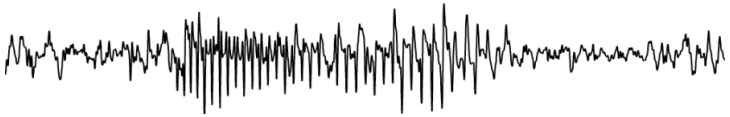
Targeting Voltage-Gated Sodium Channels for the Treatment of Epilepsy



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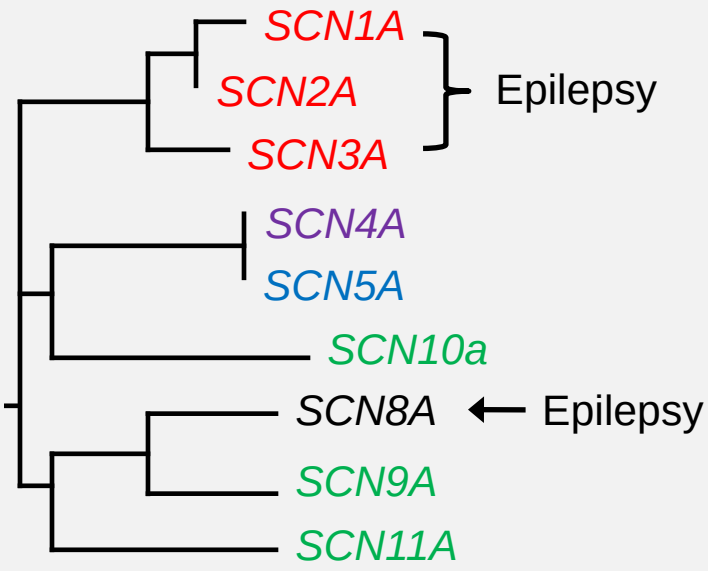
Epilepsy Overview

- Excessive neuronal activity and hypersynchrony
- Affects ~3-4% of people in their lifetime
- Genetic vs. symptomatic epilepsy
- Co-morbidities are common in epilepsy
- ~30% of patients do not respond well current treatments

