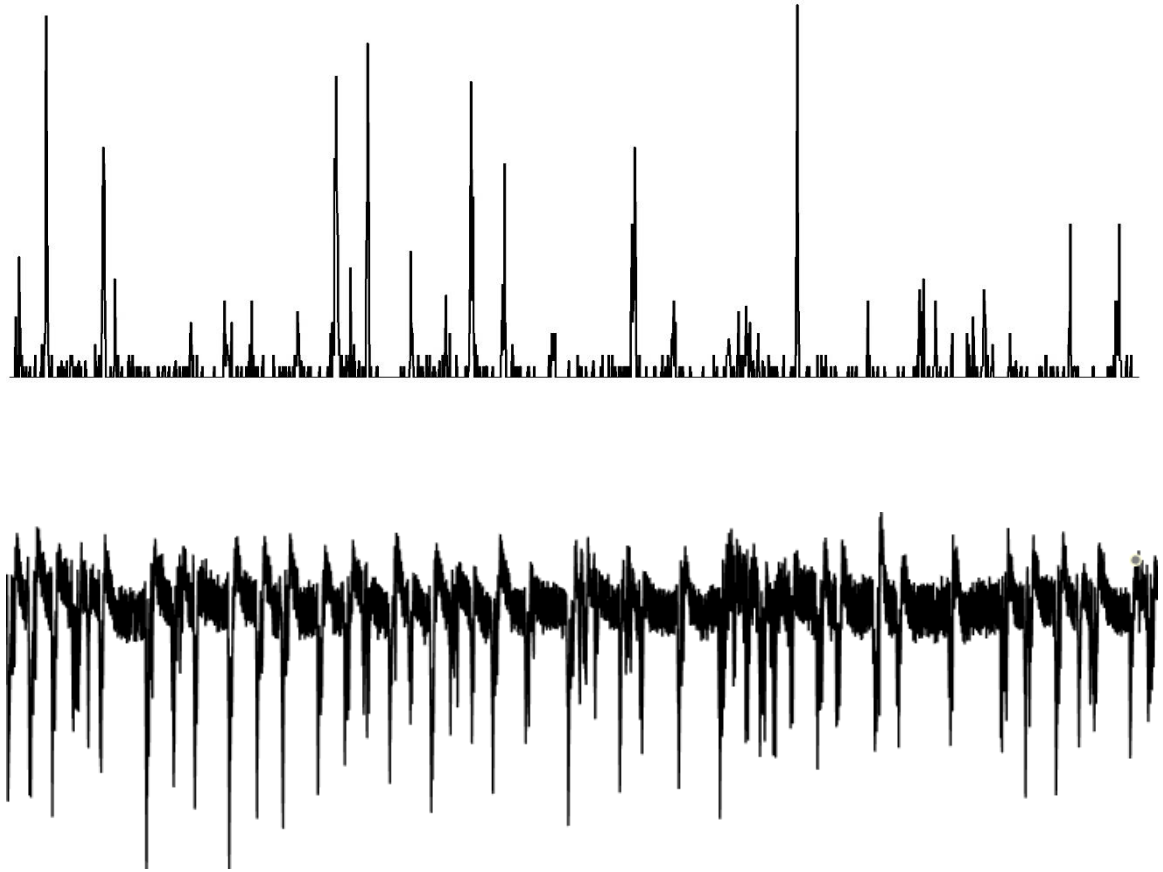


30 µm

Combined calcium imaging and LFP recordings in vivo



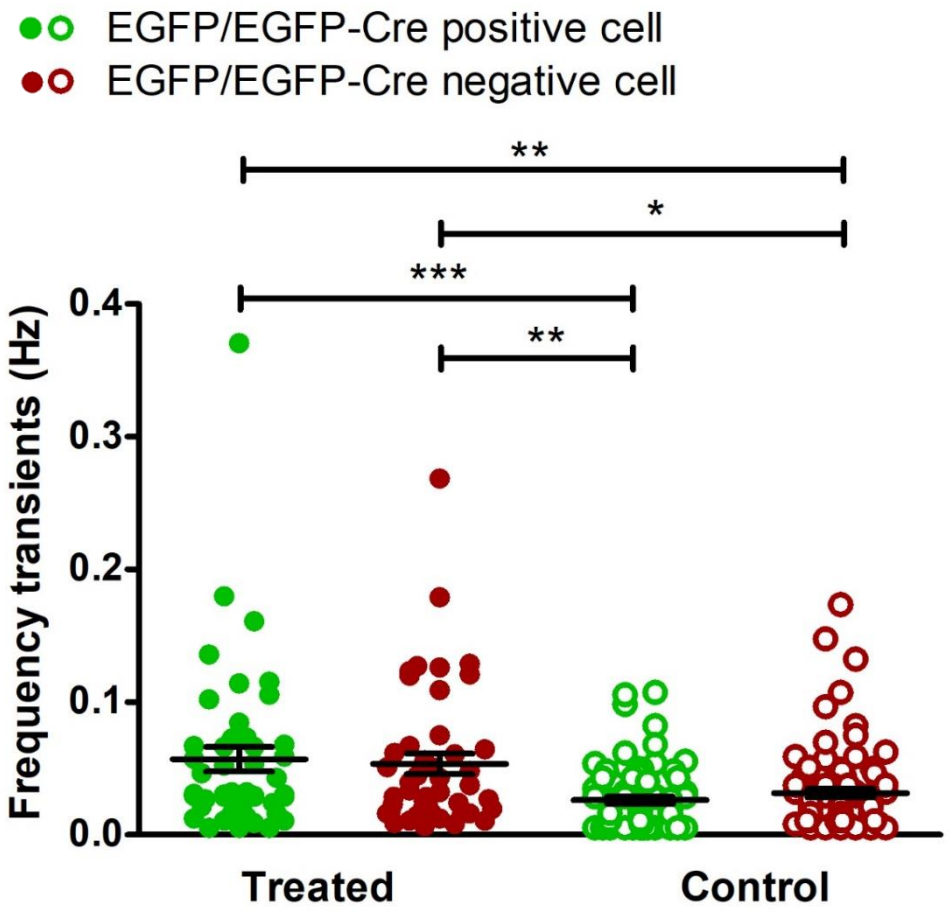
30 µm



