The vicious circle between neuronal hyperexcitability and AD

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Alzheimer's disease and seizures

- Epilepsy is a common condition in the elderly
  1.1/1000 ages 65-69
  1.6/1000 ages >80
- Prevalence of epilepsy in Alzheimer's disease(AD) is significantly higher (~8-fold) than in age-matched control populations (Scarmeas N et al., Arch Neurol 2009)
- Risk of epilepsy is particularly high in FAD patients with early-onset dementia:
  - seizures (16-67 %), highest in *APP* duplication
  - myoclonus (9- 31 %), highest in *PSEN1* mutation

  (Vossel K, Lancet Neurology 2017)

Epileptic seizures – the tip of an iceberg ?

seizures

hyperexcitability

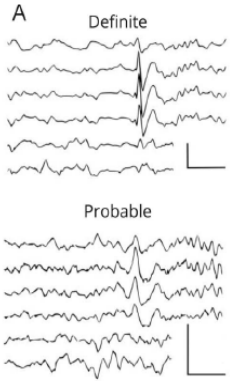
Subclinical epileptiform spiking during sleep is common in early-stage AD

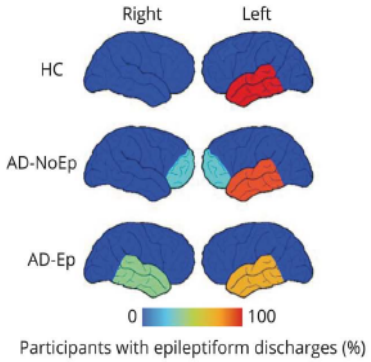
So far, three overnight EEG studies on AD patients have been reported:

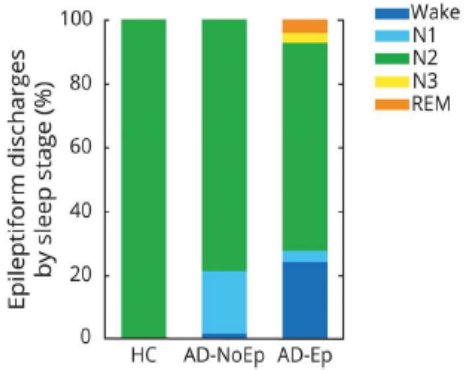
AD 42%, Healthy controls 11%
Vossel K et al., Arch Neurol 2016

AD 22 -53 %, Healthy controls 5%
Lam A et al., Neurology 2020

AD 54 %, Healthy controls 25%
Horvath A et al., Clin Neurophys 2021

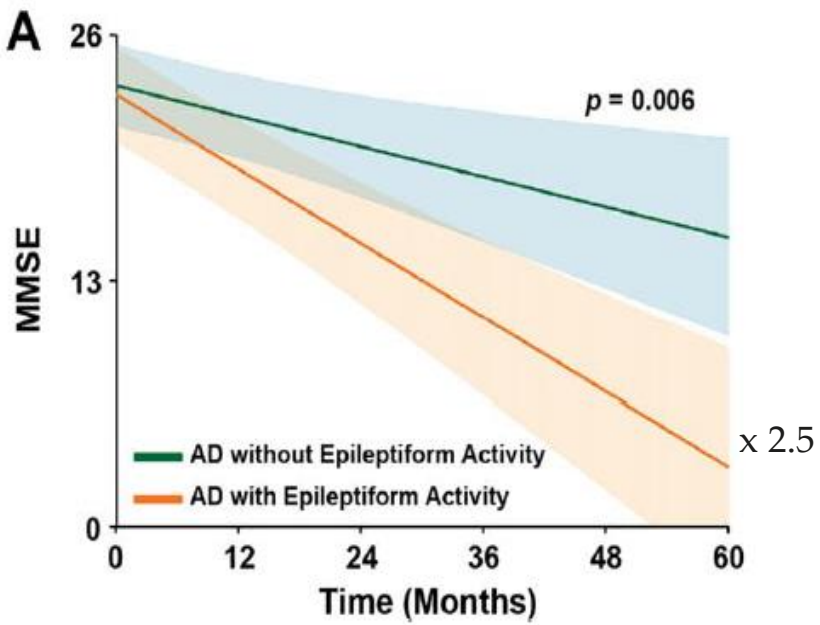






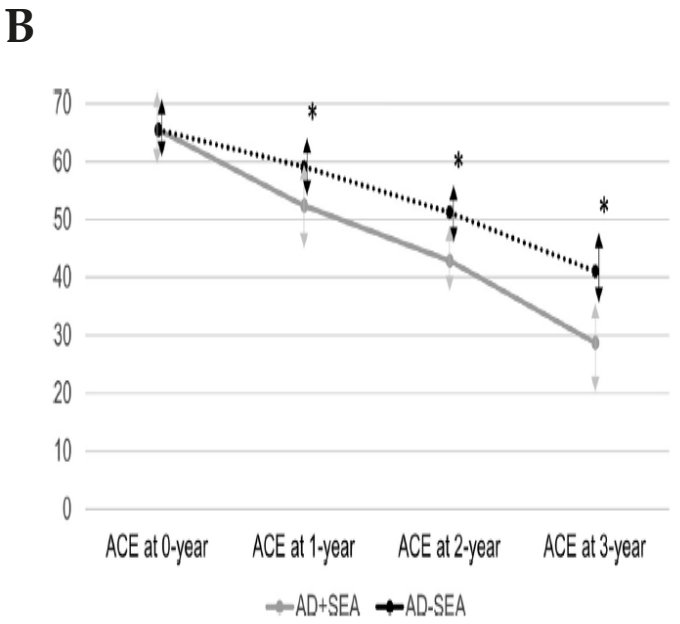
The epileptiform activity will be easily missed in routine daytime EEG examination !

Epileptiform spiking during sleep associates with faster cognitive decline



x 2.5

Vossel K et al., Arch Neurol 2016



x 1.5

Horvath A et al., Clin Neurophys 2021

Open questions

- Is hyperexcitability/epilepsy caused by core AD pathology, amyloid plaques and tau tangles ?
- Is hyperexcitablity/epilepsy an independent co-morbility that aggravates amyloid and tau pathology in AD ?
- Does hyperexcitability/epilepsy directly impair memory ?
- Should we treat AD patients with sleep associated epileptiform activity with anti-epileptic drugs ?

