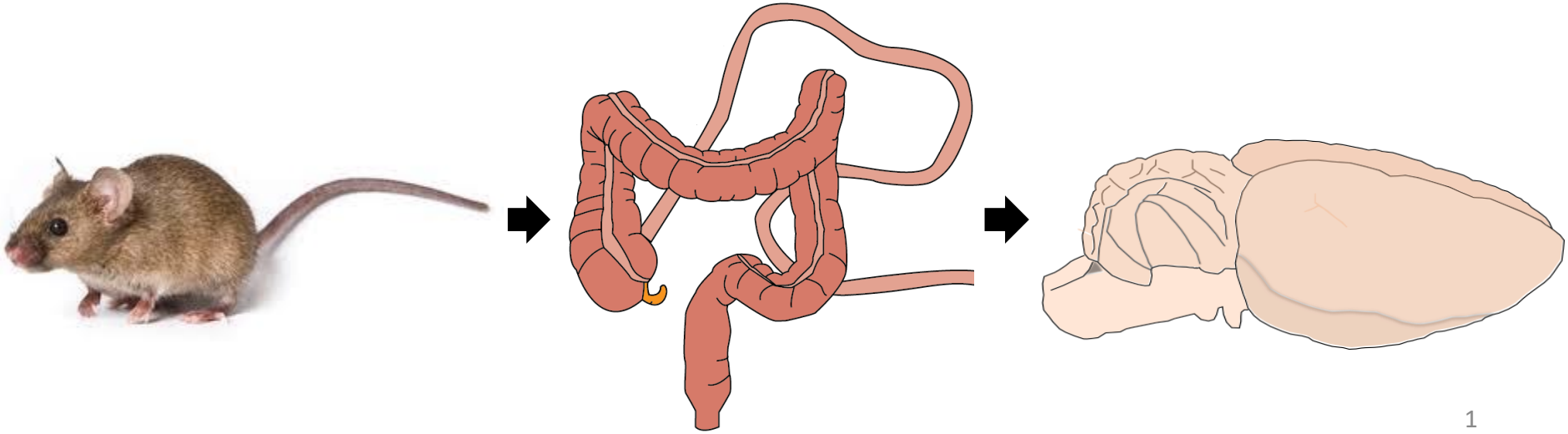
ECM 2020
The 1st International Electronic Conference on Microbiology
02–30 NOVEMBER 2020 | ONLINE
microorganisms
MDPI

"Enhanced gut microbiota-produced propionate associates with neuroinflammation and cognitive impairment in a murine model of Alzheimer´s disease "

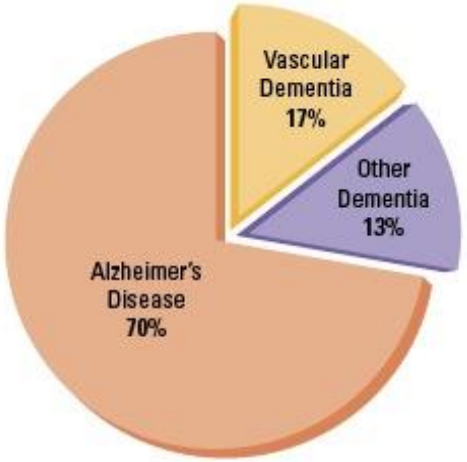
M. Sc. Daniel Cuervo Zanatta
Center for Research and Advance Studies (CINVESTAV)
Mexico



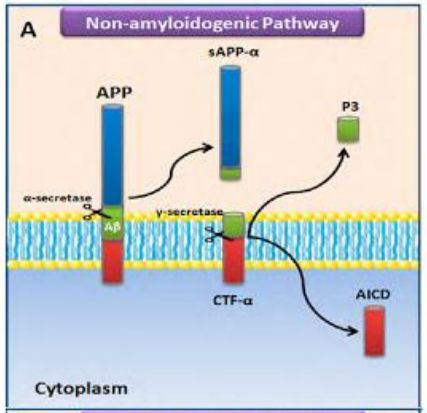
October, 2020

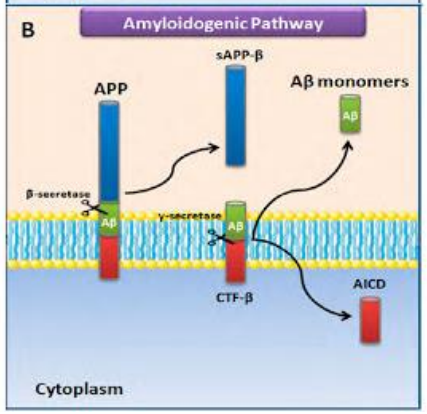
Alzheimer´s disease

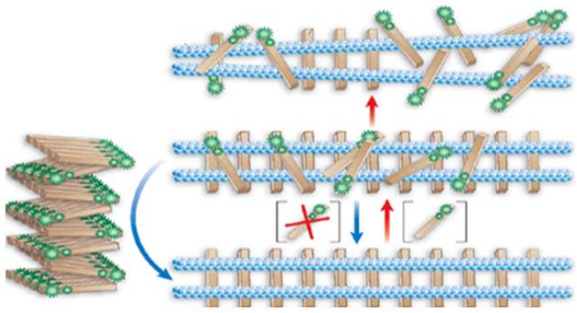
- Slowly progressive neurodegenerative disorder characterized by cognitive decline. It is also the most common form of age-related dementia.
- It affects about 30 million people worldwide and an increase to 100 million is expected by 2050.

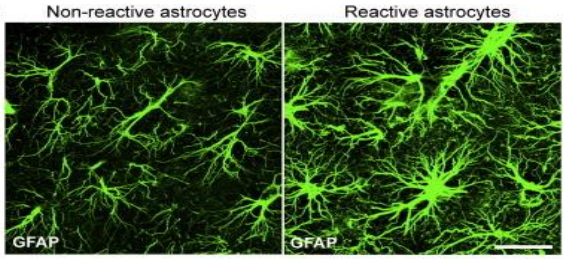


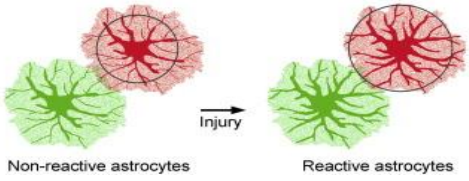
Source: Plassman, BL; Langa, KM; Fisher, GG; Heeringa, SG; Weir, DR; Ofstedal, MB, et al. "Prevalence of Dementia in the United States: The Aging Demographics, and Memory Study. *Neuroepidemiology* 2007; 29:125-132.[31]



