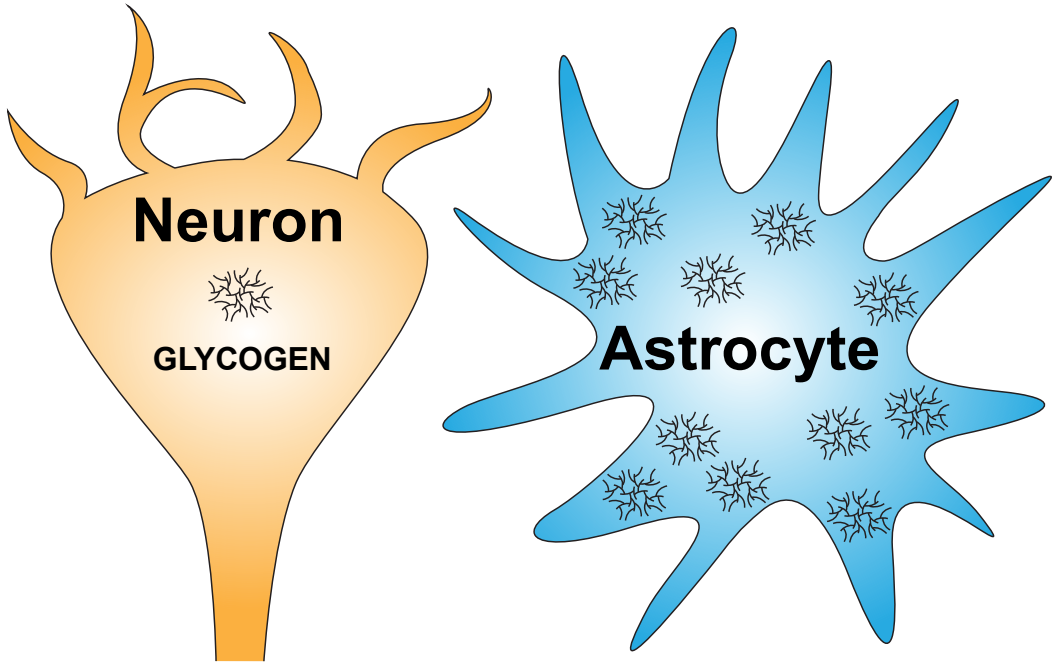
INSTITUTE FOR RESEARCH IN BIOMEDICINE

IRB BARCELONA

The physiological roles of glycogen in astrocytes and neurons



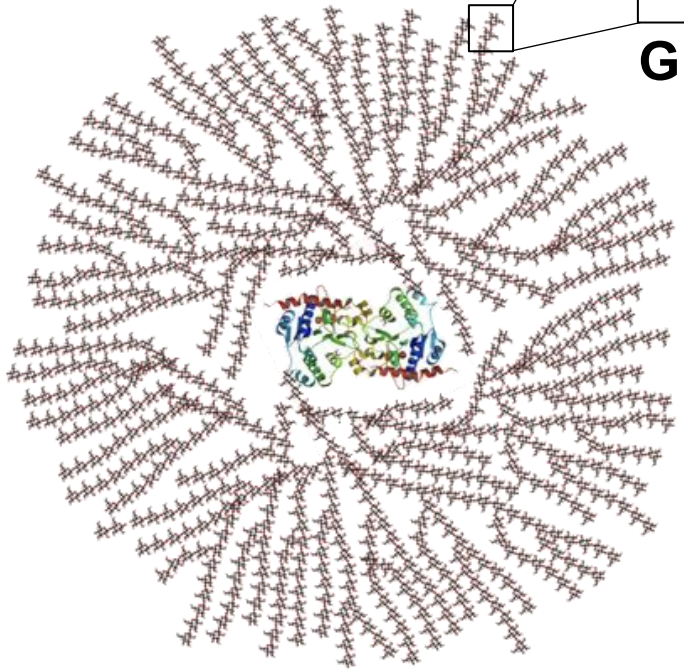
IRB Node Seminar

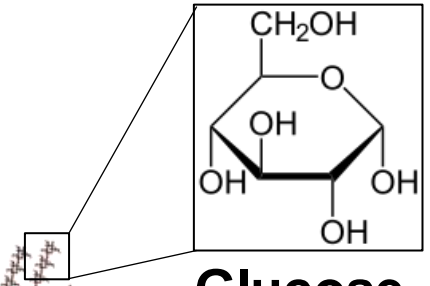
Mary Kathryn Brewer

2 March 2020

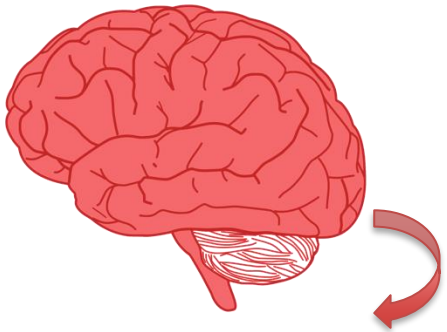
Introduction to glycogen

Glycogen





Glucose

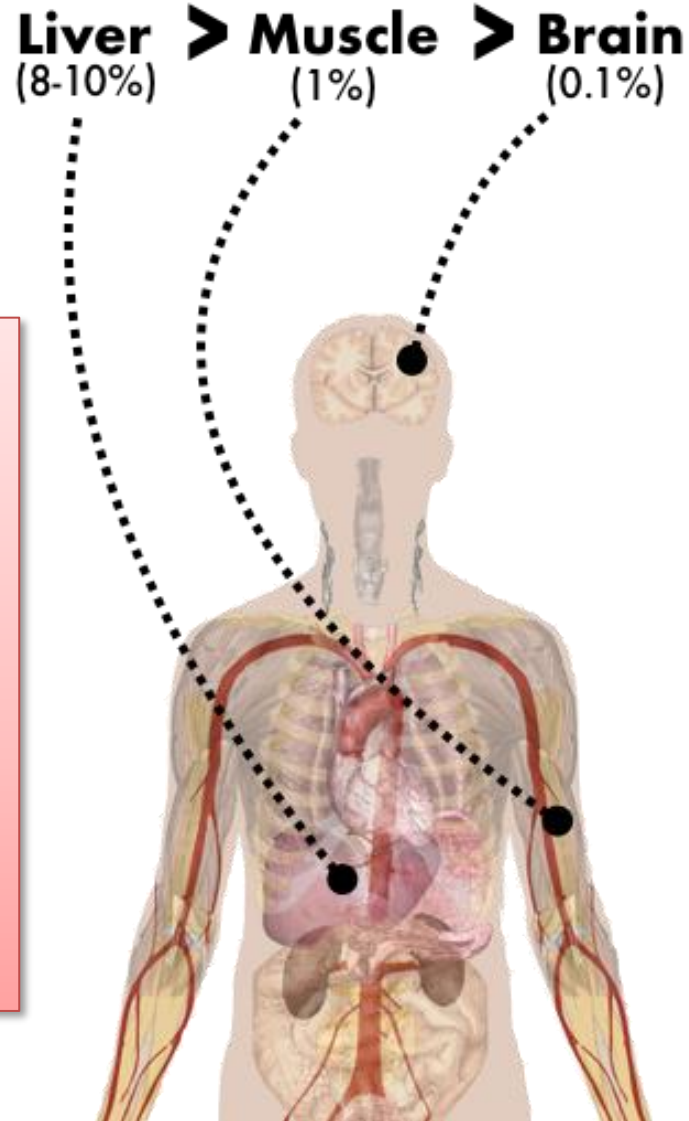


Learning and memory
- Gibbs et al. (2007)
- Suzuki et al. (2011)
- Duran et al. (2013)
- Duran et al. (2019)

Aging
- Duran et al. (2012)
- Sinadinos et al. (2014)

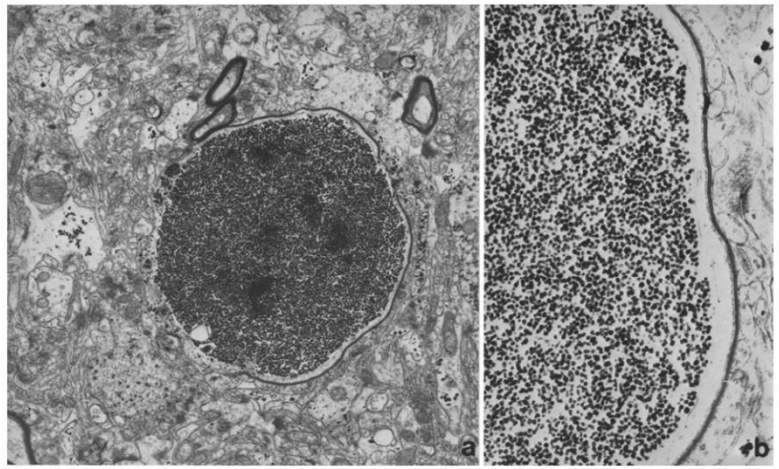
Neuronal excitability
- Lopez-Ramos et al. (2015)

Hypoxia tolerance
- Saez et al. (2014)
- Lopez-Ramos et al. (2015)



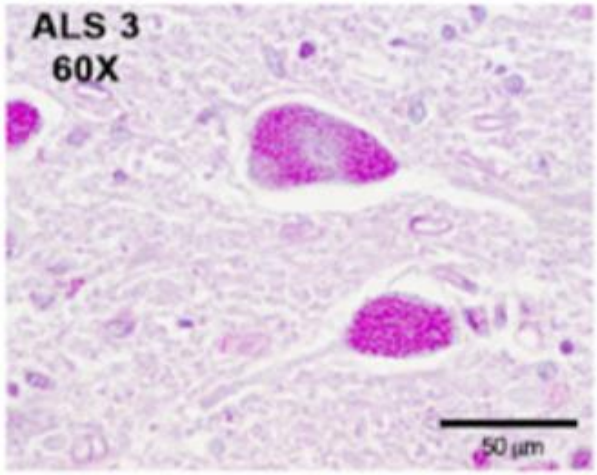
Cerebral glycogen accumulation in neurological diseases

Alzheimer's Disease



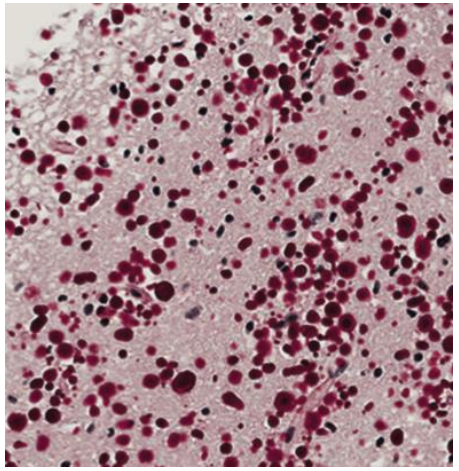
Mann, et al. *Acta Neuropathologica* (1987).

Amyotrophic Lateral Sclerosis

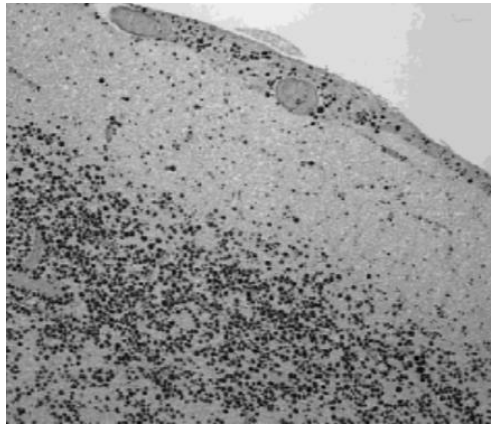


Dodge, et al. *PNAS* (2013).

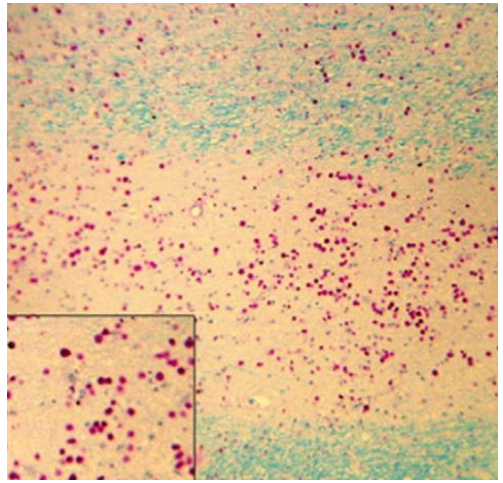
Temporal Lobe Epilepsy



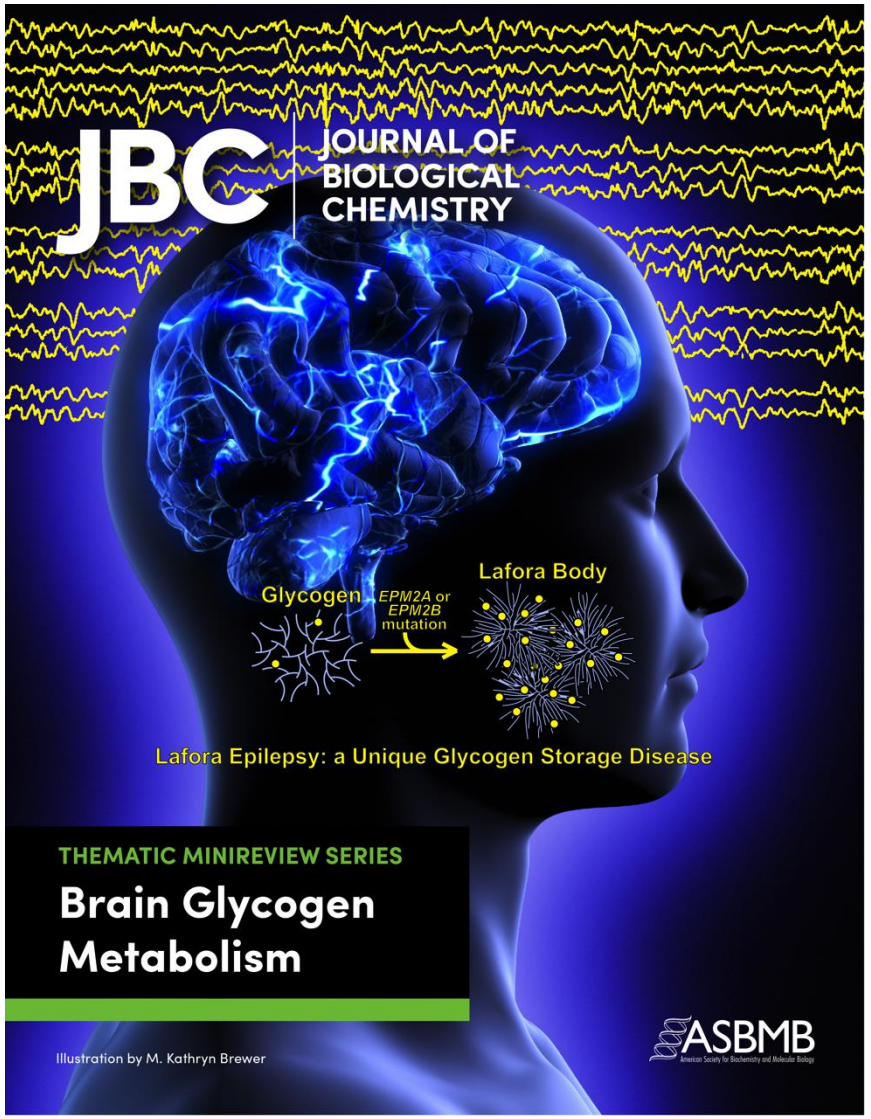
Lee, et al. *SNI* (2017).



Nishio, et al. *Epilepsia* (2001).



Radhakrishnan, et al. *Epilepsy Research* (2007).



