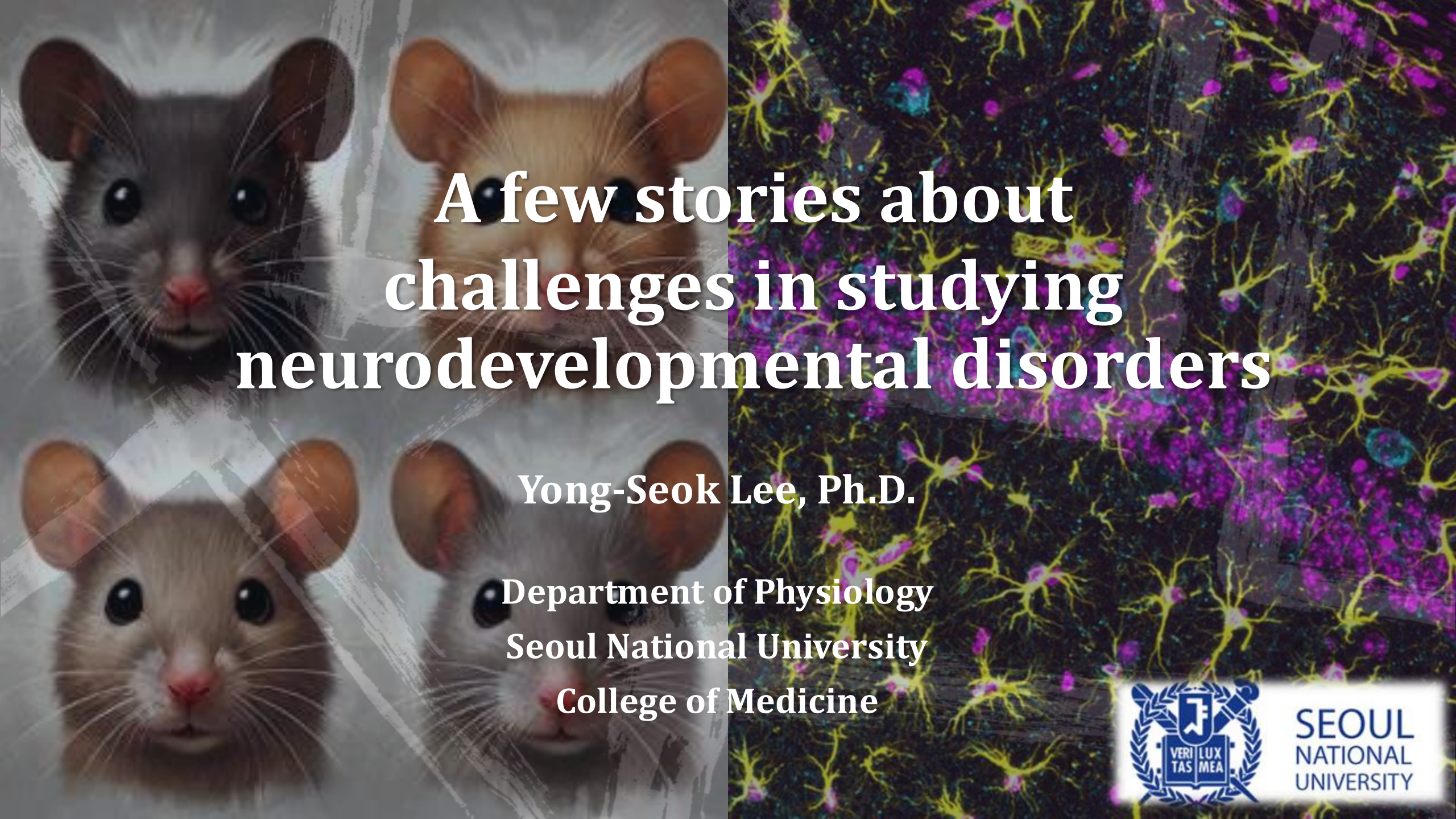




A few stories about challenges in studying neurodevelopmental disorders

Yong-Seok Lee, Ph.D.

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College of Medicine



SEOUL
NATIONAL
UNIVERSITY

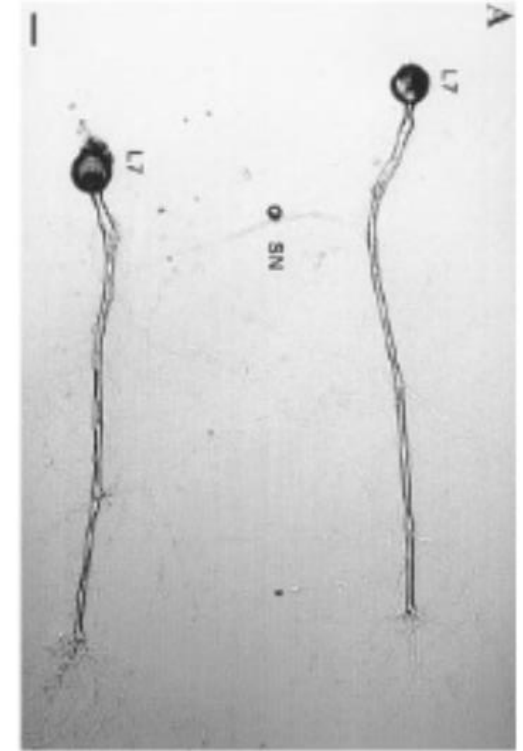
My Neurotree



Started with a simple nervous system

Eric R.
Kandel
Columbia

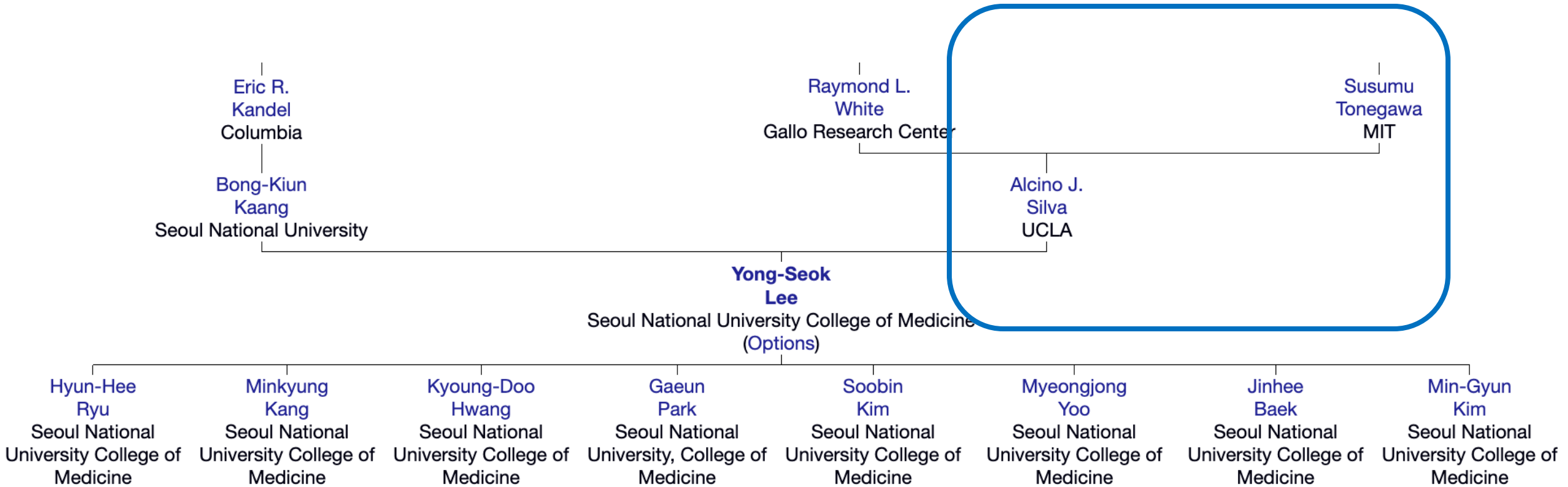
Bong-Kiun
Kaang
Seoul National University



https://en.wikipedia.org/wiki/California_sea_hare

Martin et al., 1998

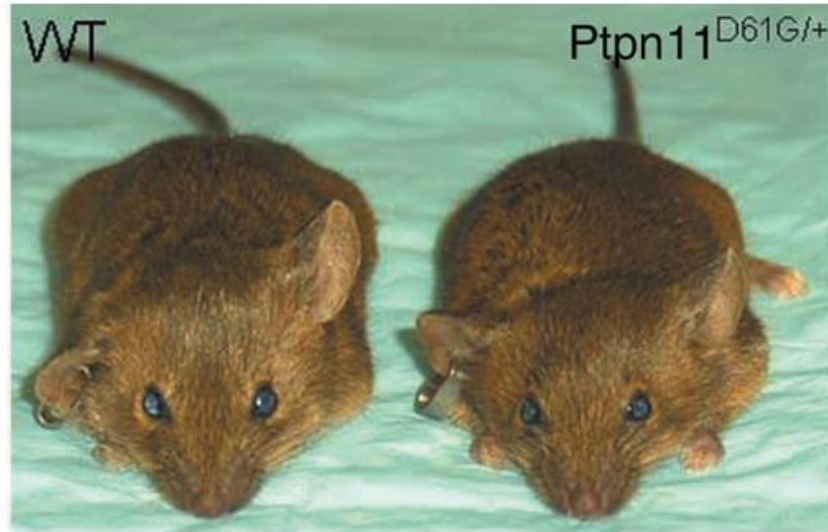
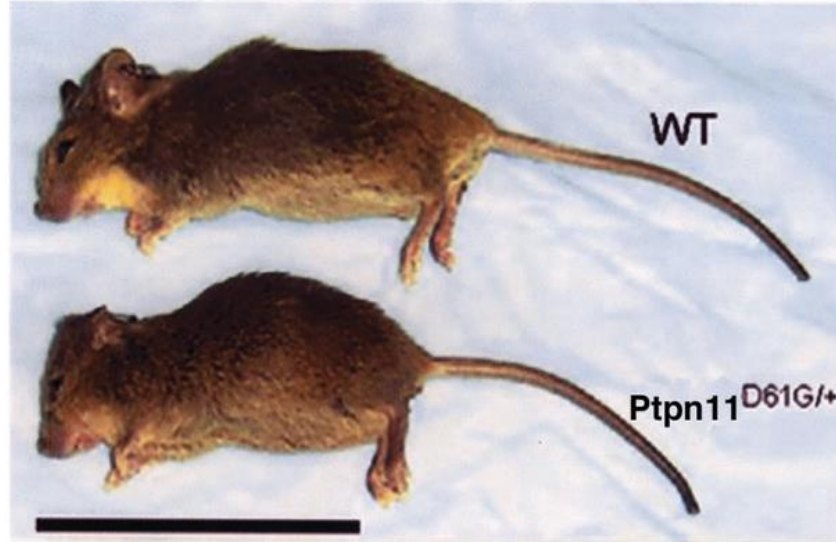
Move to mice