APP transgenic mice display epileptic seizures

Aberrant Excitatory Neuronal Activity and Compensatory Remodeling of Inhibitory Hippocampal Circuits in Mouse Models of Alzheimer's Disease

Jorge J. Palop,[1,3,*] Jeannie Chin,[1,3] Erik D. Roberson,[1,3] Jun Wang,[1,3] Myo T. Thwin,[1] Nga Bien-Ly,[1,2] Jong Yoo,[6] Kaitlyn O. Ho,[1] Gui-Qiu Yu,[1] Anatol Kreitzer,[1,2,3,4,5] Steven Finkbeiner,[1,2,3,4,5] Jeffrey L. Noebels,[6] and Lennart Mucke[1,2,3,5,*]

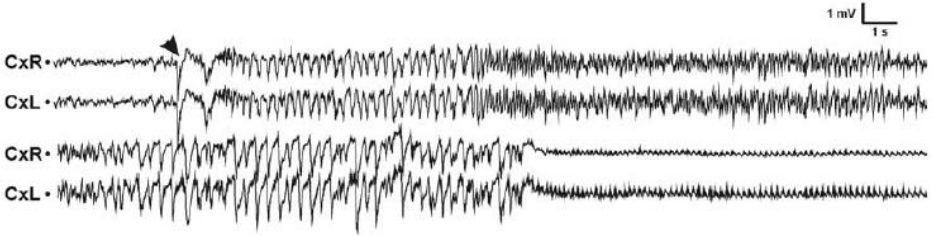
Neuron 2007

Amyloid β-Induced Neuronal Hyperexcitability Triggers Progressive Epilepsy

Rimante Minkeviciene,[1*] Sylvain Rheims,[3*] Marton B. Dobszay,[5*] Misha Zilberter,[5] Jarmo Hartikainen,[1] Lívia Fülöp,[6] Botond Penke,[7] Yuri Zilberter,[4,5] Tibor Harkany,[5,8] Asla Pitkänen,[1,2] and Heikki Tanila[1,2]

J Neuroscience 2009

Generalized seizures are easy to detect but rare



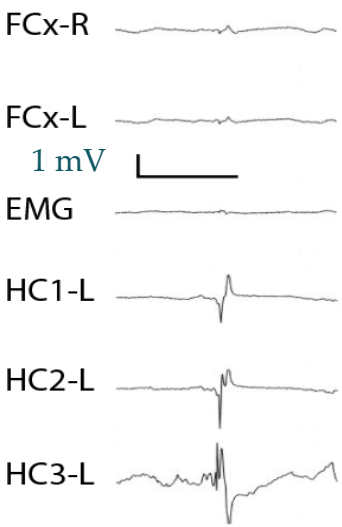
Need for surrogate markers in preclinical treatment trials

	Mouse ID	Seizures in total	Seizures per week			Mean dur. (s)	Mean beh. score	Gen. sz. (%)
			Per 1	Per 2	Per 3			
1	021	23	7	6	10	27	2.2	53
2	251	8	7	0	1	26	1.9	50
3	328	4	0	0	4	32	4.5	100
4	036	4	0	0	4	21	0.5	0
5	339	3	2	1	0	29	1.8	33
6	035	3	0	0	3	37	0	0
7	003	1	0	1	0	15	3	100
8	018	1	0	1	0	19	1	0
9	020	1	0	0	1	27	0	0
10	324	1	0	0	1	14	2	0
11	327	1	0	0	1	40	0	0
12	335	1	0	0	1	54	2	0
13	346	1	0	0	1	19	0	0
Average		4.0	1.2	0.7	2.1	28	1.5	26
14	004	0	0	0	0	0	0	0
15	006	0	0	0	0	0	0	0
16	033	0	0	0	0	0	0	0
17	200	0	0	0	0	0	0	0
18	338	0	0	0	0	0	0	0
19	353	0	0	0	0	0	0	0
20	396	0	0	0	0	0	0	0

Minkeviciene R et al., J Neurosci 2009

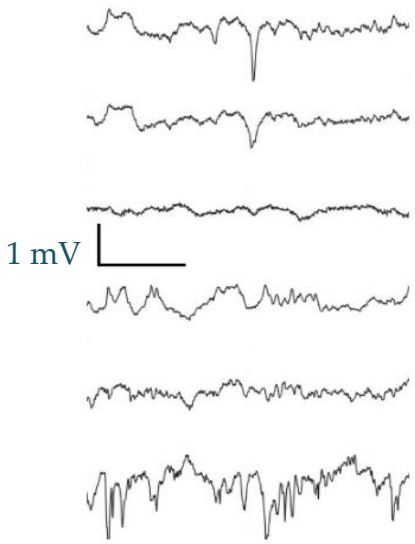
APP/PS1 mice display 3 types of epileptiform activity

Epileptiform discharges, HC



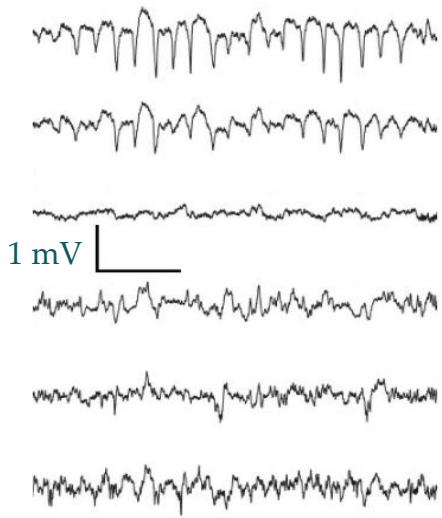
APP/PS1 specific
resemble spikes in AD
N2/3 and REM

