



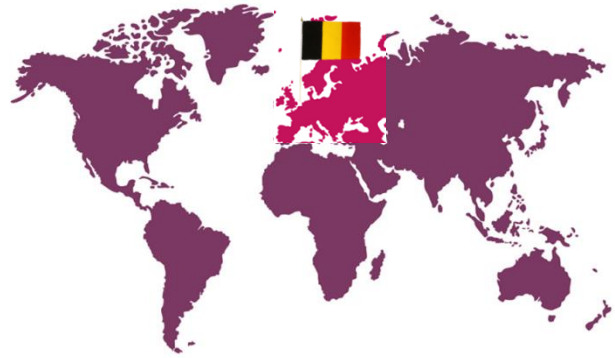
Role of the gut microbiota and feeding behaviour in alcohol use disorder : a specific impact on socialization impairments

Philippe de Timary, MD, PhD



EUFAS 22 - Lisbon





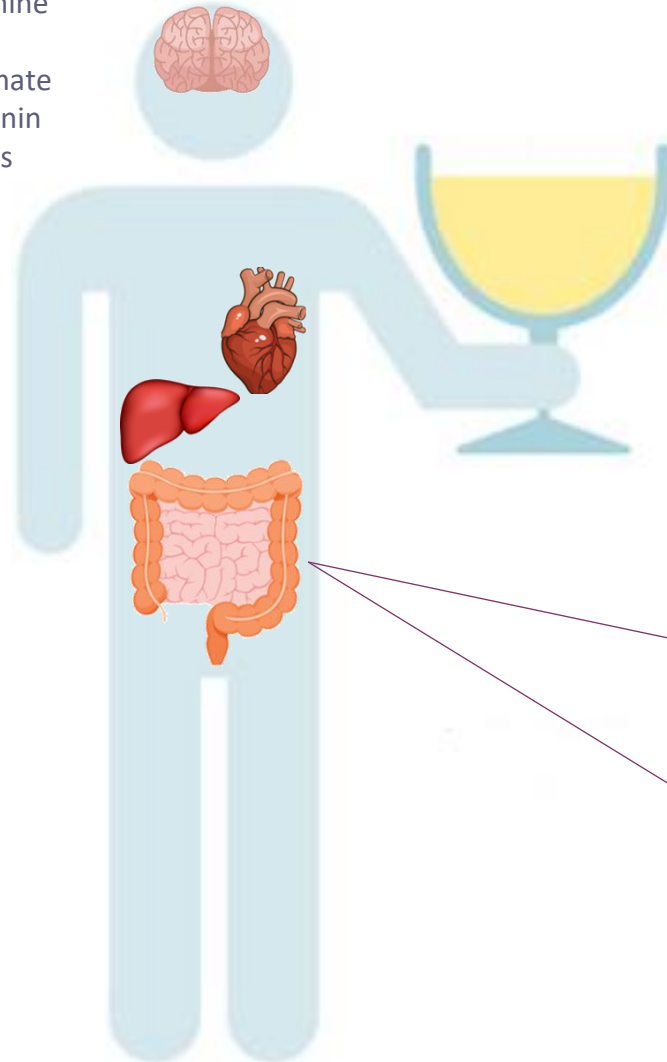
5.1 % of AUD in the world
8.1% in Belgium (12% in men)



No efficient
treatment
High rate of
relapse (70%)

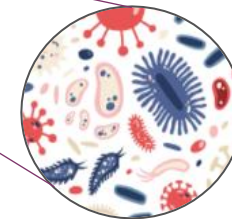
Alcohol use disorder

Dopamine
GABA
Glutamate
Serotonin
Opioids



AUD is a **chronic relapsing** brain disease characterized by **compulsive alcohol use**, **loss of control** over alcohol intake, and a **negative emotional state**.