All began with Dr. Ehninger



2008



Araki et al., 2004

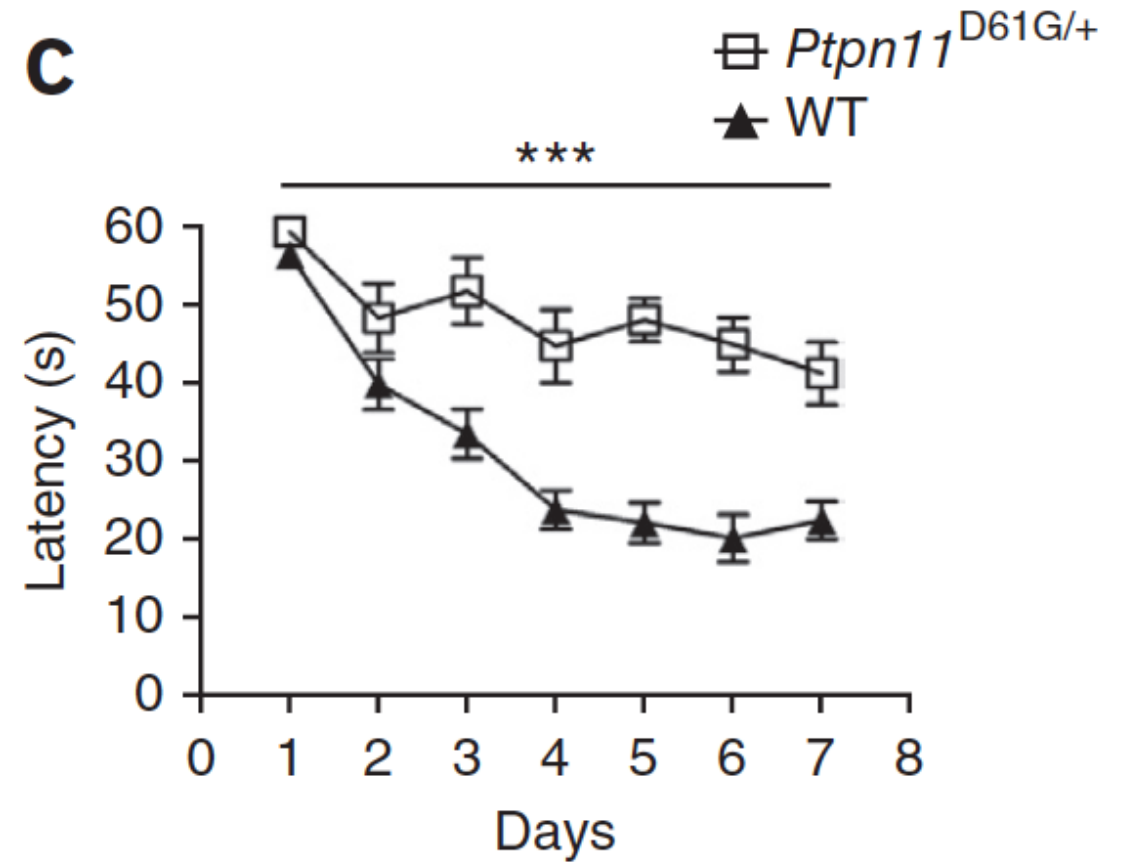
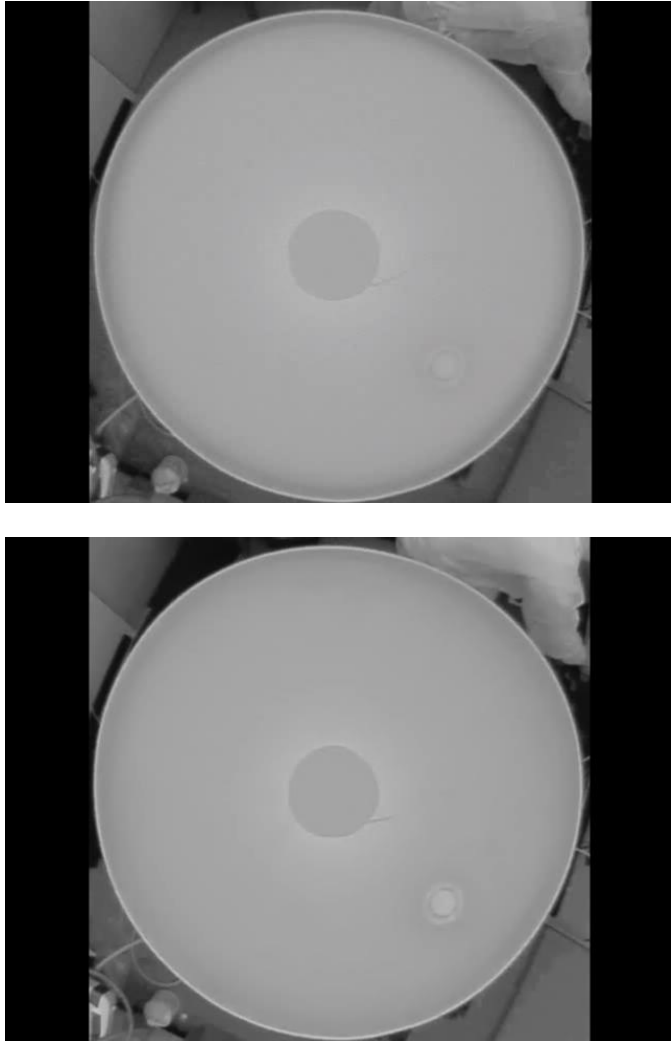
Noonan syndrome (NS)

- NS is an autosomal dominant disorder characterized by short stature, facial dysmorphism, and a wide spectrum of congenital heart defects.
- Mutations in *Ptpn11* and other RAS signaling genes
- Cognitive impairments such as learning disabilities are also common.
- Also, associated with ASD

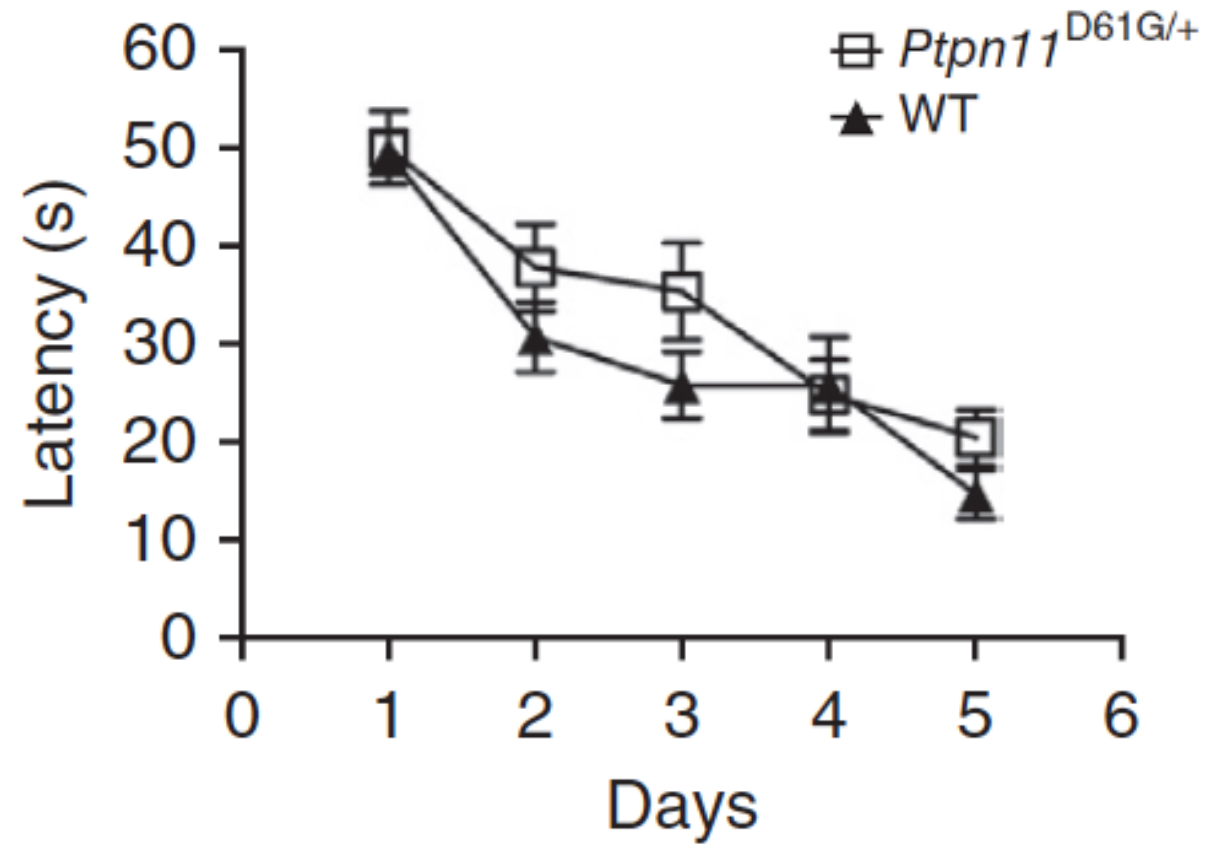
Challenge 1: Impact of genetic background



Severe learning & memory deficits in NS mutant



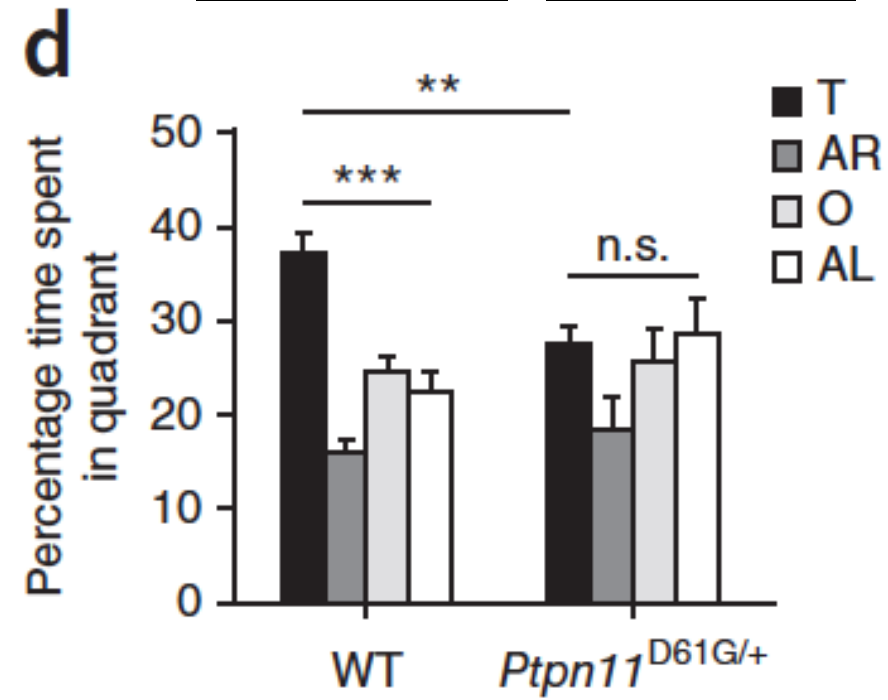
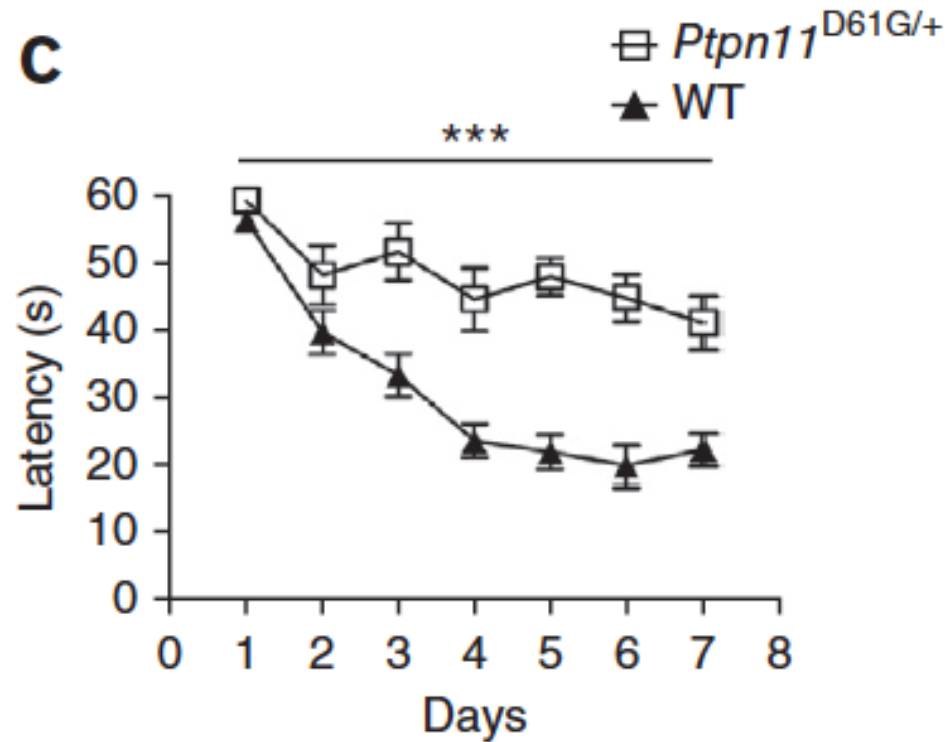
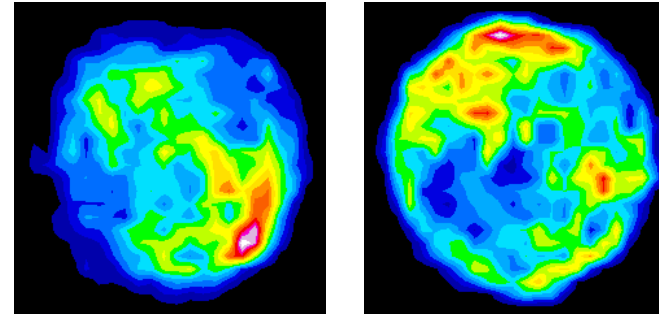
NO learning & memory deficits in NS mutant