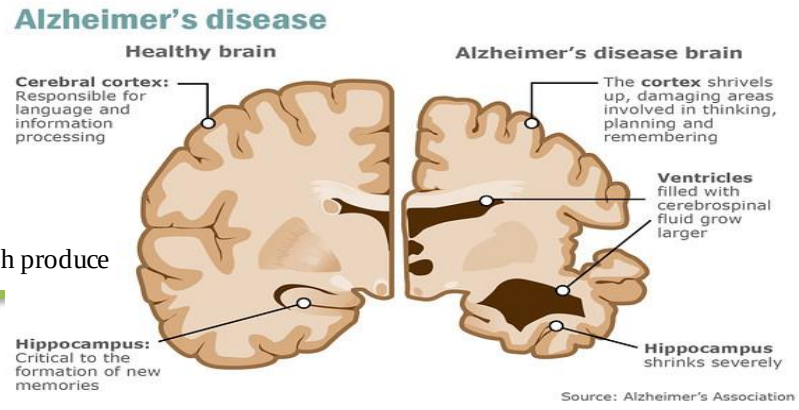


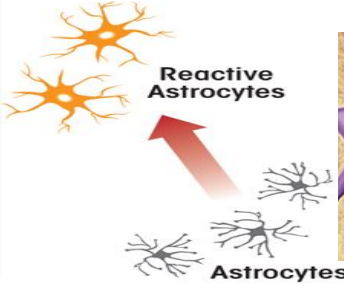


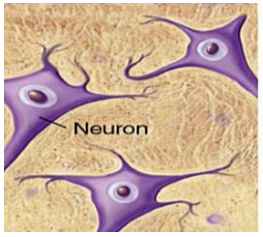


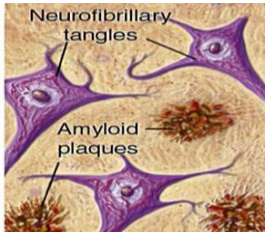


Which produce



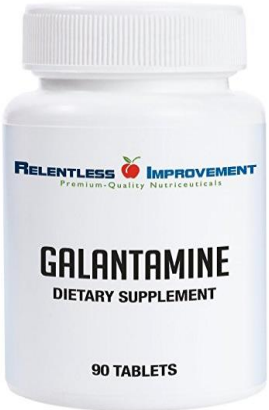


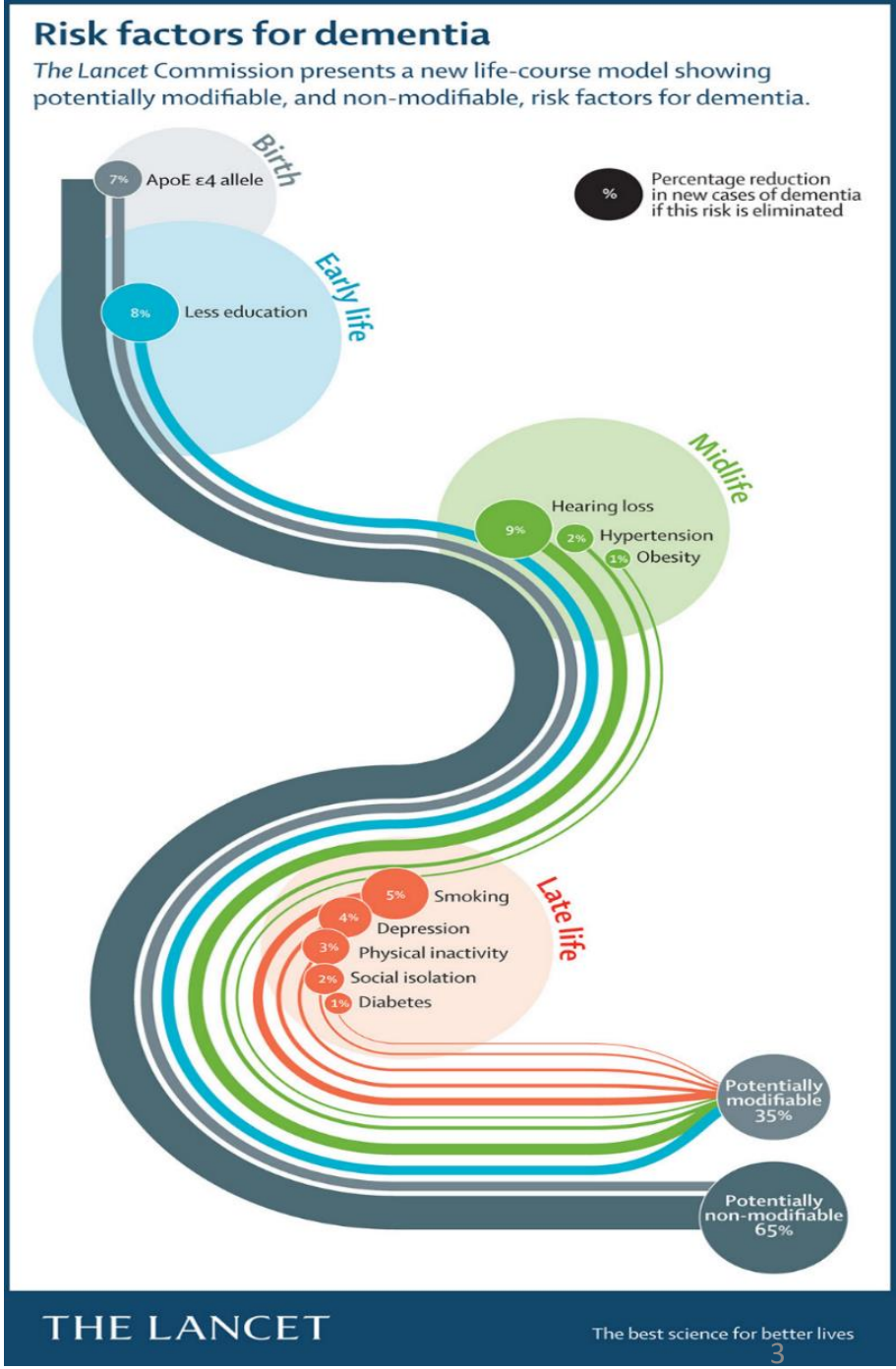




Alzheimer's Association, 2017; Bélanger et al., 2009; Birch, 2014; Gibson et al., 2008; Jahn, 2013; Neugroschl and Wang, 2011; Mena López et al., 2009; Serrano-Pozo et al., 2011.

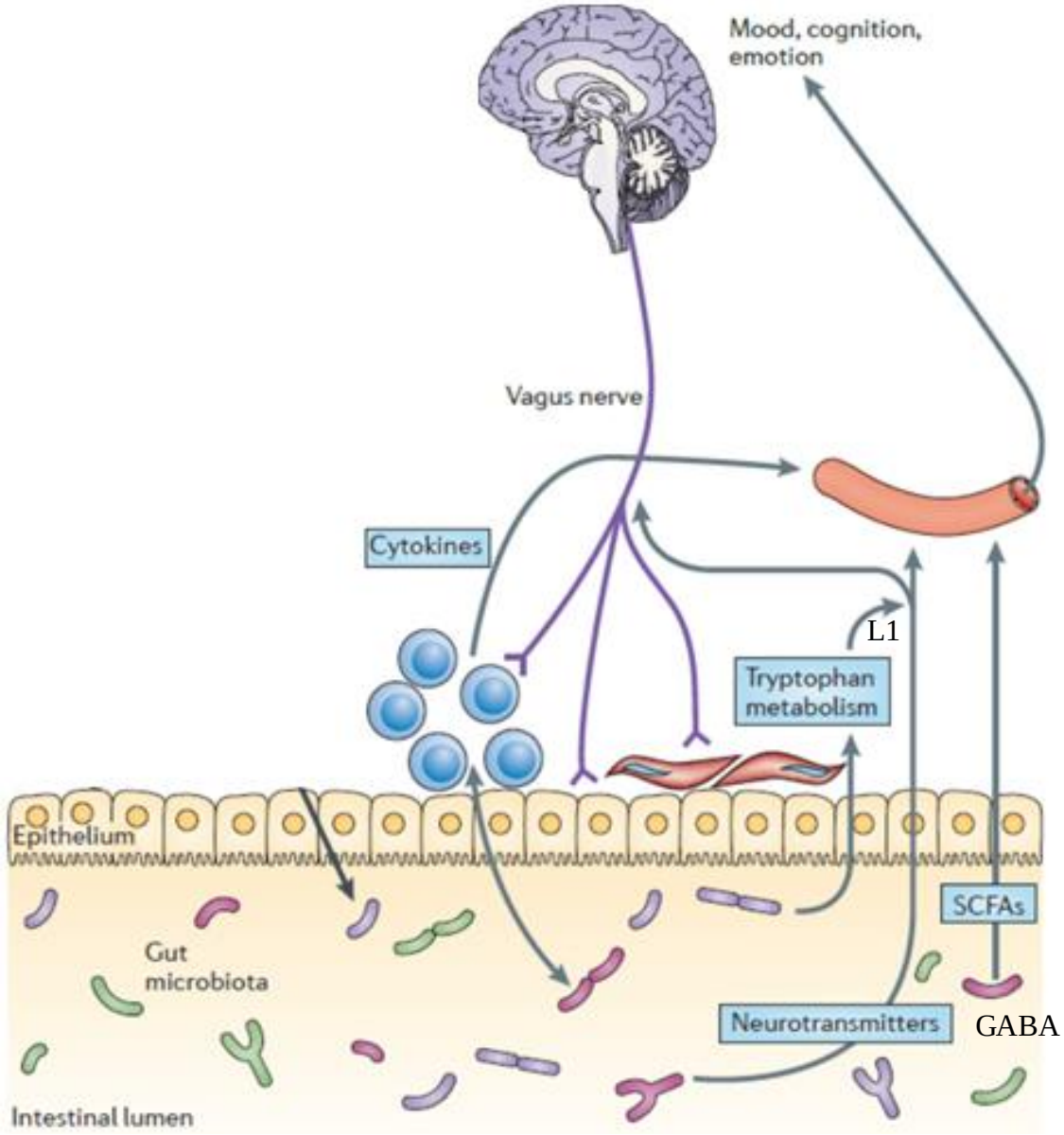
There is no treatment





FDA, 2013; Lancet commission, 2017.

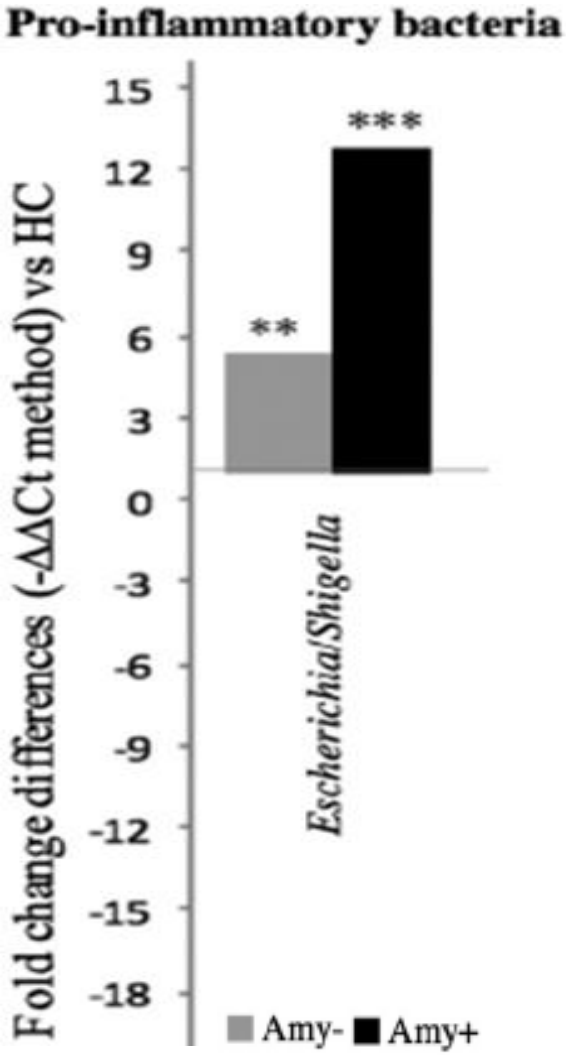
Gut microbiota are all the living microorganisms in the intestine (bacteria ≈ 90%) with great influence on host´s health. The imbalance between mutualistic, commensal and parasitic bacteria (dysbiosis) is characteristic in obesity, type 2 diabetes, and Alzheimer´s disease.



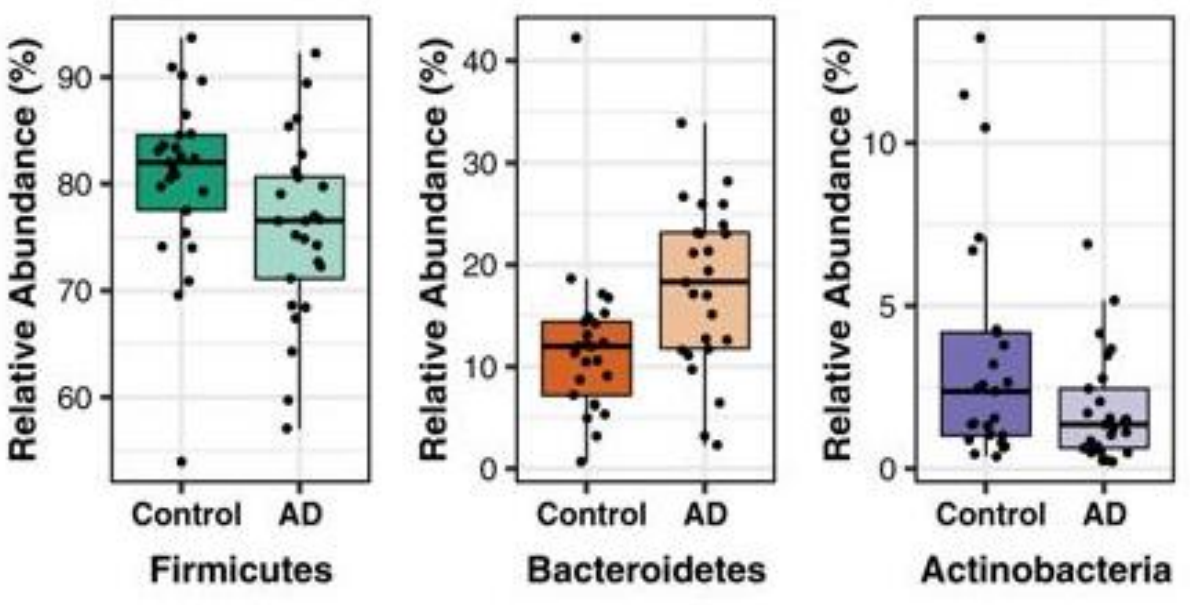
GABA (GAT2)/Choline (OCT1)

Vinolo et al., 2011; Vadder et al., 2015.

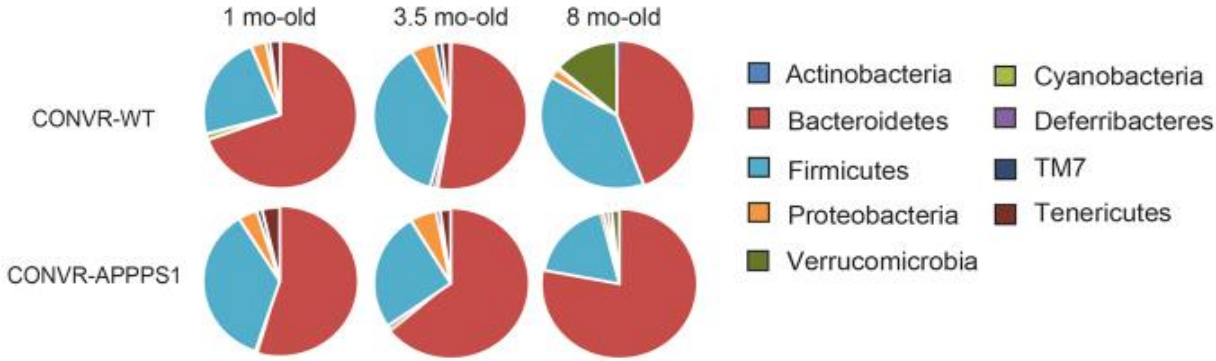
Gut dysbiosis in Alzheimer´s disease has been described in patients and animal models.