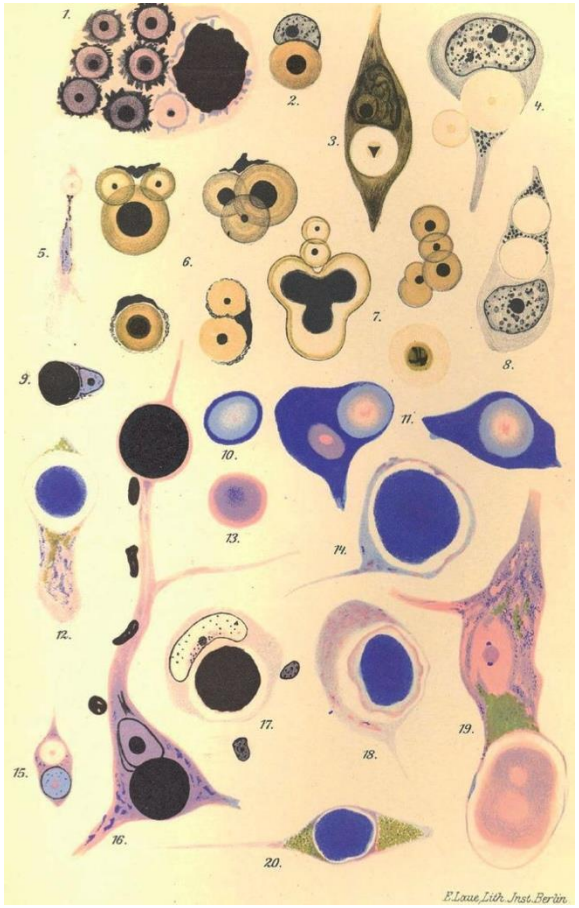
Lafora disease (LD): a glycogenosis of the brain

Late-stage LD patient

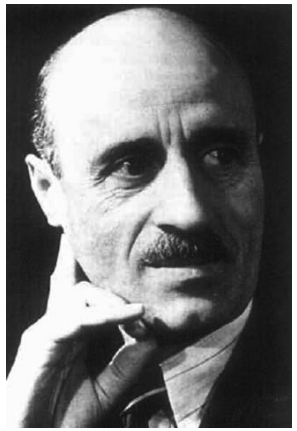


Beagle with LD



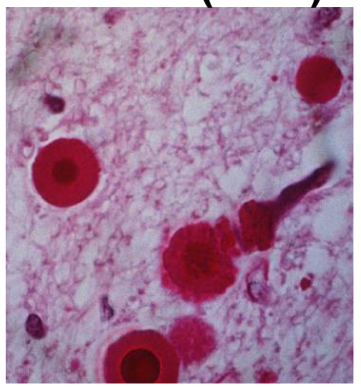


Lafora, *Virchows Arch Pathol Anat Physiol Klin Med* (1911).



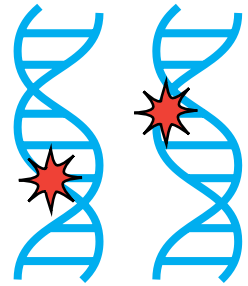
Gonzalo Rodriguez Lafora (c. 1930)

Periodic acid-Schiff (PAS)

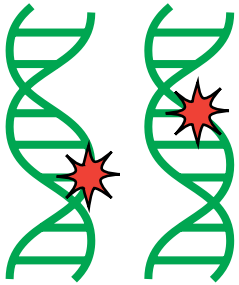


Courtesy of Jose Serratosa

the Epilepsy, Progressive Myoclonus type 2 (EPM2) genes

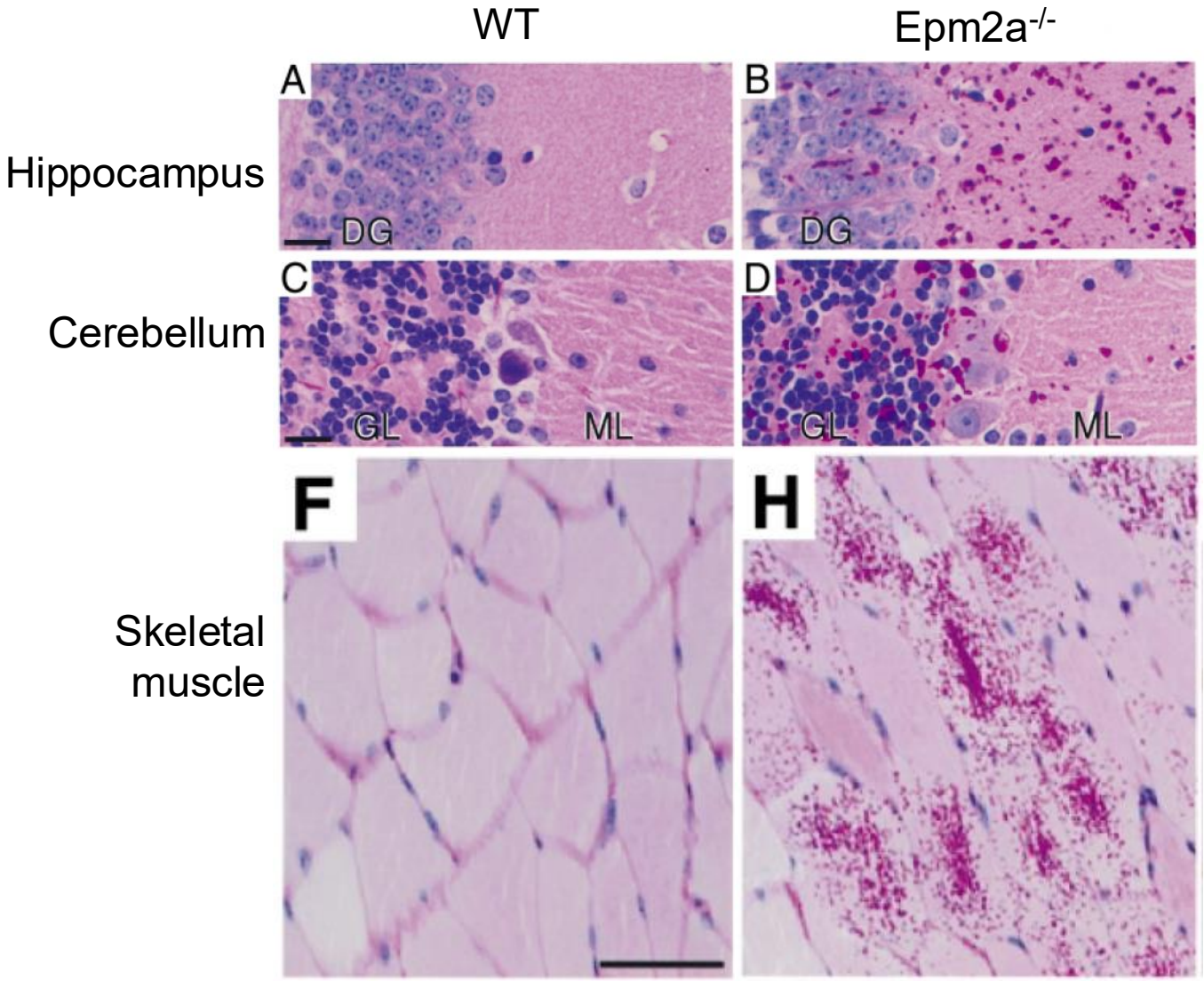


EPM2A



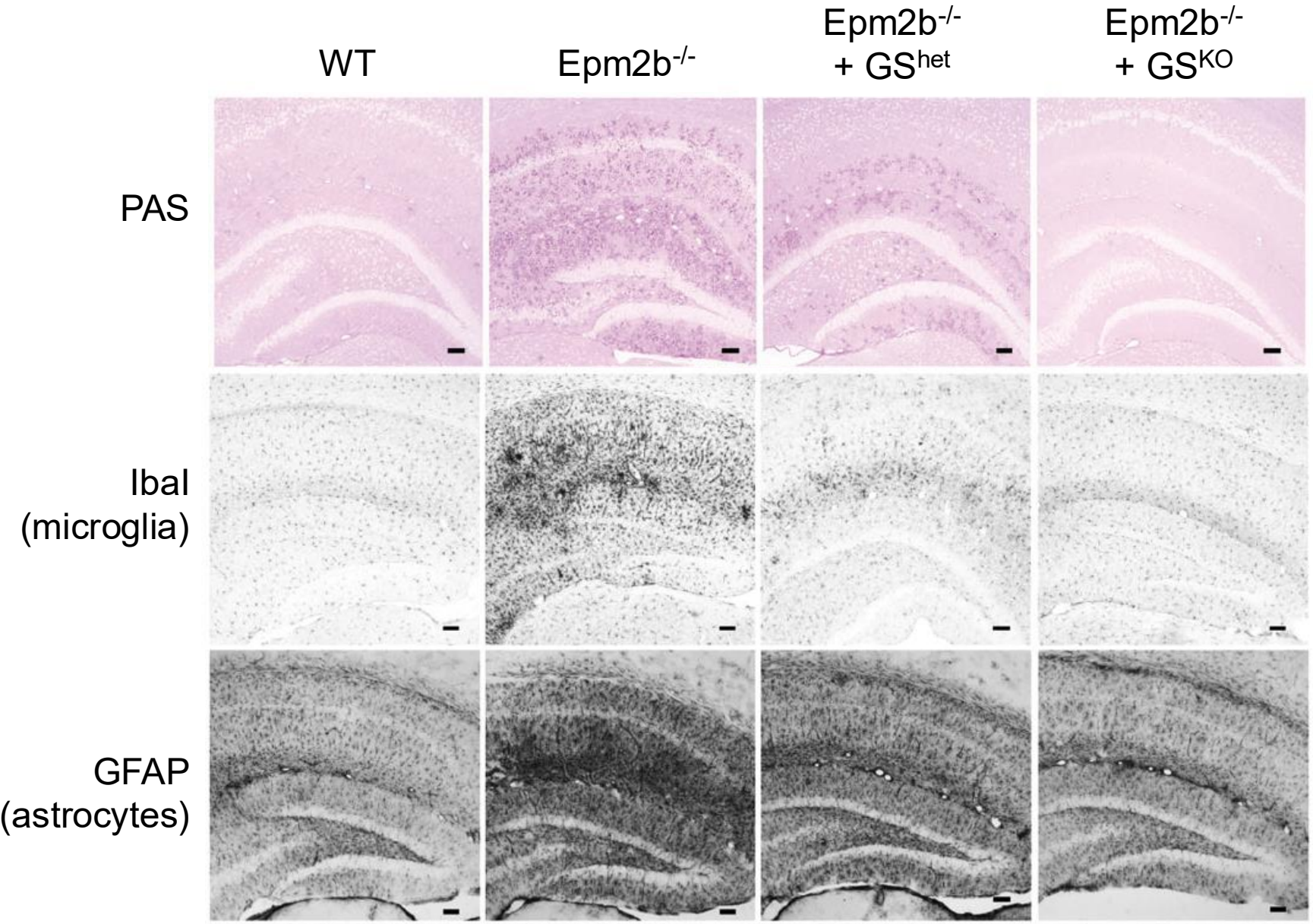
EPM2B

Lafora bodies drive disease pathology



Ganesh, et al. *Human Molecular Genetics* (2002).

Lafora bodies drive disease pathology



GS = glycogen synthase

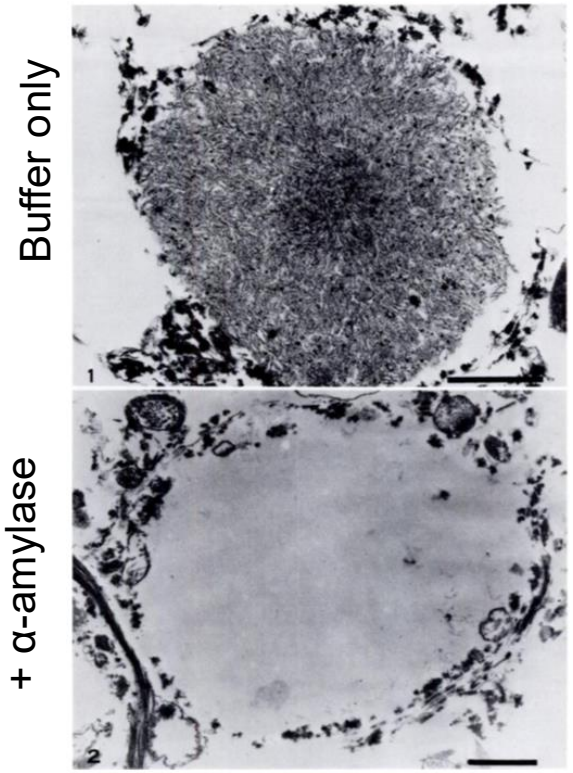
PTG = Protein Targeting to Glycogen (activator of GS)

<u>Double KOs</u>

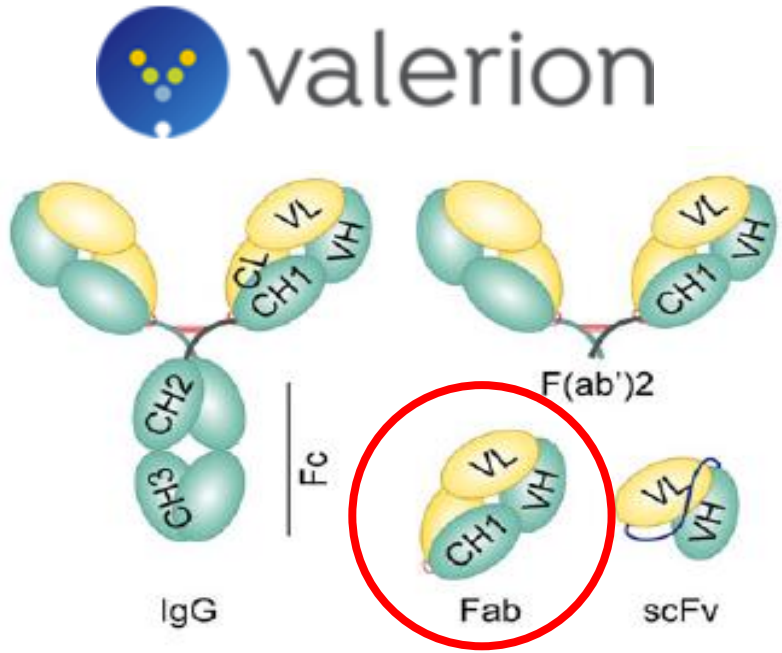
Epm2a / PTG – Turnbull et al., 2011
Epm2a / GS – Pedersen et al., 2013
Epm2b / PTG – Turnbull et al., 2014
Epm2b / GS – Duran et al., 2014

A delivery system for α-amylase

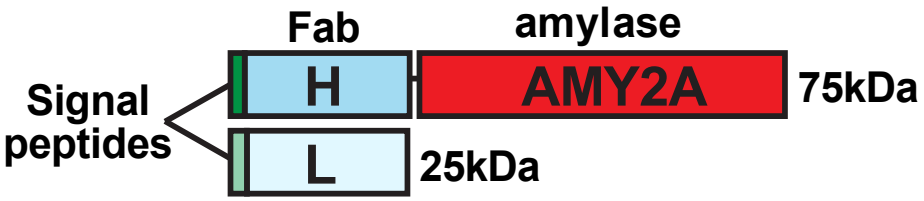
Lafora body
(fixed human tissue)



Nikaido et al. 1971. *J Histochem Cytochem*.