CURE
Citizens United for Research in
EPILEPSY

Background: Voltage-gated sodium channel (VGSC) epilepsies

VGSC genes: Epilepsy risk genes

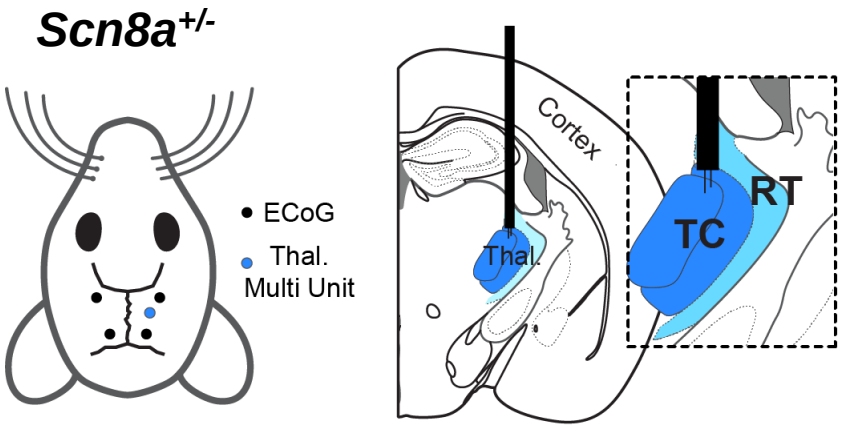


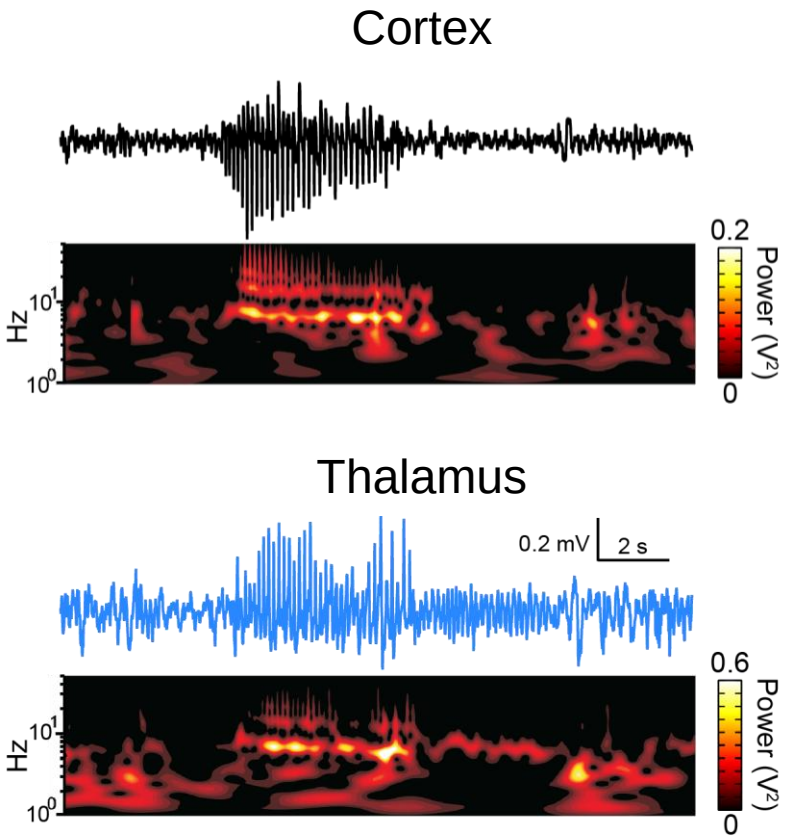
Red – Brain
Purple – Skeletal Muscle
Blue – Heart
Green – PNS
Black - Ubiquitous

VGSC blockers: Antiepileptic drugs

Phenytoin
Carbamazepine
Lamotrigine
Felbamate
Topiramate
Oxcarbazepine
Zonisamide
Rufinamide
Lacosamide
Eslicarbazepine acetate