Patients with amyloidosis show an increase in pro-inflammatory bacteria. Cattaneo et al., 2017.

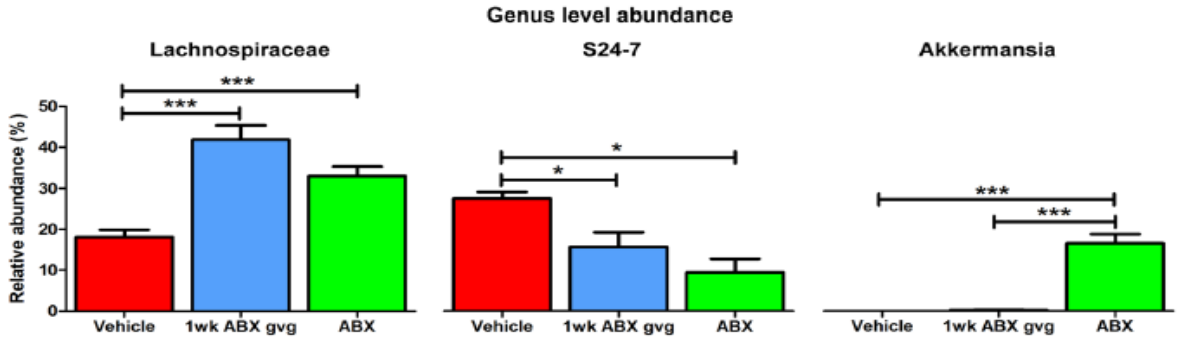


Patients with Alzheimer´s disease present bacterial *phyla* variations in their gut microbiota. Vogt et al., 2017.

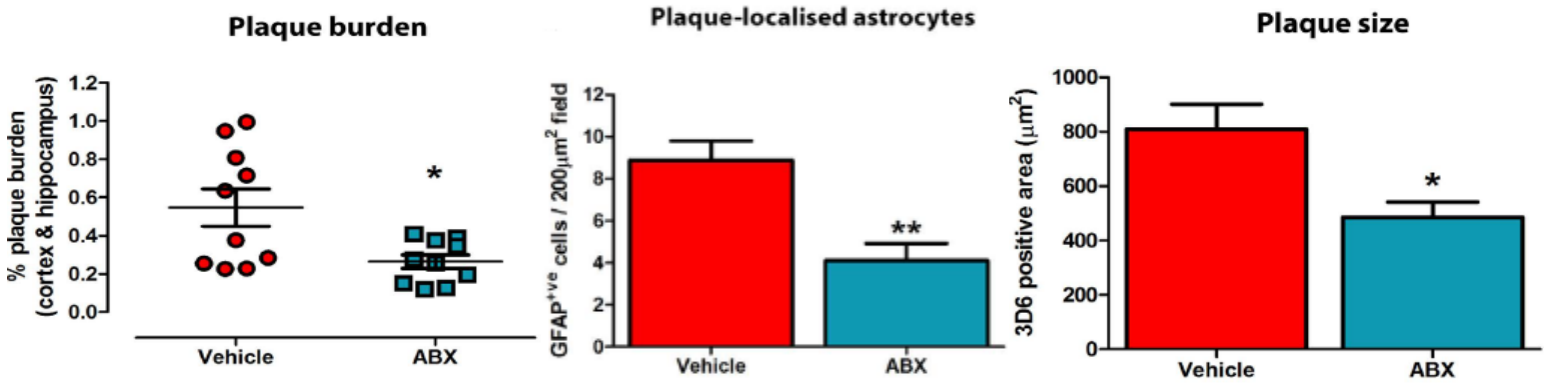


Tg mice show a different bacterial ratio compared to the wild strain through time. Harach et al., 2017.

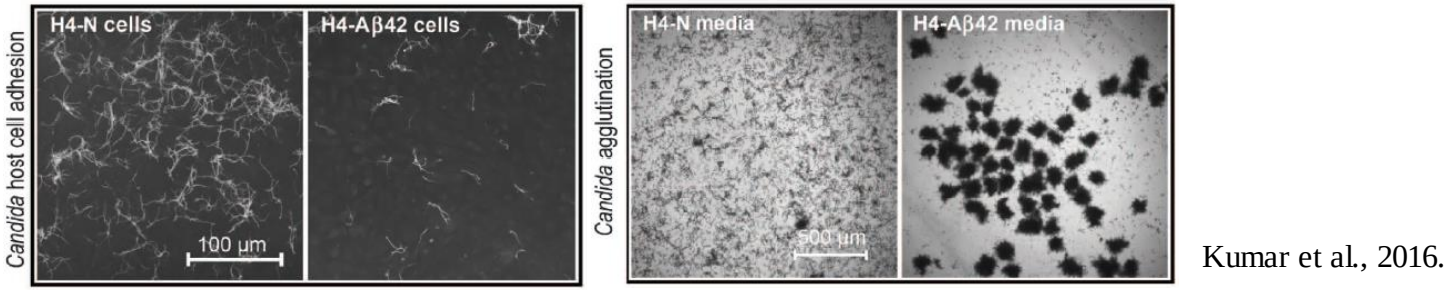
We know that gut microbiota alterations have an impact in Alzheimer´s disease hallmarks.



Antibiotics significantly modified the gut microbiota of Alzheimer´s disease transgenic mice. Minter et al., 2016.



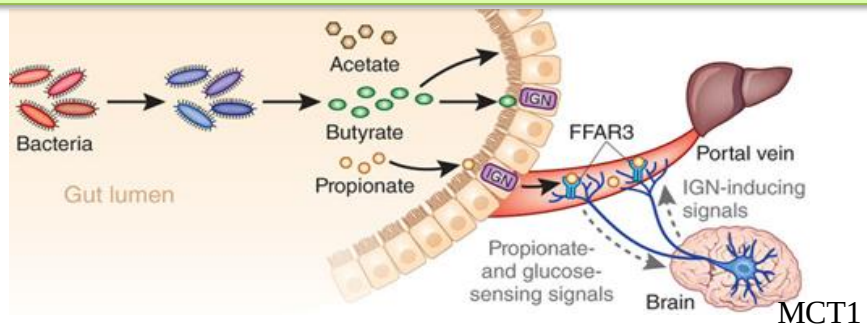
Antibiotics reduced pathological hallmarks in Alzheimer´s disease. Minter et al., 2016.



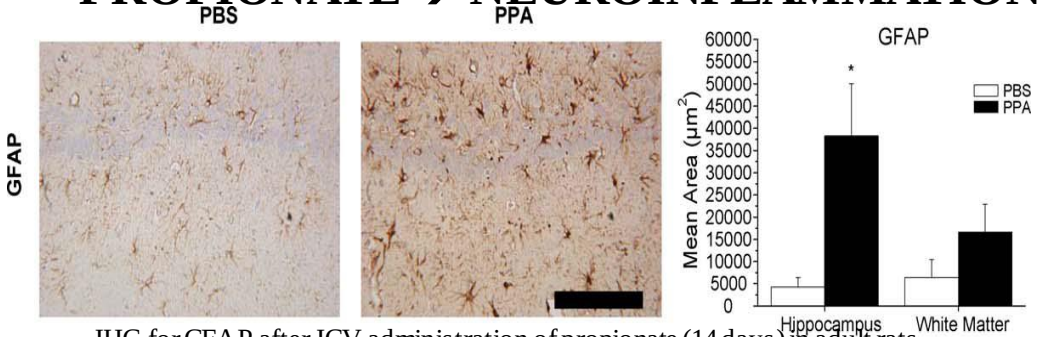
Kumar et al., 2016.

This is important because gut microbiota related products could modify cognition in Alzheimer´s disease.

Short chain fatty acids

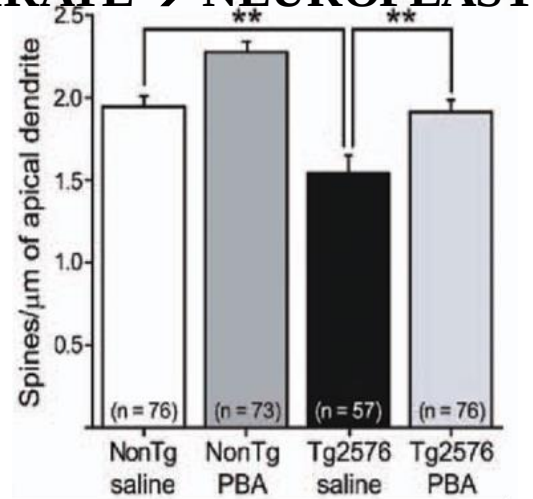


PROPIONATE → NEUROINFLAMMATION



IHC for GFAP after ICV administration of propionate (14 days) in adult rats.