Cortical single spikes

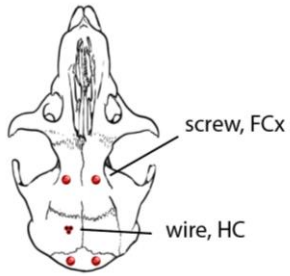


also in wild-type mice
resemble spikes in AD
N2/N3

Spike-wave discharges, S1 cortex

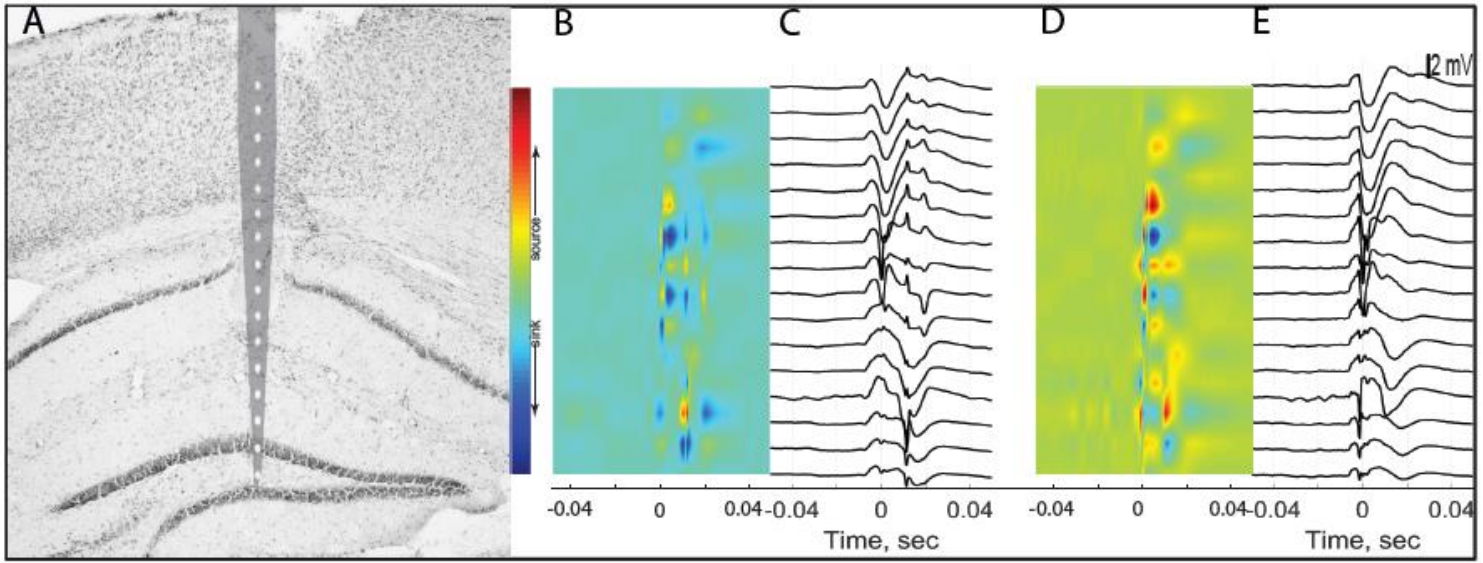


APP/PS1 specific
never reported in AD
Drowsiness, N1



Jin N et al. Alzheimer's Dementia 2022

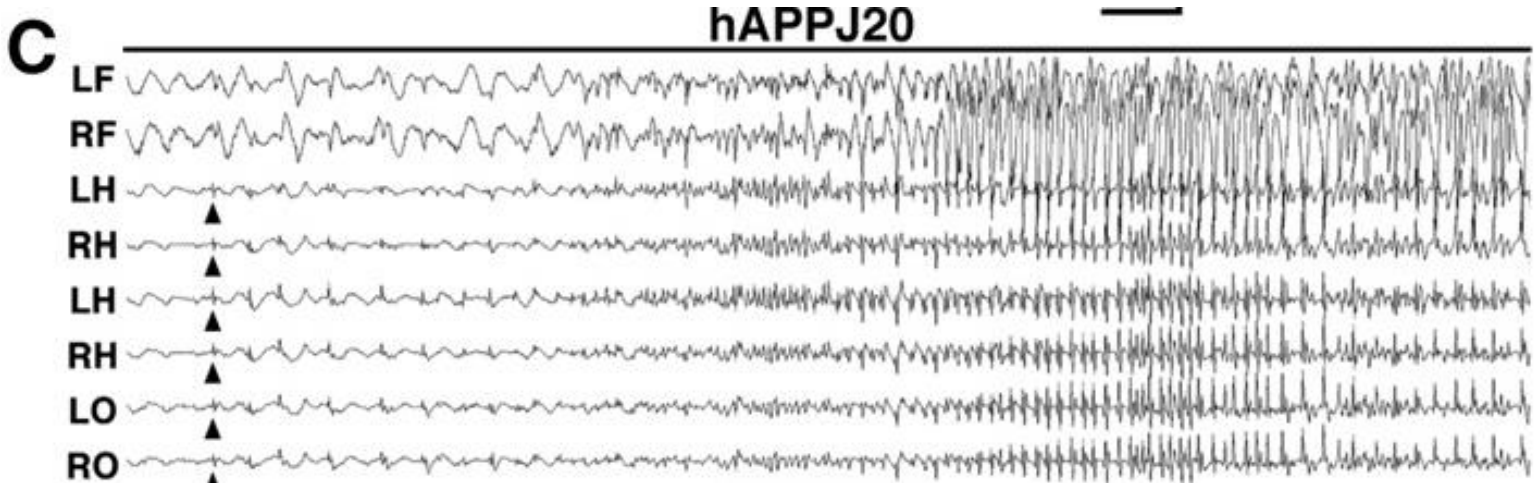
Epileptiform discharges show multiple sinks and sources in the hippocampus -> complex shape



Gureviciene I et al. Front Neurology 2019

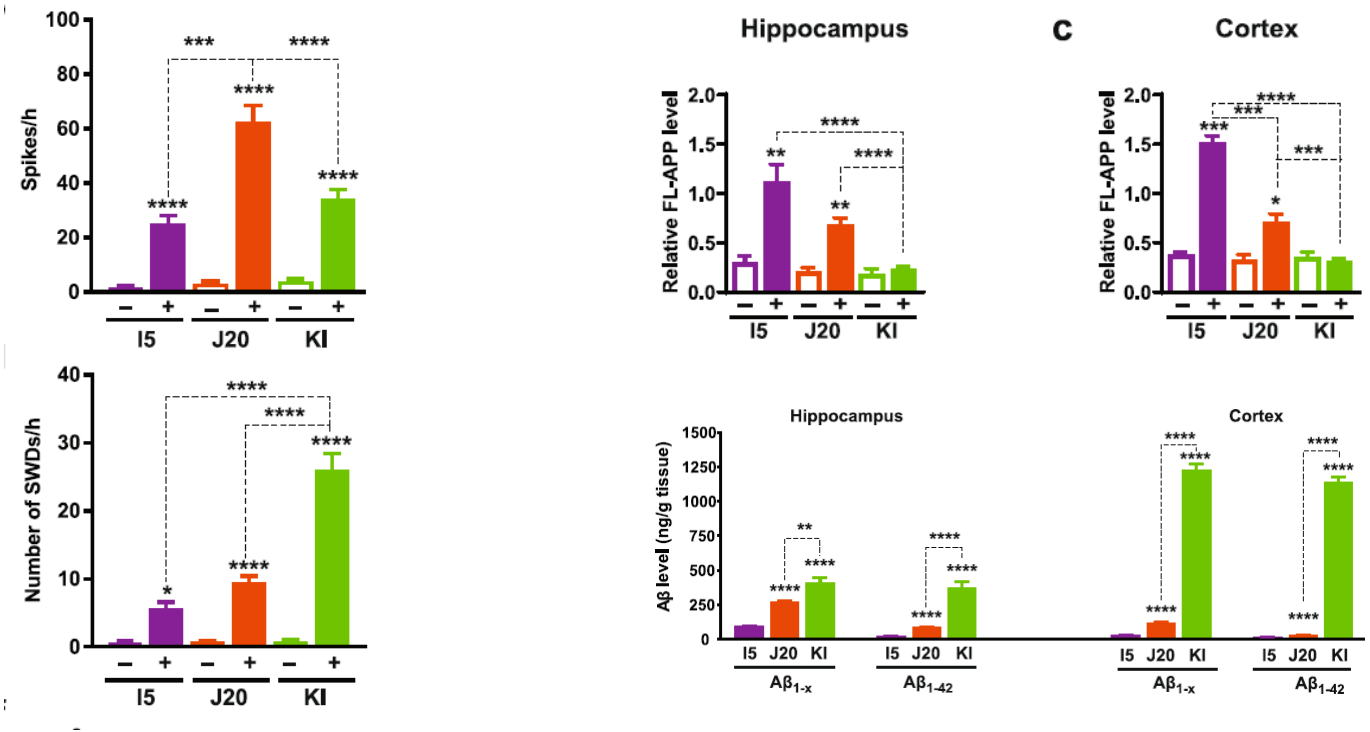
Origin of seizures ?