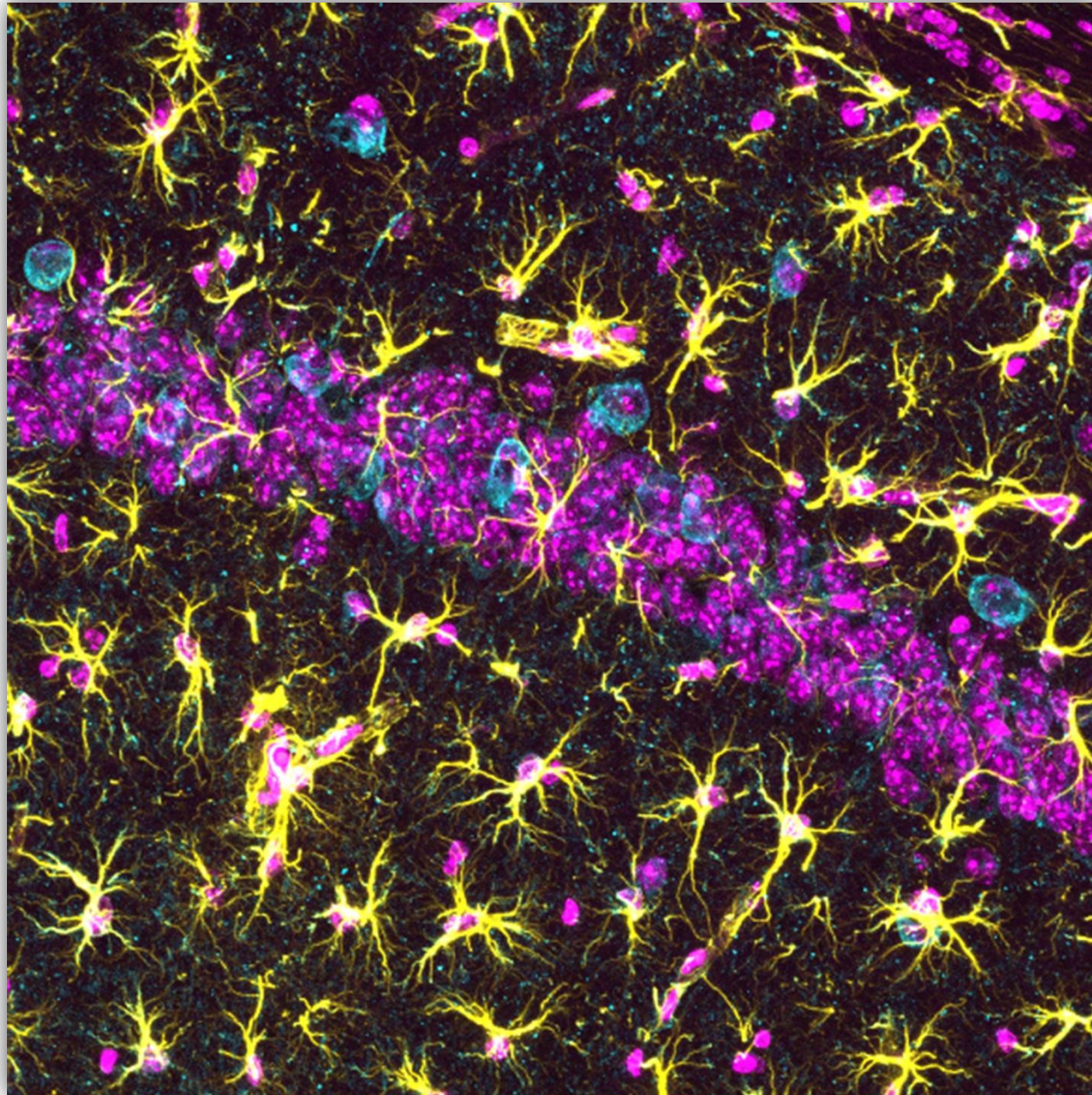
Challenge 1: Impact of genetic background



Got the phenotypes back in 129SvEv background

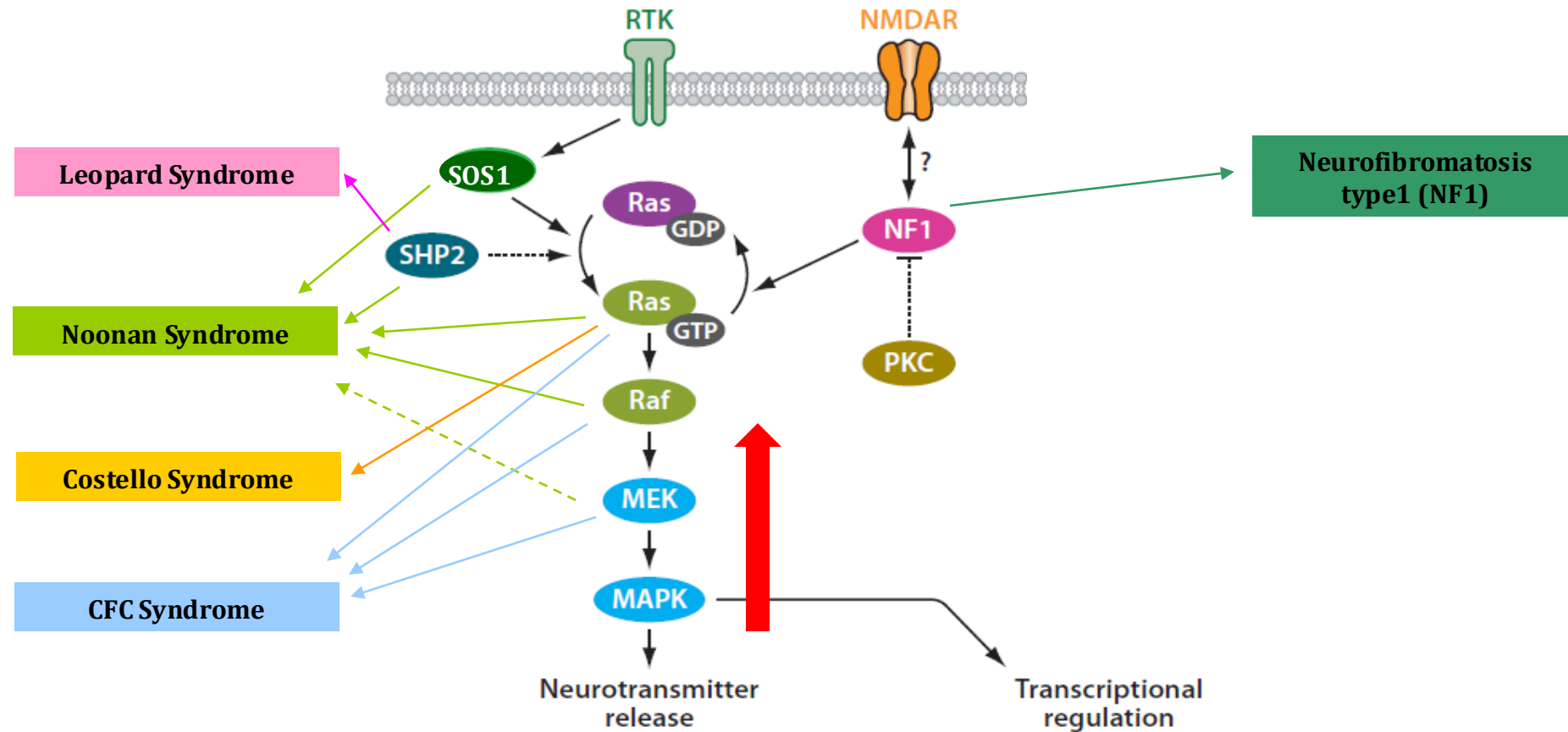


Challenge 2: Impact of cell types

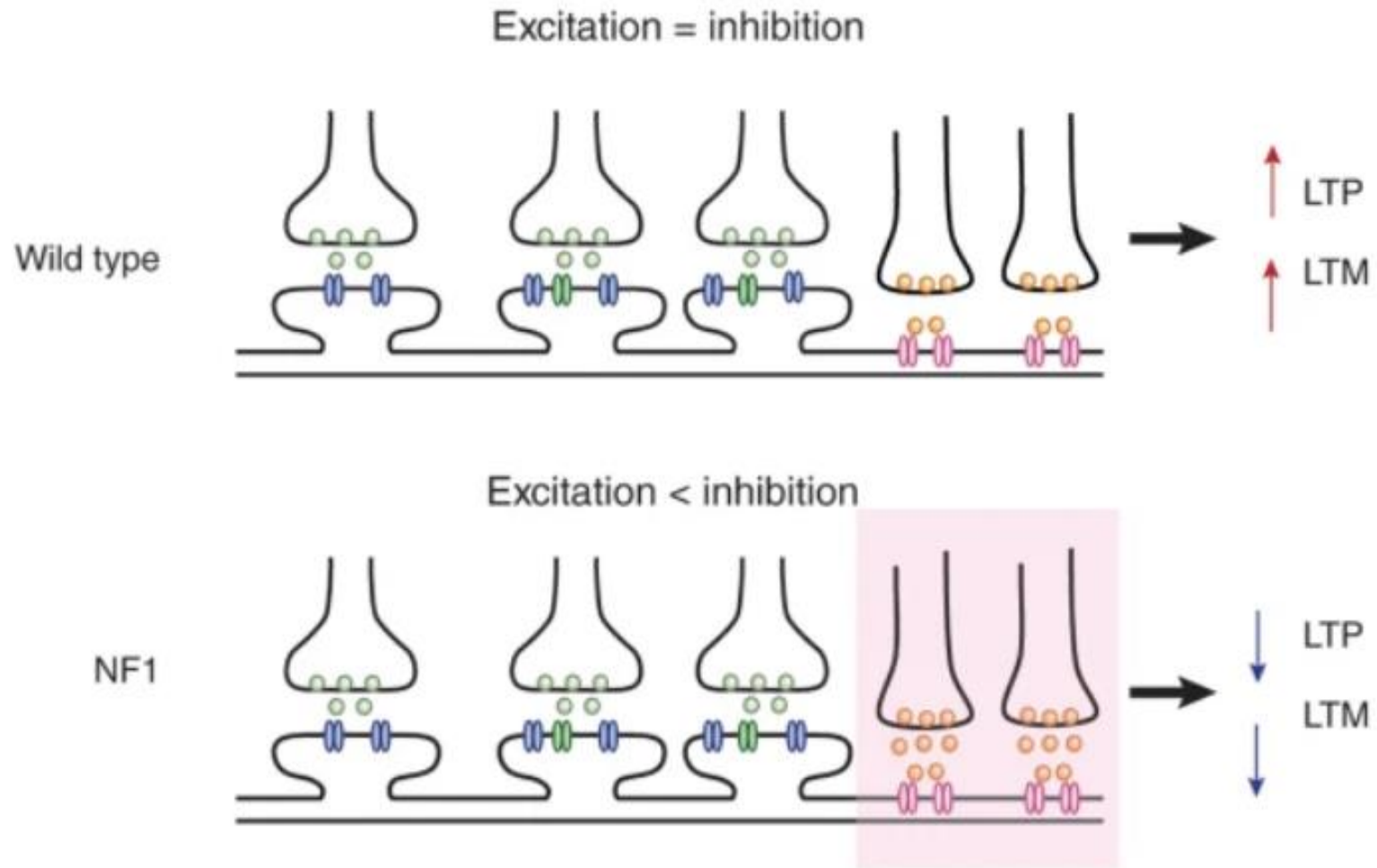


Common synaptic mechanism for all RASopathy?