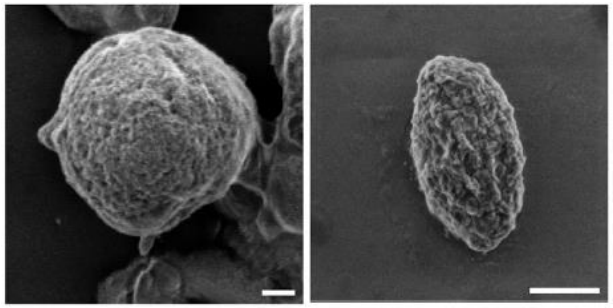


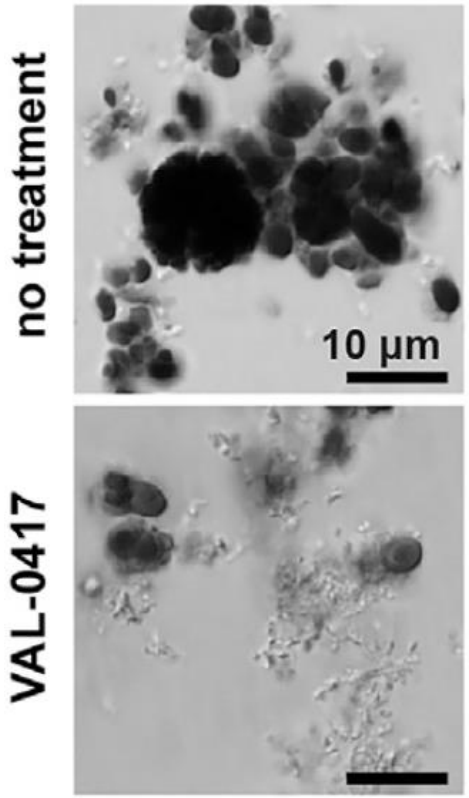
VAL-0417



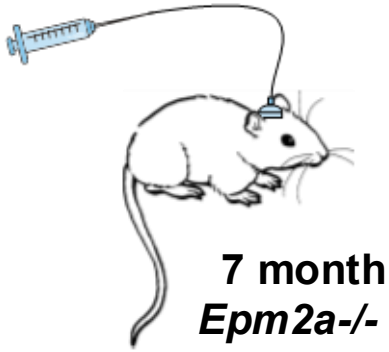
VAL-0417 degrades LBs *in vitro* and *in vivo*

Purified LBs





Intracerebroventricular (ICV) administration



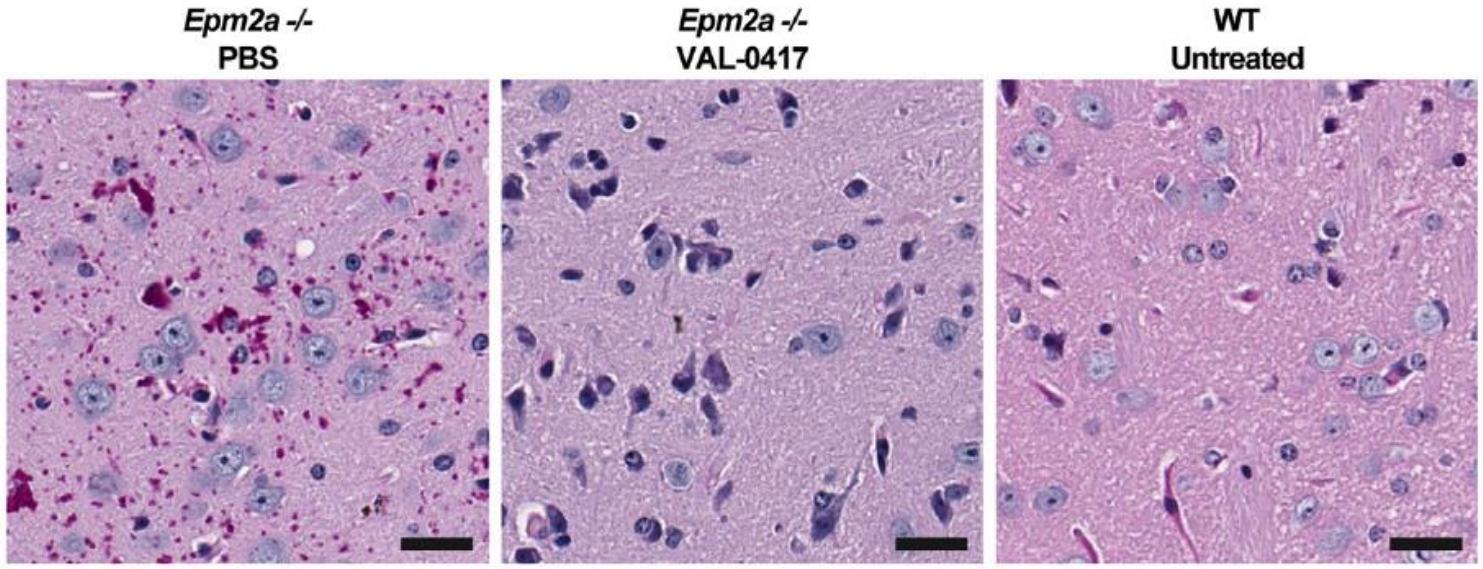
7 month old *Epm2a-/-* mice

Continuous infusion of VAL-0417 (0.08mg/day) or PBS for 8 days

→ **Euthanized on 9th day**

→ **Metabolomics via GCMS**

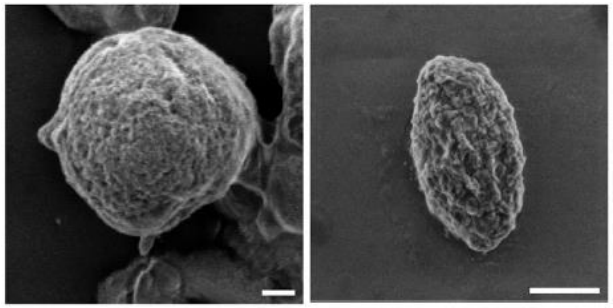
→ **PAS staining**

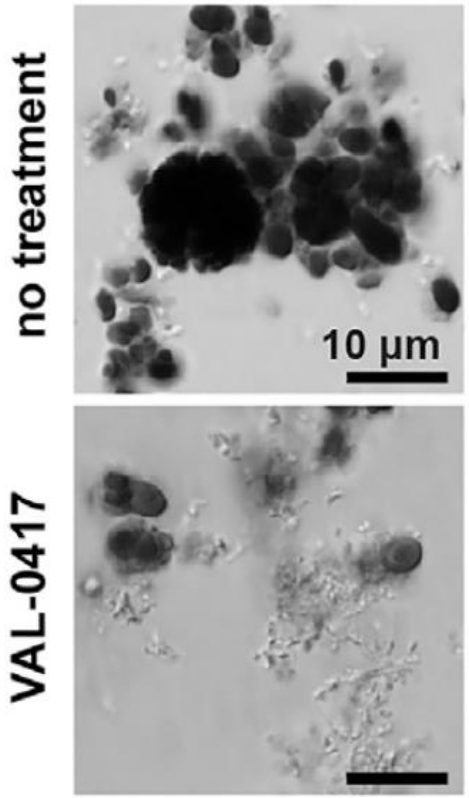


Brewer et al. *Cell Metabolism* (2019).

VAL-0417 degrades LBs *in vitro* and *in vivo*

Purified LBs





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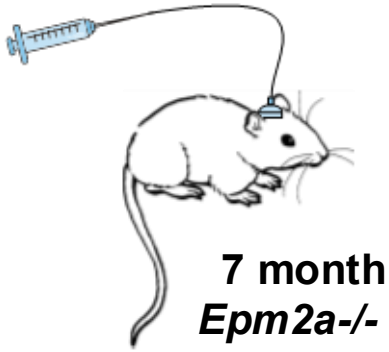

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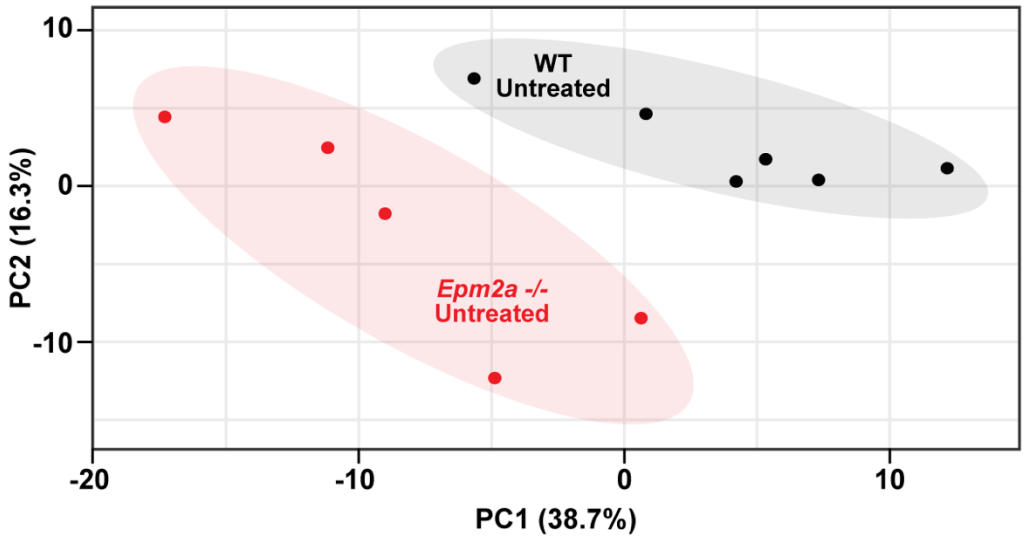
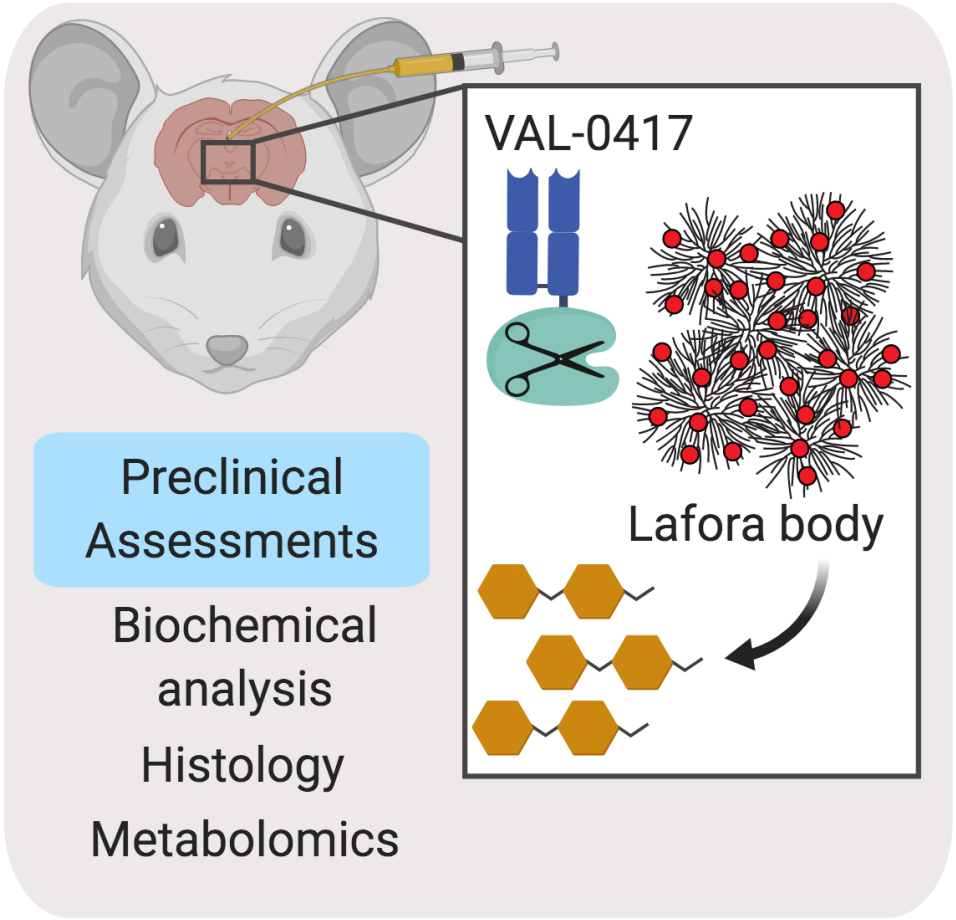
Principle Component (PC) analysis

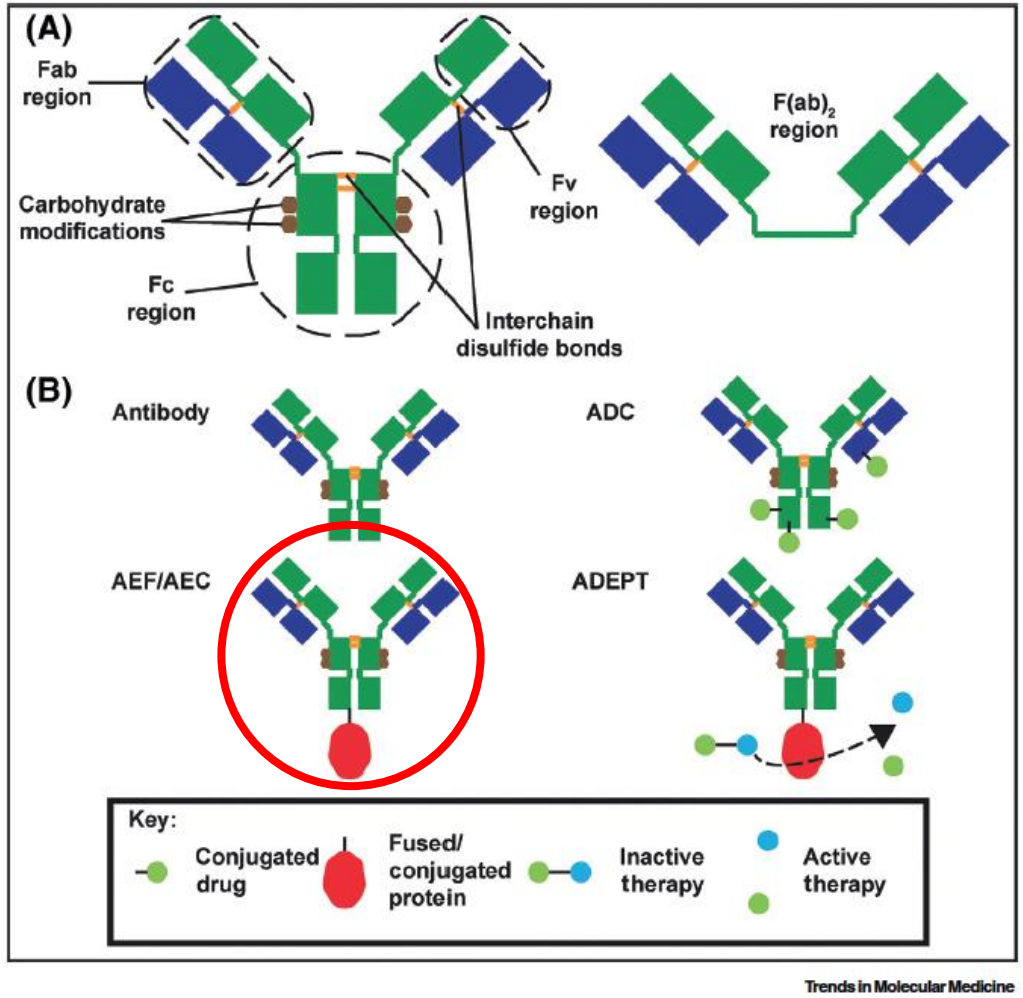


Brewer et al. *Cell Metabolism* (2019).

VAL-0417 is a putative therapeutic



Brewer et al. *Cell Metabolism* (2019).

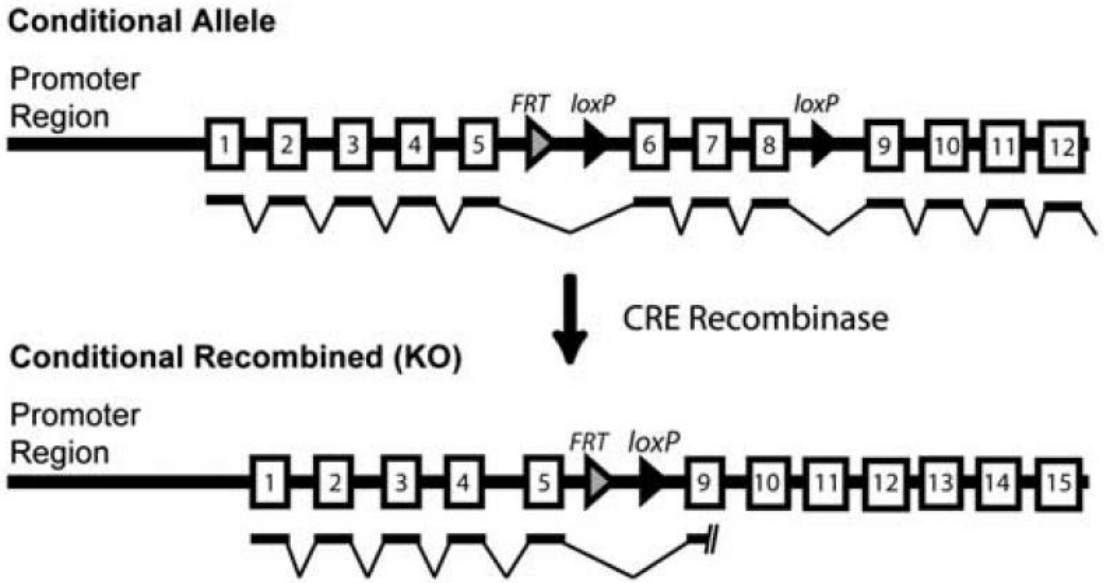


Zhou et al. *Trends in Molecular Medicine* (2019).