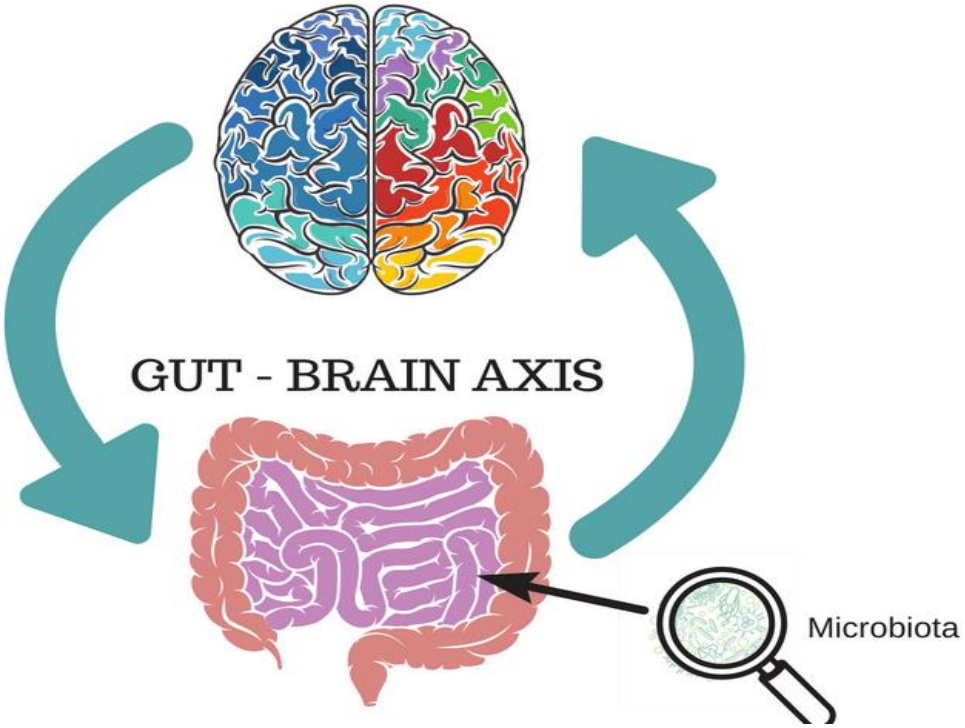
BUTIRATE → NEUROPLASTICITY

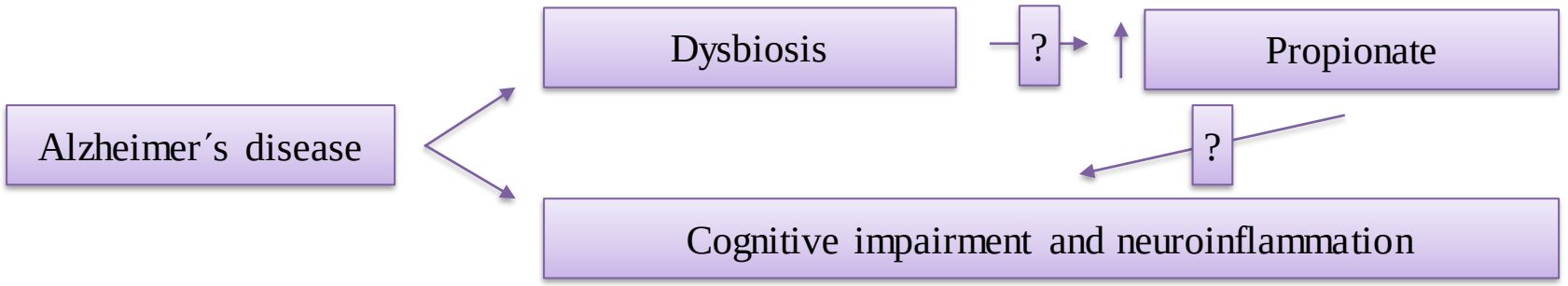


Golgi stain after daily (5 weeks) i.p. phenylbutyrate administration in 6-month-old mice.

Brüssow and Parkinson, 2014; Macfabe et al., 2015; Pessione et al., 2014 and Ricobaraza 2010.

So, we know that there is a bidirectional comunication system between enteric, and central nervous system…





In order to answer this question…

WT
n = 9

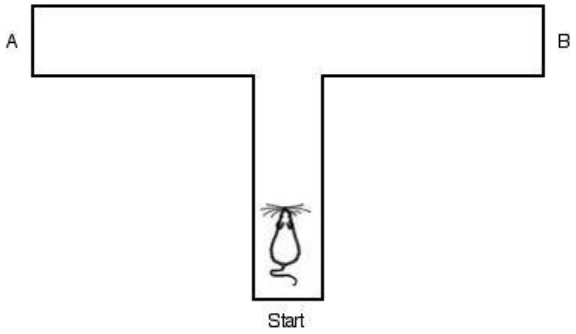
Tg
n = 8

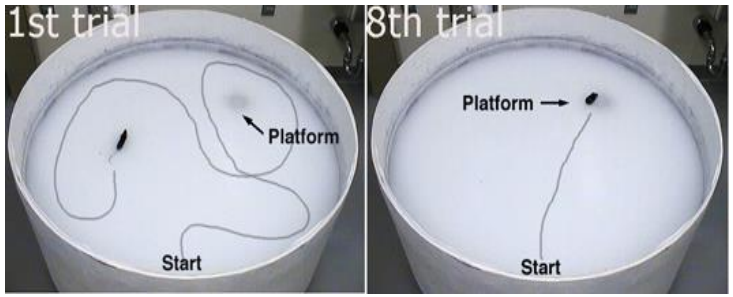
4-month-old males.

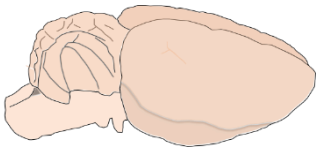
Individualization.
Diet and water *ad libitum*.

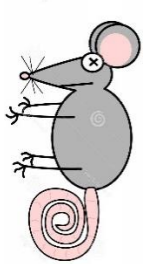
Weight and feeding monitoring.

8 weeks.

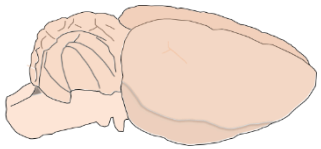




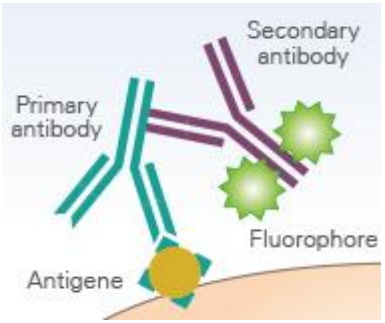




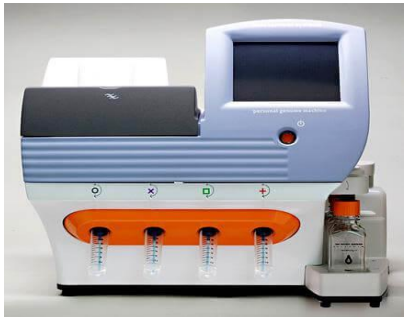
Neuroinflammation
(Glial fibrillary acidic protein).

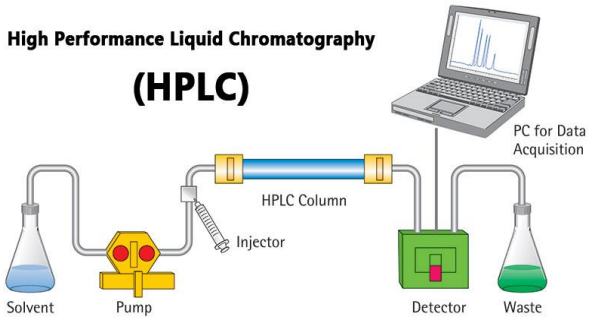


Brain



Feces



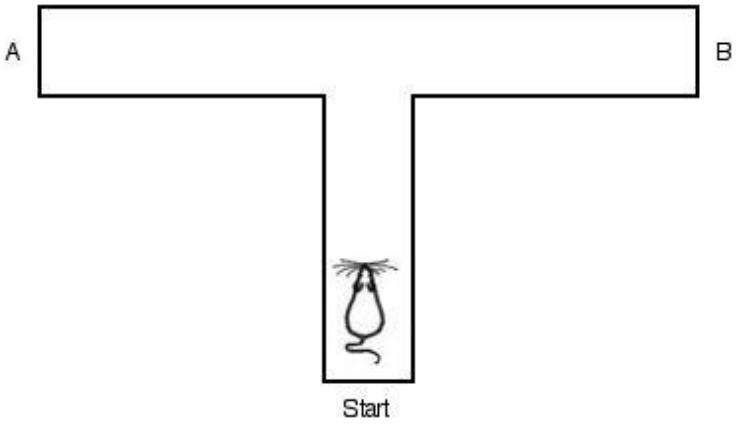


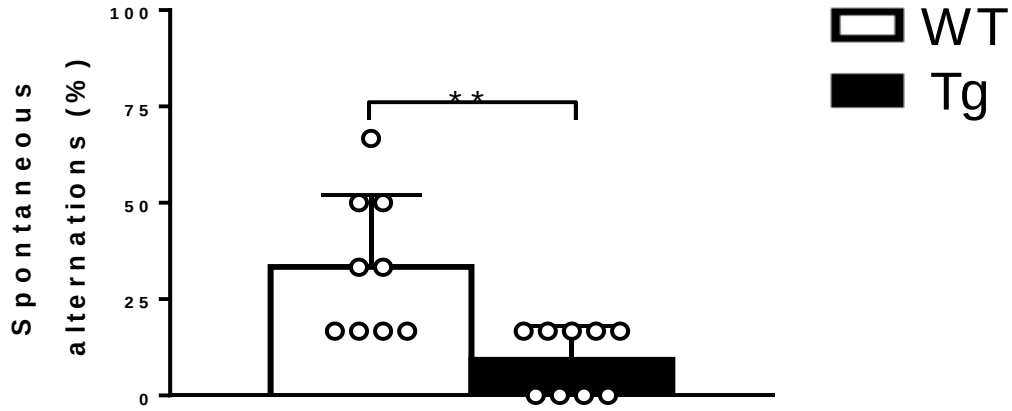
DNA Massive sequencing: Abundance, diversity, enrichment and predicted metabolic pathways related to bacterial taxa.