Nutrition
Gut microbiota





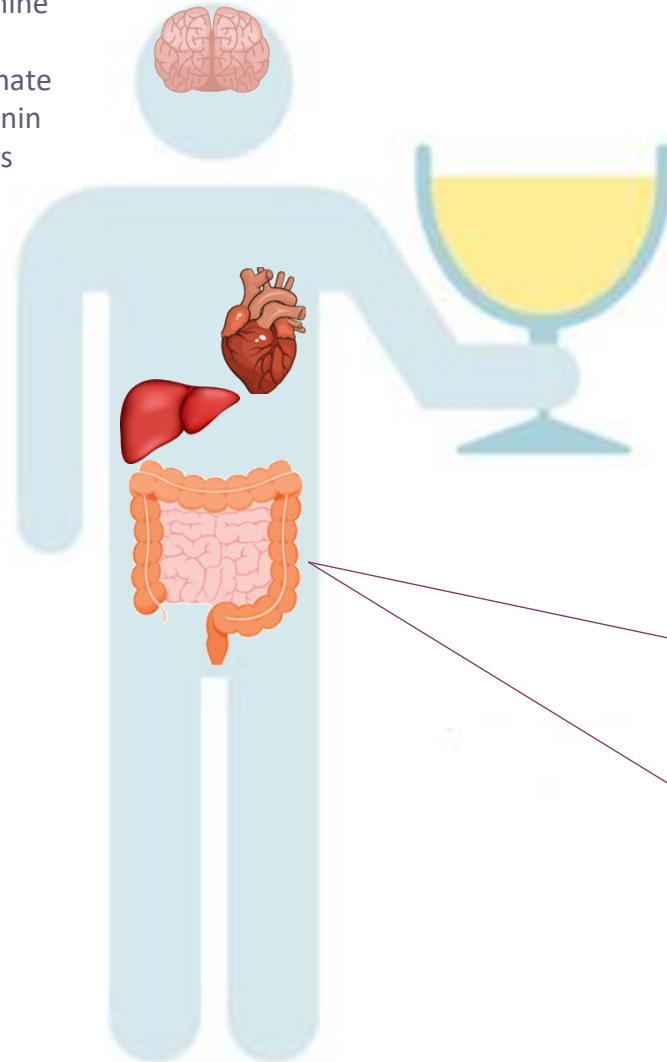
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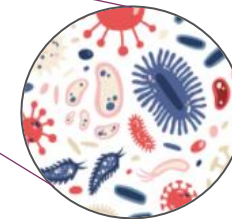
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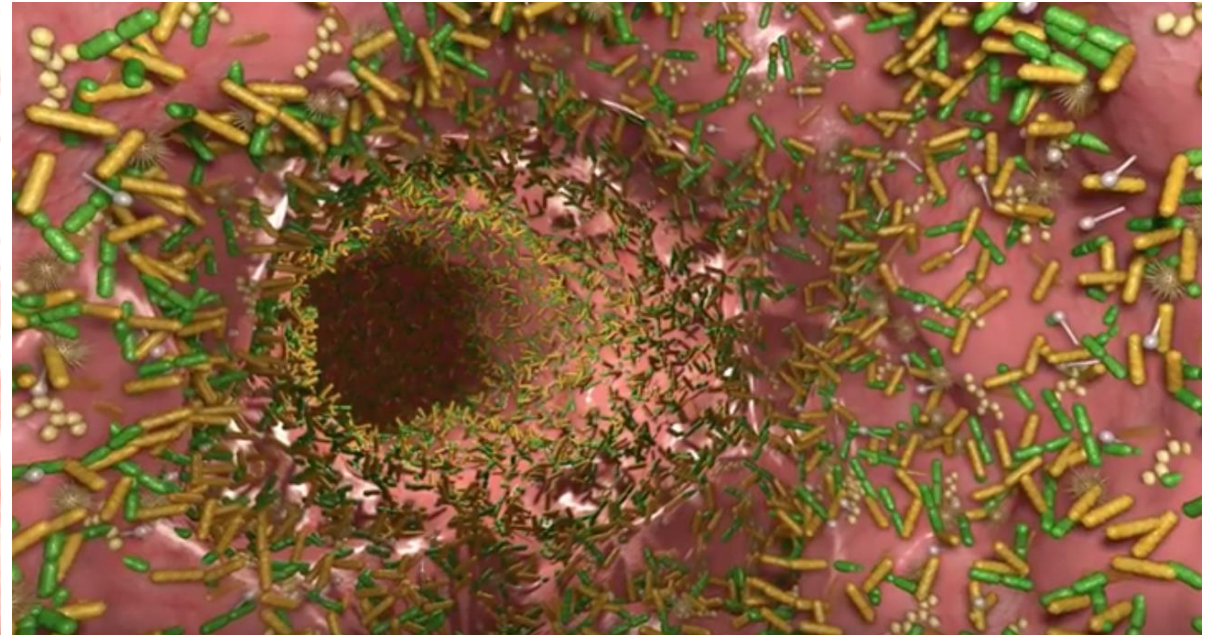
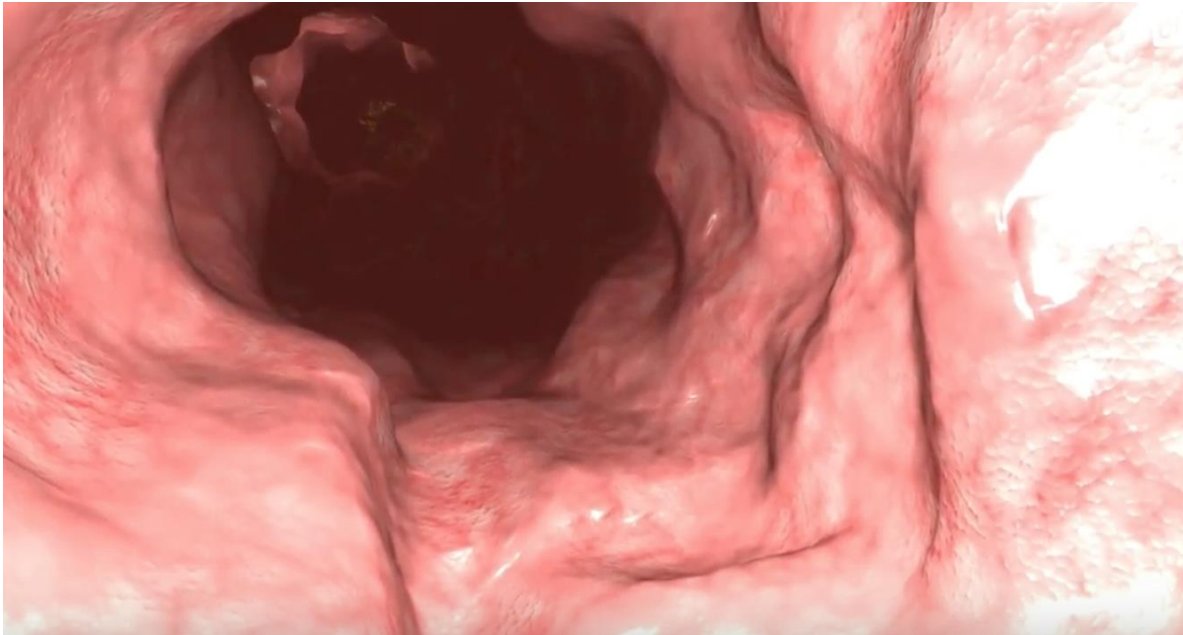


AUD is a **chronic relapsing** brain disease characterized by **compulsive alcohol use**, **loss of control** over alcohol intake, and a **negative emotional state**.