Lack of brain glycogen impairs associative memory



Lack glycogen in entire CNS



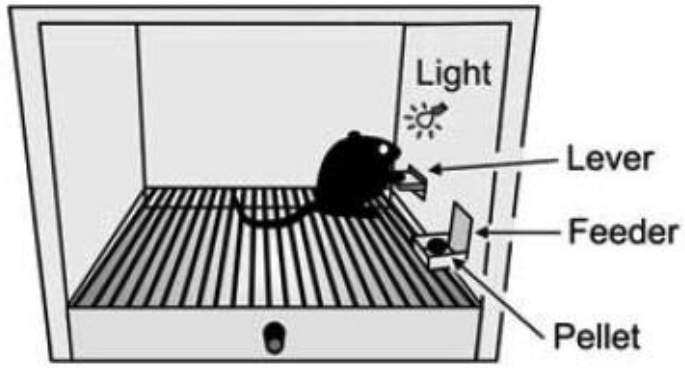
Duran et al. *JCBFM* (2013).

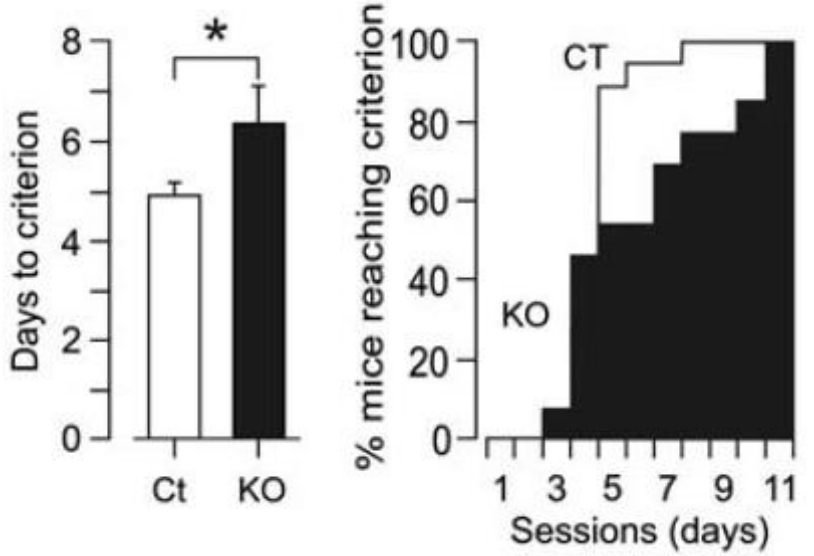
Lack of brain glycogen impairs associative memory

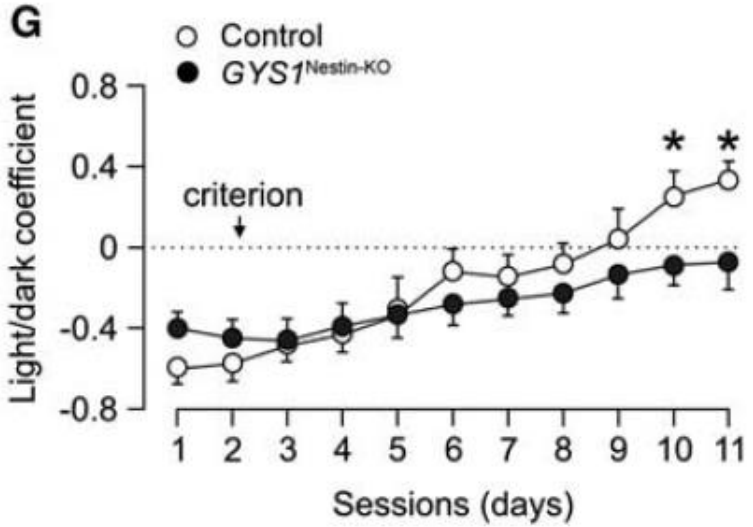


Lack glycogen in entire CNS

Skinner Box







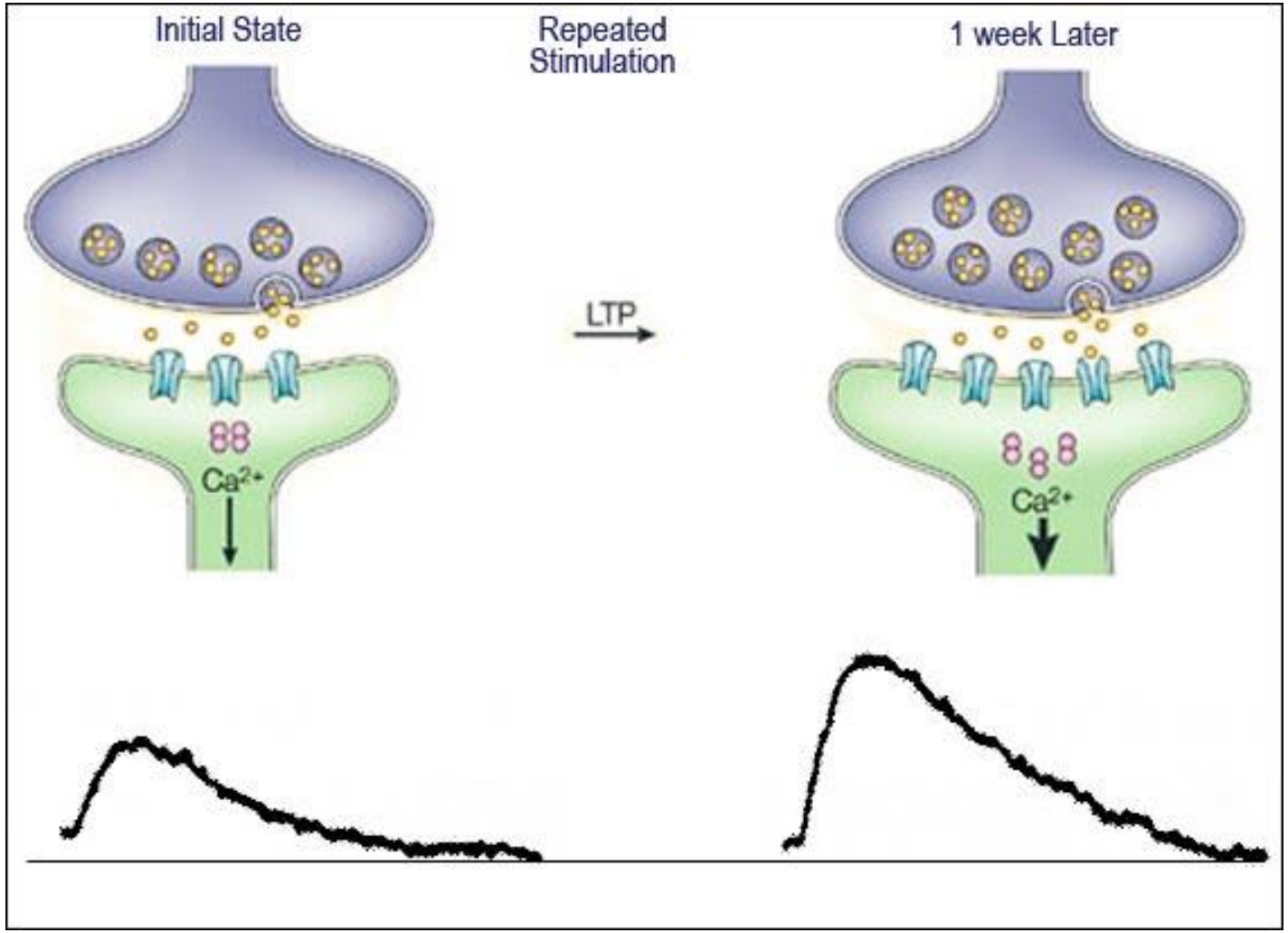
Duran et al. *JCBFM* (2013).

Lack of brain glycogen impairs LTP



Lack glycogen in entire CNS

Long term potentiation (LTP)

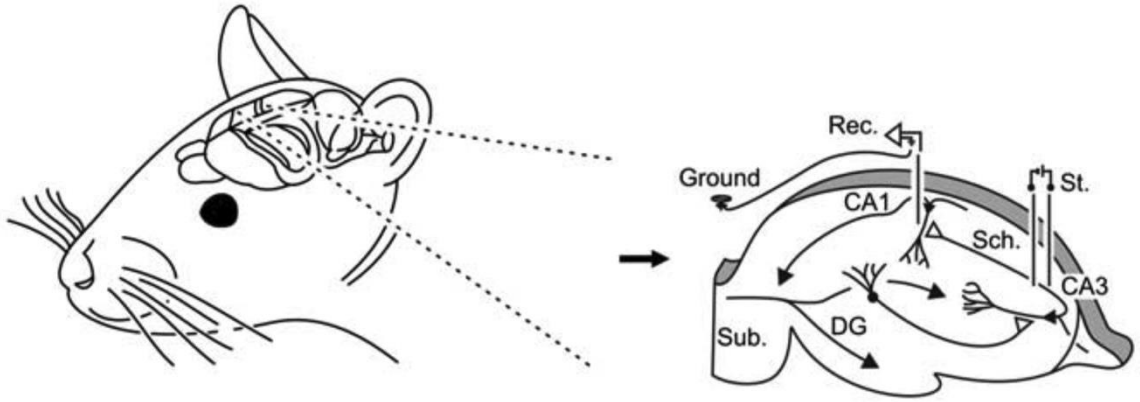


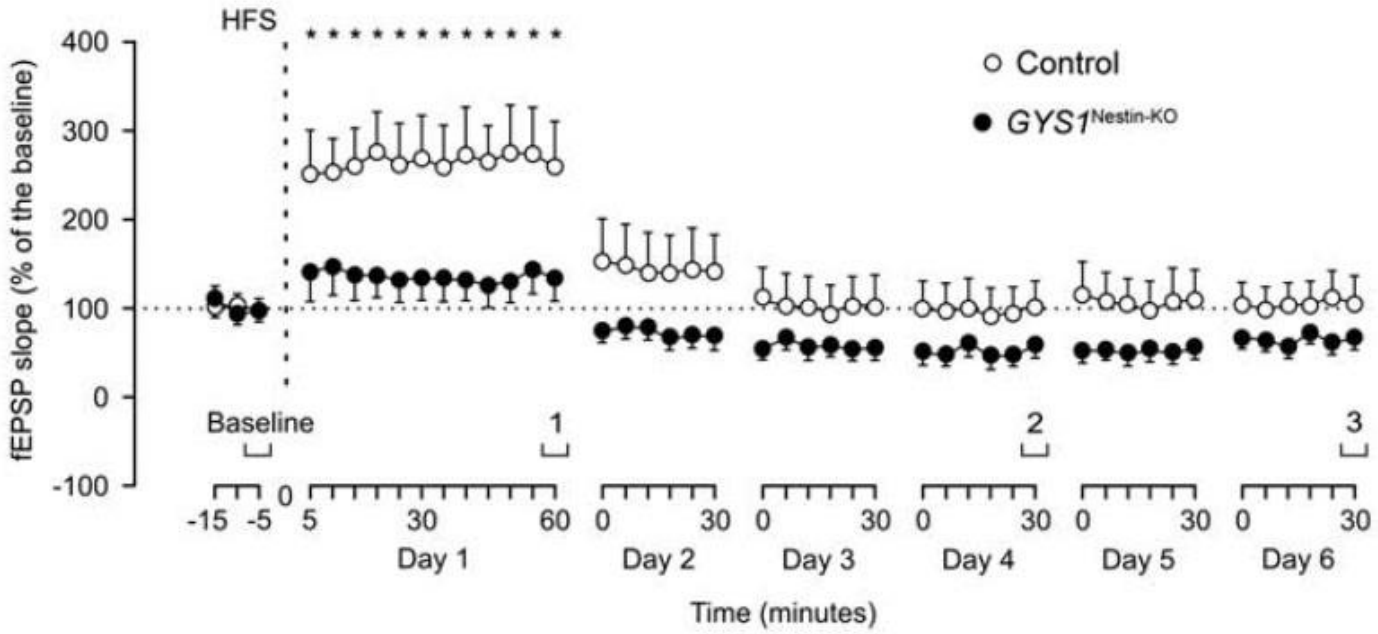
https://sites.google.com/site/mcauliffeneur493/home/synaptic-plasticity

Phenotype of GS$^{Nestin\text{-}KO}$ mice



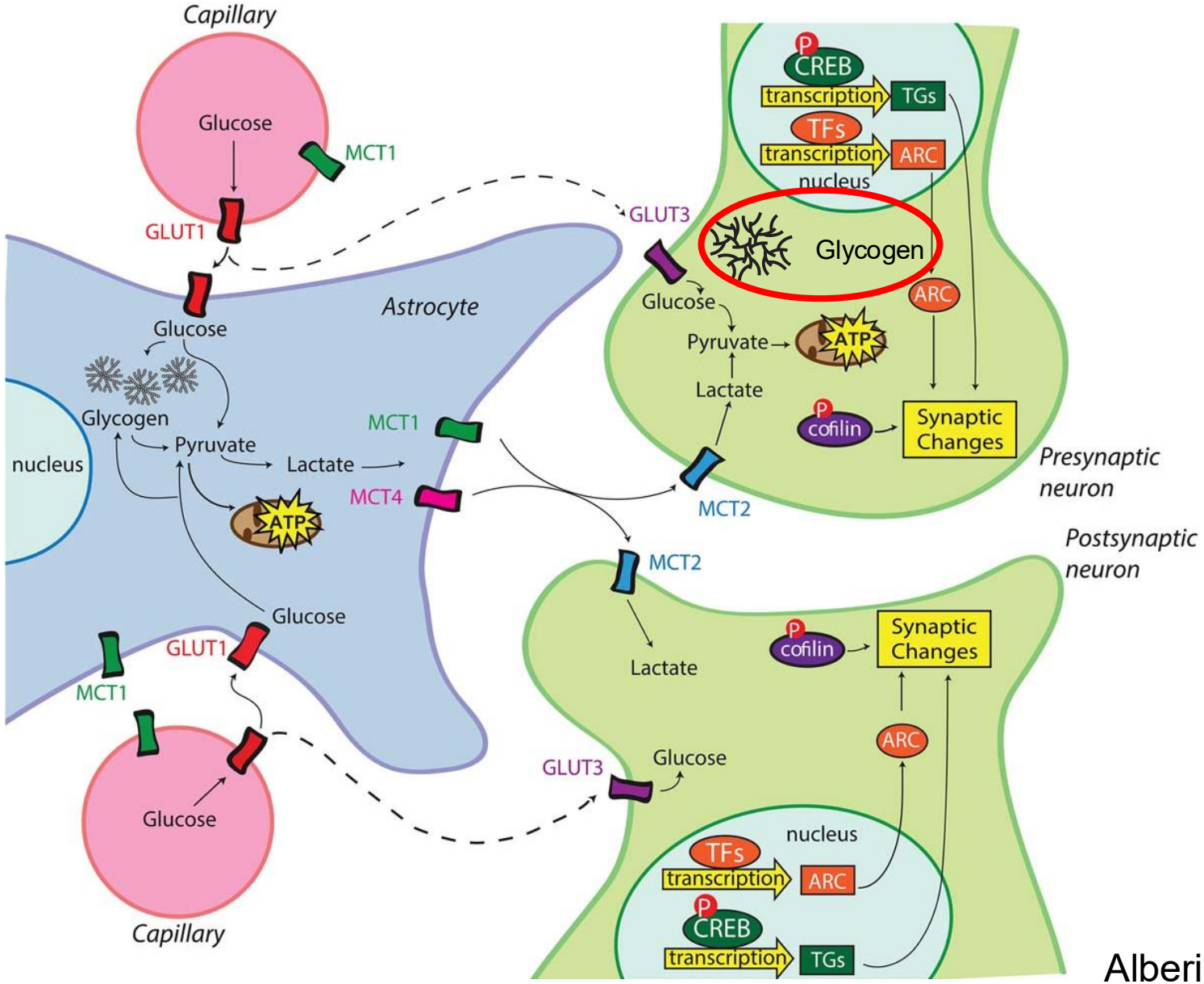
Lack glycogen in entire CNS





Duran et al. *JCBFM* (2013).