Thalamocortical seizures by loss of *Scn8a*

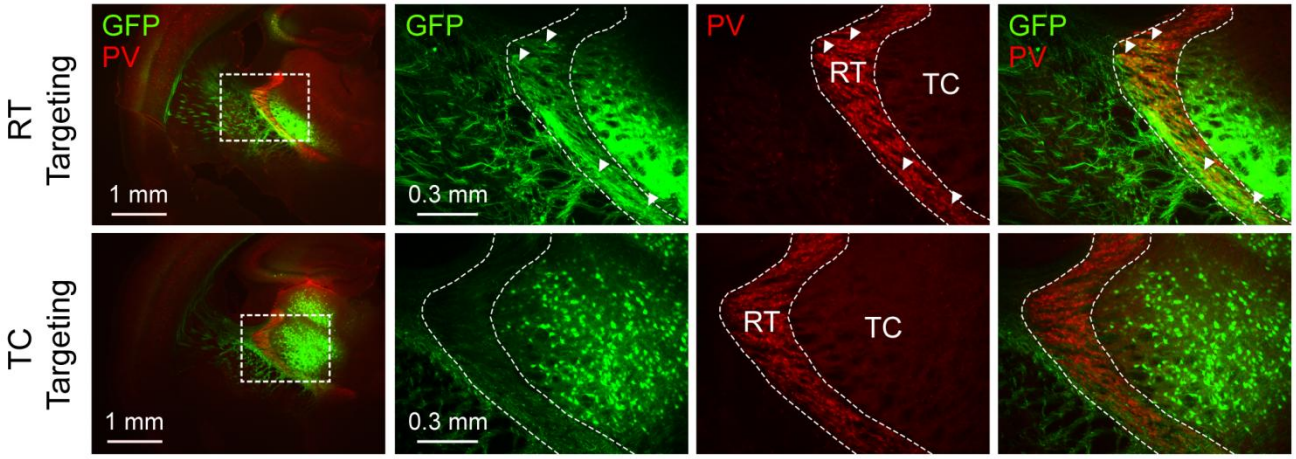




Absence seizures detected in the cortex and thalamus

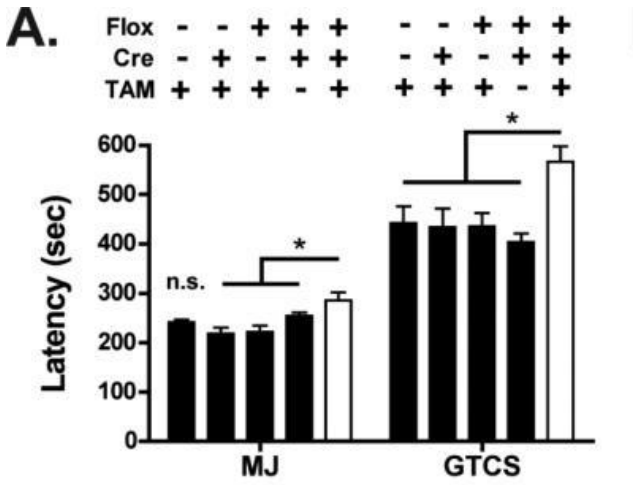
Makinson et al., *Neuron* 2017

Knockdown of *Scn8a* in RT causes thalamocortical seizures