Nutrition
Gut microbiota



What is the gut microbiota?



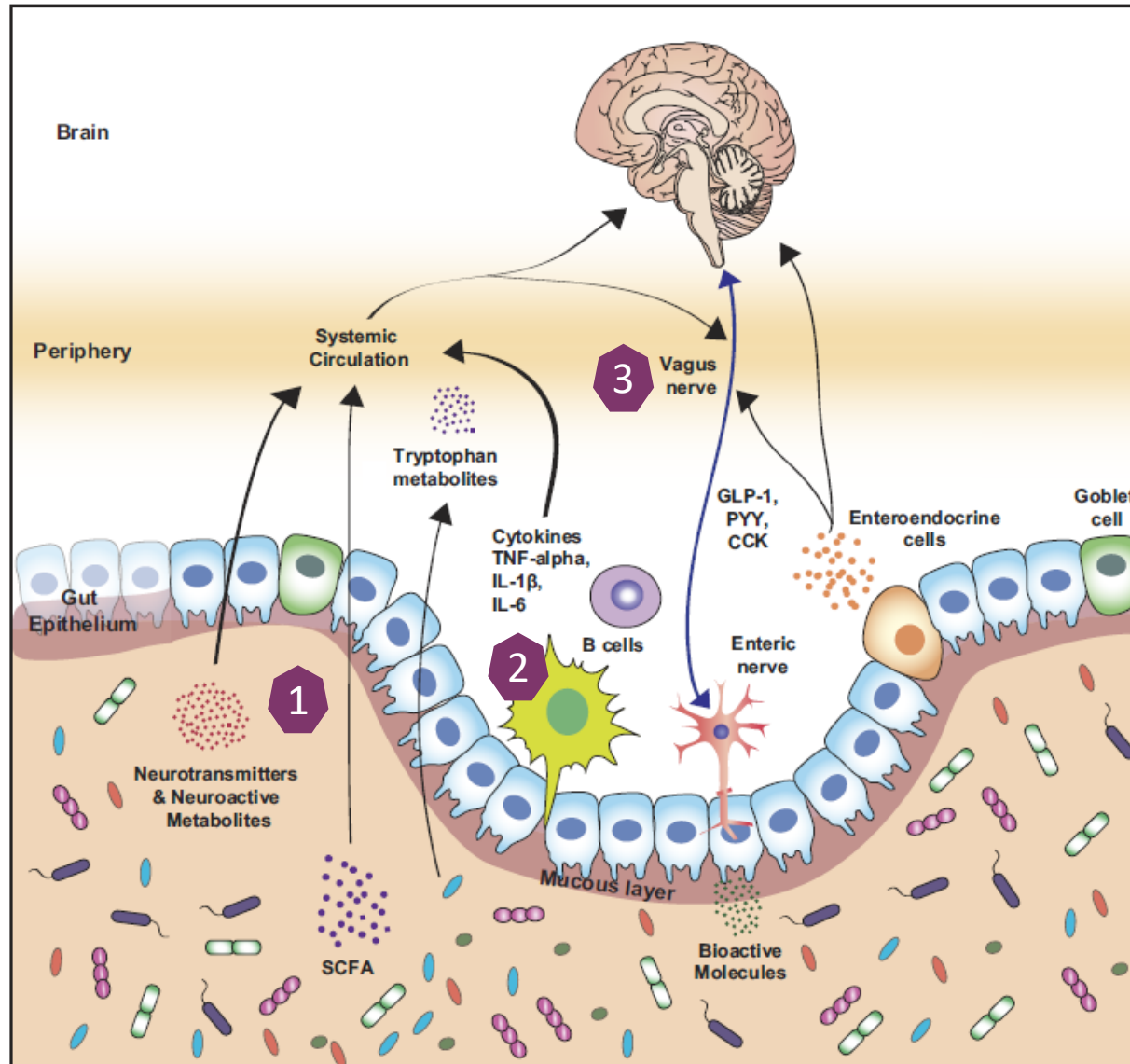
Bacteria Viruses Fungi Yeasts

100 000 000 000 000

Microbial composition is unique...