A group of disorders caused by mutations in the key elements of RAS/MAPK signaling, associated with cognitive deficits

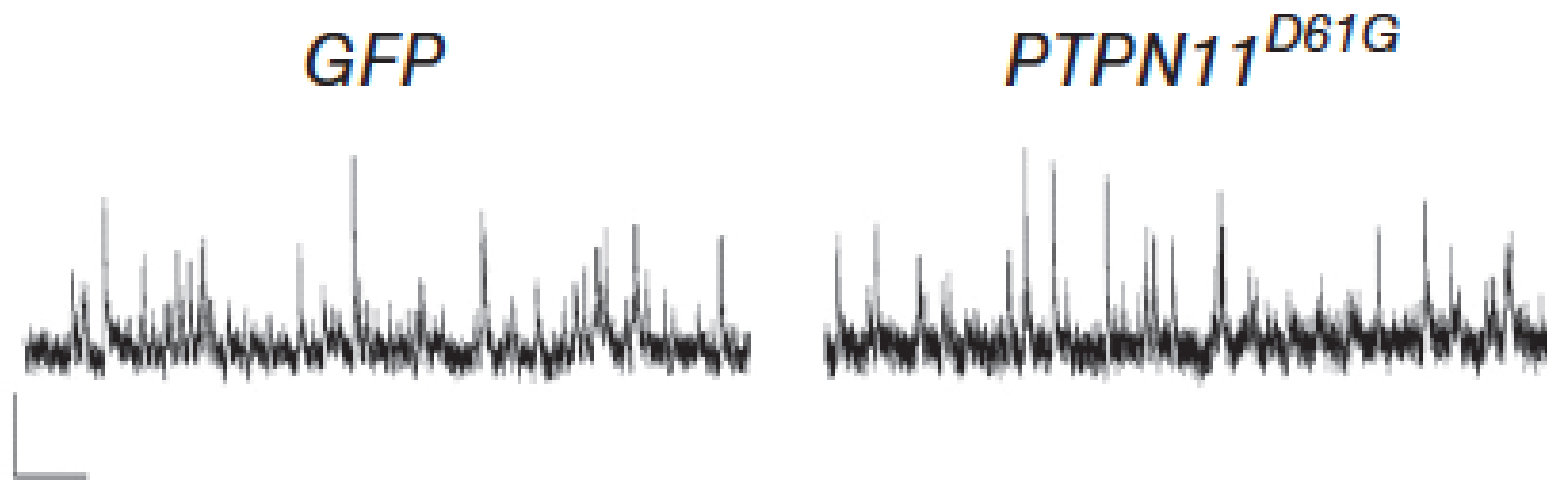


Selective increase in inhibitory synaptic transmission in NF1

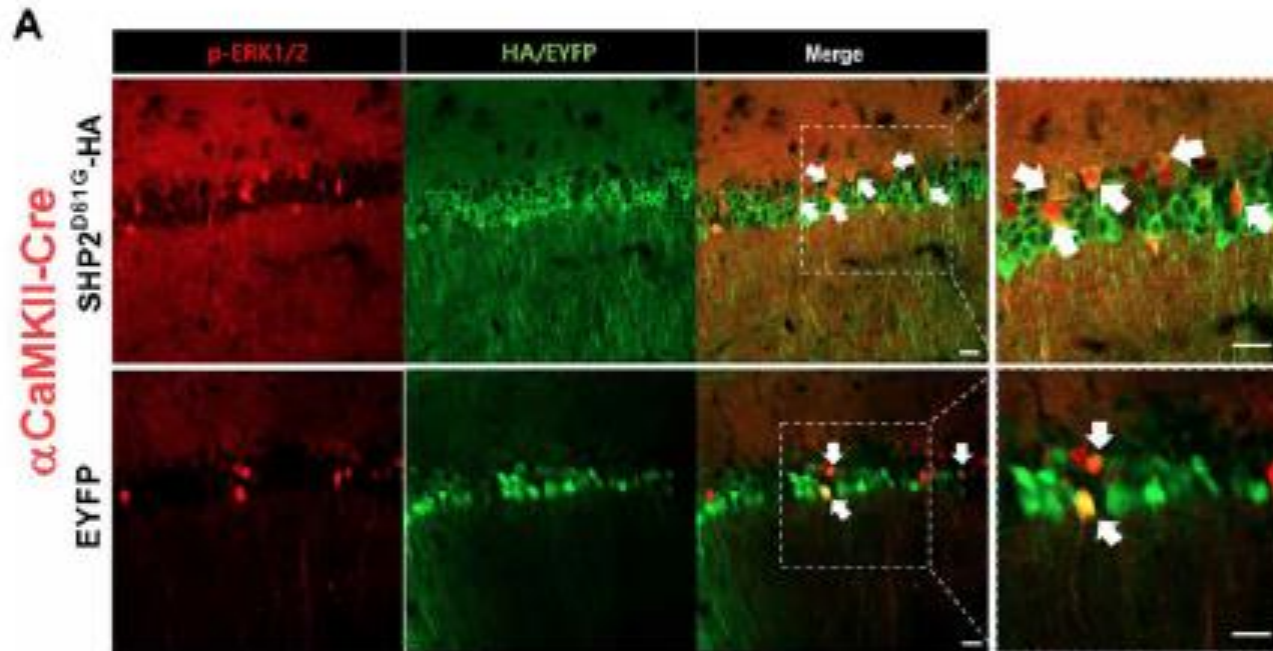
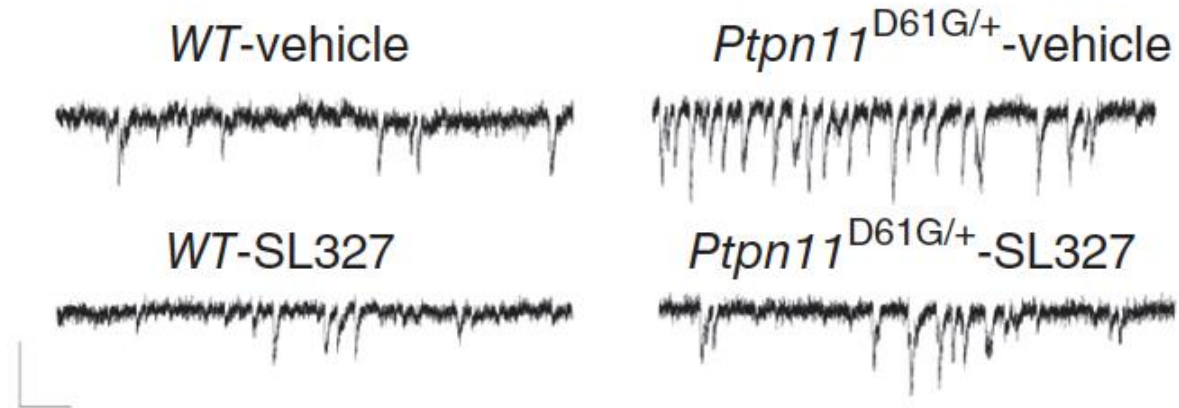


Costa-Mattioli, 2014
Costa et al., 2002
Cui et al., 2008
Shilyansky et al., 2000

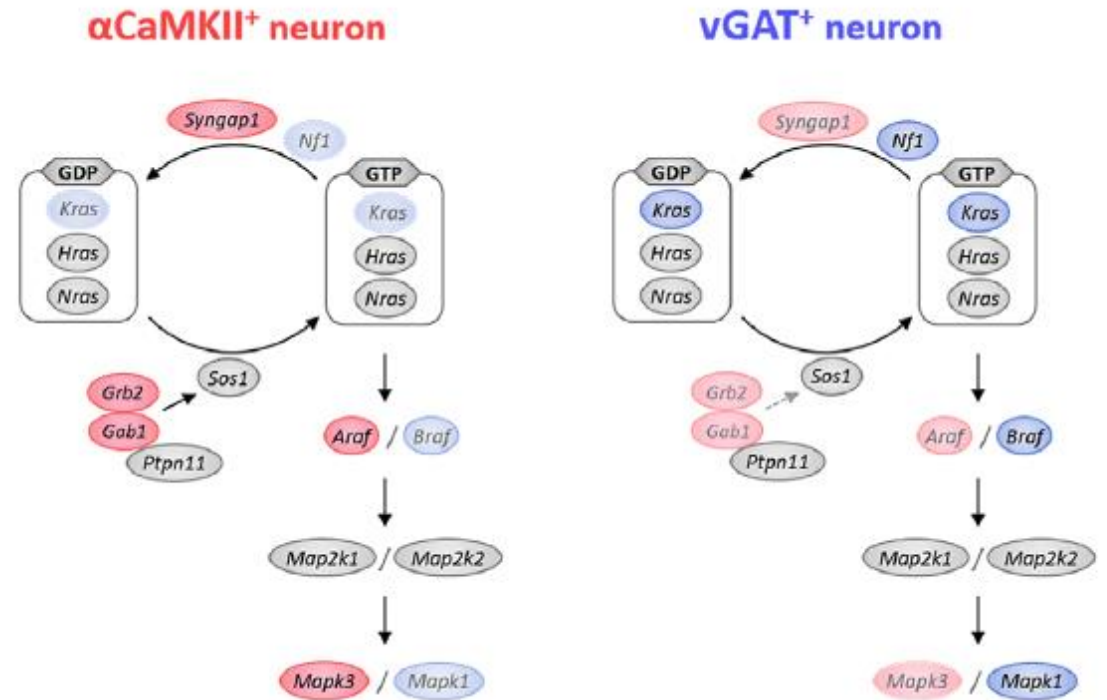
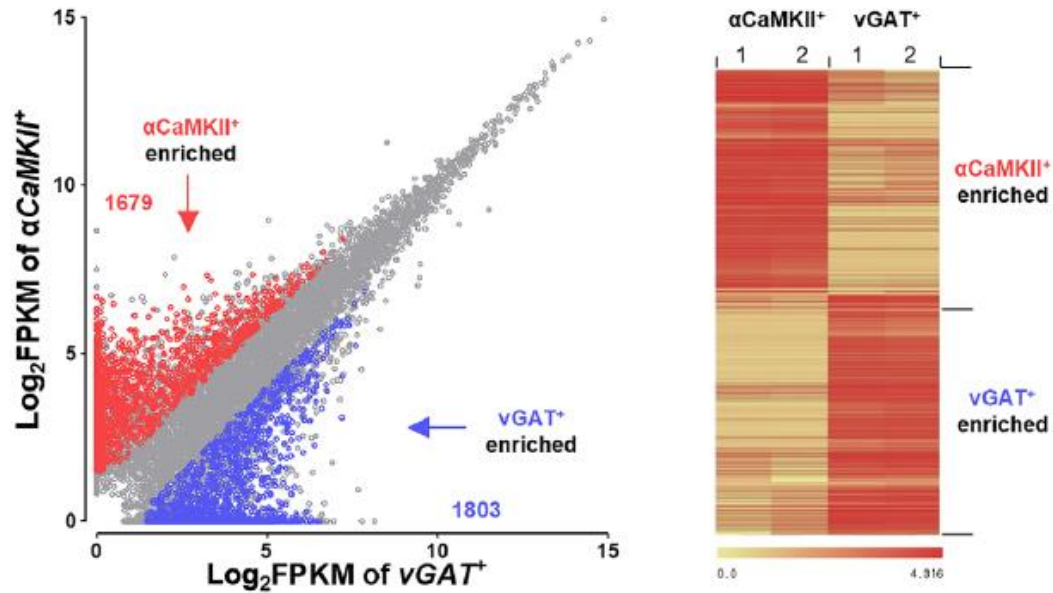
NO increase in inhibitory synaptic transmission in NS



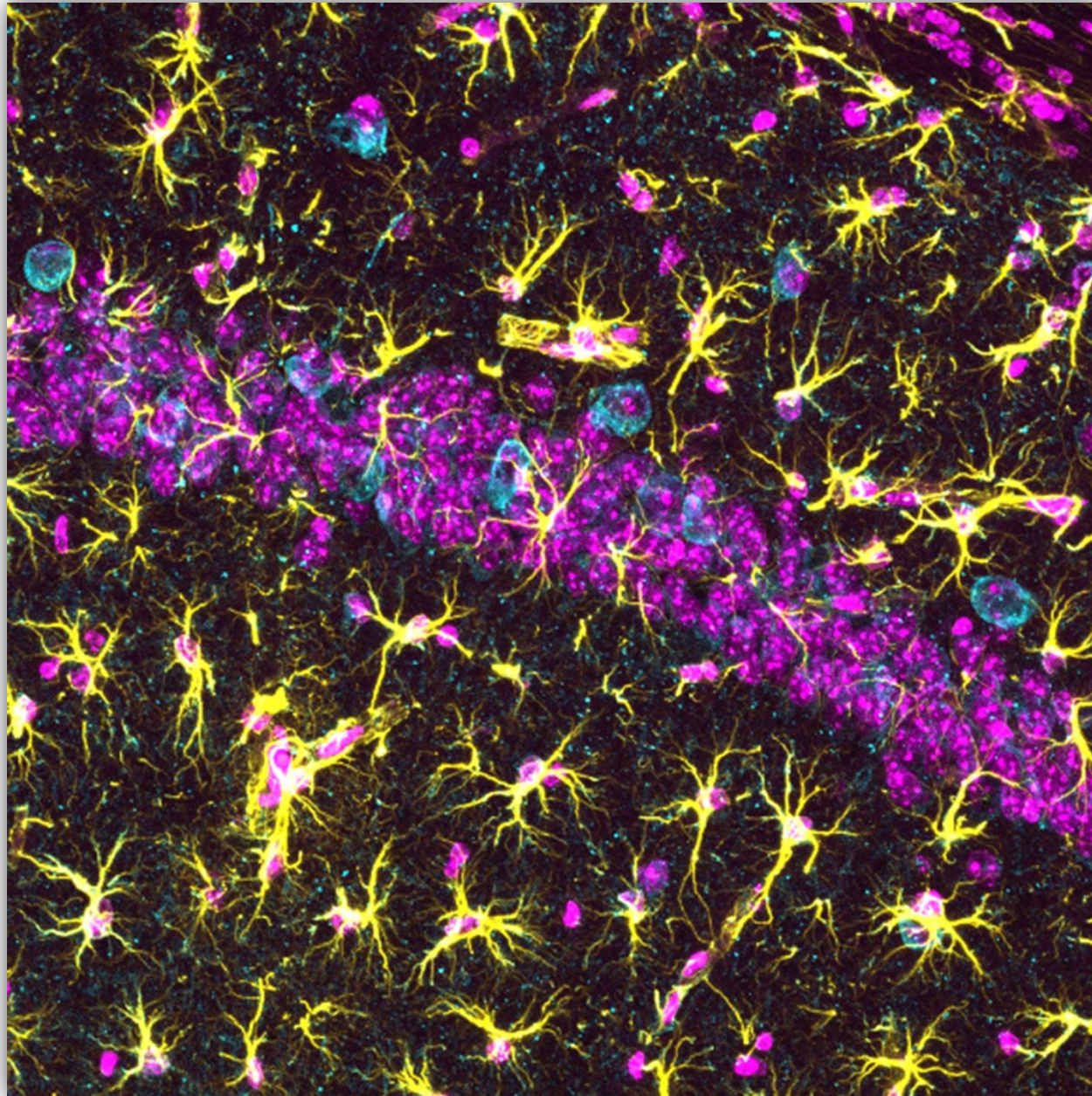
Selective increase in excitatory synaptic transmission in NS