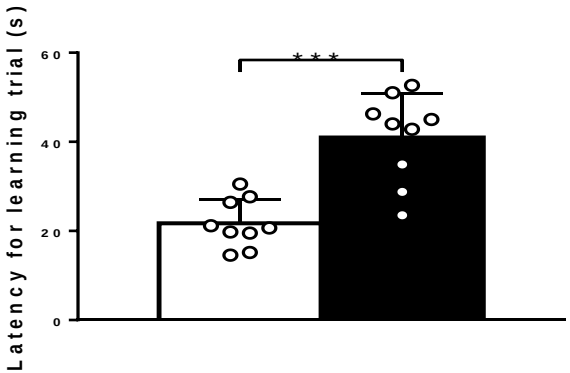
Short chain fatty acids concentration

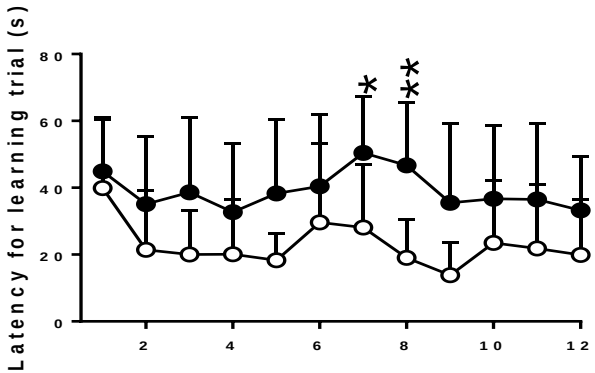
RESULTS

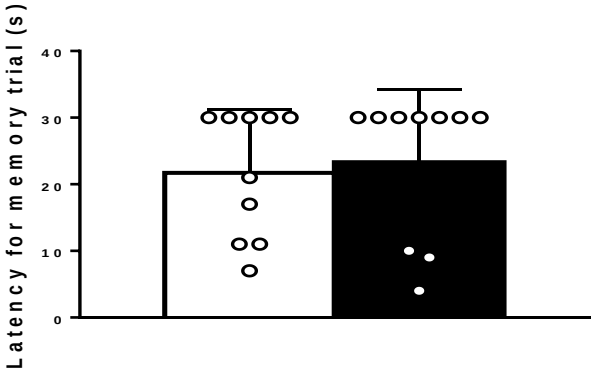
Behavior

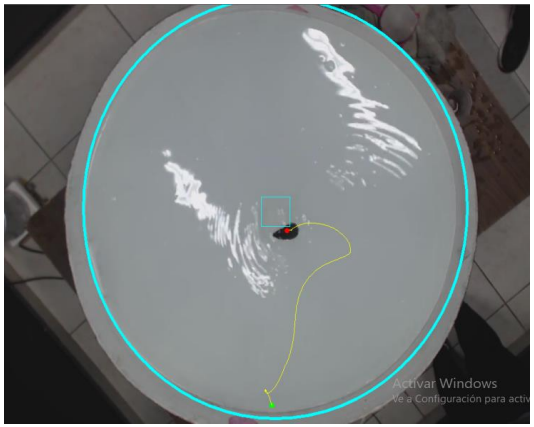

A
B
Start

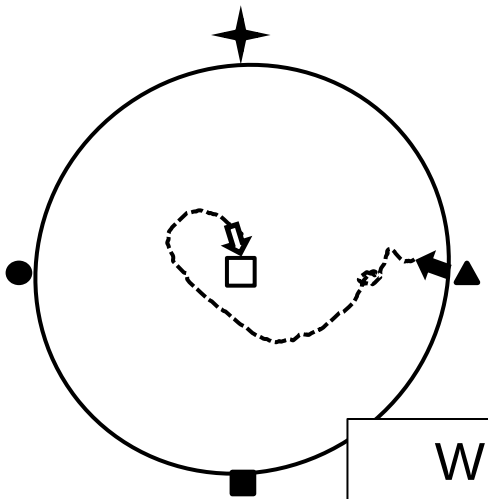

WT
Tg
Spontaneous alternations (%)
100
75
50
25
0
**

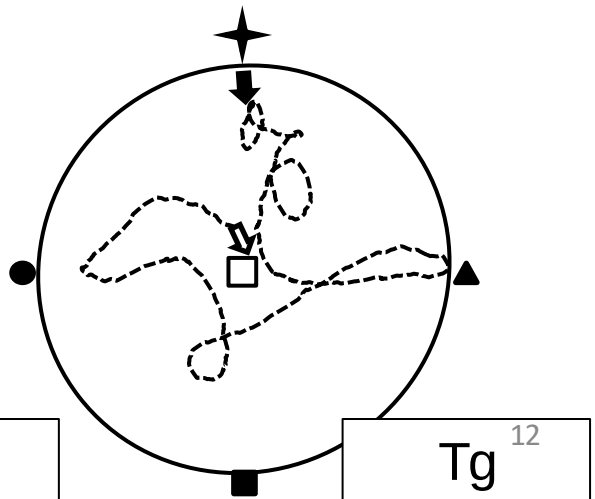

Latency for learning trial (s)
60
40
20
0
***

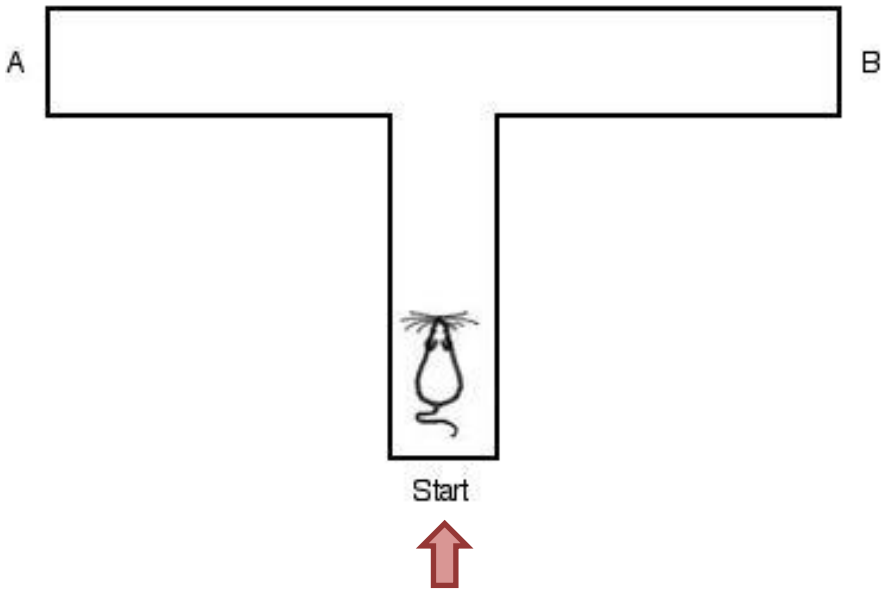

Latency for learning trial (s)
80
60
40
20
0
2
4
6
8
10
12
*
**


Latency for memory trial (s)
40
30
20
10
0

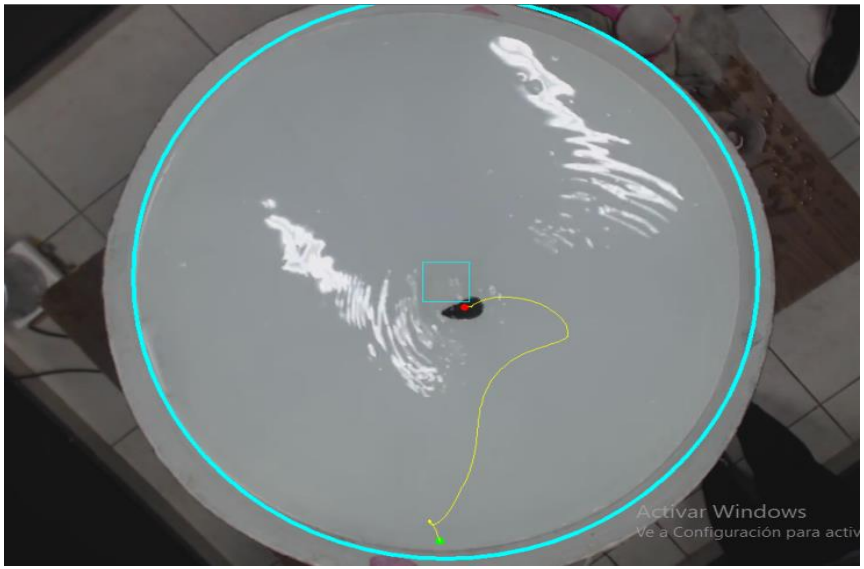

Activar Windows


WT


Tg

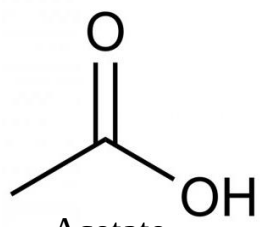


Working memory and spatial learning are impaired in Tg compared to control mice.

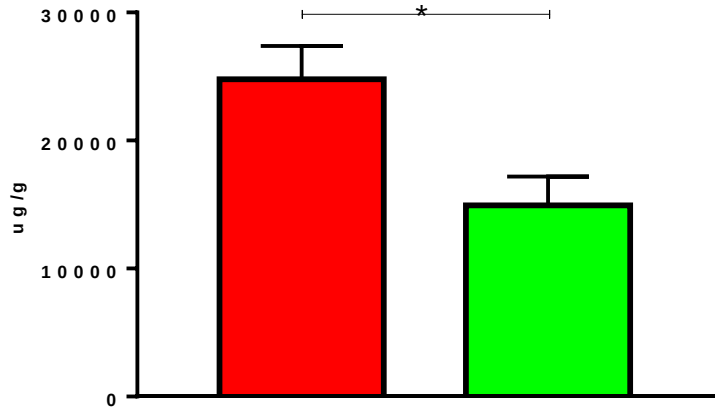


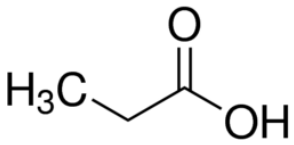
Does the levels of short chain fatty acids in feces differ between WT and Tg mice?

Short chain fatty acids (concentration)

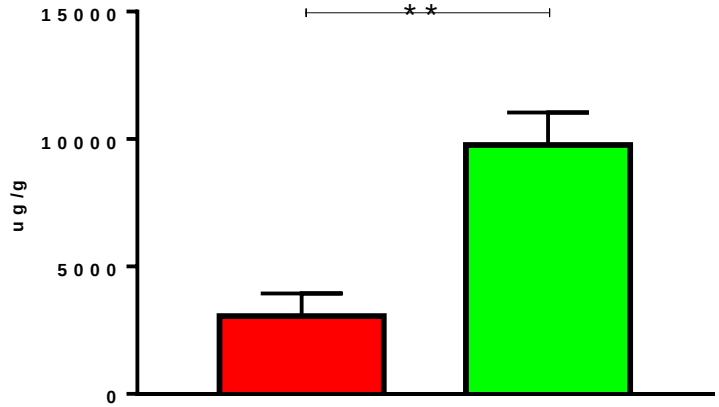


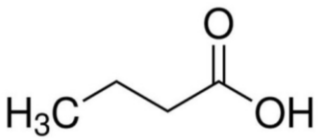
Acetate



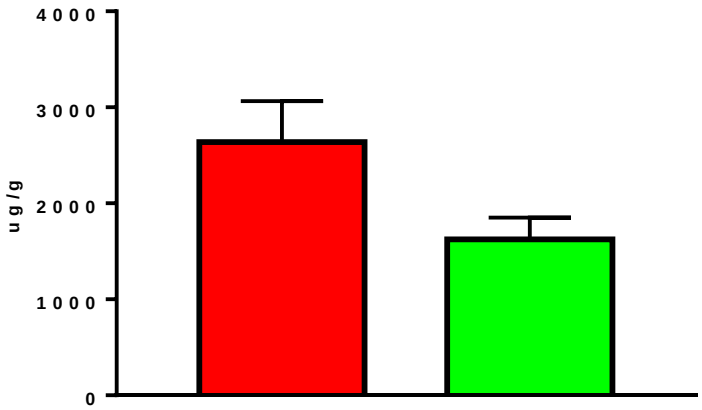


Propionate





Butirate



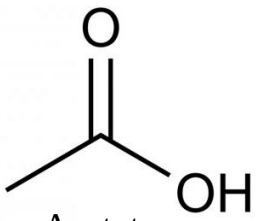
WT

Tg

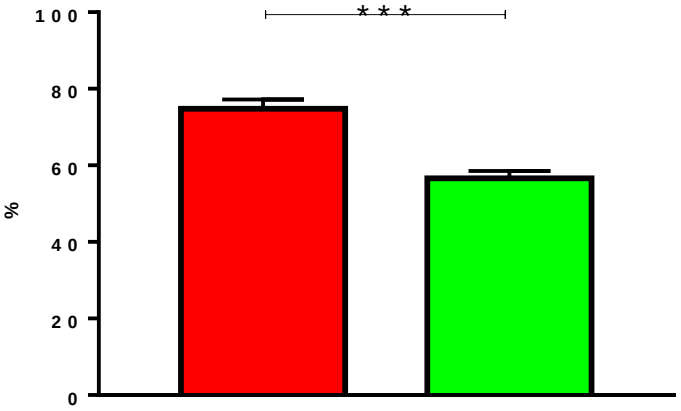
Short chain fatty acids (proportion)

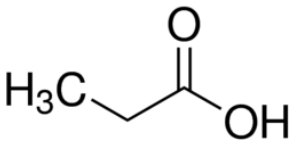
Group	Acetate (%)	Propionate (%)	Butirate (%)
WT	80.34	9.30	10.36
Tg	55.80	37.56	6.64

Short chain fatty acids (proportion)