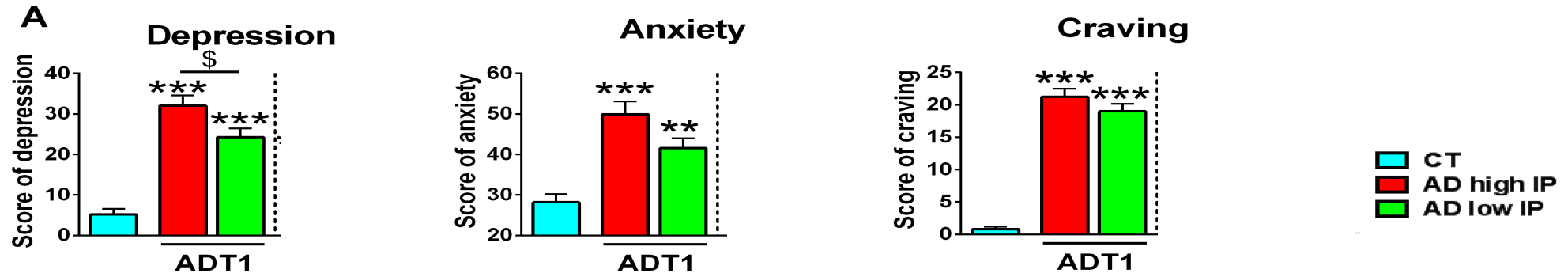
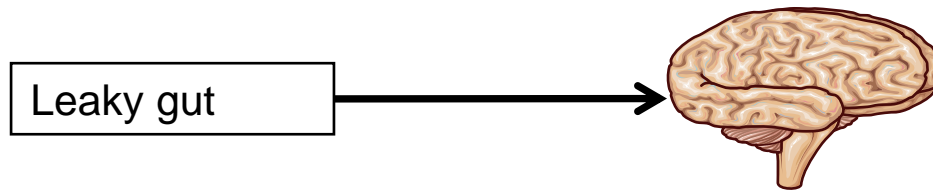
How can the gut communicate with the brain ?



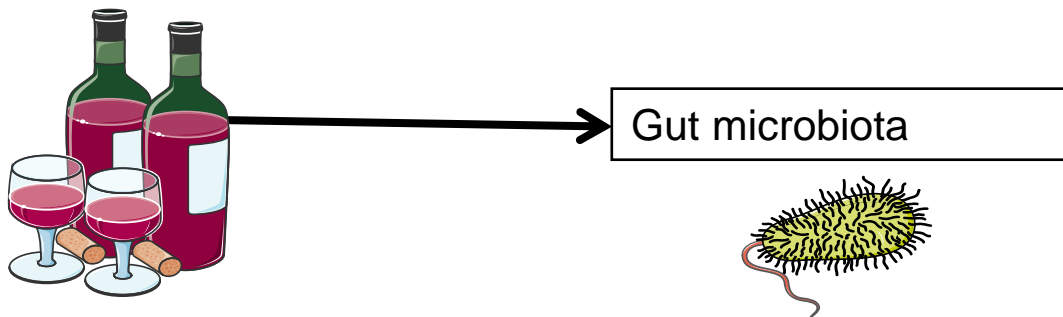
- 1 Microbial metabolites
- 2 Inflammation
- 3 Vagus nerve

Methods

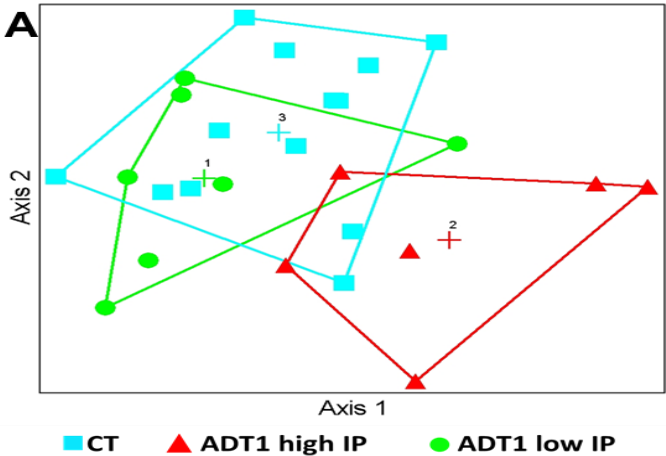
- Alcohol dependent subjects tested at the beginning and end of detox
- Interstitial permeability assessed by ^{51}Cr -EDTA technique
- Gut microbiota analysis by pyrosequencing and qPCR
- Metabolomic analysis of volatile organic compounds by gas chromatography-mass spectrometry



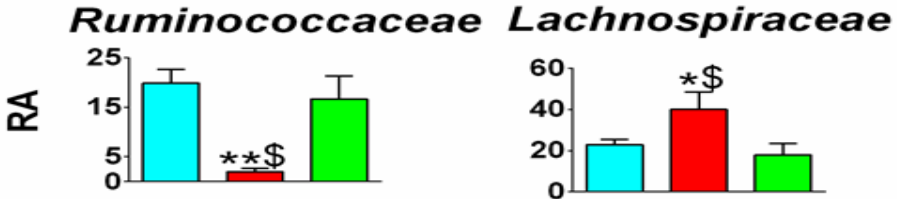
- The gut barrier function is related to the psychological symptoms of alcohol dependence at the end of detoxification