Typically monitored in mice with two cortical epidural electrodes over weeks
→ little spatial resolution



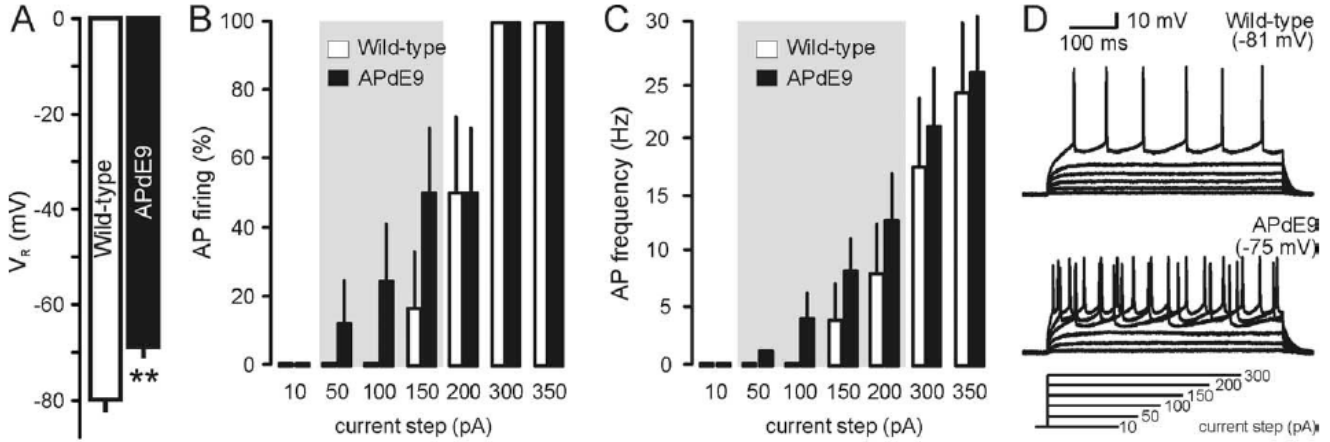
Two mice in the first Palop J et la., 2007 Neuron paper had single hippocampal electrodes (LH, RH).

hAPP overexpression or Aβ formation behind neuronal hyperexcitability/epilepsy ?

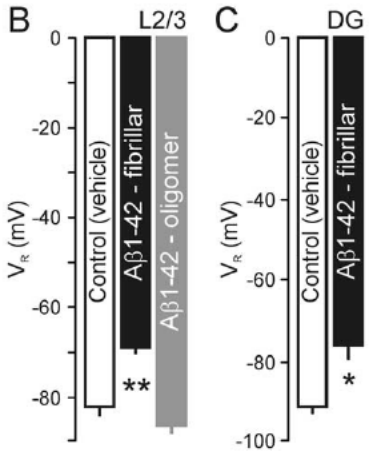


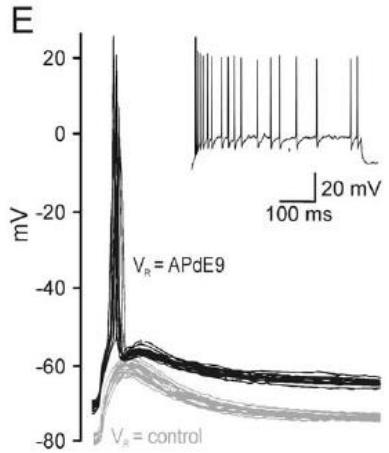
Johnson E, …, Mucke L Mol Neurodeg 2020

Protofibrillar Aβ increases excitability



L2/3 cortical pyramidal neurons





DG granule neurons

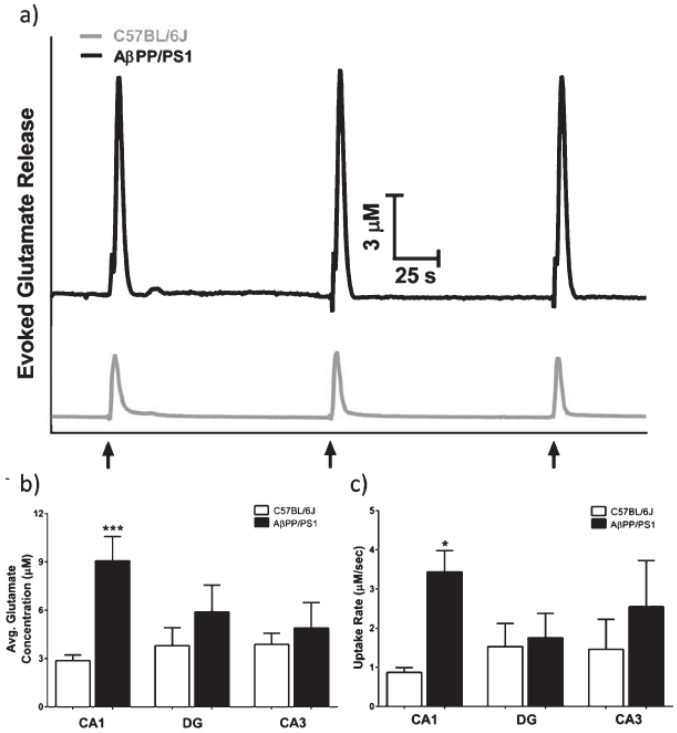
Minkeviciene R et al., J Neurosci 2009

Possible sources of amyloid induced hyperactivity

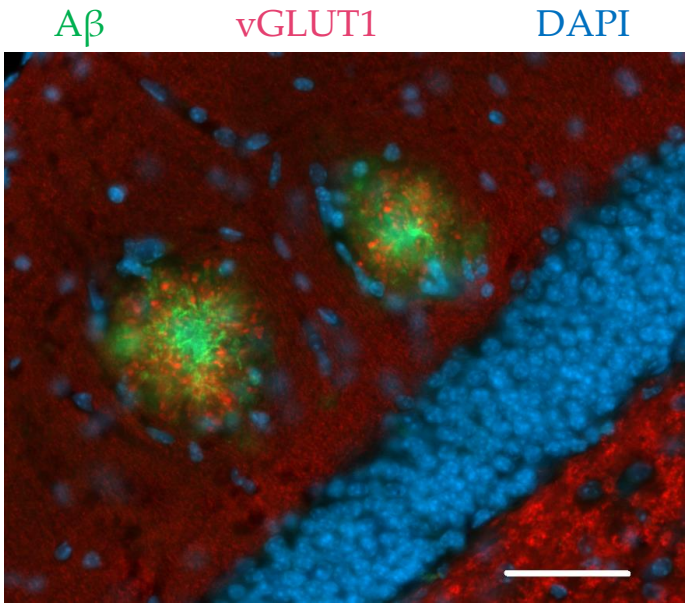
- Direct excitation of neurons through ion channels
- Increased presynaptic glutamate release
- Decreased inhibition by GABAergic interneurons