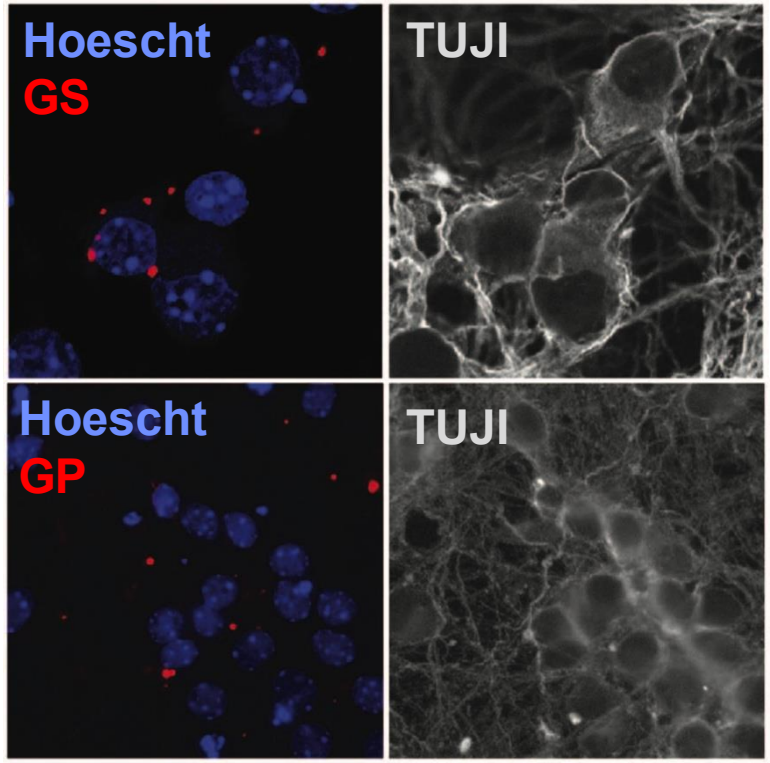
Glycogen in astrocytes and neurons

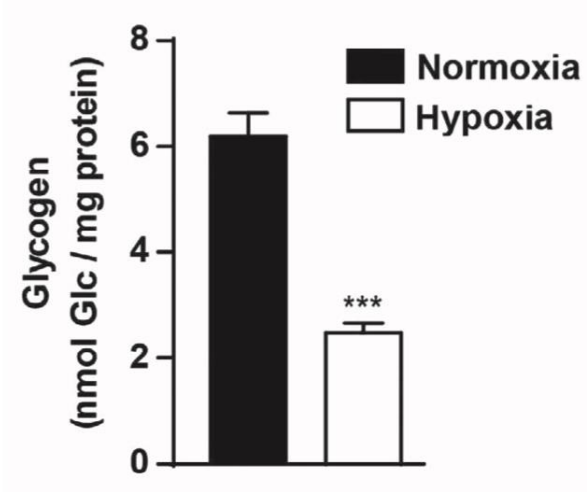


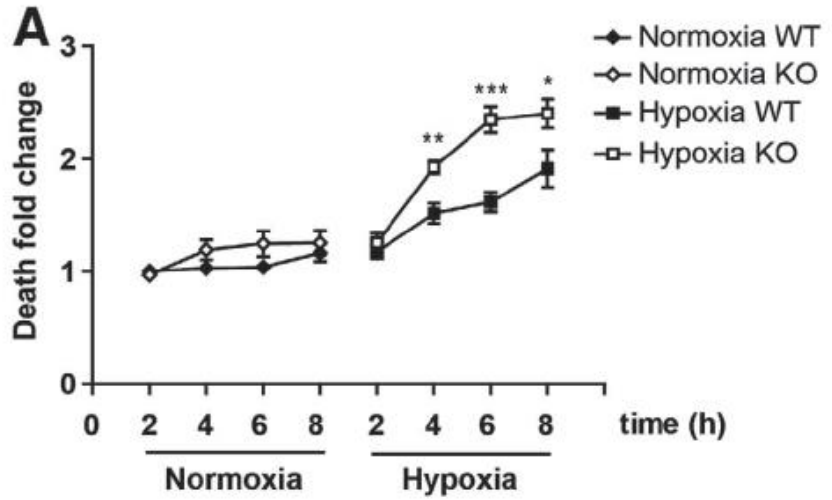
Alberini et al., *GLIA* (2017)

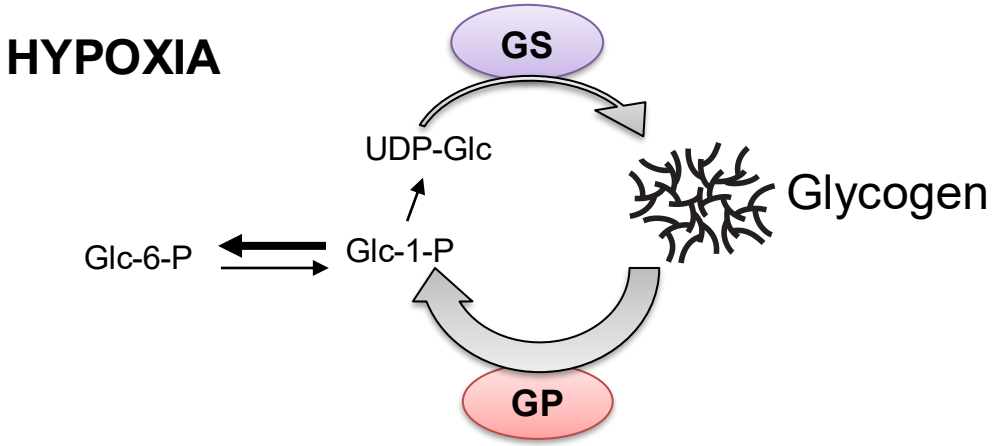
Glycogen protects neurons during hypoxia

GS = glycogen synthase
GP = glycogen phosphorylase
TUJI = neuronal marker





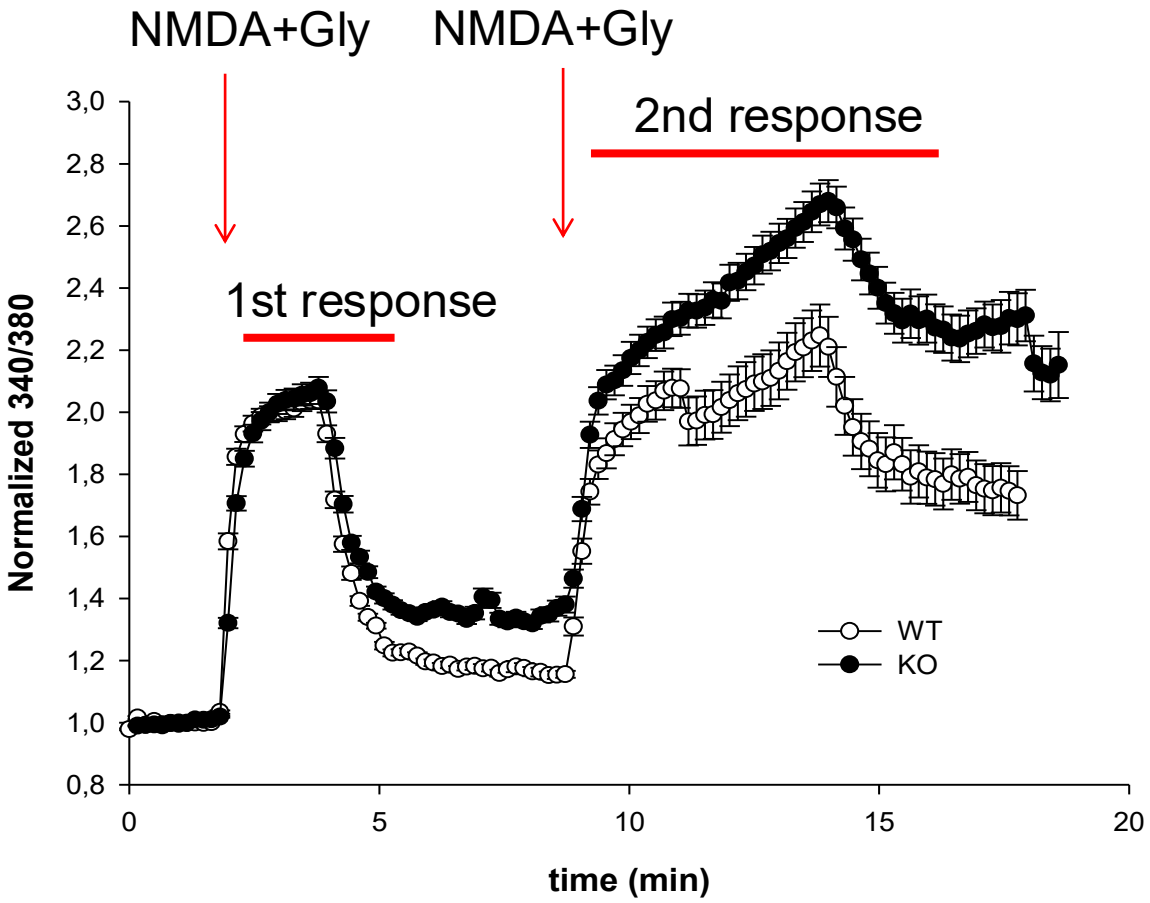




Saez et al., *JCBFM* (2014).

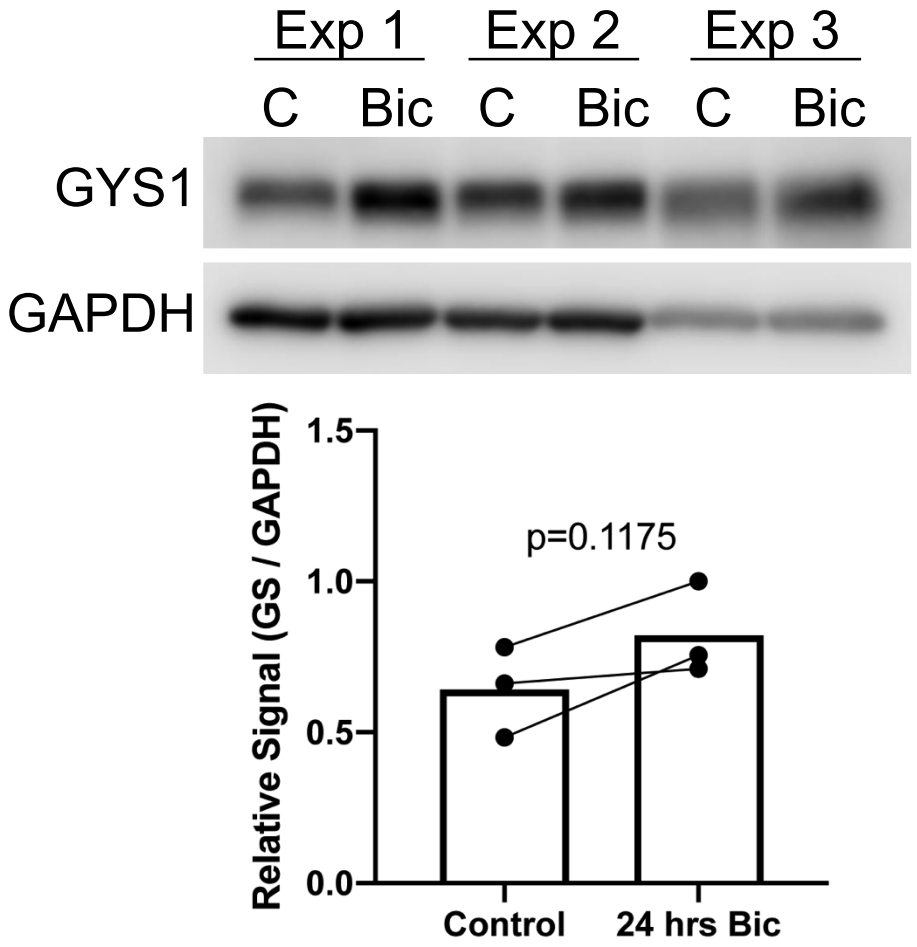
Neuronal glycogen metabolism during synaptic activation

NMDA + glycine (Gly) = NMDA receptor agonist



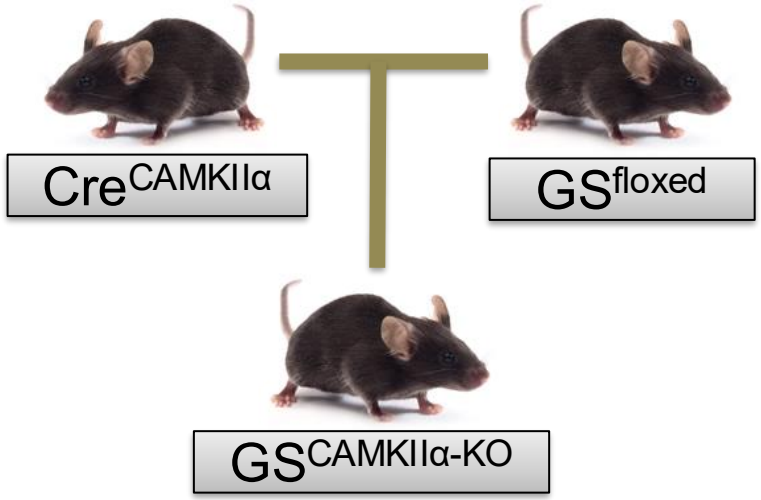
Collaboration with Eva Ramos (UPF)

Bicuculline (Bic): GABA receptor antagonist

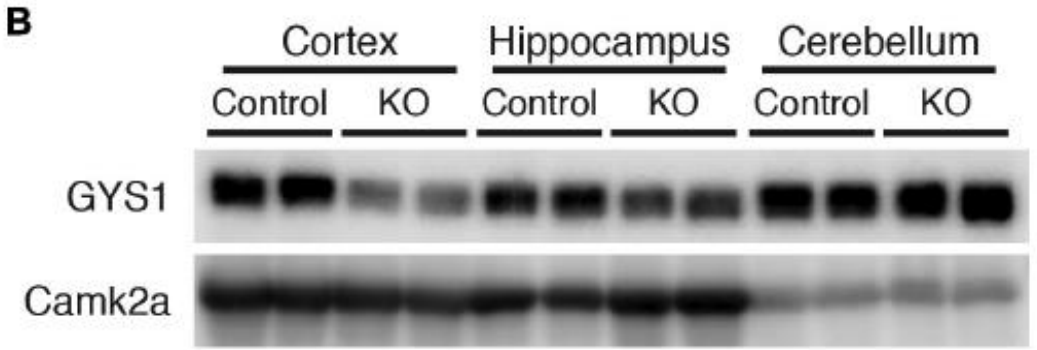


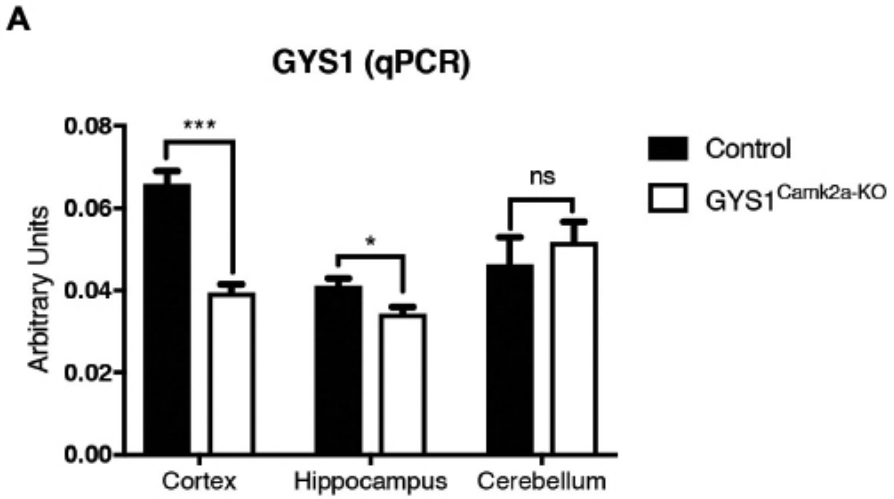
Collaboration with Francesc Soriano (UB)