Makinson et al., *Neuron* 2017

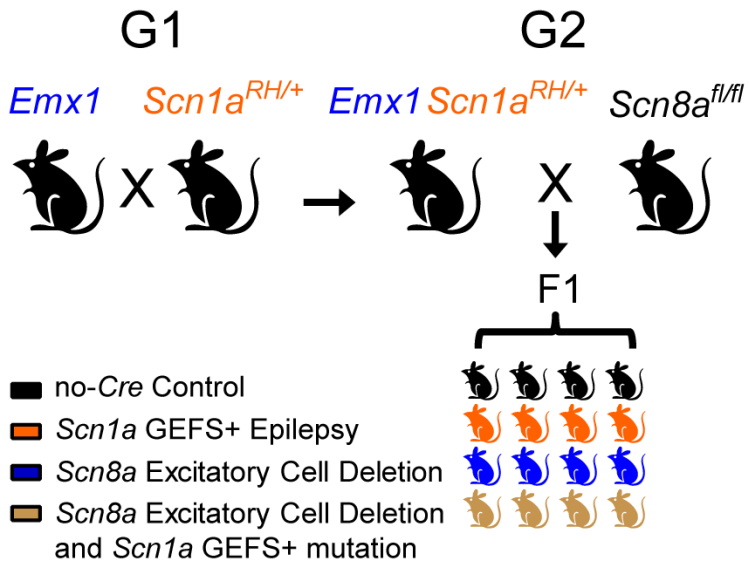
Targeting *Scn8a* in adult animals confers resistance to proconvulsants



Makinson et al., *Neurobiol Dis 2014*

Deletion of *Scn8a* confers resistance to *Scn1a* epilepsies

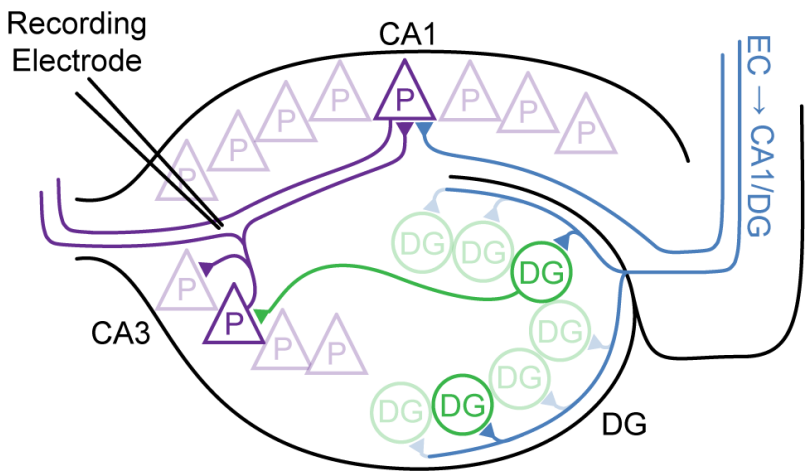
A.