Combined calcium imaging and LFP recordings in vivo

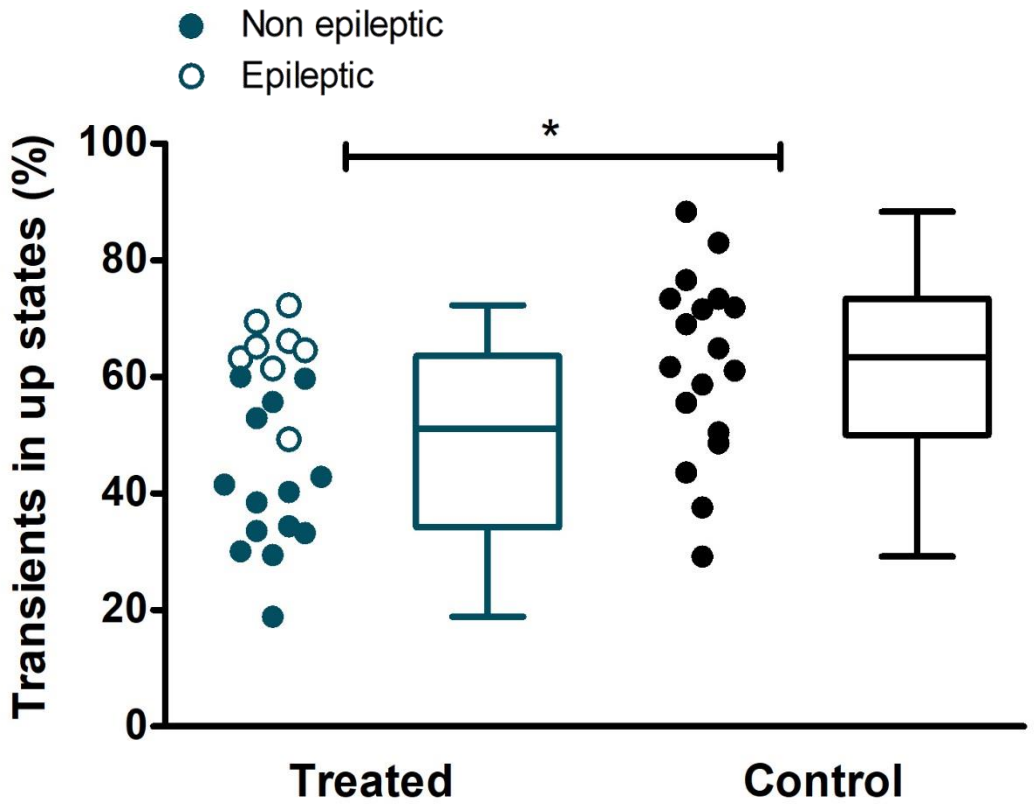
On average higher activity in mosaic animals, but also a larger variance of activity