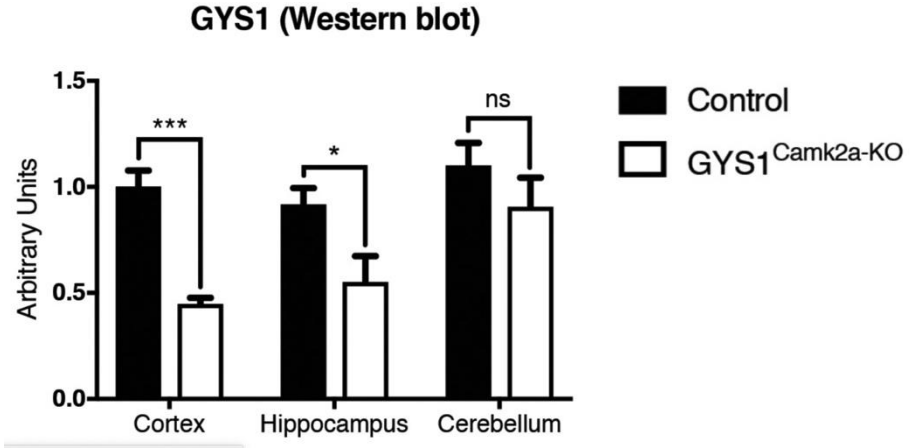
Neurons have an active glycogen metabolism



Lack glycogen in excitatory (glutamatergic) neurons

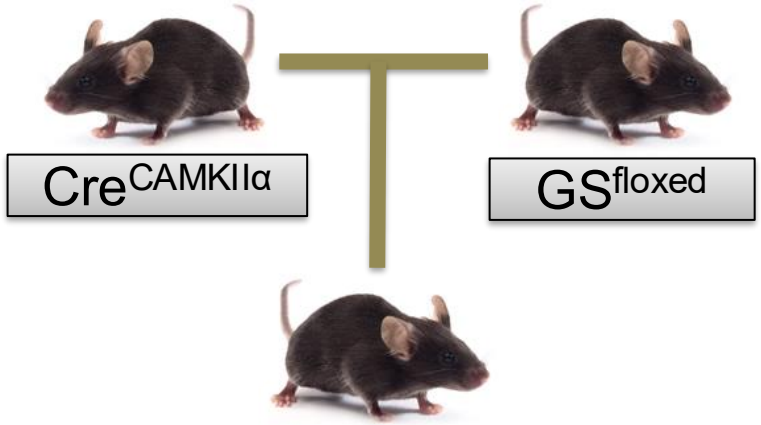






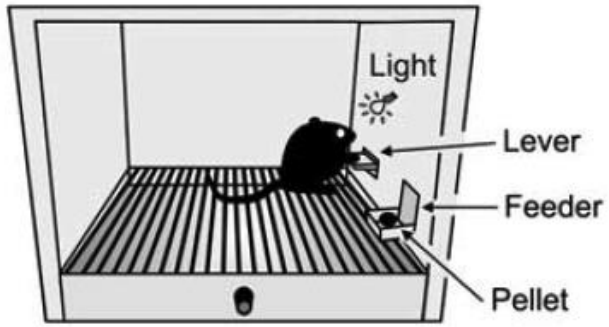
Duran et al., *Frontiers in Cellular Neuroscience* (2019).

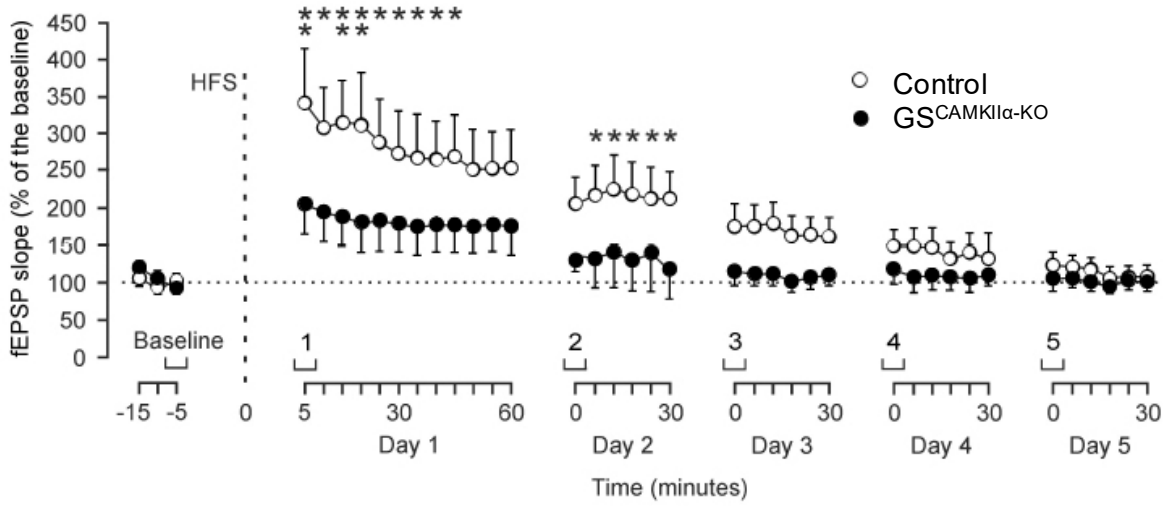
Impaired LTP and associative memory in GS$^{CAMKIIα\text{-}KO}$ mice

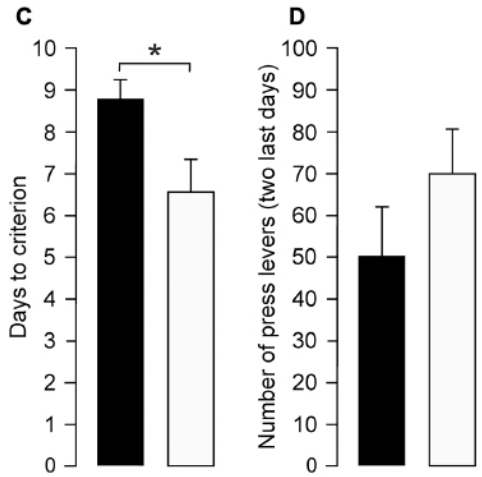


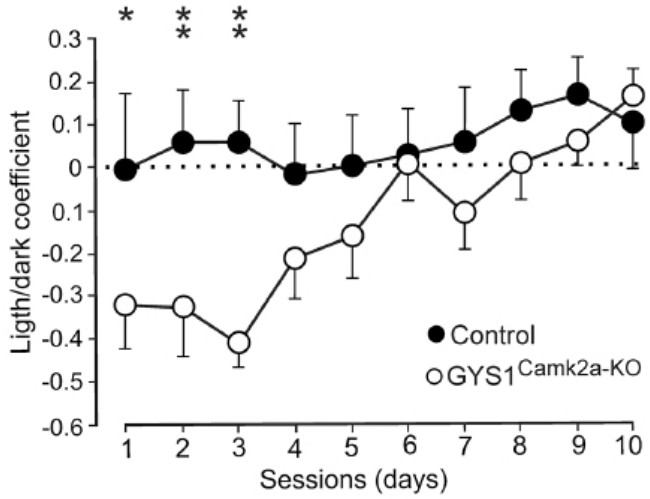
Lack glycogen in excitatory (glutamatergic) neurons

Skinner Box



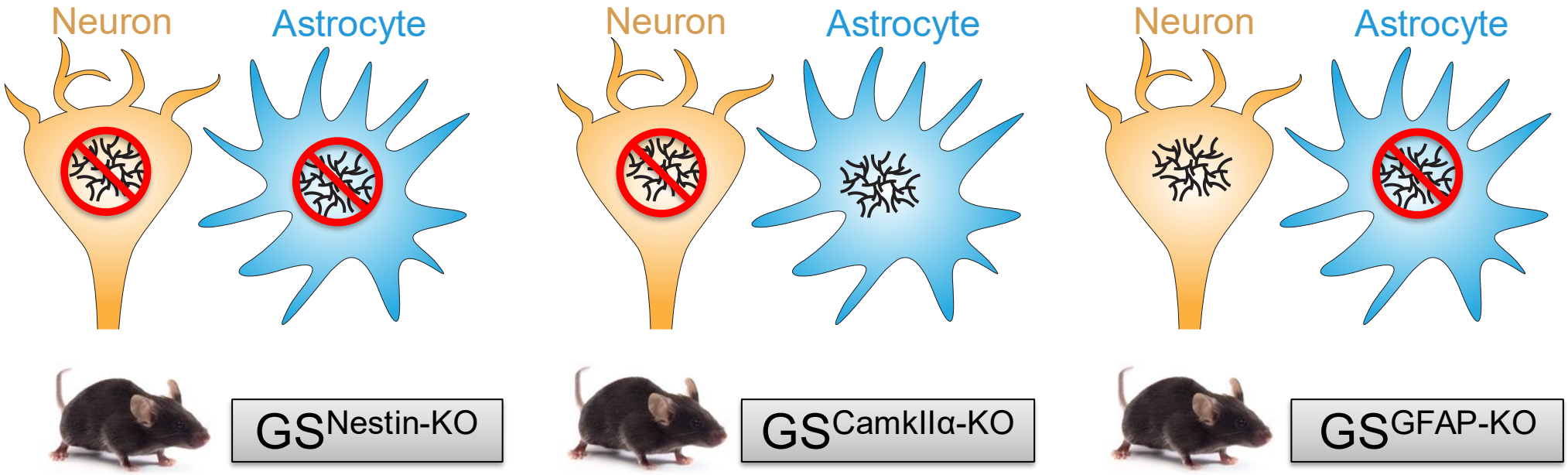






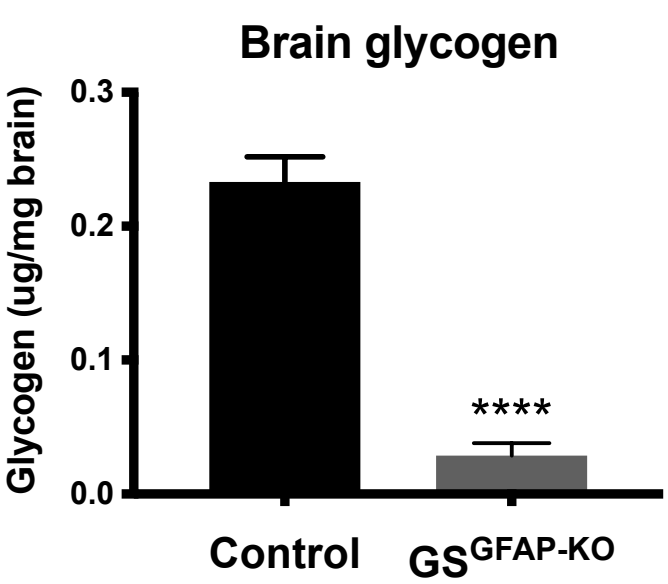
Duran et al., *Frontiers in Cellular Neuroscience* (2019).

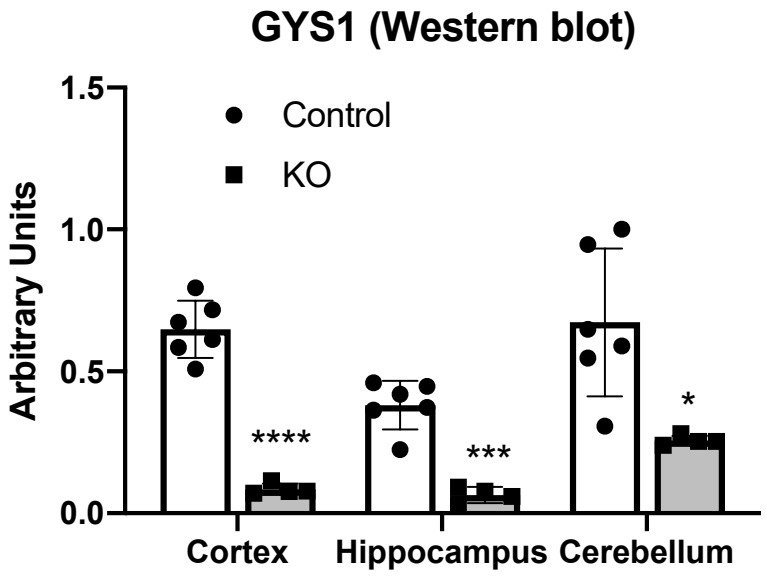
Mouse models to study brain glycogen

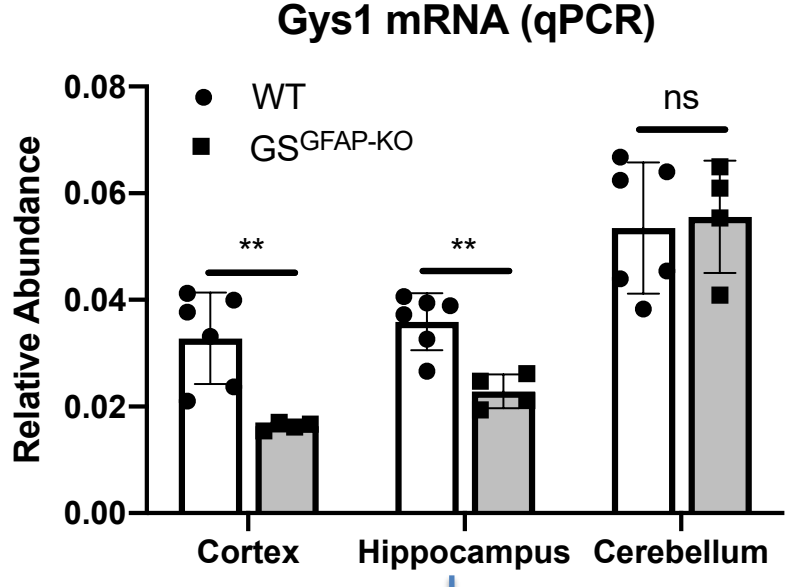


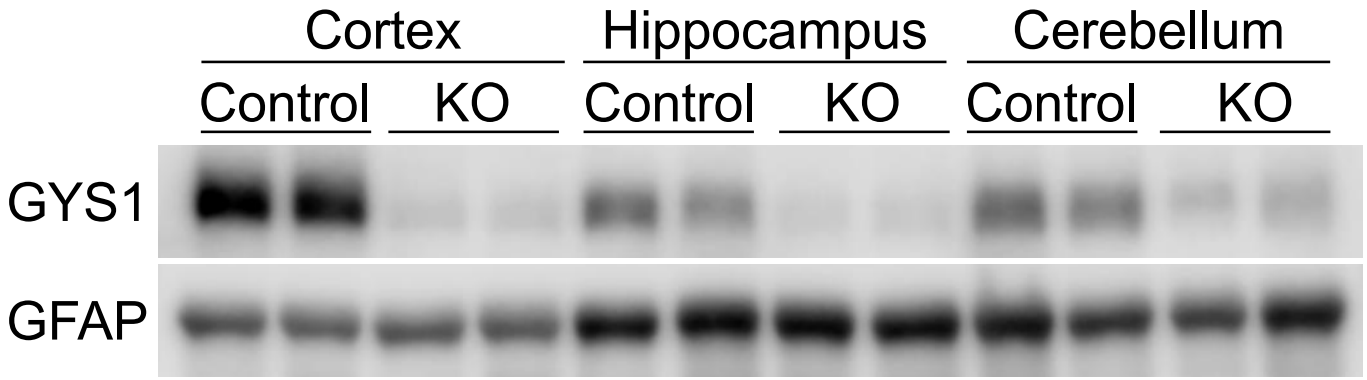
GS deletion in:	Whole brain	CAMKIIα-positive excitatory neurons	GFAP-positive astrocytes
Associative memory:	Impaired	Impaired	?
Long-term potentiation:	Reduced	Reduced	?
Reference(s):	Duran, et al. (2013) Lopez-Ramos, et al. (2015)	Duran et al. (2019)	