- The bacterial profile is altered in AD subjects with high IP



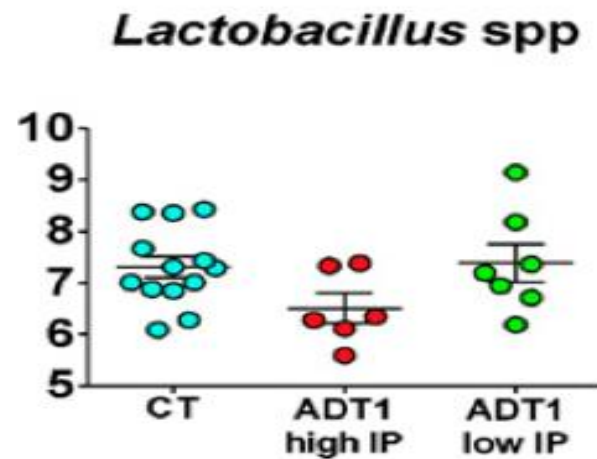
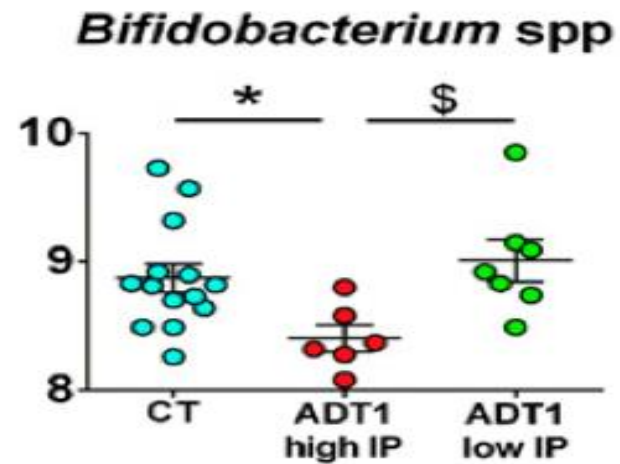
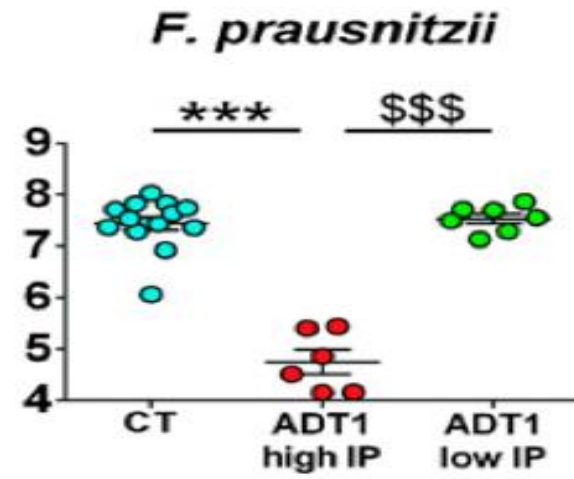
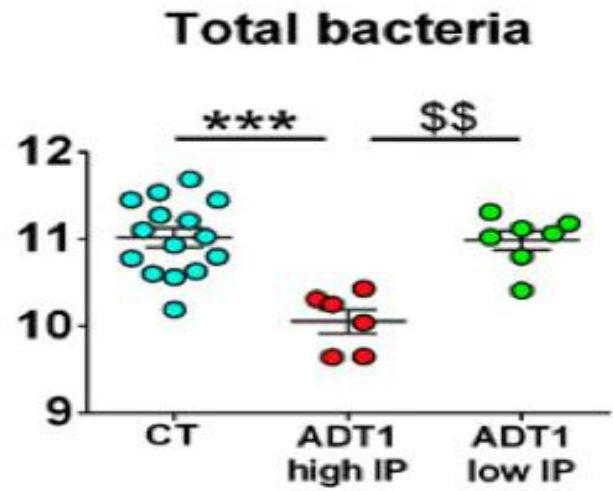
B Families