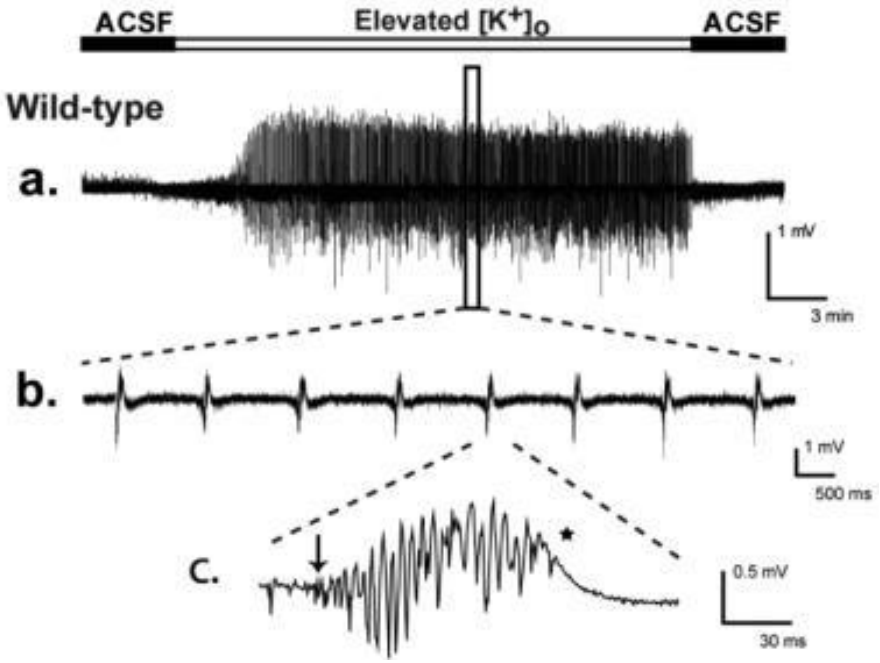


Makinson et al., *Neuron* 2017

Targeting *Scn8a* for the treatment of temporal lobe epilepsy

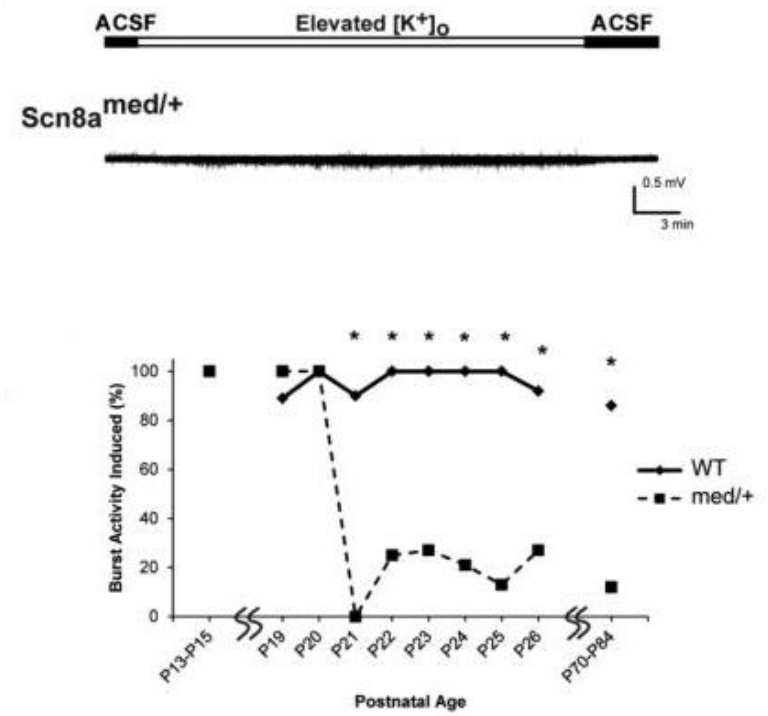
Hippocampus slice





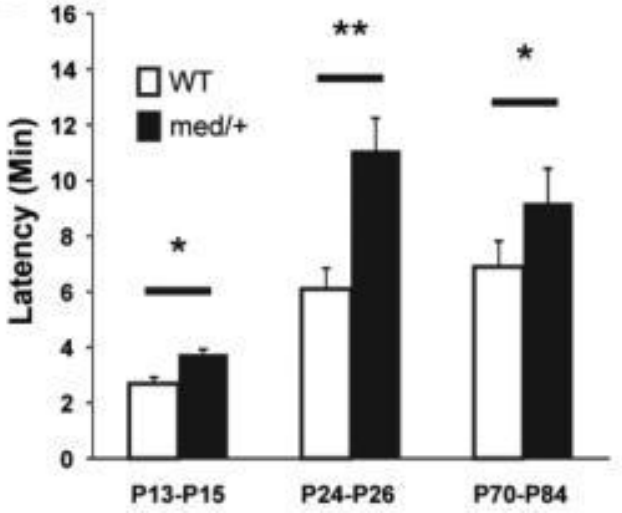
Makinson et al., *Neurobiol Dis 2014*

Targeting *Scn8a* reduces epileptiform hippocampal bursting *in vitro*