Increased presynaptic glutamate release in APP/PS1 mice

KCl stimulation

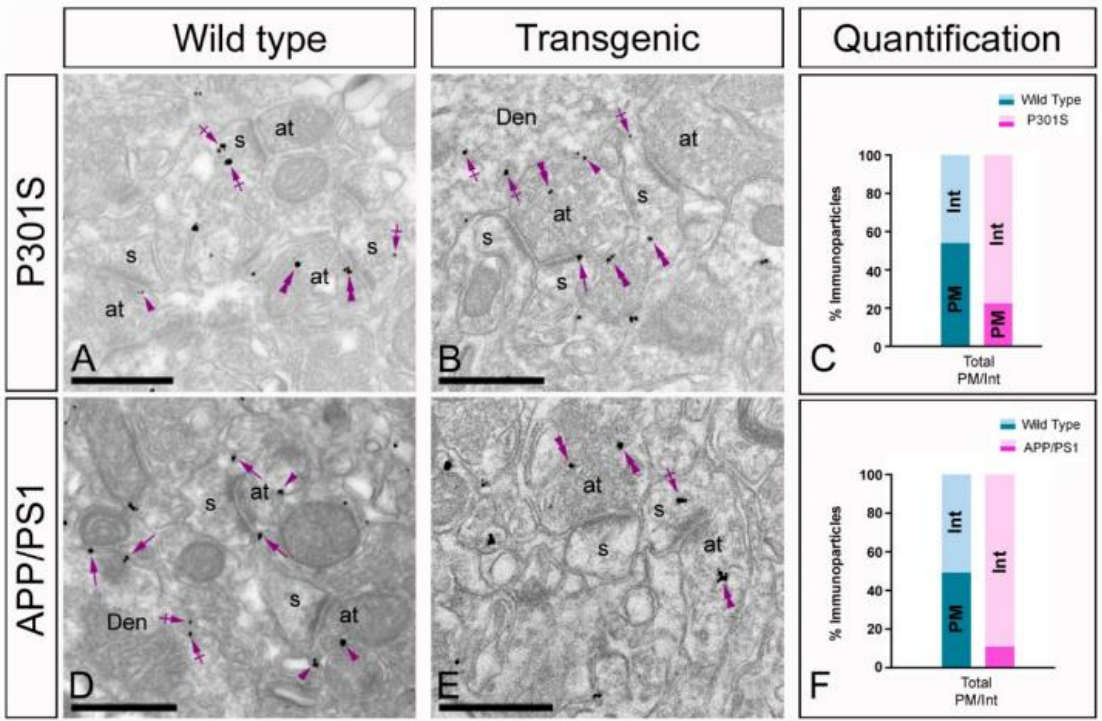


K & E Hascup, JAD 2015



Jin N et al. Alzheimer's Dementia 2022

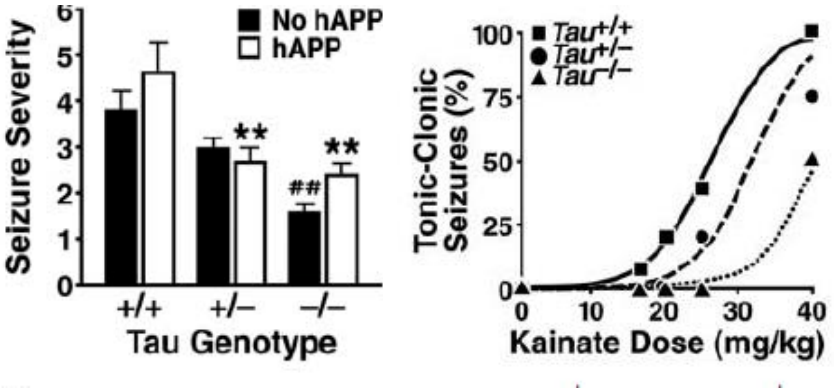
Loss of membrane-bound GIRK2 K^+ channels on presynaptic Glu terminals in CA1 pyramidal cells



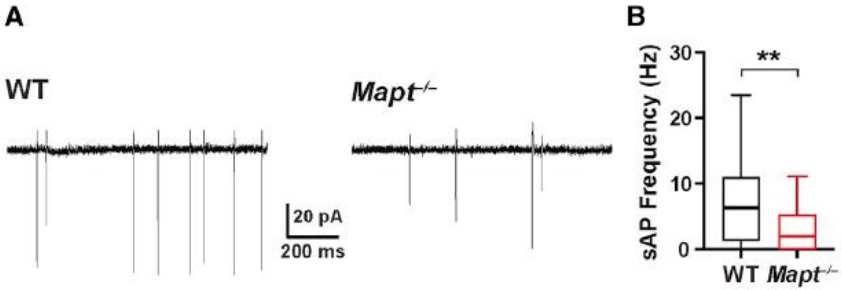
Alfaro-Ruiz et al., Int J Mol Sci 2021

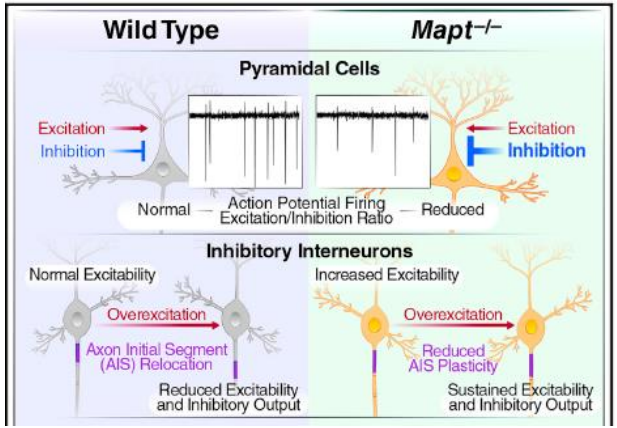
Reduction of endogenous tau attenuates seizures by decreasing network E/I balance