Cell type-specific RAS signaling networks in nervous system



Challenge 2: Impact of cell types



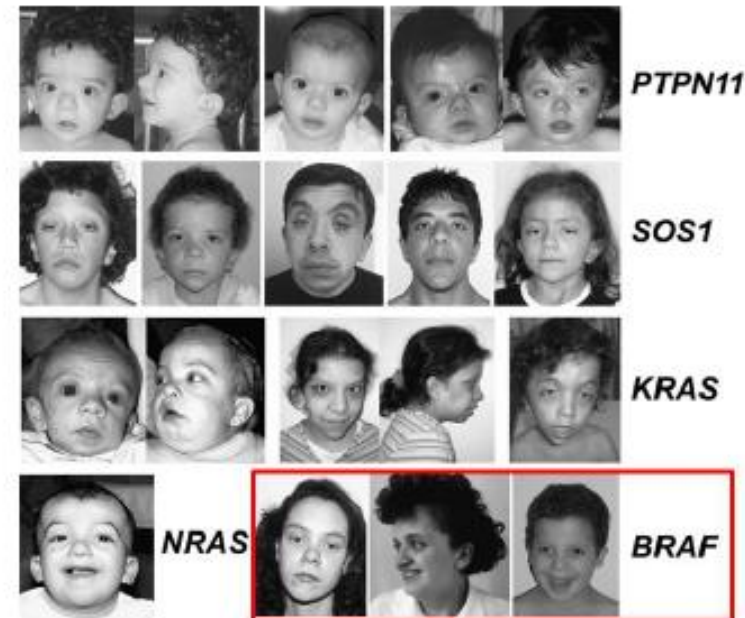
Cardio-Facio-Cutaneous (CFC) syndrome

- Rare RASopathy affecting many parts of the body, particularly the heart (cardio-), facial features (facio-), and the skin and hair (cutaneous)
- Varying degrees (mostly severe) of **cognitive deficits and intellectual disabilities**
- Associated with mutations in **BRAF** (~70%), KRAS, MEK1/2



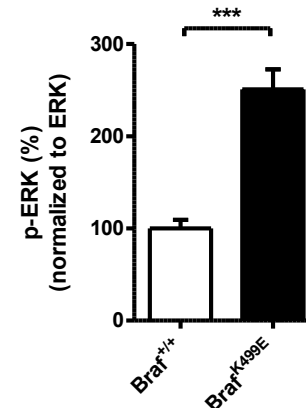
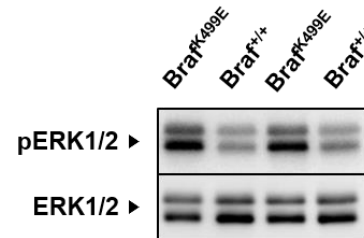
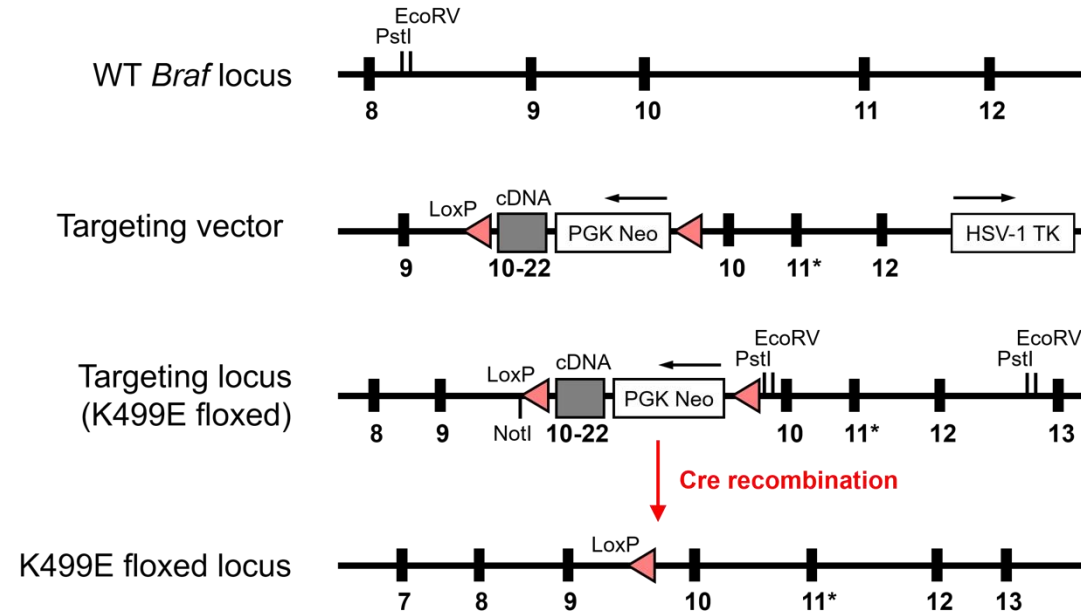
Tartaglia et al., 2011

Niihori et al., 2006



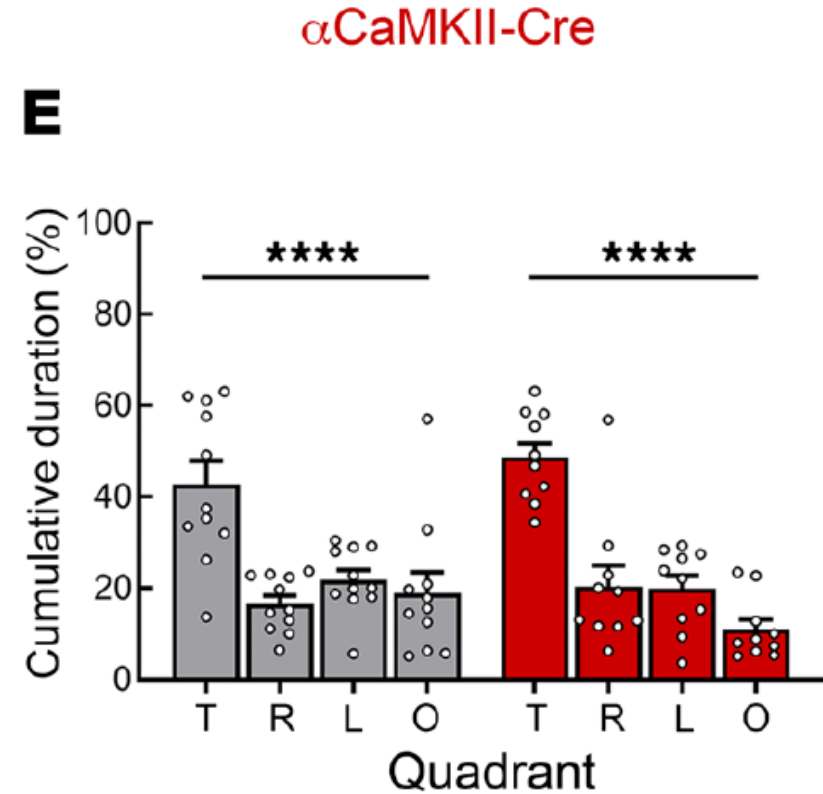
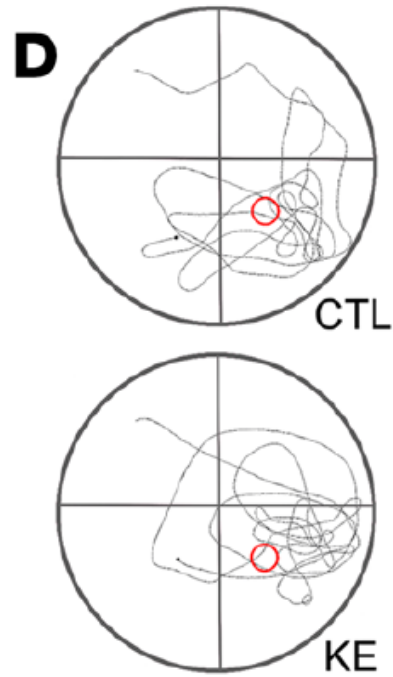
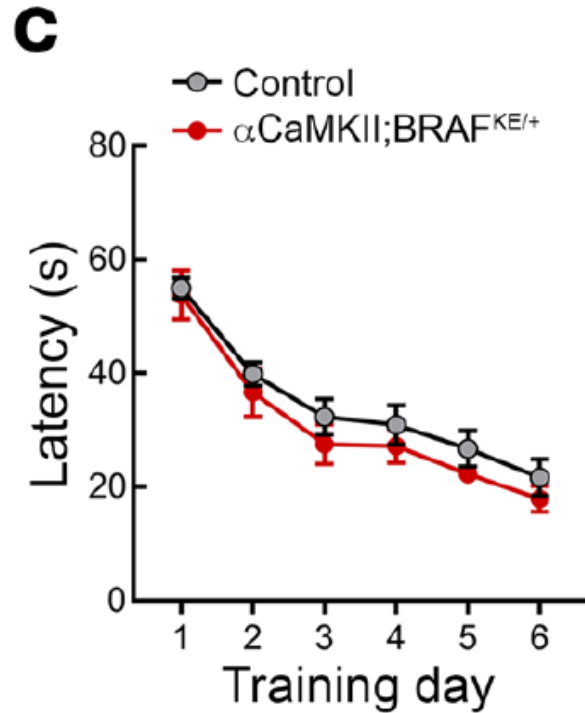
CFCS animal model: Gain-of-function *Braf* mutant mice

Conditional knock-in mouse *Braf* **K499E** (Kinase-activated)

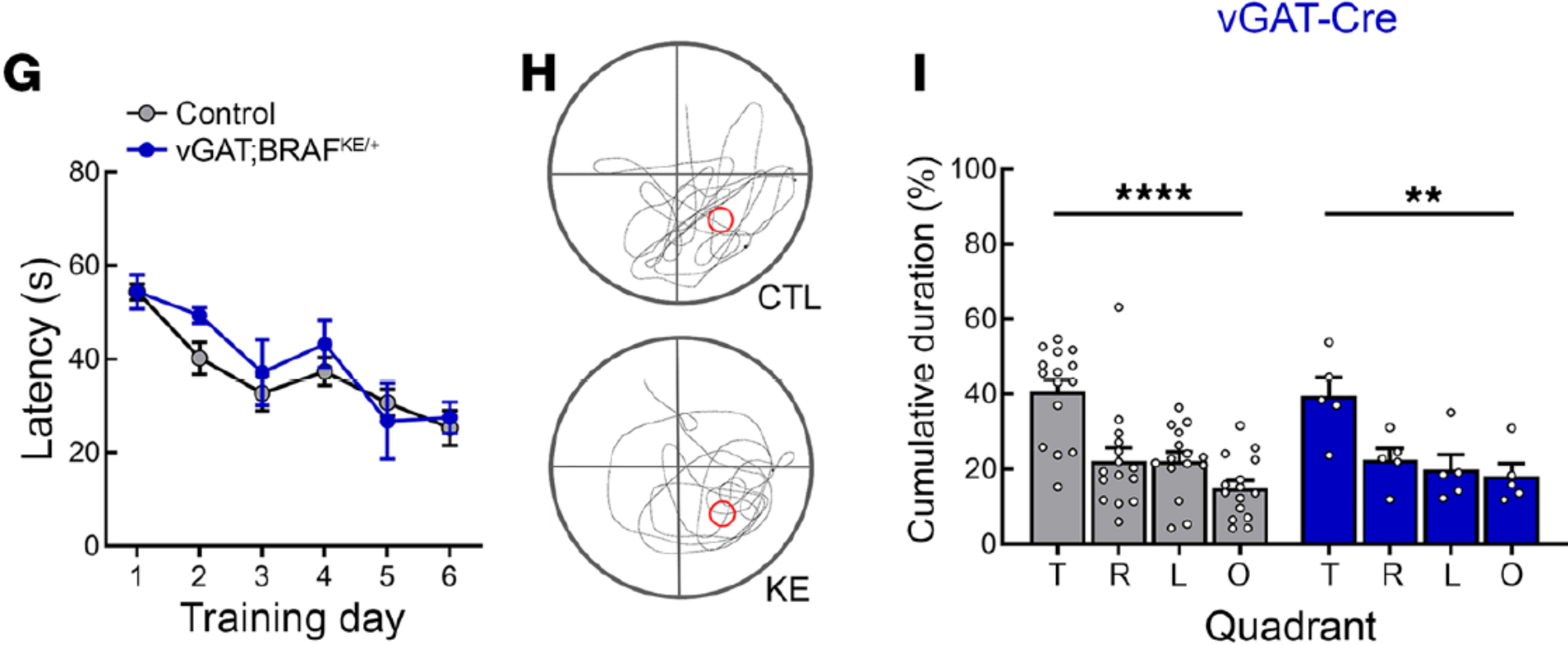


flox mice from Neel lab (NYU)