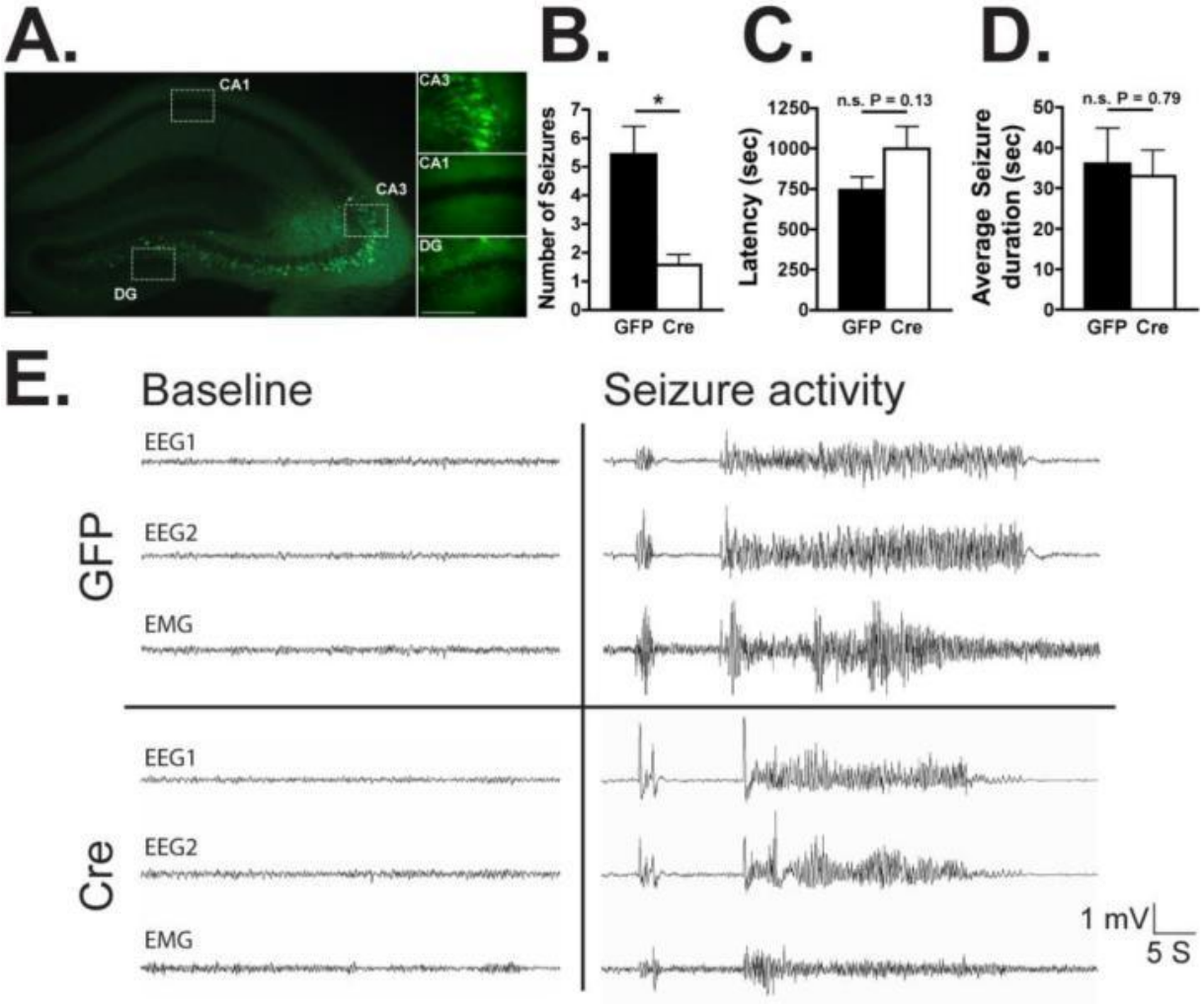
	P13-P15		P19	P20	P21	P22	P23	P24	P25	P26		P70-P84
WT	100 % (5, 2)		89 % (9, 3)	100 % (9, 3)	90 % (10, 5)	100 % (11, 4)	100 % (8, 3)	100 % (10, 4)	100 % (8, 3)	92 % (12, 4)		86 % (7, 4)
med/+	100 % (4, 2)		100 % (5, 2)	100 % (4, 2)	0 % (6, 3)	25 % (8, 7)	27 % (11, 4)	21 % (14, 5)	13 % (16, 5)	27 % (15, 4)		12% (17, 6)

(# of slices, # of mice)