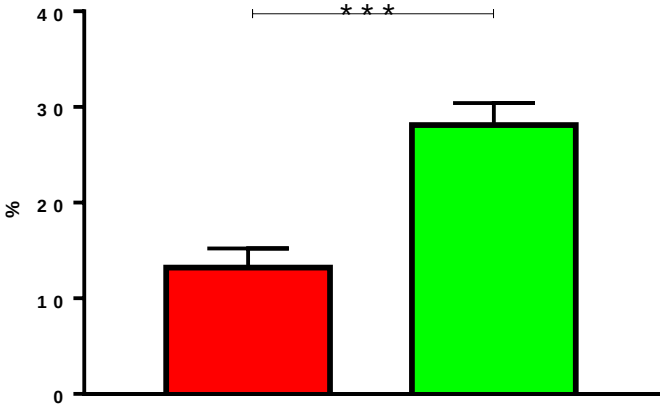


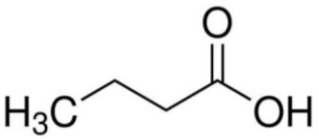
Acetate



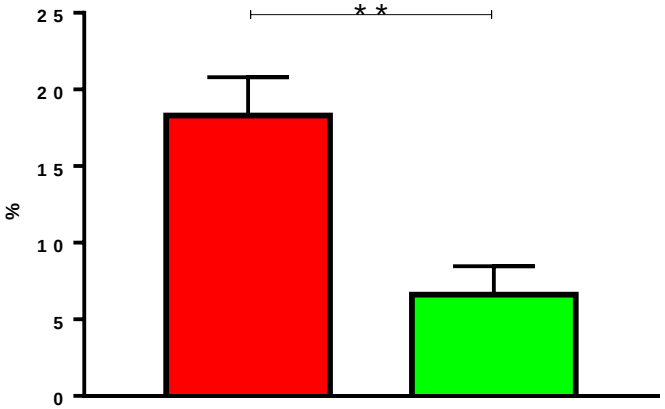


Propionate



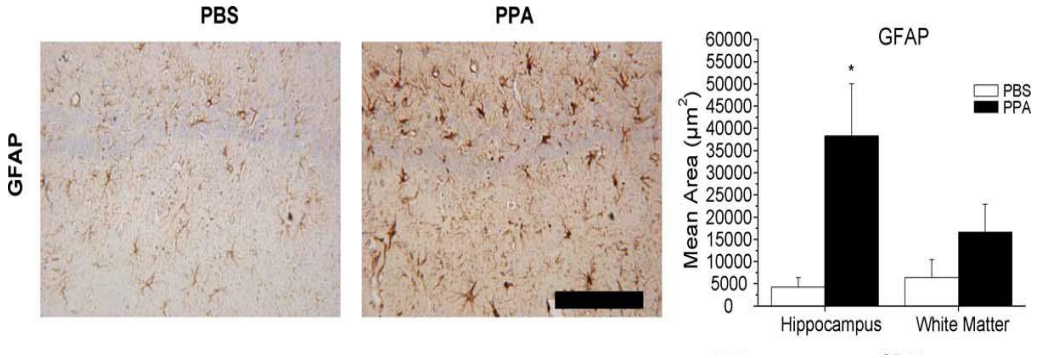


Butirate

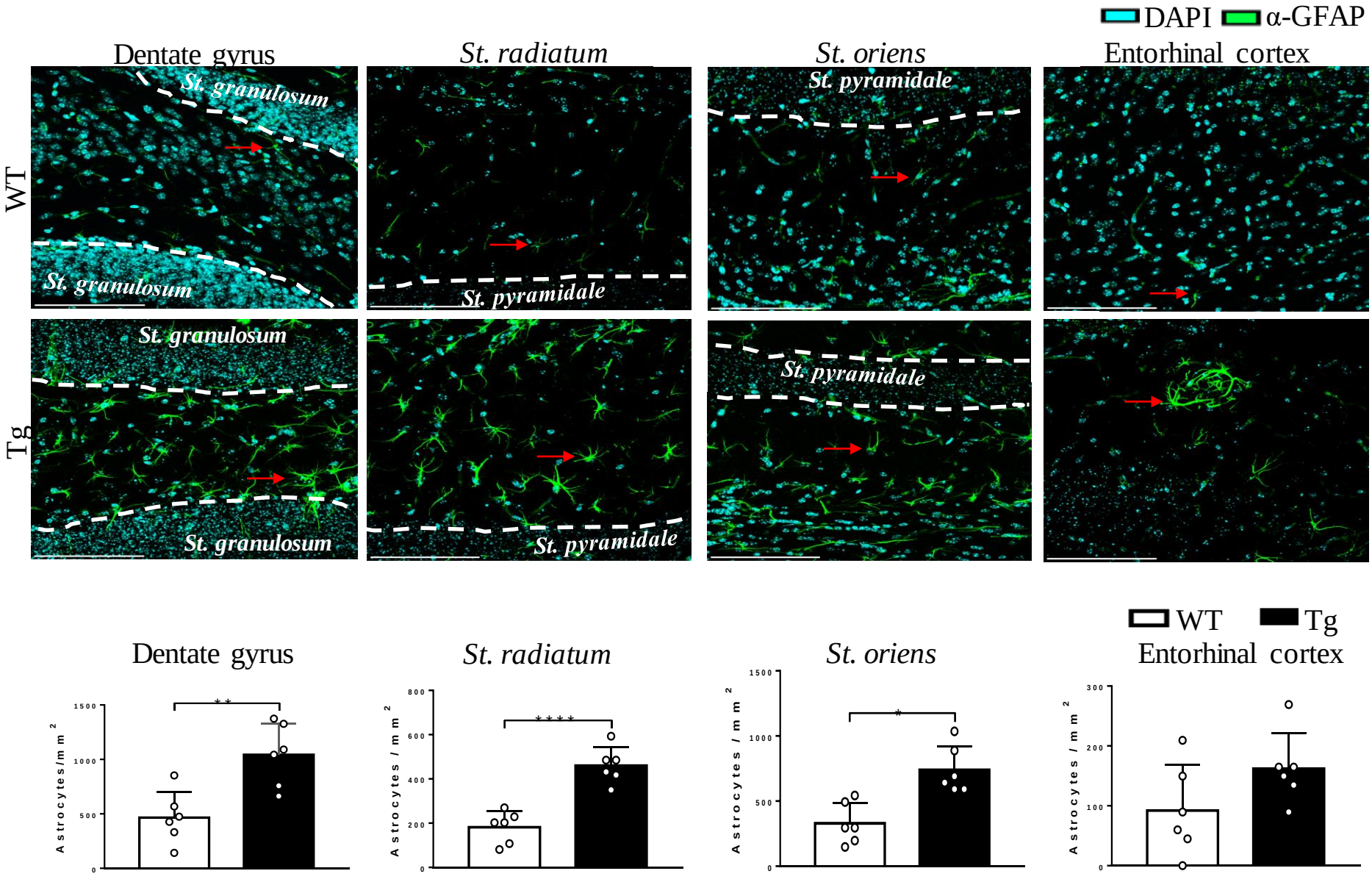


Acetate and butyrate proportions were decreased in Tg compared to WT mice.

Propionate concentration and proportion were increased in Tg animals compared to WT mice.



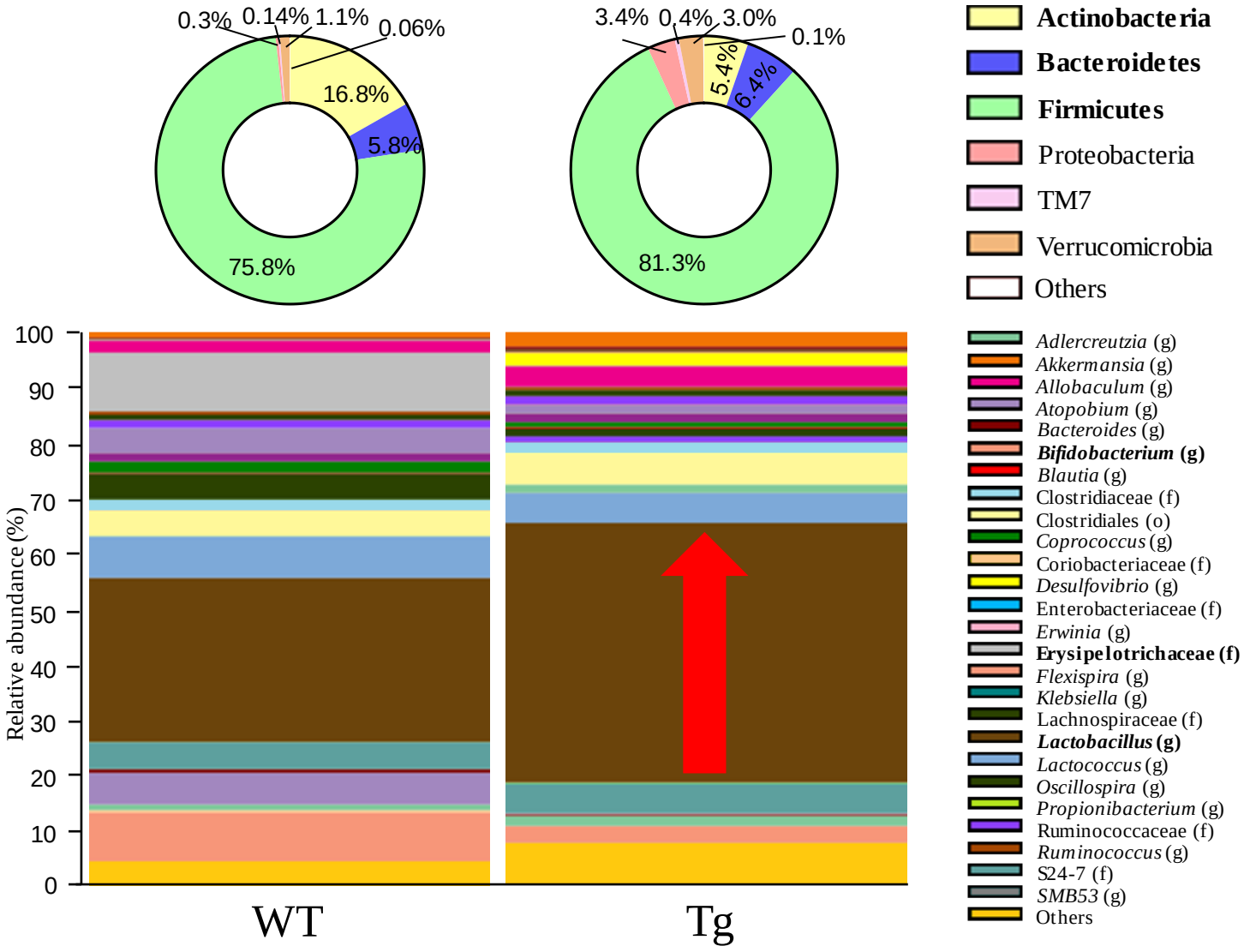
Is neuroinflammation more pronounced in Tg than in WT mice?