Pentylene tetrazole



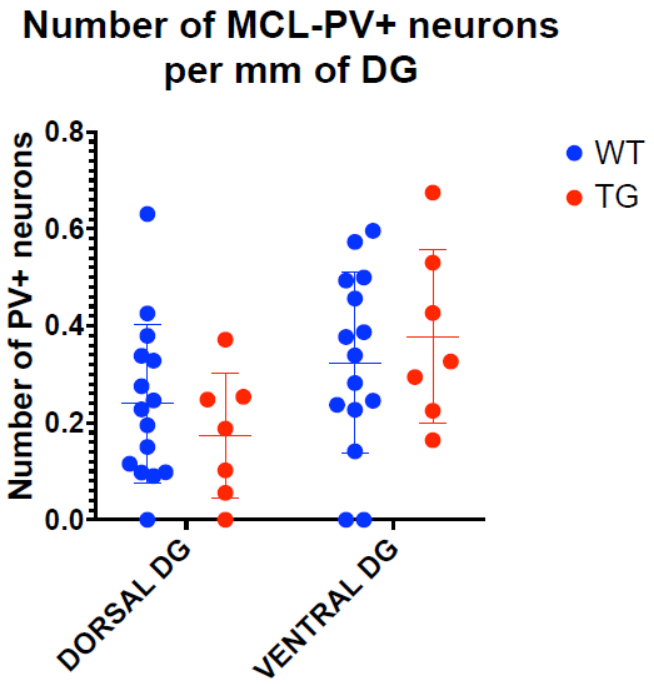
Roberson E, …, Mucke L Science 2007

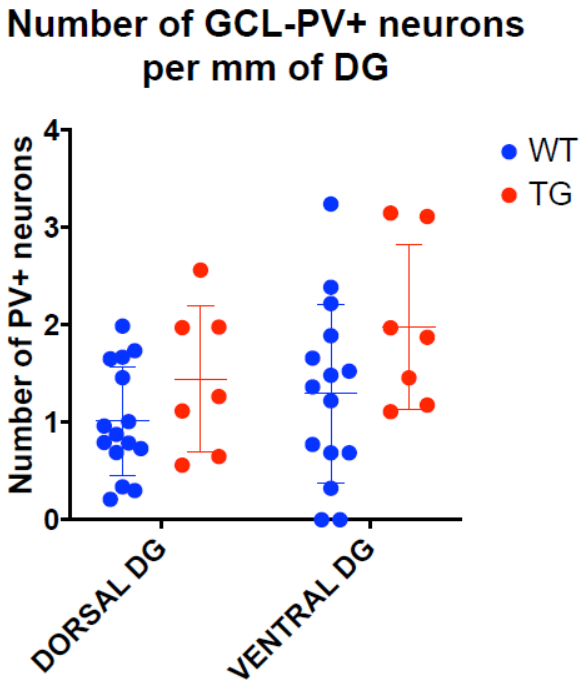




Chang C-W,…, Mucke L Cell Rep 2021

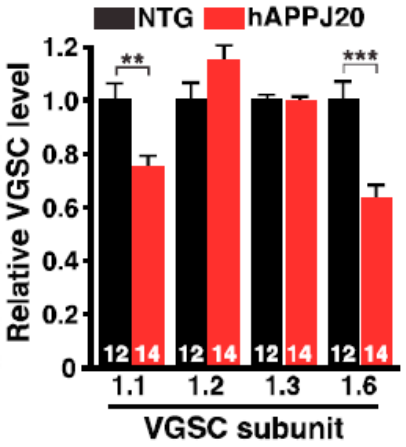
No loss of parvalbumin interneurons in APP/PS1 mice

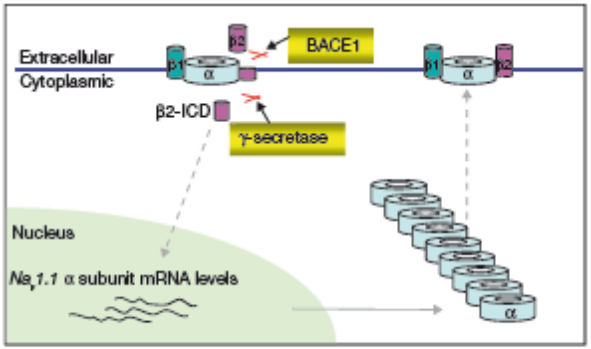




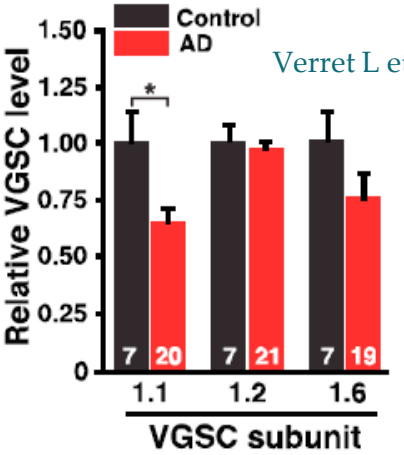
Vartiainen T, …, Tanila H (unpublished)