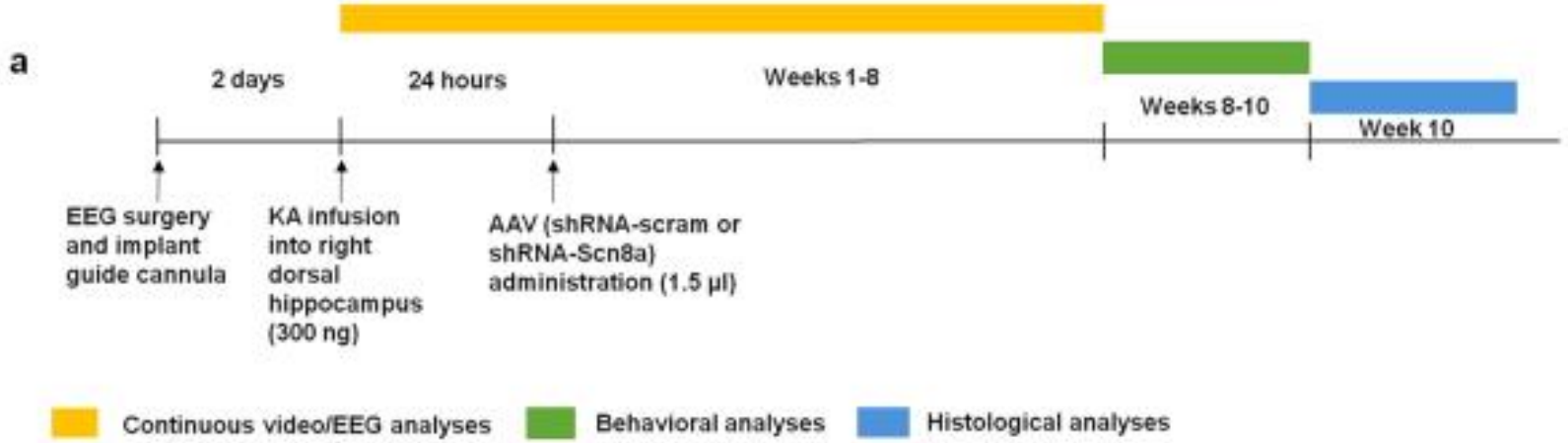
Makinson et al., *Neurobiol Dis 2014*

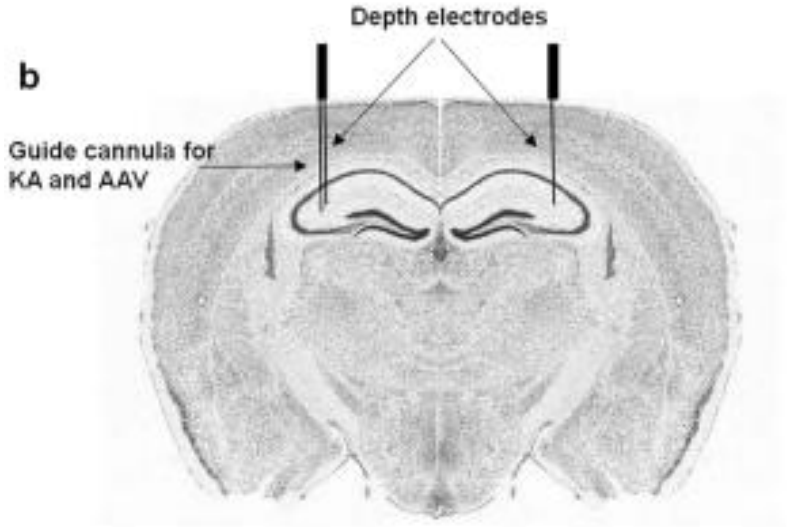
Targeting *Scn8a* in the hippocampus reduces seizures *in vivo*