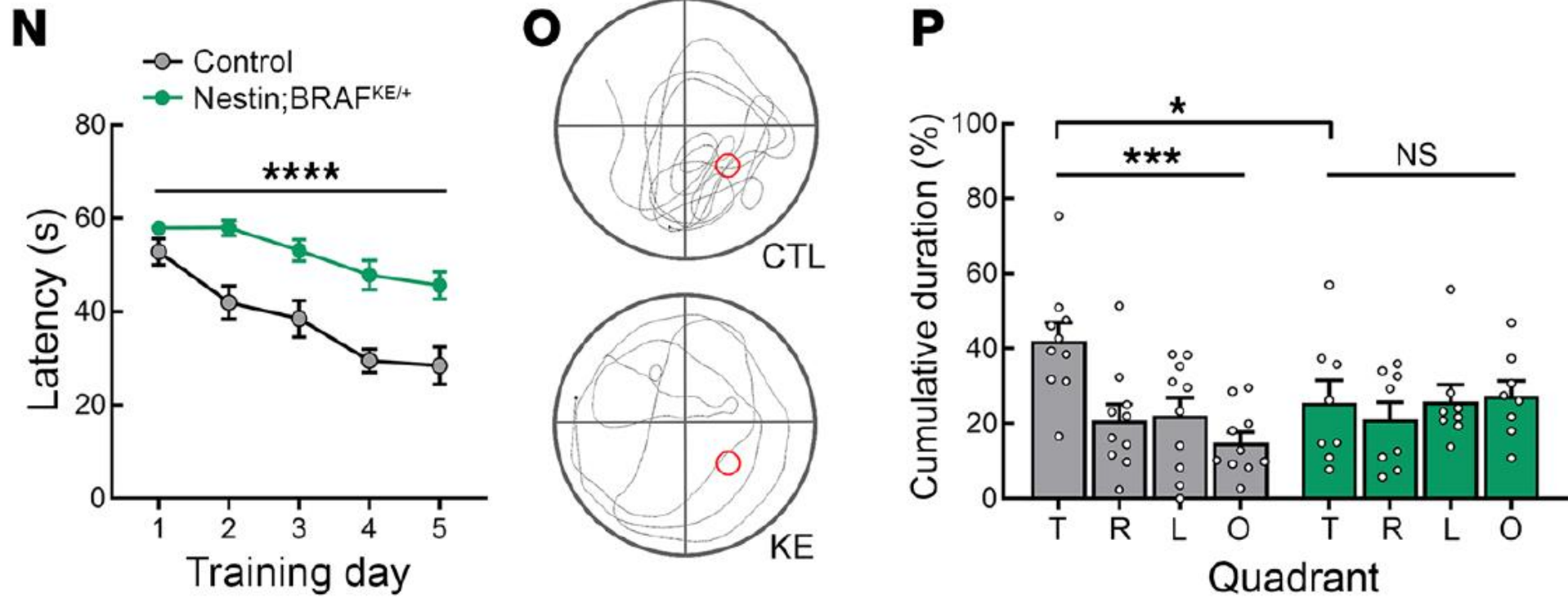
α CaMKII;Braf^{K499E/fl} mice show normal hippocampal L&M



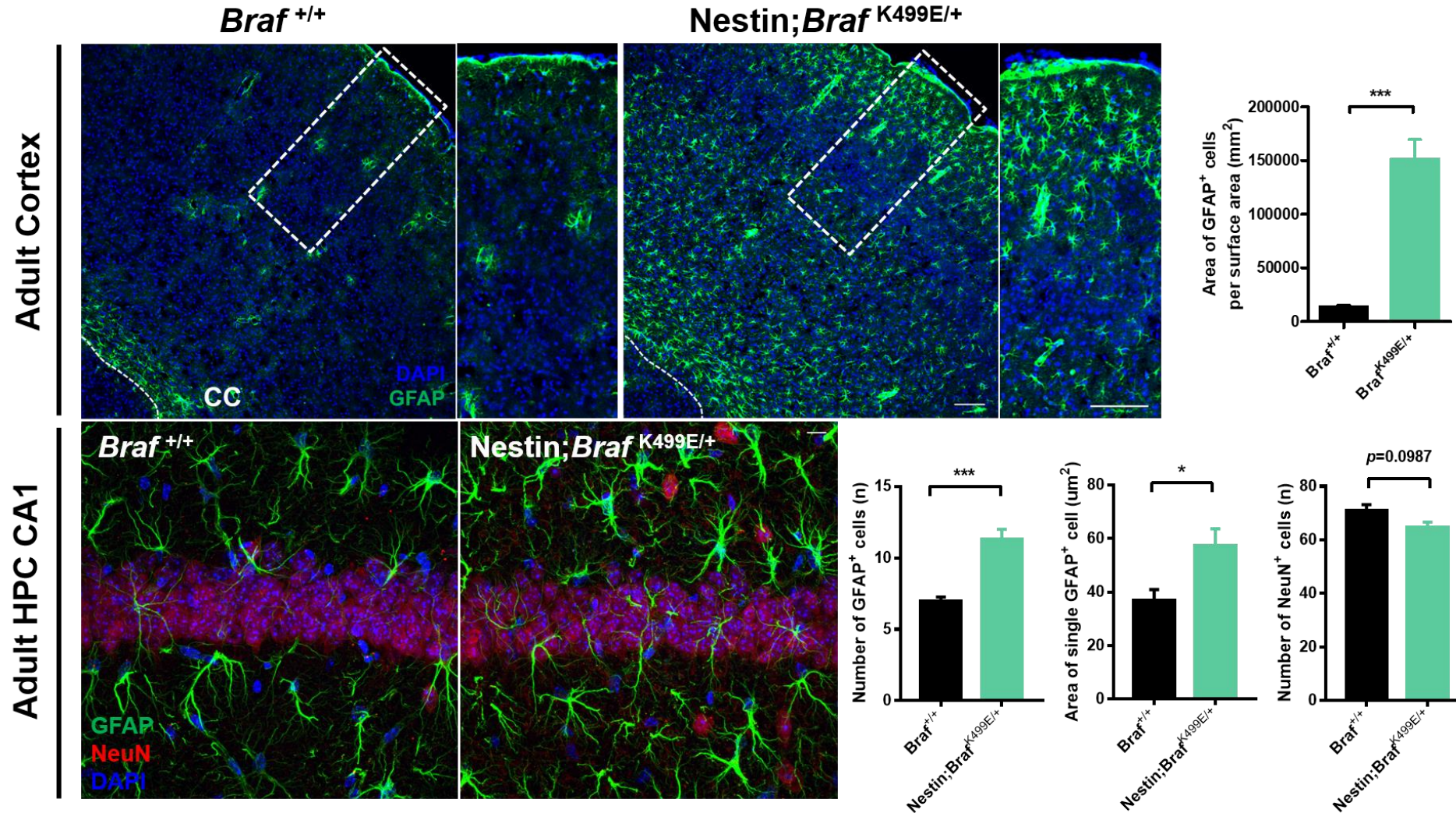
vGAT;Braf^{K499E/fl} mice show normal hippocampal L&M



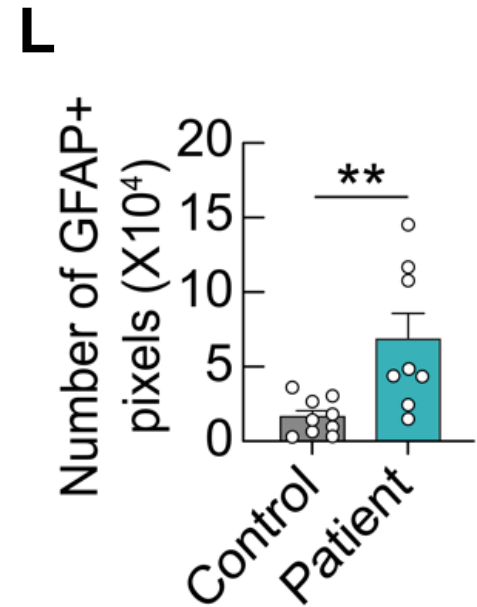
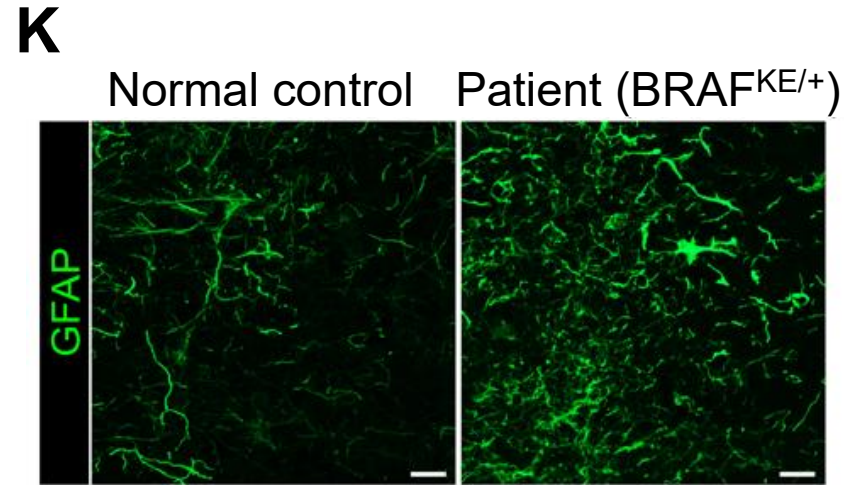
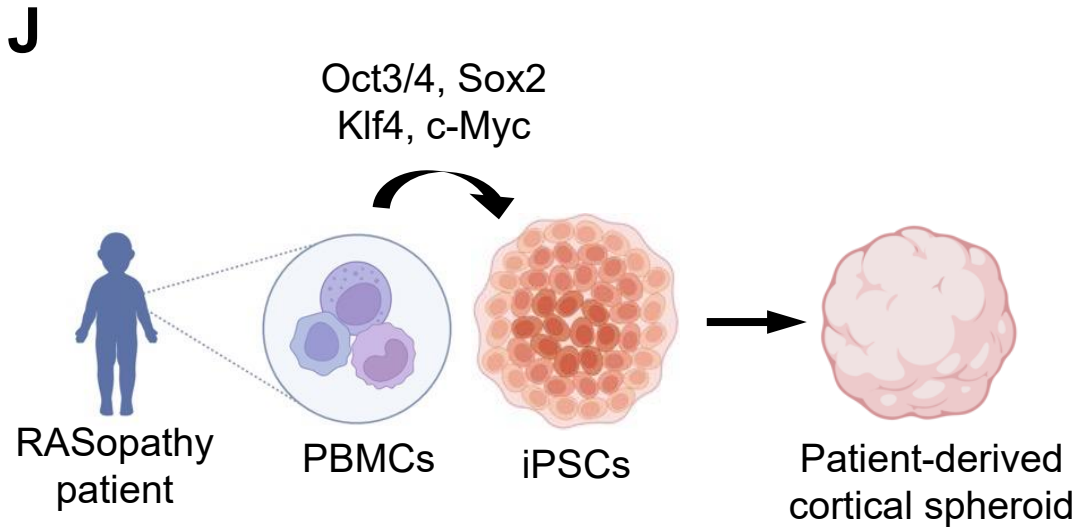
Nestin;Braf^{K499E/fl} mice show severe learning and memory deficits