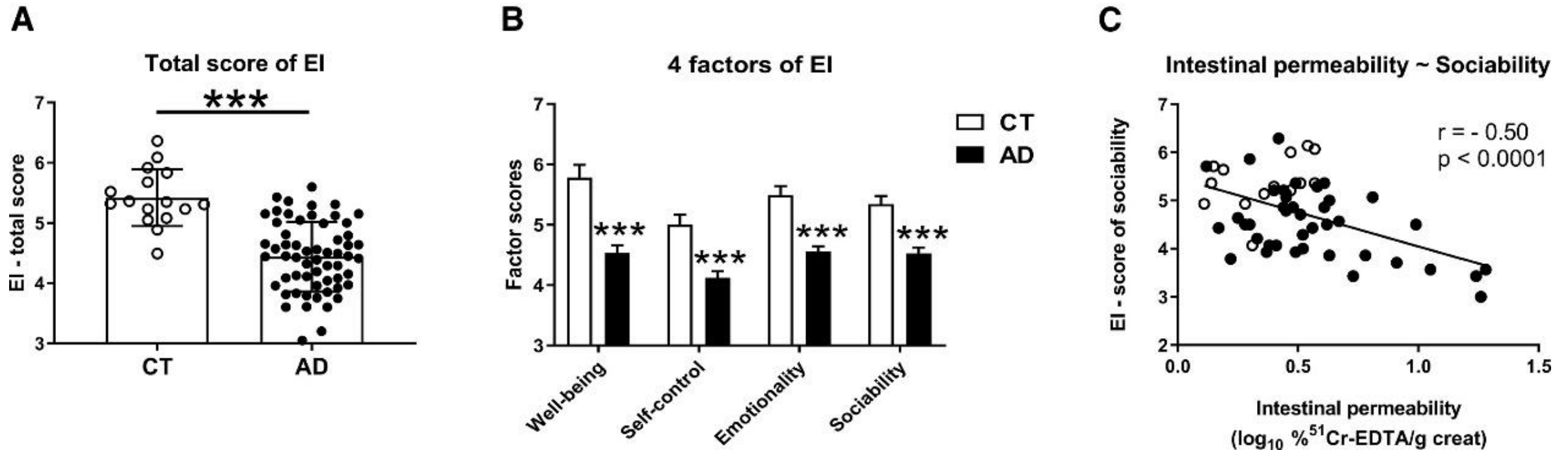
Pyrosequencing

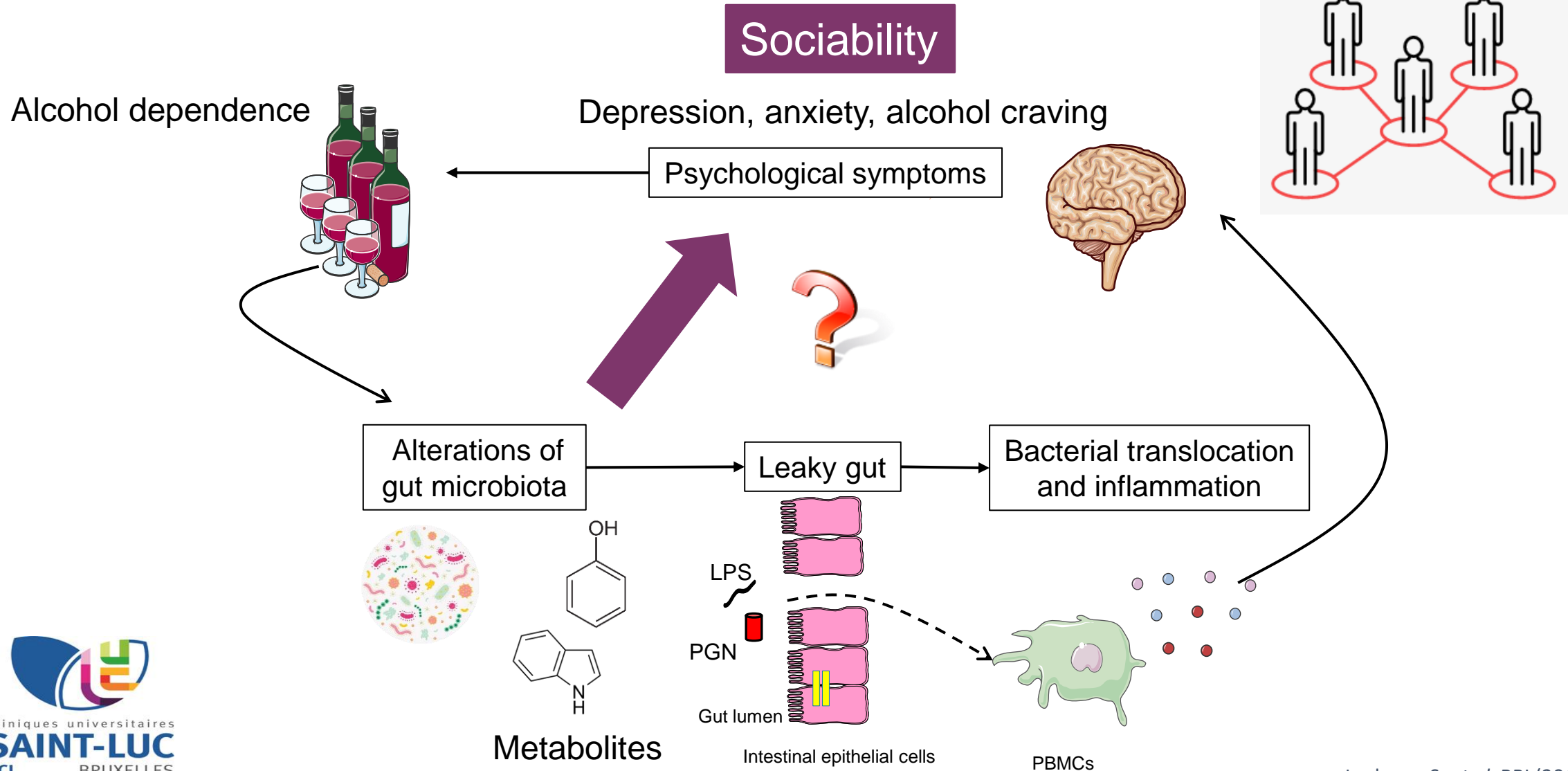
- Persistence of dysbiosis at the end of detoxification
 \$ p < 0,05 vs AD-low IP, \$\$\$ p < 0,001 vs AD-low IP, ** p < 0,01 vs CT *** p < 0,001 vs CT