Reduced levels of Nav1.1 channel in PV interneurons



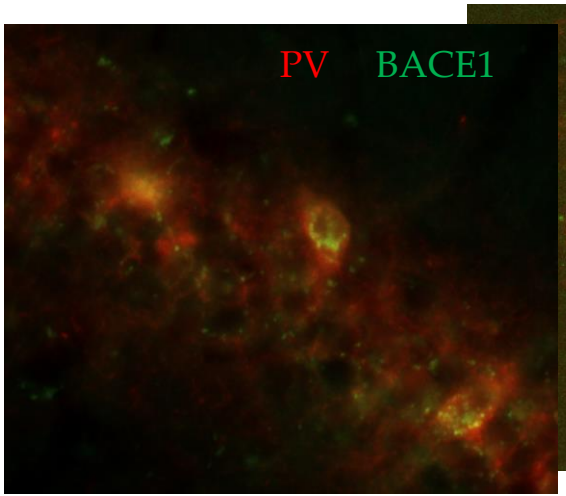


Kim DY, ..., Kovacs D,
Nature Cell Biol. 2007

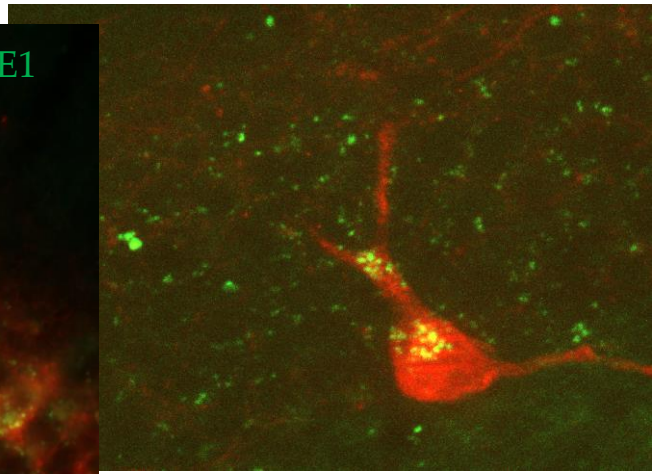


Verret L et al., Cell 2012

BACE1 overexpression in PV neurons in APPswe/PS1dE9 mice

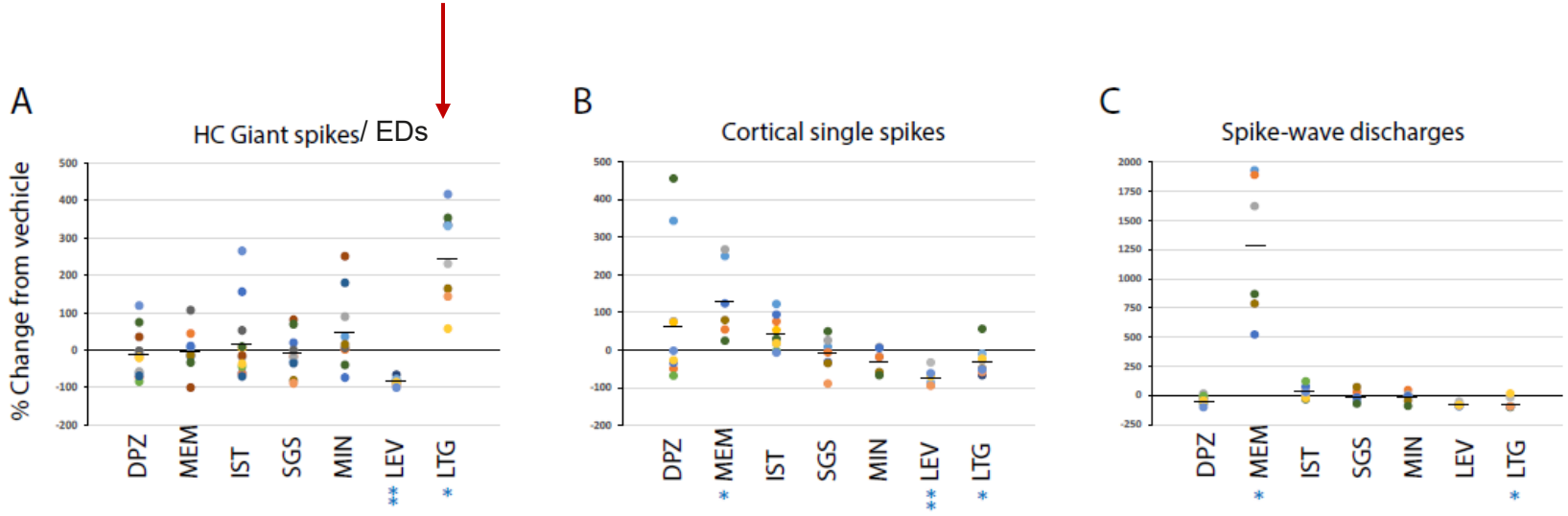


CA1



DG

Drug responses



DPZ = donepezil
MEM = memantine
IST = instraphylline

SGS = semagacestat

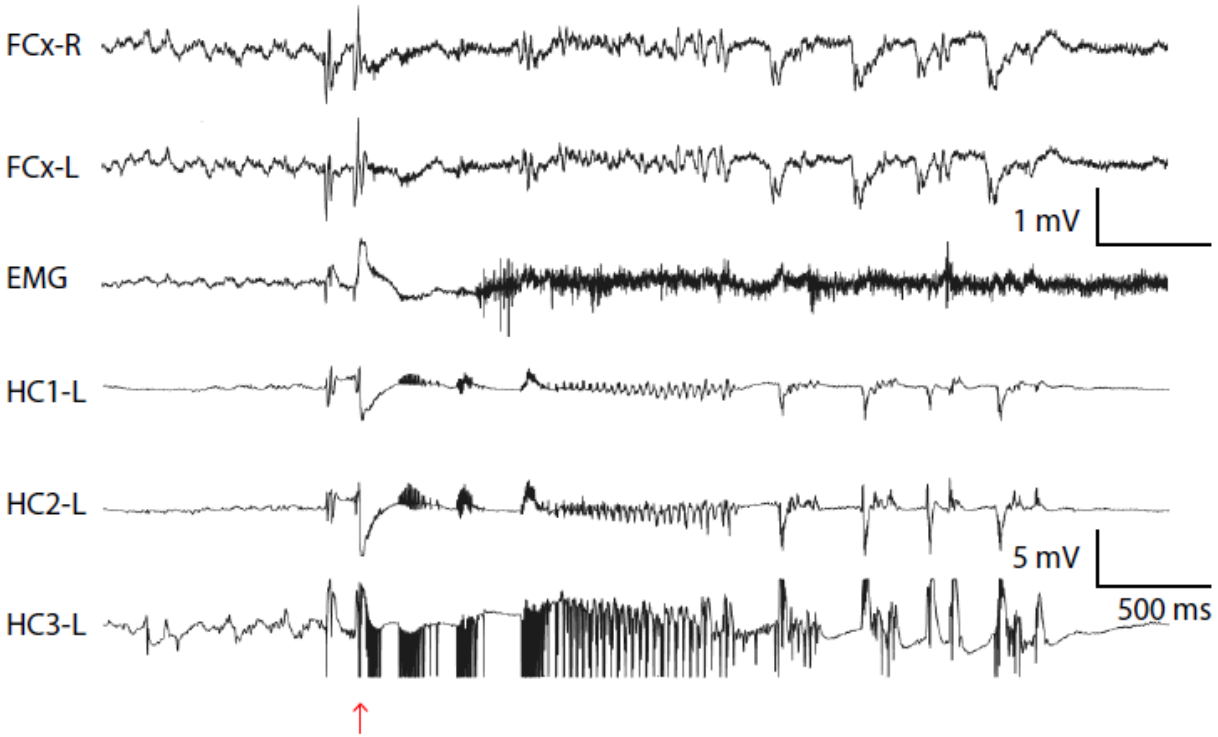
MIN = minocycline

LEV = levetiracetam

LTG = lamotrigine

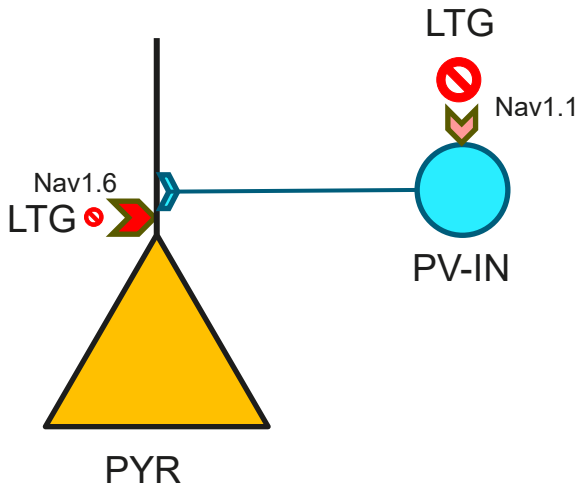
Jin N et al., Alz & Dem 2022

Lamotrigine induced a generalized seizure in two mice

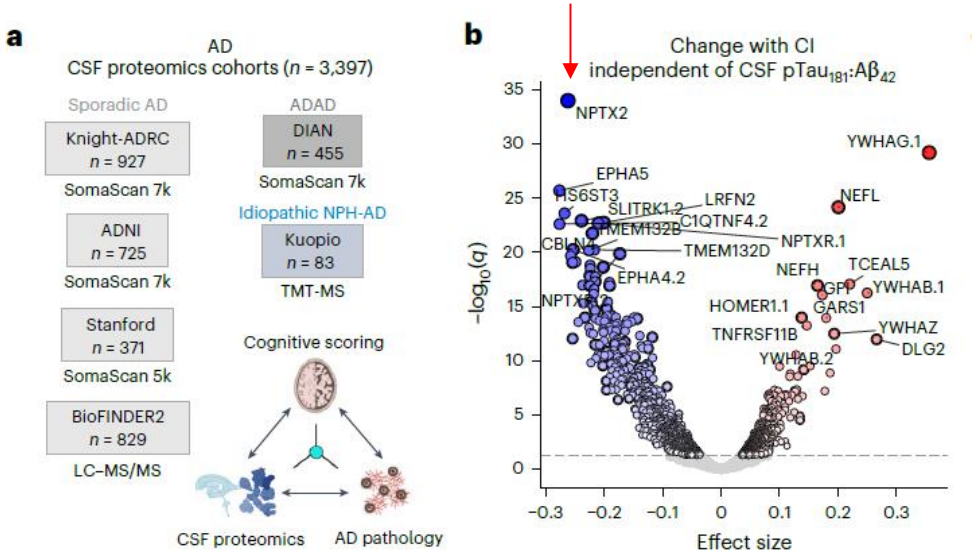


Jin N et al., Alz & Dem 2022

Model: Reduced number of functional Nav1.1 channels in PV-INs in AD mice
→ blockade by a small dose of LTG acts stronger on PV-INs than PYRs



NPTX2 – a new player in the game



> 7000 proteins/sample

The strongest predictor of cognitive decline during 15 years:

Aβ+Tau+ normal cognition

↓

Mild cognitive impairment

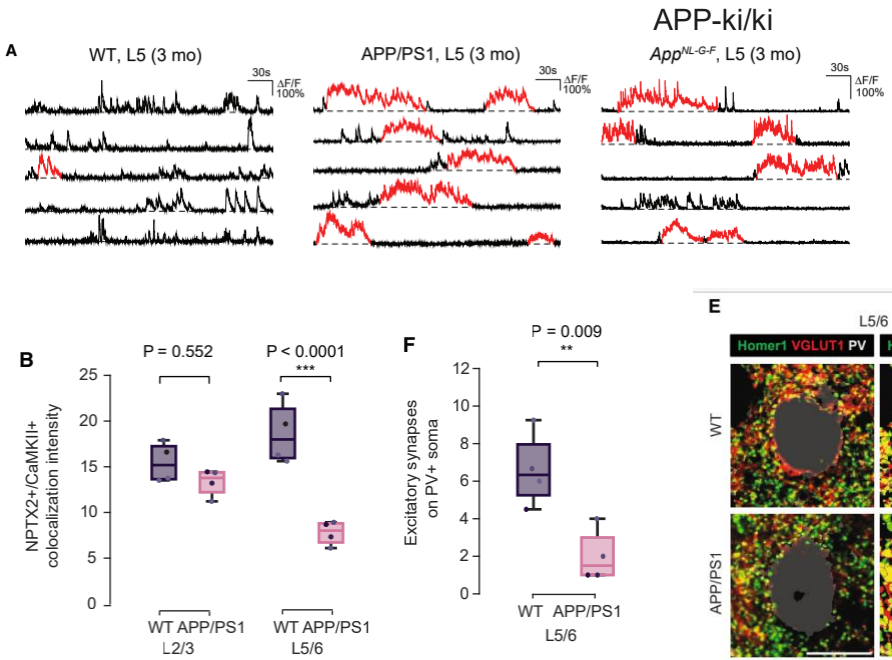
↓

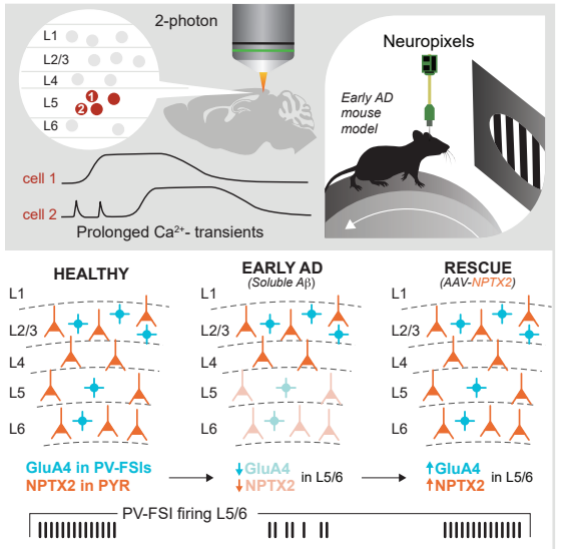
AD dementia

Low CSF levels of NPTX2 (neuronal pentraxin 2)

Oh H,…., Wyss-Corey T, Nat Med 2025

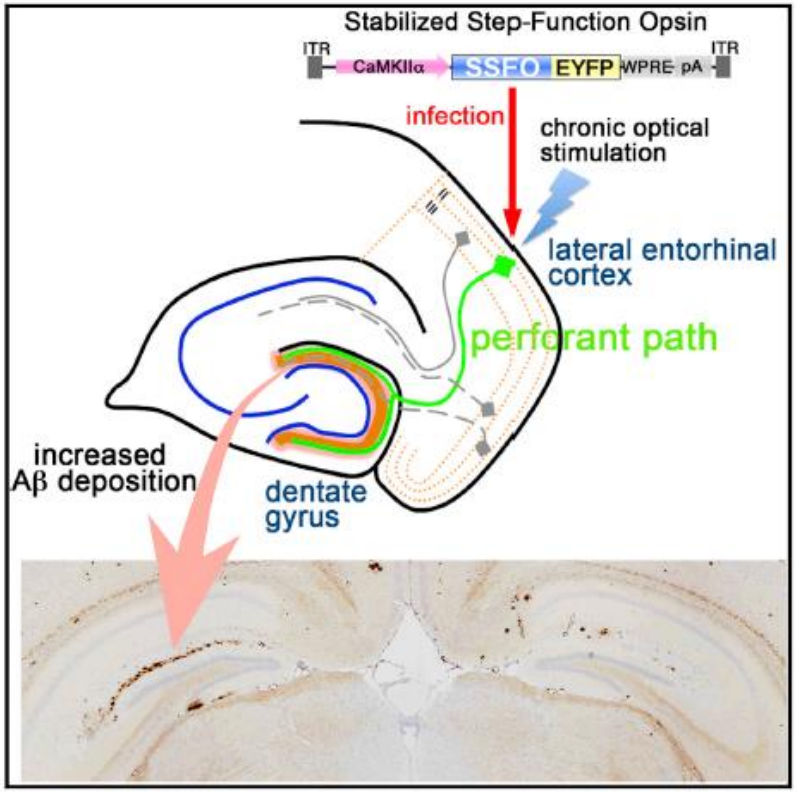
Loss of NPTX2 reduces GluA4-Rs on PYR-PV synapses in two AD model mice





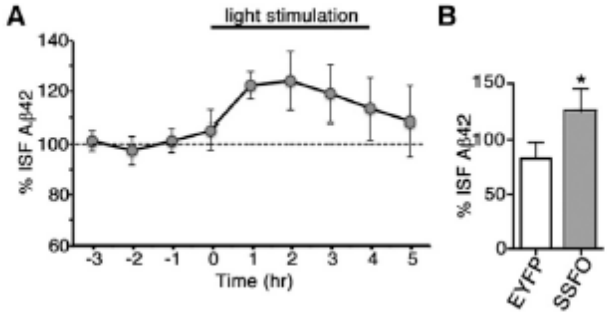
Papanikolaou A, …, Busche M-A Neuron 2025

Chronic optogenetic activation increases local amyloid accumulation in an APP tg mouse

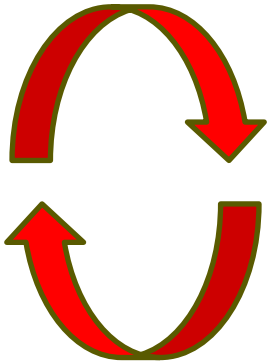


Yamamoto K, Cell Rep. 2015

In vivo microdialysis, increased Abeta secretion to ISF



Neuronal hyperexcitability



Aβ accumulation

Conclusions

- Neuronal hyperexcitability/hyperactivity is an integral part of AD neuropathology
- It may manifest as seizures but more often as subclinical epileptiform activity, mostly in medial temporal lobe. DG may be a special hotspot.
- Amyloid-β (protofibrils) increase neuronal excitability
- There are also other contributing factors, such as hAPP overexpression (in mouse models), alterations in Nav1.1 channels and reduced neuronal NPTX2 levels in PV-INs
- Hyperexcitability is associated with increased brain amyloid load and fast cognitive decline

Acknowledgements

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