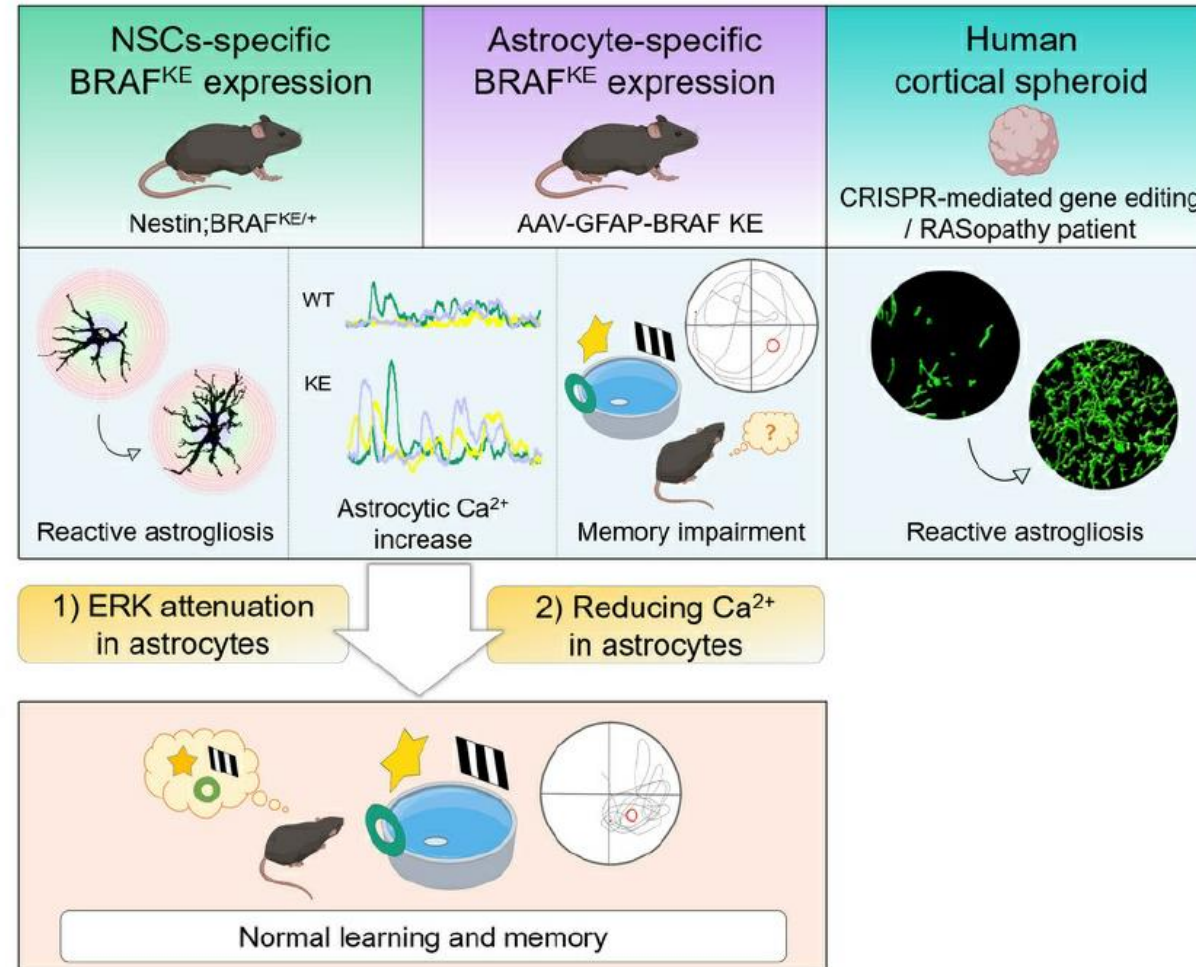
Increased GFAP(+) astrocytes in Nestin;*Braf*^{K499E/fl} mice



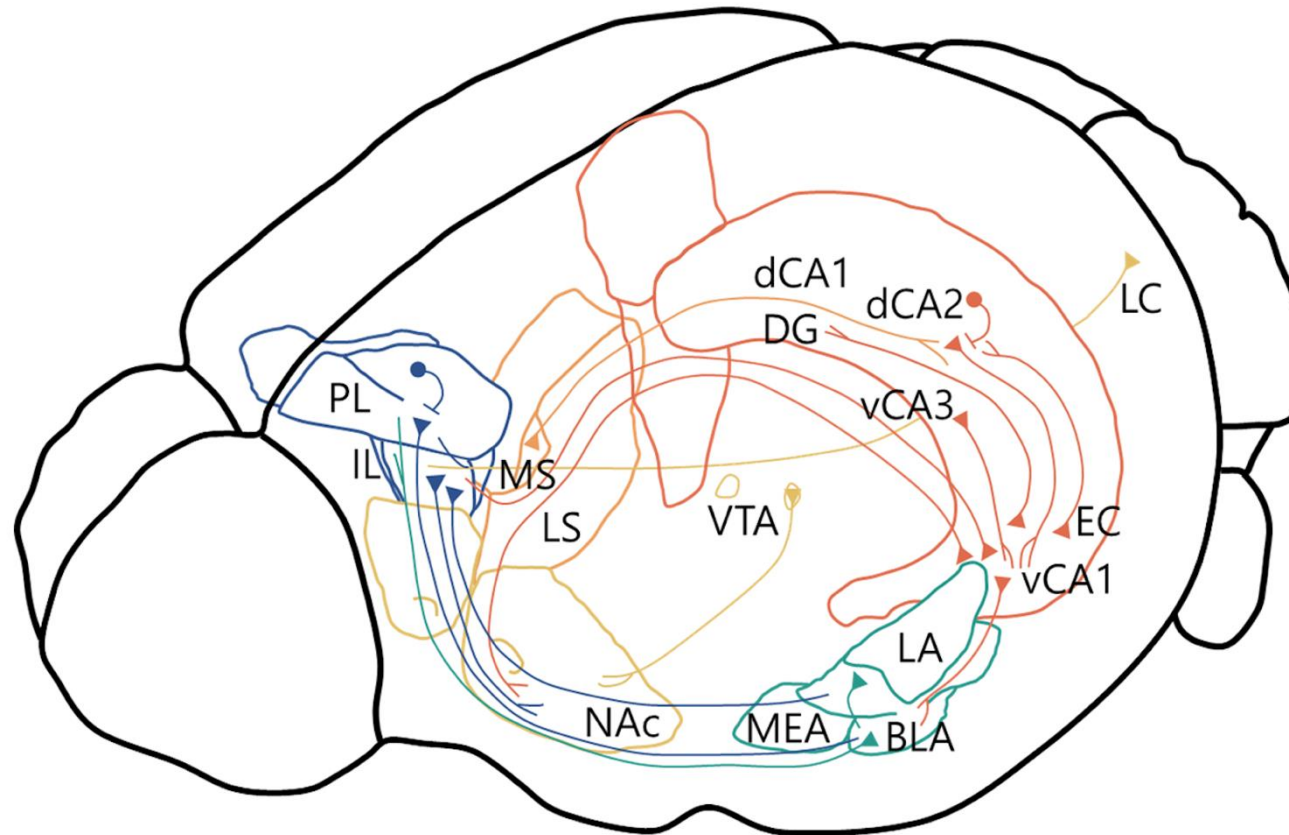
Korean patient-derived brain organoid showed similar phenotypes



Quick summary of CFCS-astrocyte project



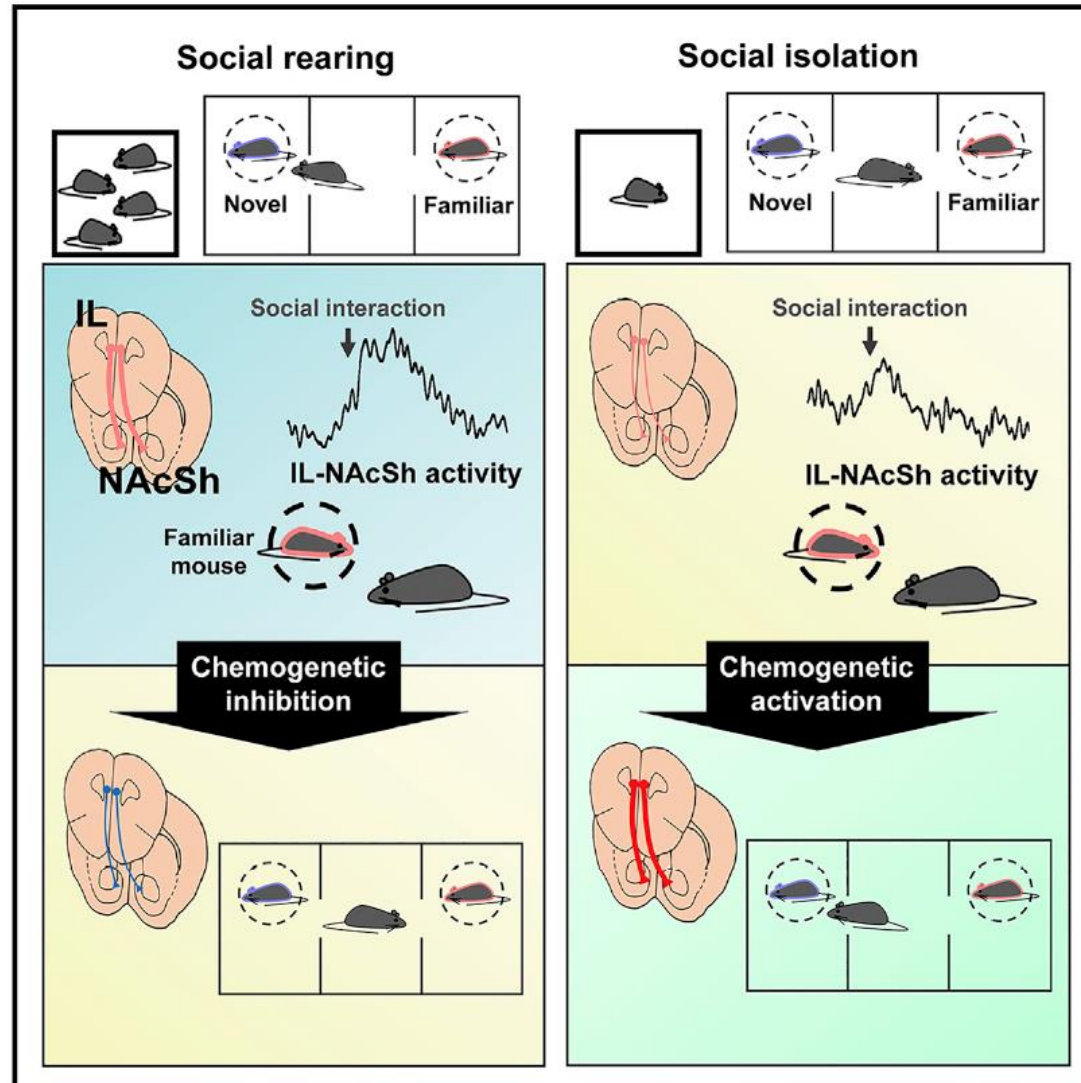
Challenge 3: Brain cells/regions do not work alone