DAPI
α-GFAP
Dentate gyrus
St. radiatum
St. oriens
Entorhinal cortex
WT
Tg
St. granulosum
St. granulosum
St. pyramidale
St. pyramidale
St. granulosum
St. granulosum
St. pyramidale
St. pyramidale
WT
Tg
Dentate gyrus
St. radiatum
St. oriens
Entorhinal cortex
Astrocytes/mm 2
Astrocytes / mm 2
Astrocytes / mm 2
Astrocytes / mm 2
**
****
*

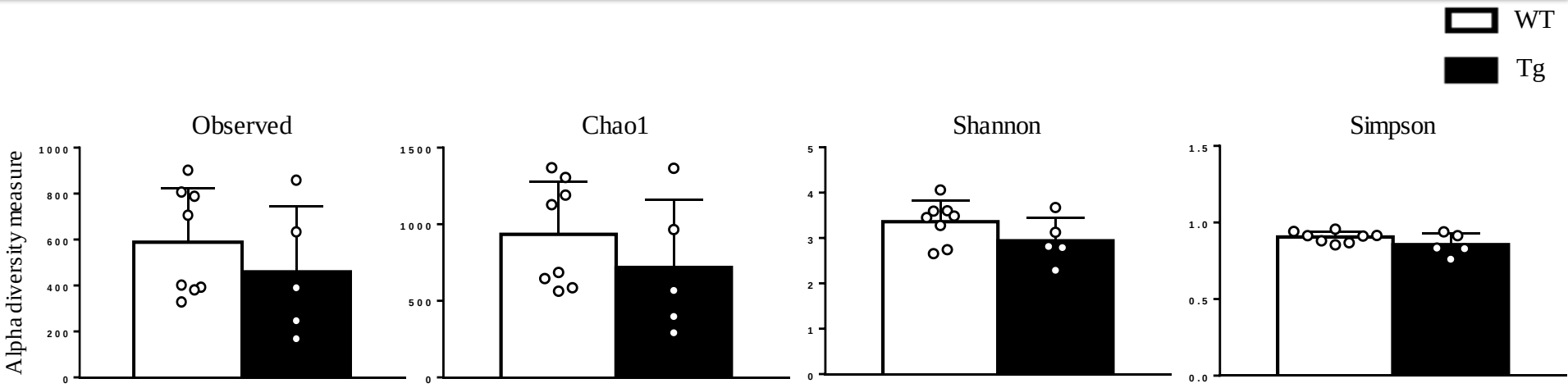
GFAP-positive astrocytes were more abundant in the dentate gyrus, *st. radiatum* and *st. oriens* of Tg compared to WT mice.

Can gut microbiota alterations be related to propionate production in Tg mice?

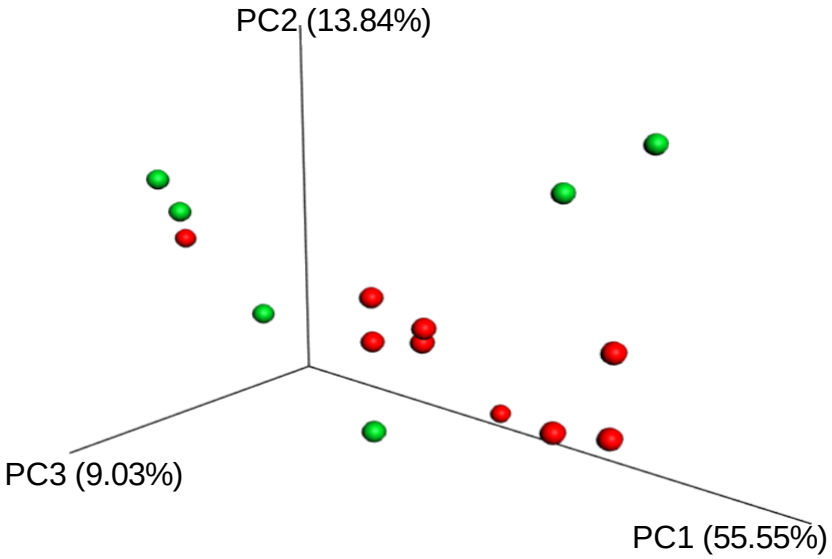
Bacterial abundance



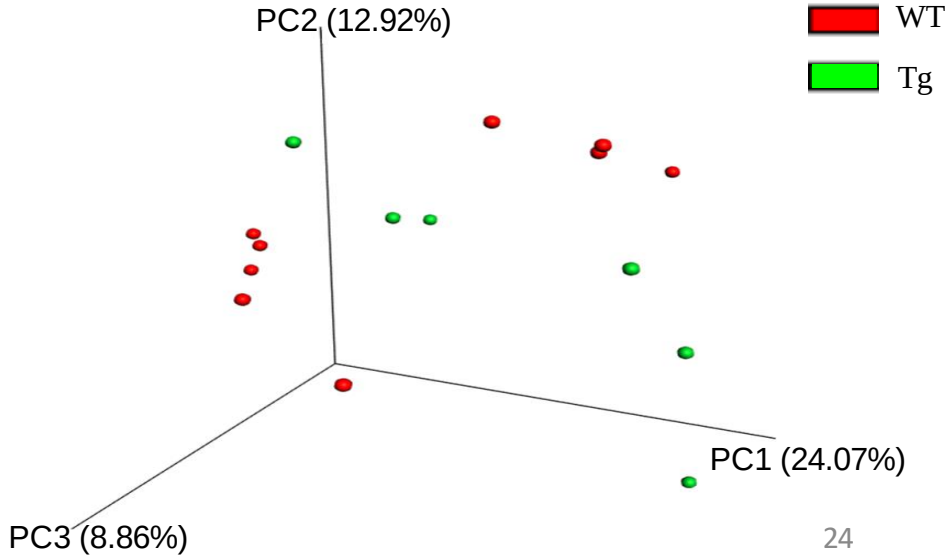
α-diversity



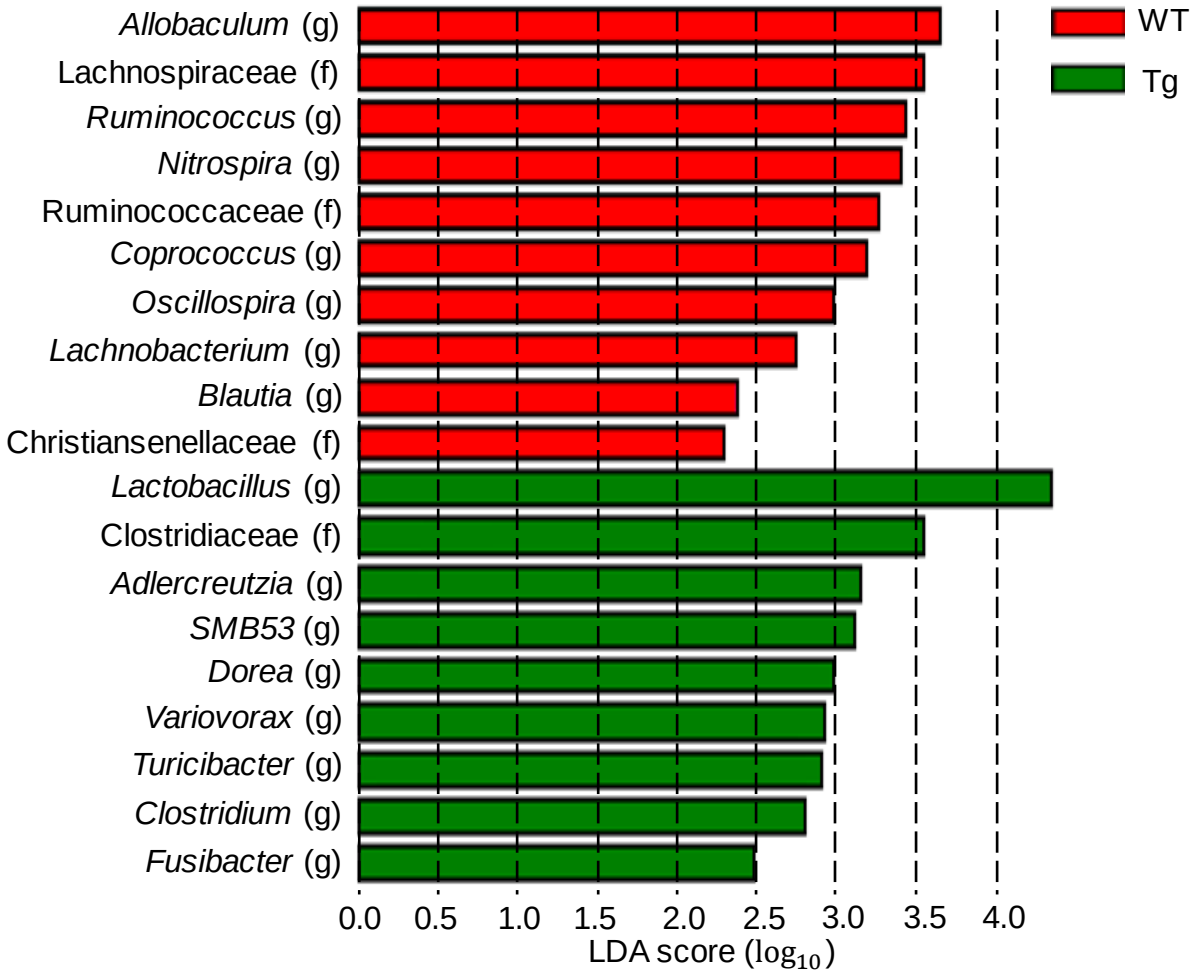
B-diversity (weighted)