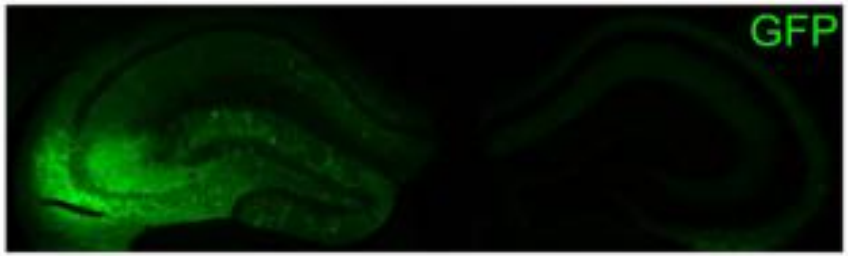


Makinson et al., *Neurobiol Dis 2014*

Targeting *Scn8a* in treatment-resistant temporal lobe epilepsy

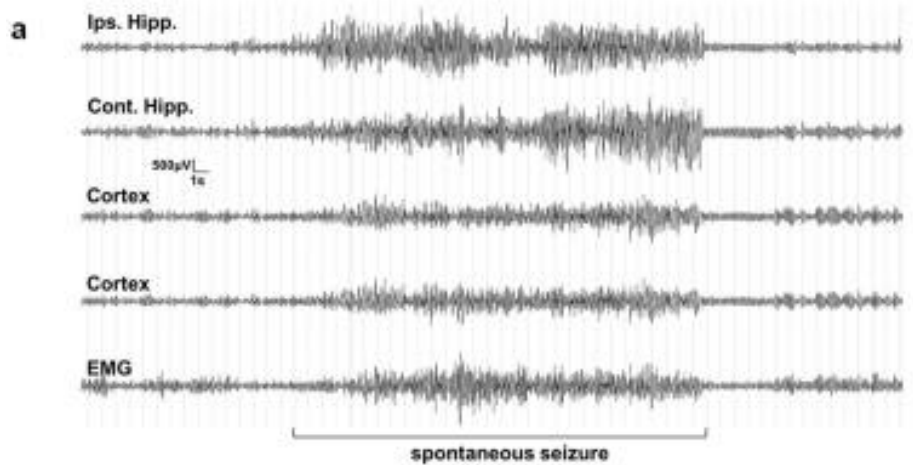






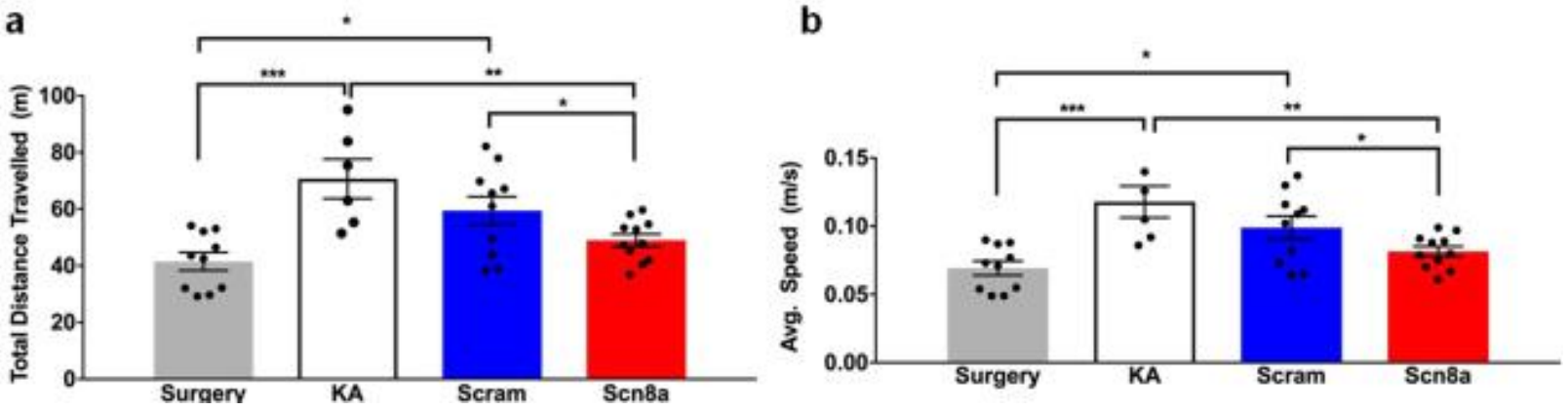
Wong, Makinson et al., *Scientific Reports* 2018

Targeting *Scn8a* in treatment-resistant temporal lobe epilepsy



Wong, Makinson et al., *Scientific Reports* 2018

Targeting *Scn8a* in treatment-resistant temporal lobe epilepsy



Wong, Makinson et al., *Scientific Reports* 2018

Conclusions

↓ *Scn8a* in cortical circuits leads to widespread reductions in neural excitability and ↓ convulsive seizures

↓ *Scn8a* in the thalamus leads to ↑ non-convulsive thalamocortical seizures

↓ *Scn8a* selectively in the hippocampus is an effective seizure control strategy in models of temporal lobe epilepsy

Some side effects can be avoided using a brain region and cell-type selective targeting strategy

Viral-mediated RNAi approaches may represent a viable alternative to pharmacology for difficult classes of therapeutic targets (e.g. VGSCs)

Acknowledgements

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