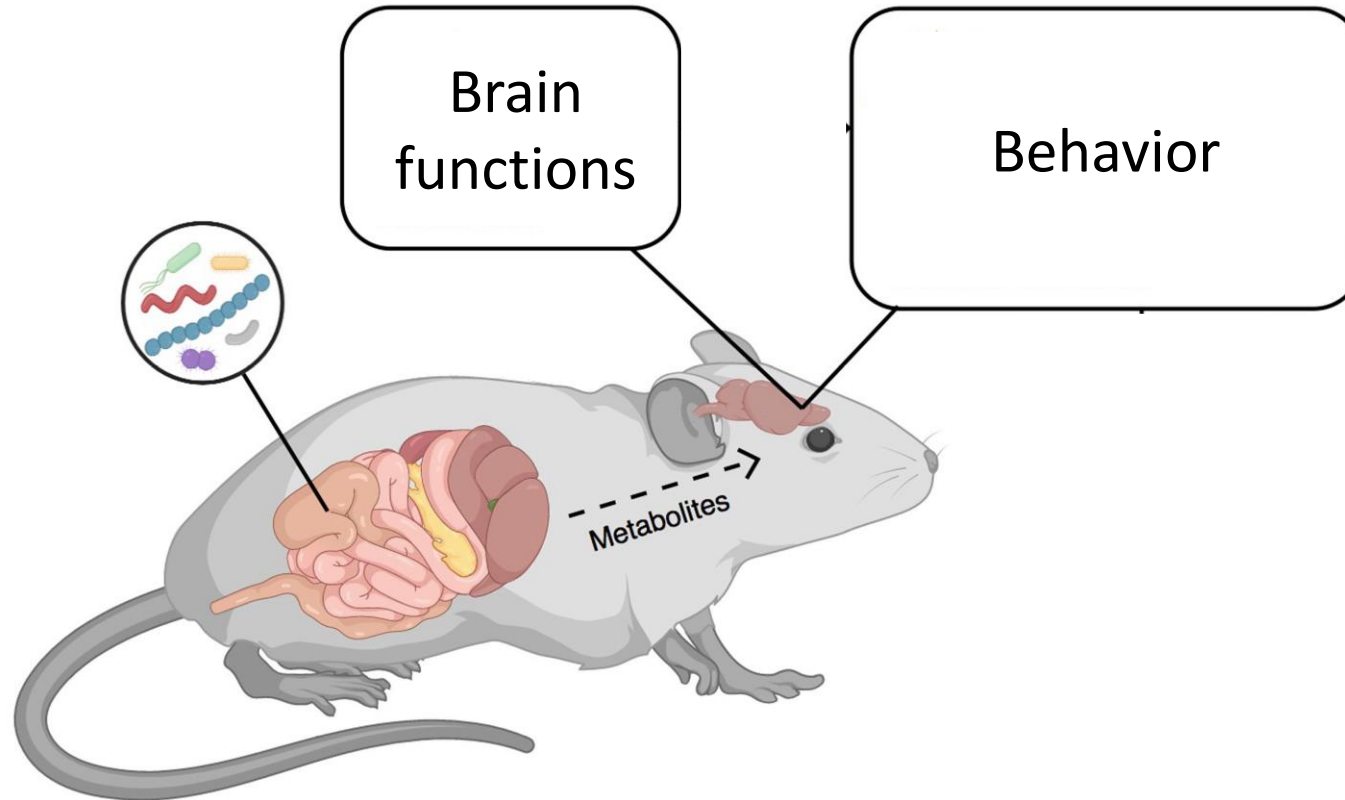
C
 \log_{10} (bacteria cells/g feces)