Increase from 6.3% (control green) to 28.3% (treated green) of hyperactive cells
(> 4 transients per minute, Busche et al. Science 2008)



Combined calcium imaging and LFP recordings in vivo

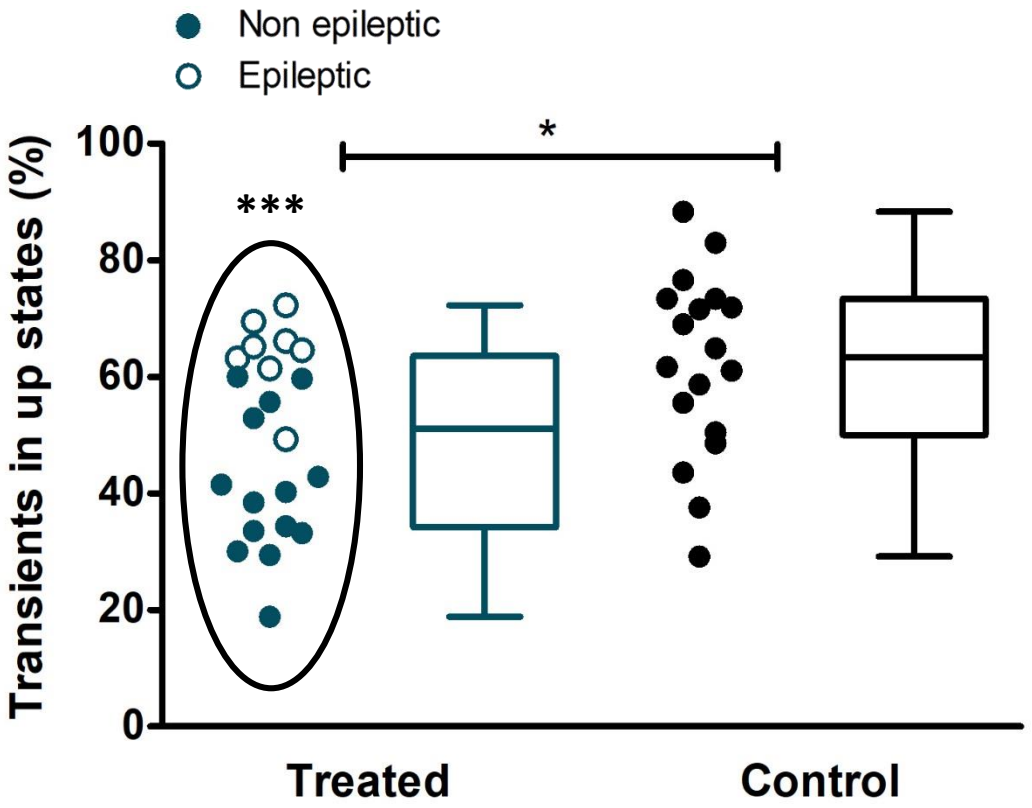
Mosaic animals have a reduced synchronicity to slow waves.



Combined calcium imaging and LFP recordings in vivo

Mosaic animals have a reduced synchronicity to slow waves.

Animals with ‘β oscillations’ have a significantly higher synchronized activity than other mosaic animals



Conclusions

- Our mouse model displays signs of hyperexcitability
- SWA is disrupted in a mosaic PCDH19 brain
- PCDH19 is not merely a developmental disease
- Mosaic network less synchronized and with a larger variation of activity?

Thank you!

Roberta Mezzena, Silvia Landi, Maria Passafaro, Silvia Bassani, Gian Michele Ratto