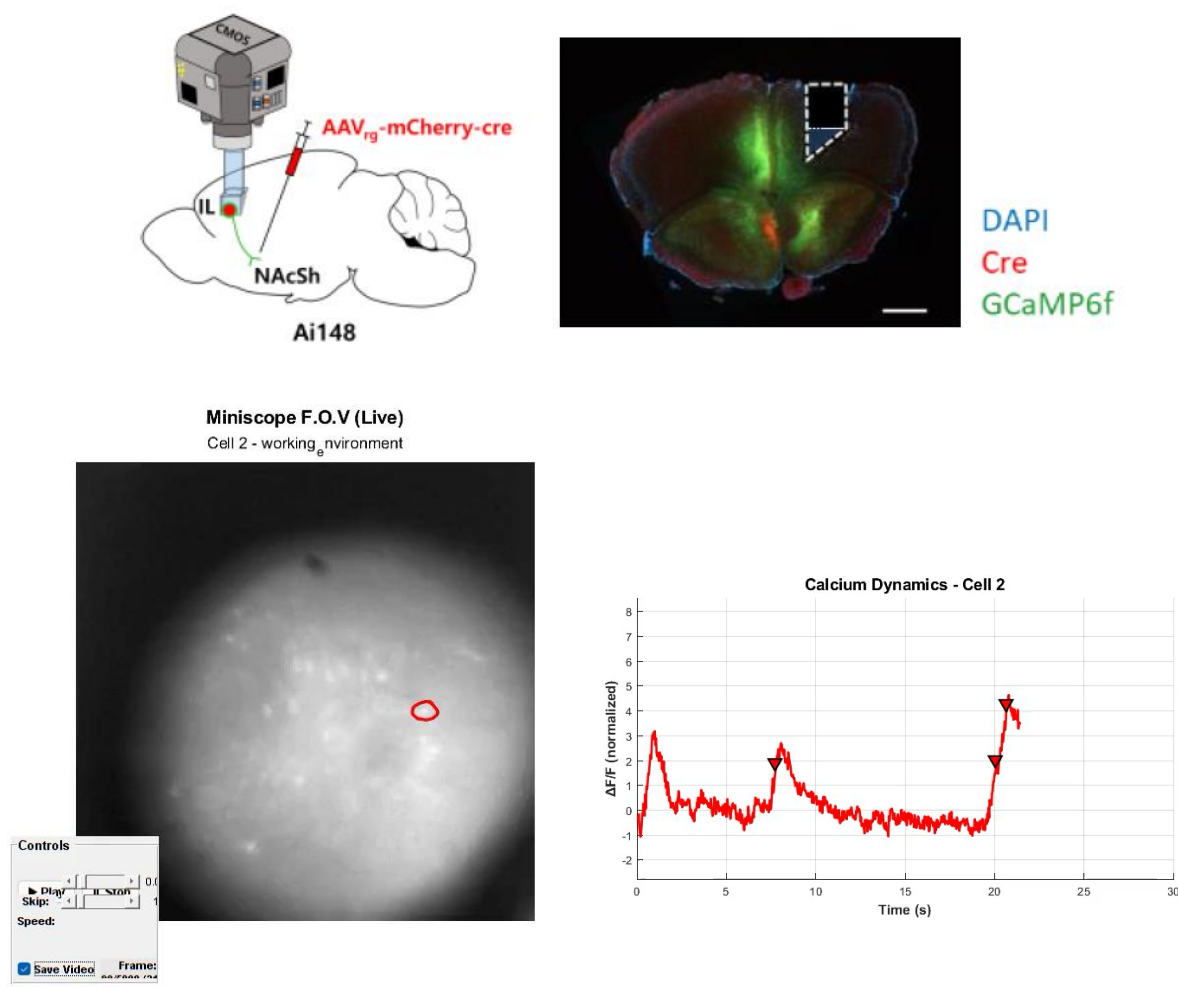
Circuit mechanisms underlying social memory consolidation



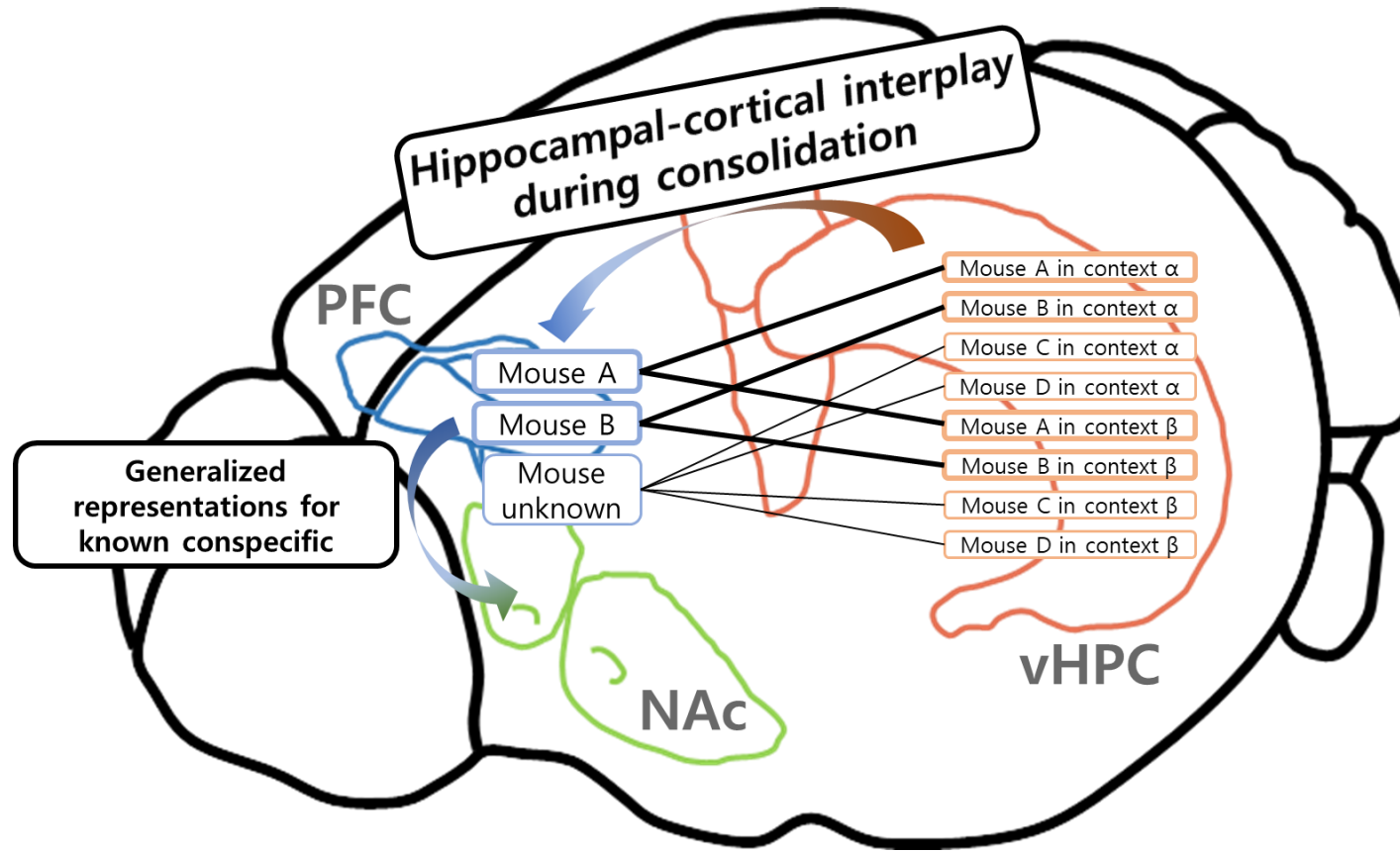
Circuit for social recognition memory in mice, affected by social isolation



We have to understand many neurons, part of a circuit



vCA1 $\rightarrow$ IL $\rightarrow$ NAcSh circuit encodes social familiarity



Research Topic 1
in my lab & future collaboration

Identification of **genetic modifiers**
affecting behavioral phenotypes in
neurodevelopmental disorders

Kim and Kim et al., *in prep*

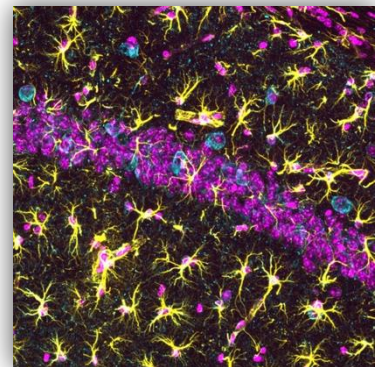


Research Topic 2

in my lab & future collaboration

Cell type-specific mechanisms of memory deficits in neurodevelopmental disorders

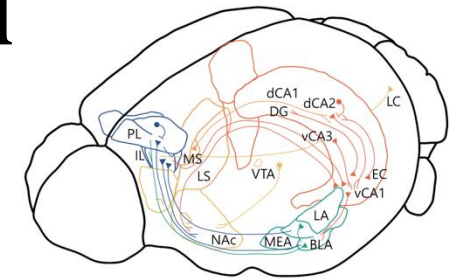
Lee et al., *Nature Neuroscience* 2014
Ryu and Lee, *Neurobiol Learn Memory* 2016
Ryu, Kim et al., *Science Signaling* 2019
Ryu, Kang et al., *Molecular Brain* 2019
Ryu, Kang et al., *Scientific Reports* 2020
Lee et al., *PNAS* 2024
Kang et al., *JCI* 2025



Research Topic 3

in my lab & future collaboration

Circuit mechanism underlying social memory and its deficits in ASD mouse model



Park et al., *Cell Report* 2021

Park et al., *Mol Brain* 2022

Jane et al., *Mol Psychiatry* 2022

Park et al., *EMM* 2023

Park et al., *BioRxiv* 2025

Research Topic 4

in my lab & future collaboration

Sex differences in neurodevelopmental disorders



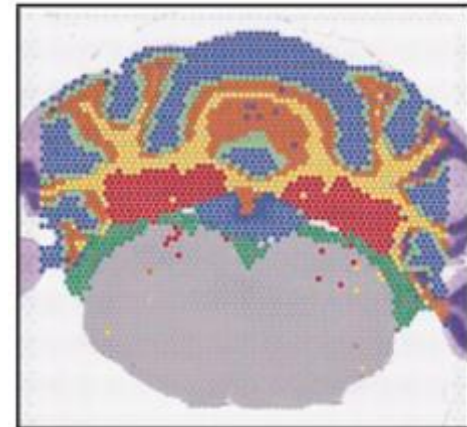
Kim et al., *in prep*
Kim, Park et al., *in prep*

Research Topic 5

in my lab & future collaboration

Non-motor functions of **the Cerebellum**

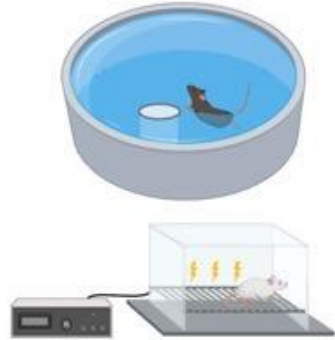
Han et al., *eLife* 2021
Hwang et al., *Frontiers* 2022
Hwang et al., *Cell Rep* 2023
Lee et al., *Mol Psy* 2023
Ji et al., under revision



Key techniques and resources I can share with you!

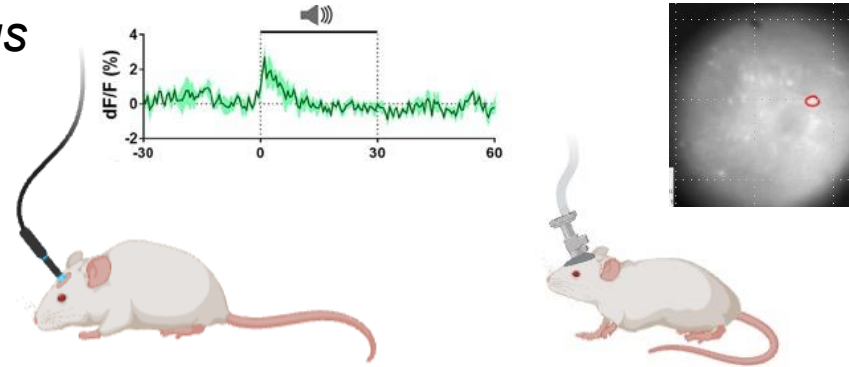
Behavioral analyses

Spatial memory
Social
Fear
Sensory
Motor



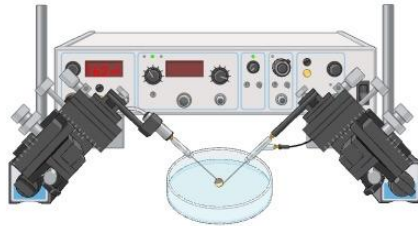
In vivo recordings

Fiber photometry
1p, 2p Miniscope
Tetrode recordings



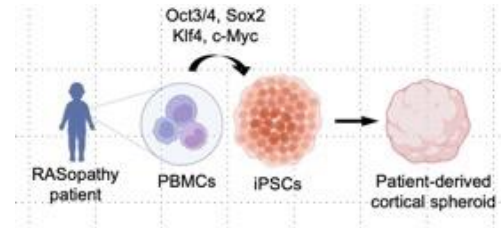
Electrophysiology

Whole cell patch
Local field recording



Clinical data and samples

Working with SNU Hospitals



Lab of Neurophysiology

<http://brain.snu.ac.kr>

Lab members

Current

Soobin Kim
Myeongjong Yoo
Jinhee Baek
Min Gyun Kim
Taewoo Kim
Yebum Shin
Hee Ju Kim

Alumni

Hyun-Hee Ryu
Minkyung Kang
Kyung-Doo Hwang
Gaeun Park
Ahbin Kim
Hanbyul Jang
Sun Yong Kim



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Teachers' appreciation day, 2024

Key Collaborators

SNU

Sang Jeong Kim
Murim Choi

SNUH

Hee Jeong Yoo
Jong-Hee Chae

Korea Univ

Joon-Yong An

U Iowa

Ted Abel

Supported by grants from



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