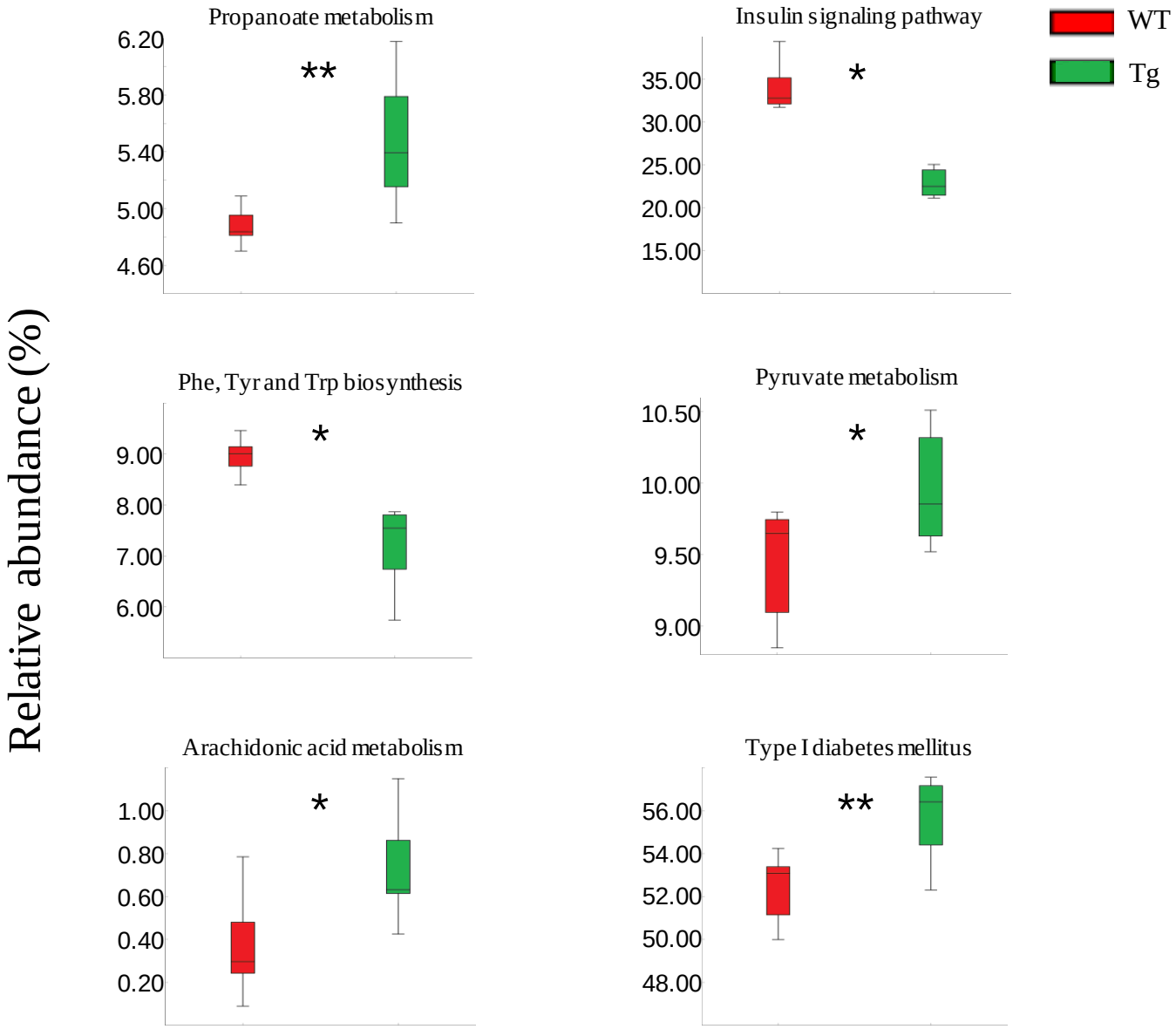
B-diversity (unweighted)



LEfSe (family and genus order)

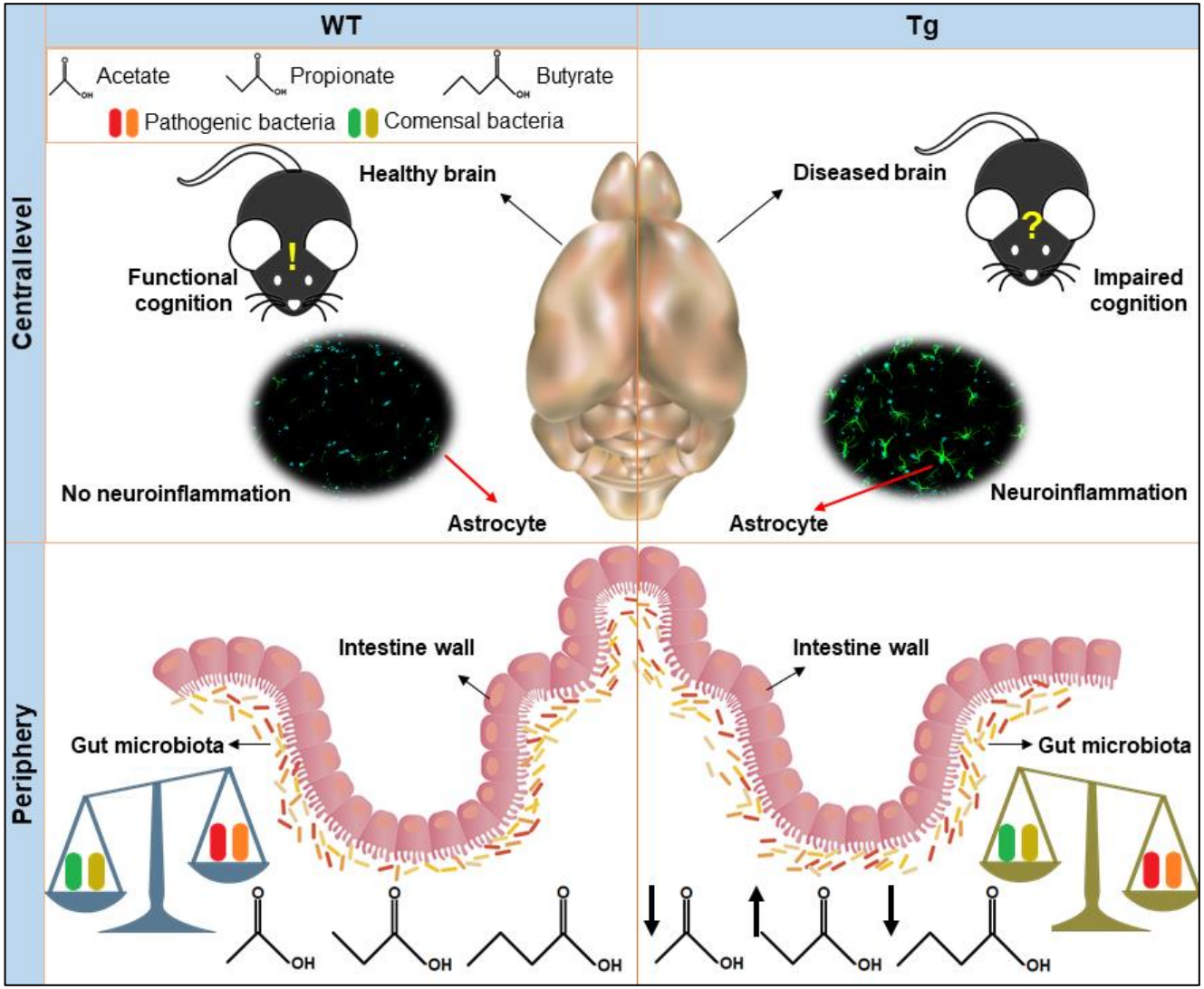


PICRUSt


Relative abundance (%)
Propanoate metabolism
6.20
5.80
5.40
5.00
4.60
**
Insulin signaling pathway
35.00
30.00
25.00
20.00
15.00
*
WT
Tg
Phe, Tyr and Trp biosynthesis
9.00
8.00
7.00
6.00
*
Pyruvate metabolism
10.50
10.00
9.50
9.00
*
Arachidonic acid metabolism
1.00
0.80
0.60
0.40
0.20
*
Type I diabetes mellitus
56.00
54.00
52.00
50.00
48.00
**

Enrichment of lactic acid bacteria in fecal samples of Tg mice is related to propionate levels, pyruvate metabolism, and inflammation.

According to PICRUSt analysis, WT´s bacterial diversity, and composition associates with enhanced Phe, Tyr and Trp biosynthesis compared to Tg mice.


WT
Tg
Central level
Periphery
Acetate
Propionate
Butyrate
Pathogenic bacteria
Comensal bacteria
Healthy brain
Diseased brain
Functional cognition
Impaired cognition
No neuroinflammation
Neuroinflammation
Astrocyte
Astrocyte
Intestine wall
Intestine wall
Gut microbiota
Gut microbiota
OH
OH
OH
OH
OH
OH

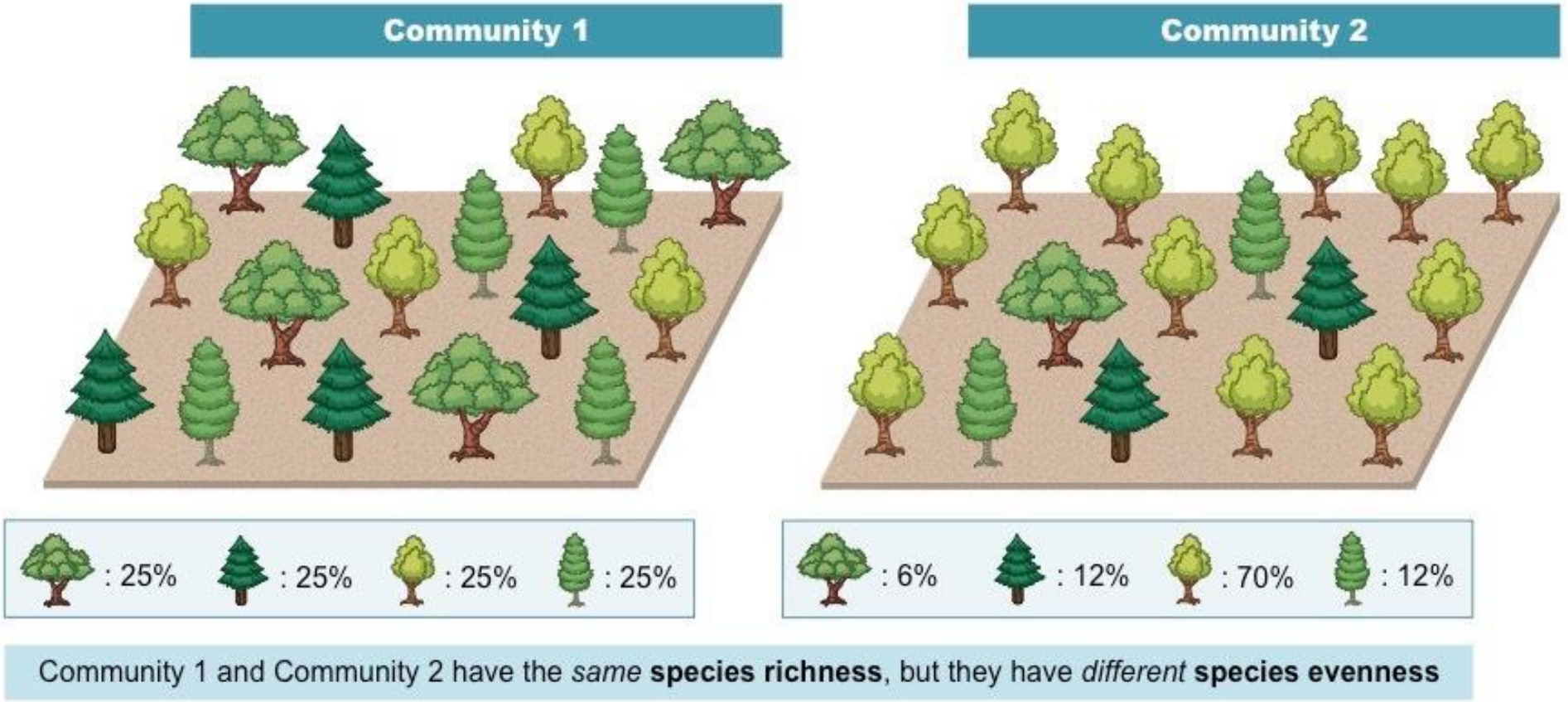
Perspectives

- To evaluate the impact of modifying/restoring the gut microbiota on cognition in Tg mice.

- To determine the presence of bacterial molecules in plasma of Tg mice.

- To quantify the levels of short chain fatty acids in the brain.


Thank you



Community 1 and Community 2 have the *same* **species richness**, but they have *different* **species evenness**