Molecular changes in GS$^{GFAP-KO}$ mice



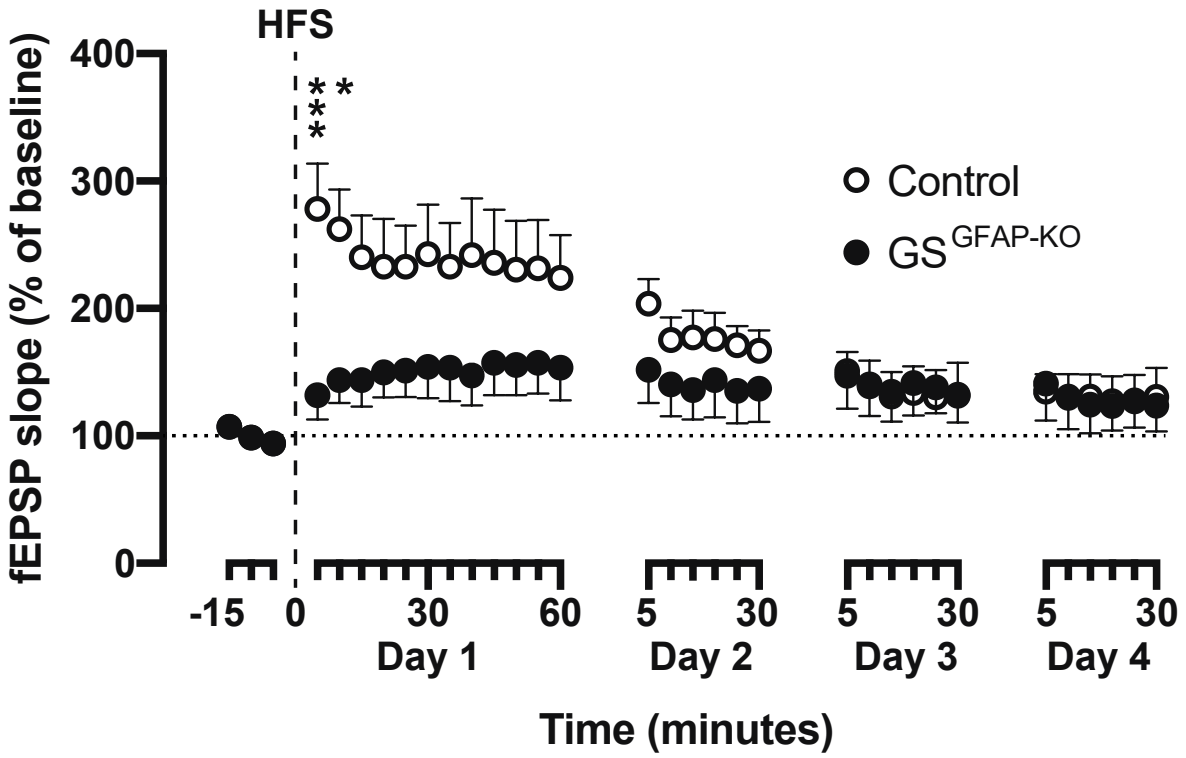


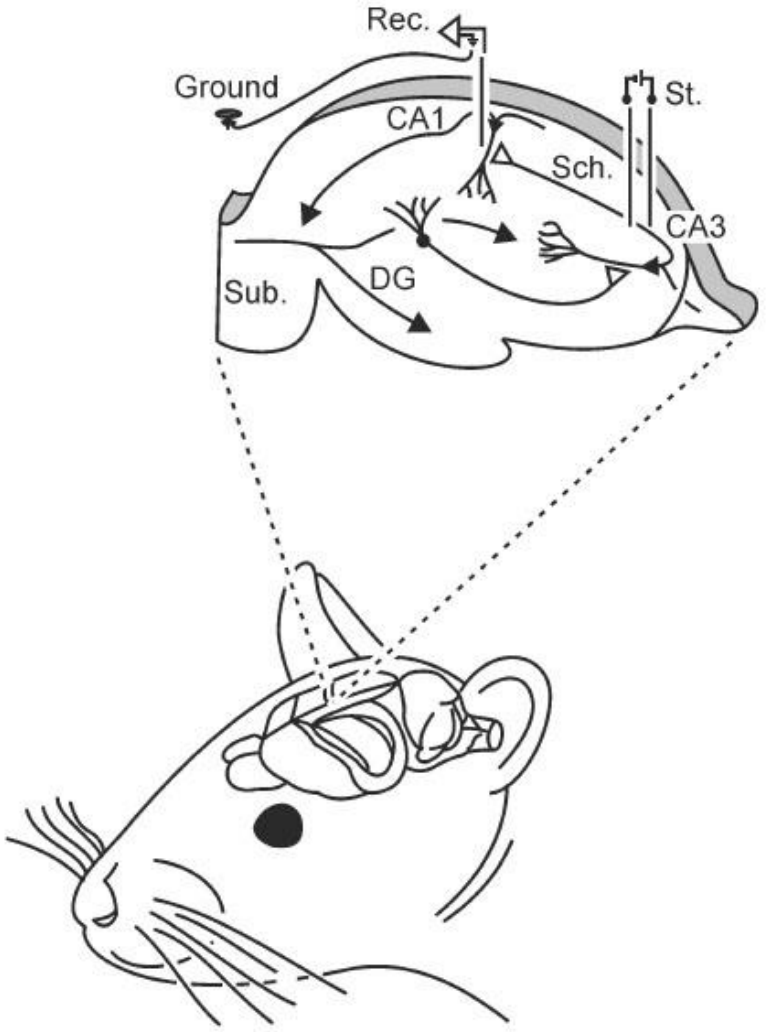




RNAseq
23% decrease

Impaired LTP in $GS^{GFAP\text{-}KO}$ mice

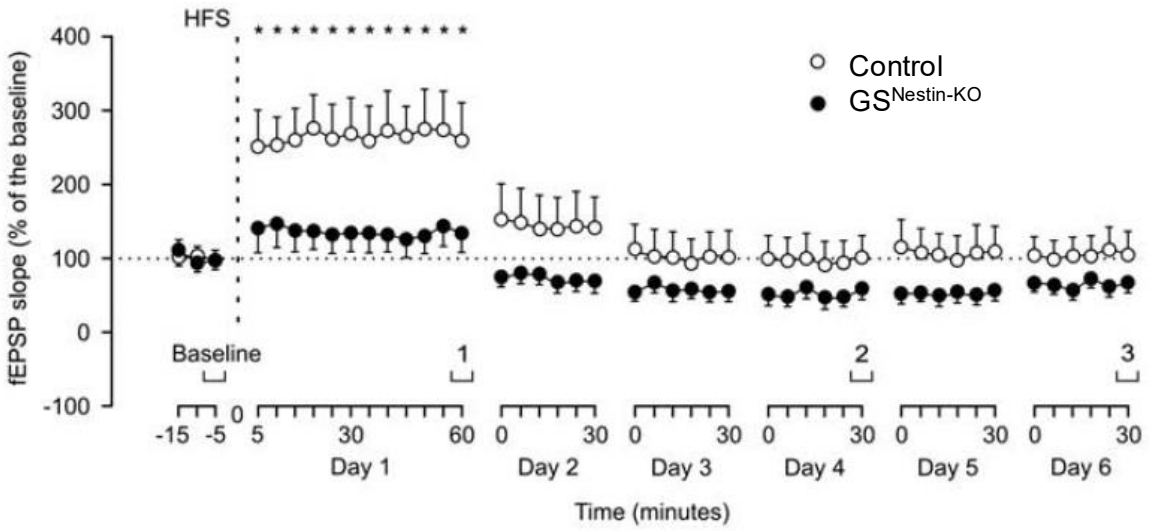




José Delgado-García, Pablo de Olavide University

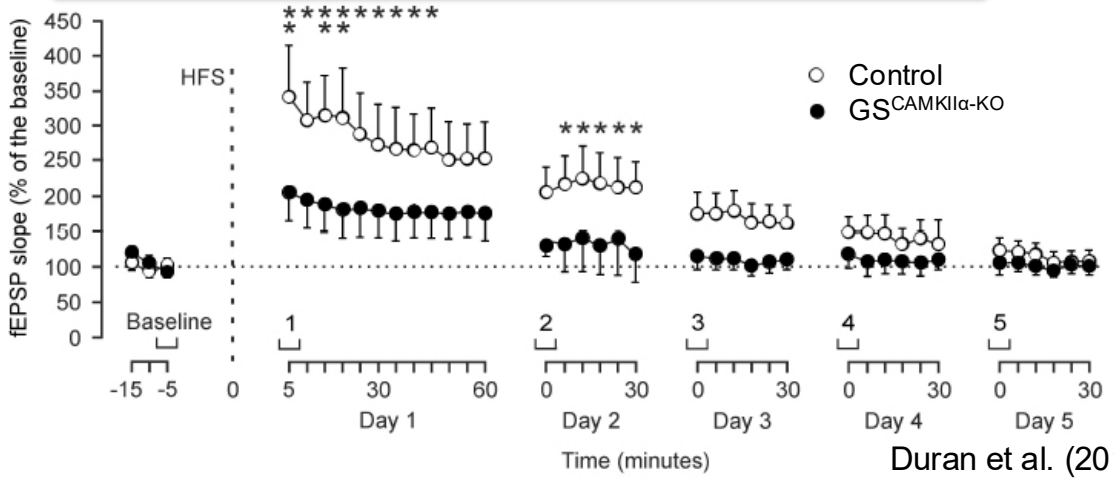
Impaired LTP in $GS^{GFAP\text{-}KO}$ mice

$GS^{Nestin\text{-}KO}$
(Lacks all brain glycogen)



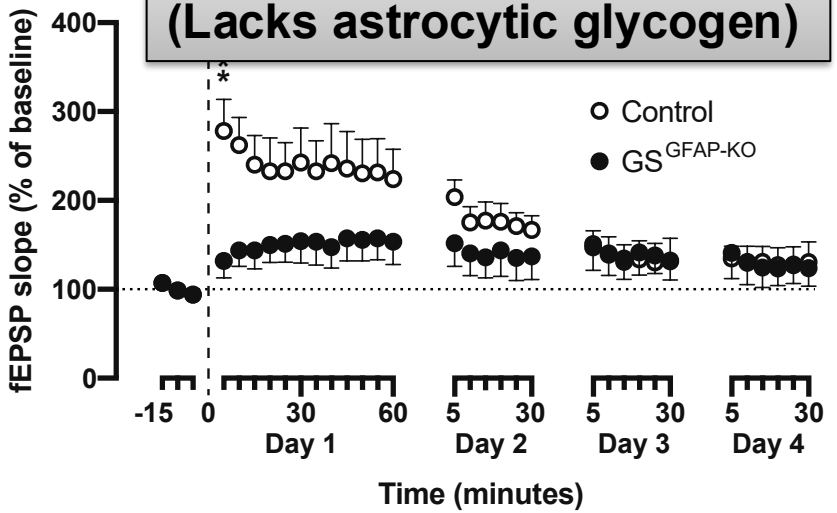
Duran et al. (2013).

$GS^{CAMKII\alpha\text{-}KO}$
(Lacks glycogen in excitatory neurons)

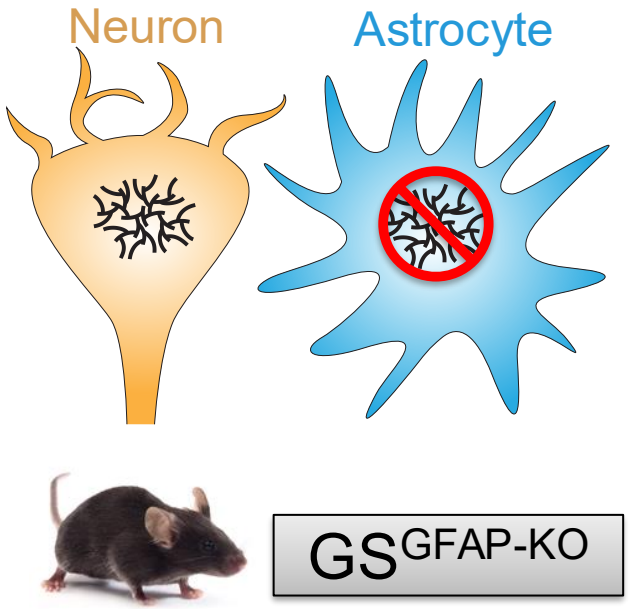


Duran et al. (2019).

$GS^{GFAP\text{-}KO}$
(Lacks astrocytic glycogen)



Mouse models to study brain glycogen



GS deletion in: GFAP-positive astrocytes

Associative memory: ?

Long-term potentiation: Reduced

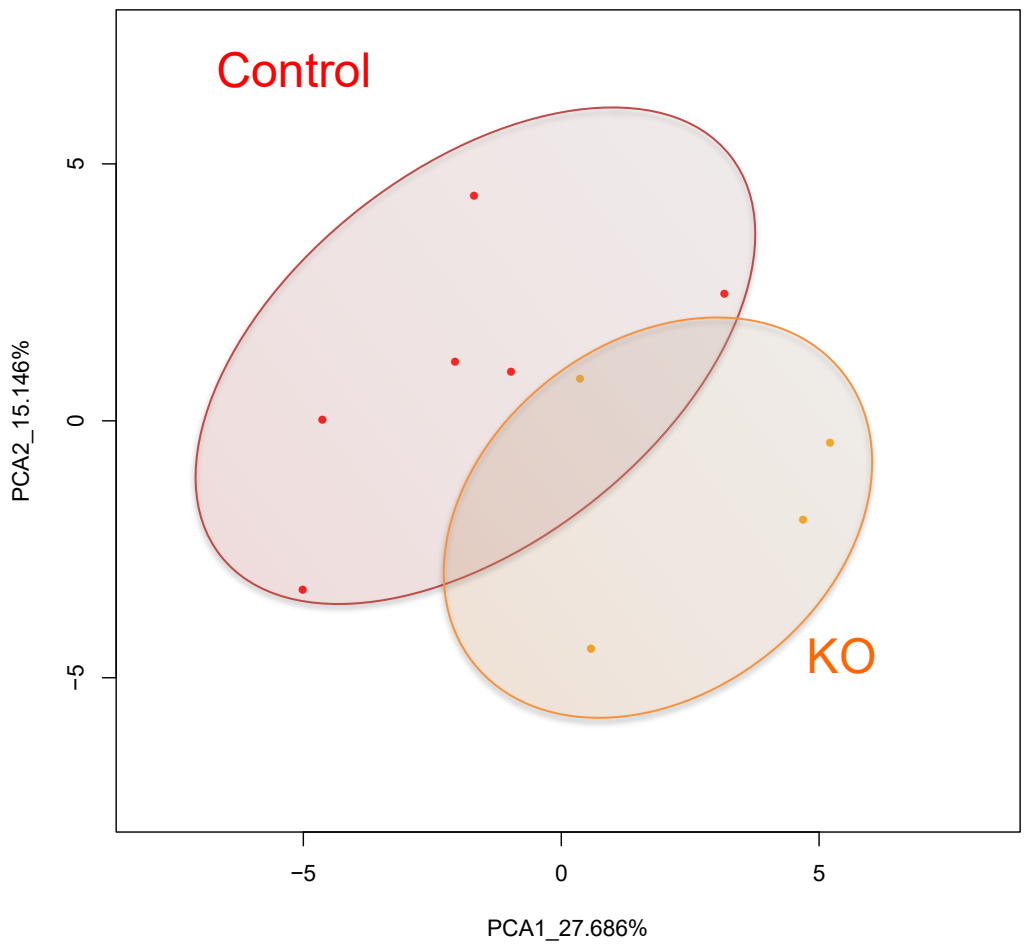
Questions:

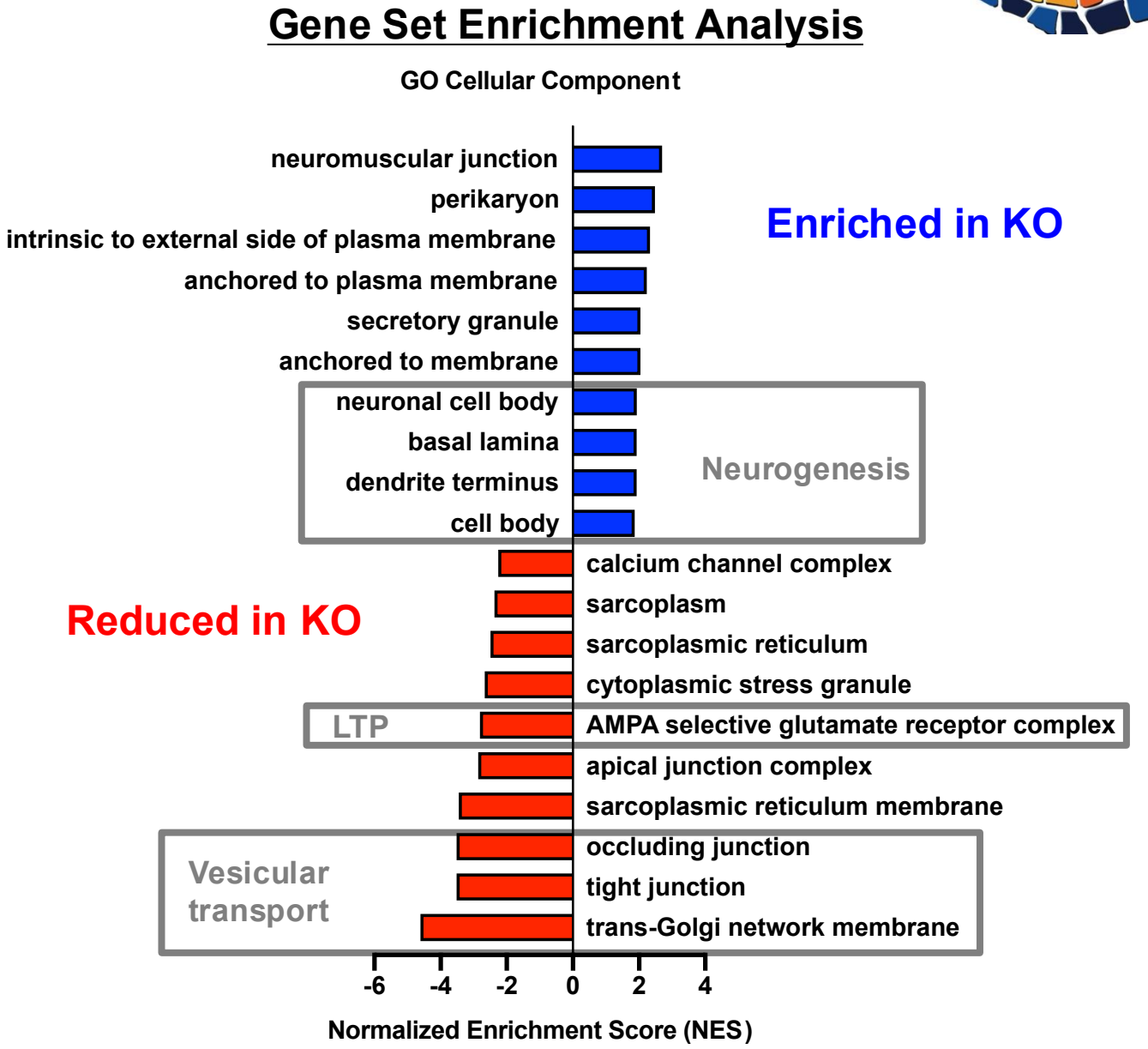
- Molecular changes underlying LTP defect
- Other molecular changes contributing to additional phenotype(s)

Approaches:

- Transcriptomics (hippocampus)
- Metabolomics (whole brain)

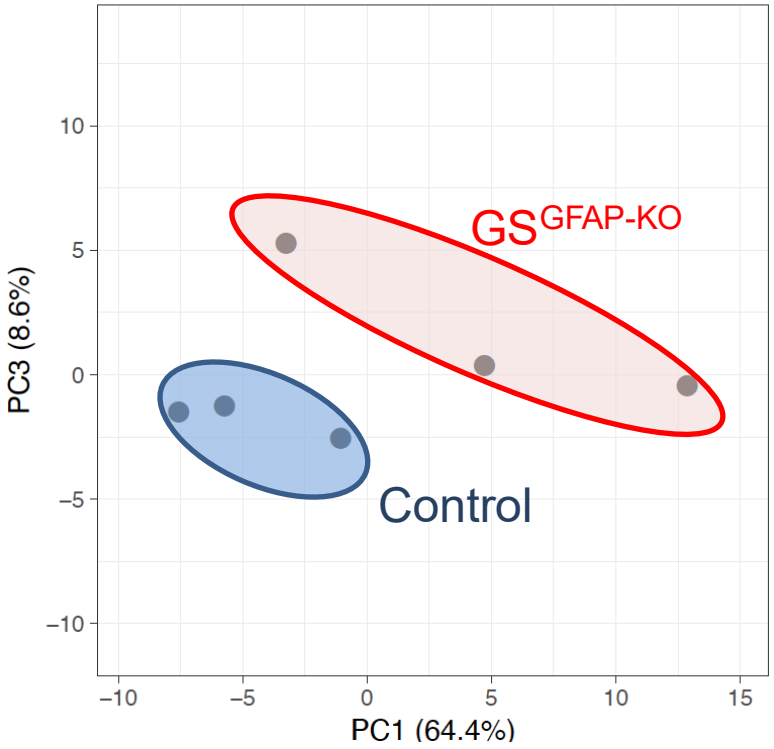
Transcriptomics on GS$^{GFAP\text{-}KO}$ hippocampus

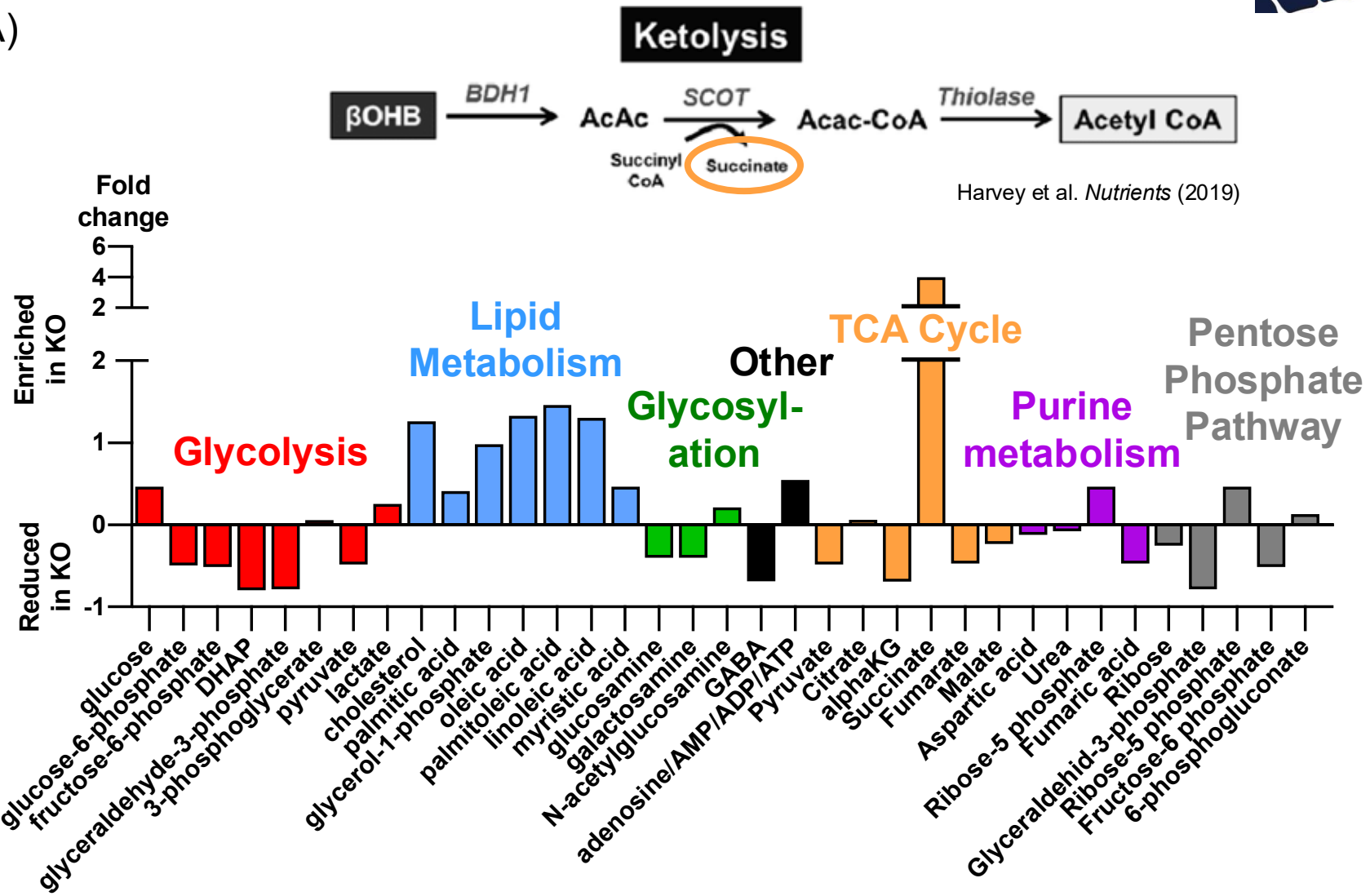




Metabolomics on GS$^{GFAP\text{-}KO}$ whole brain

Principle Component Analysis (PCA)

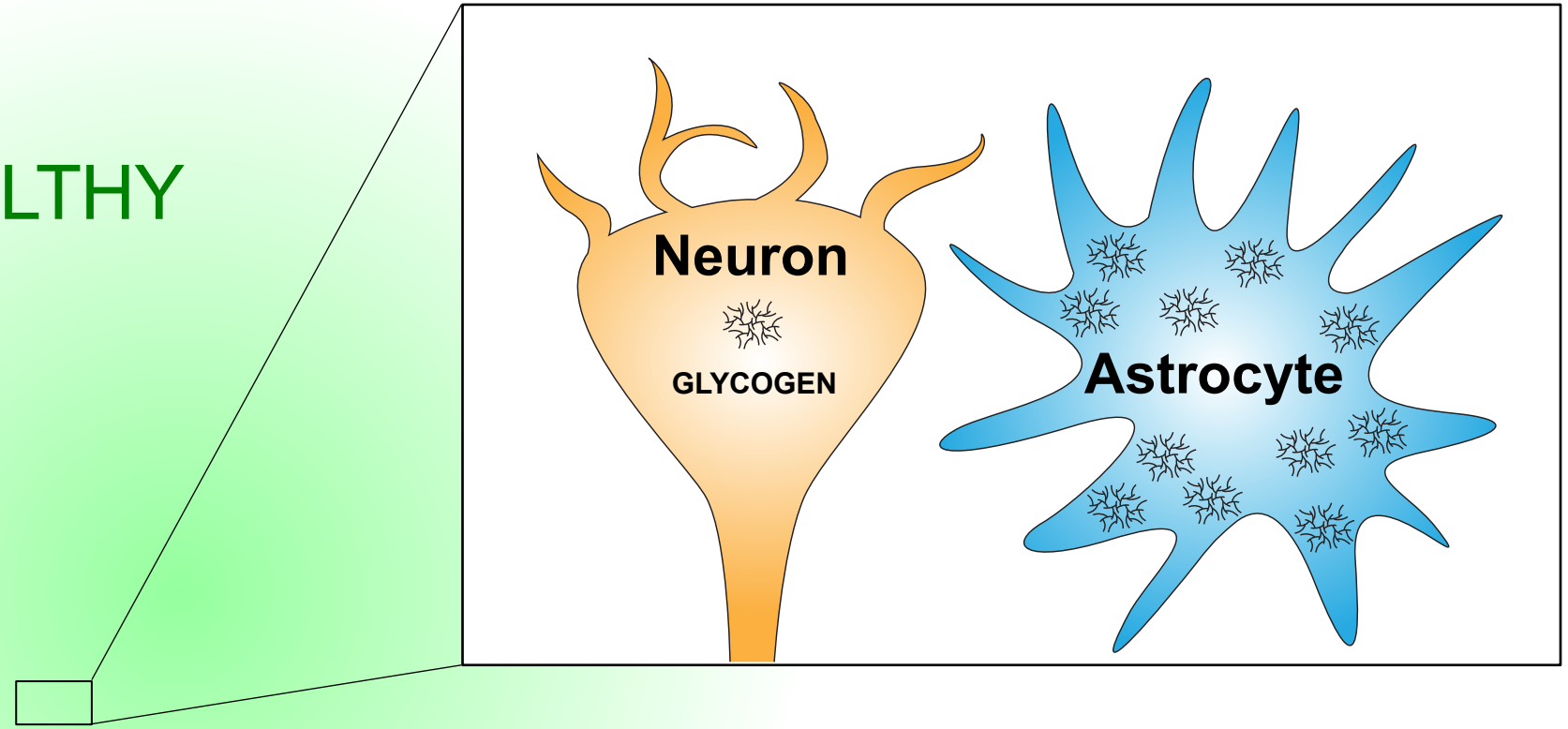




Ramon Sun, University of Kentucky

Brain glycogen in health and disease

HEALTHY

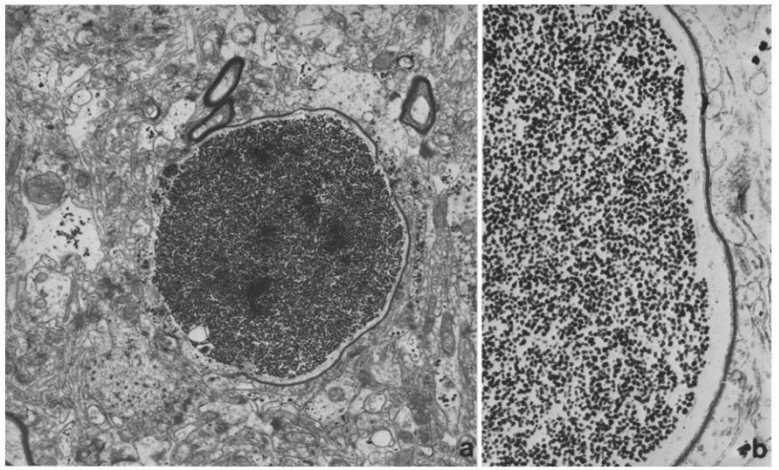


Brain glycogen in health and disease

DISEASED

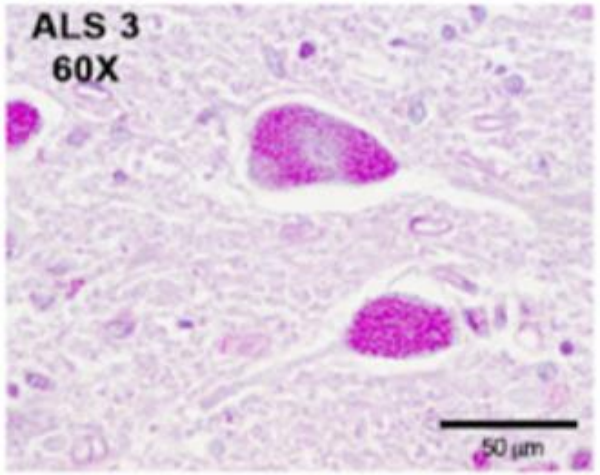


Alzheimer's Disease



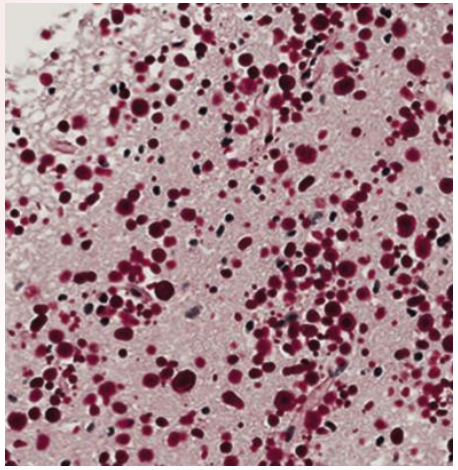
Mann, et al. *Acta Neuropathologica* (1987).

Amyotrophic Lateral Sclerosis



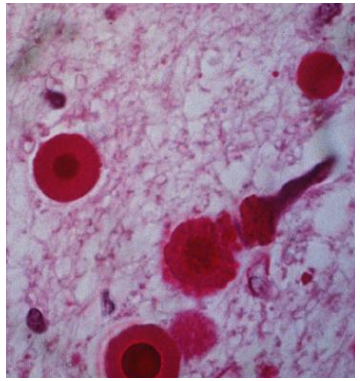
Dodge, et al. *PNAS* (2013).

Epilepsy



Lee, et al. *SNI* (2017).

Lafora disease



Courtesy of Jose Serratosa

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Gentry Lab Members
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Valerion Therapeutics