In AUD patients, sociability is related to intestinal permeability

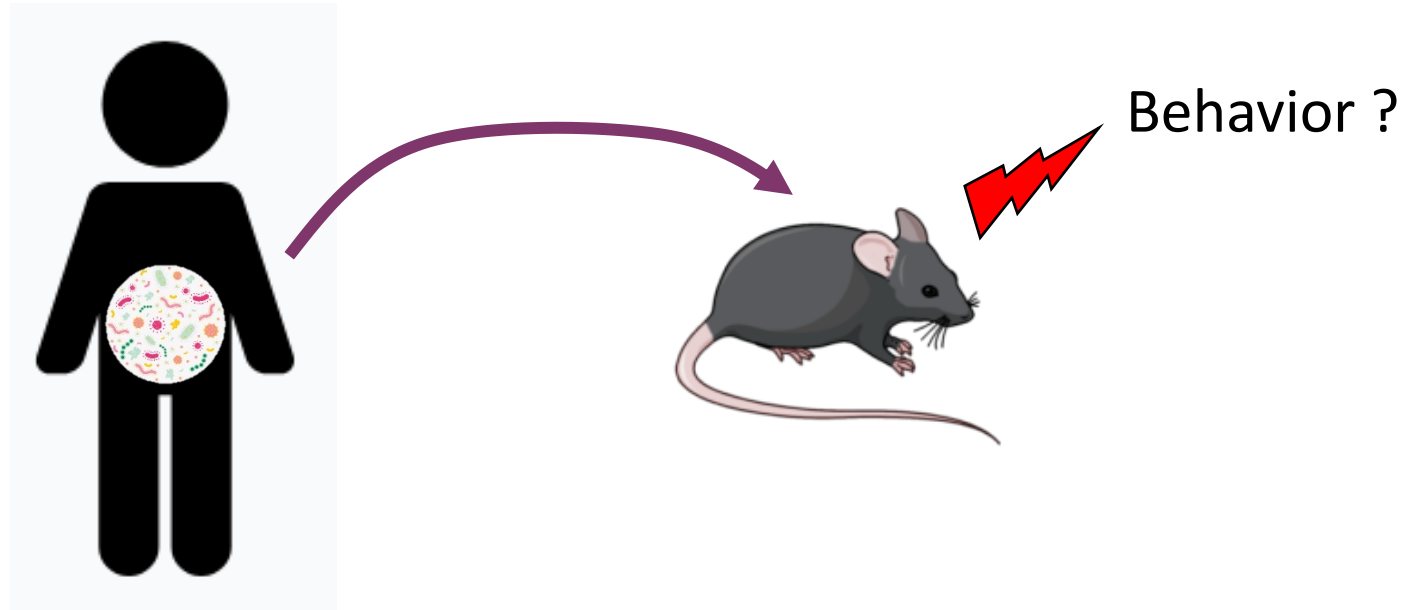




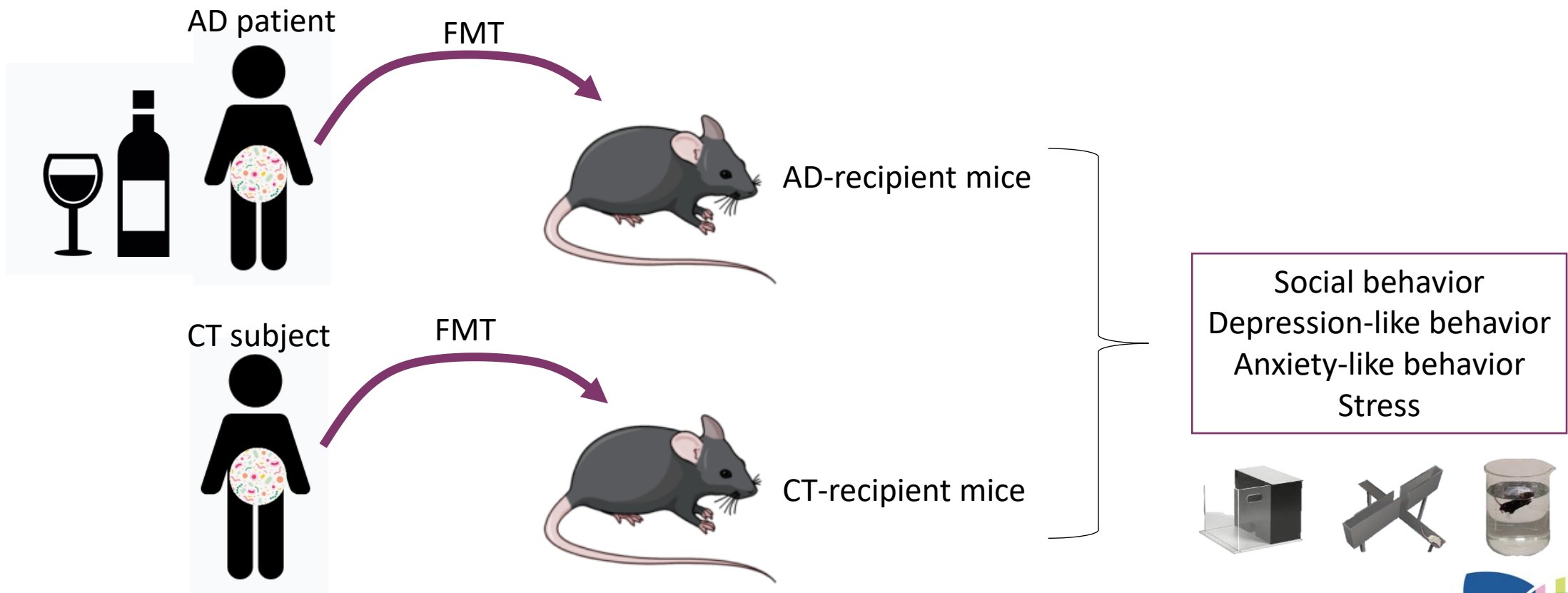
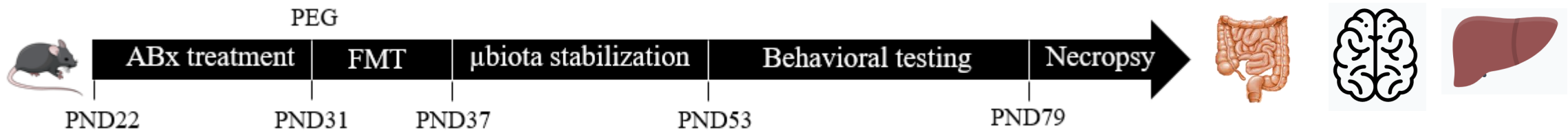


Do intestinal microbes play a **causal role** in the development of behavioral alterations associated with alcohol dependence ?

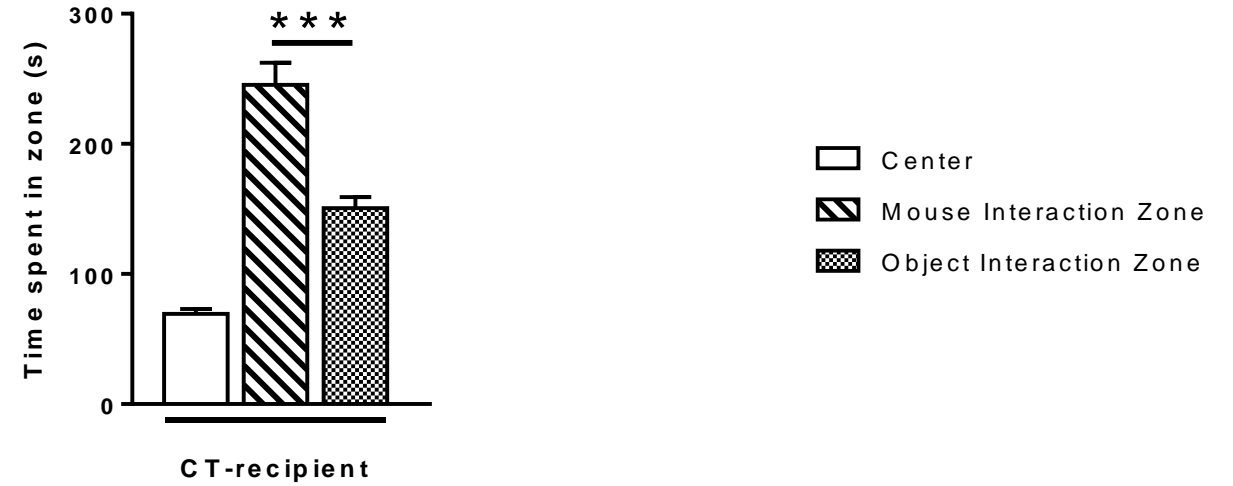
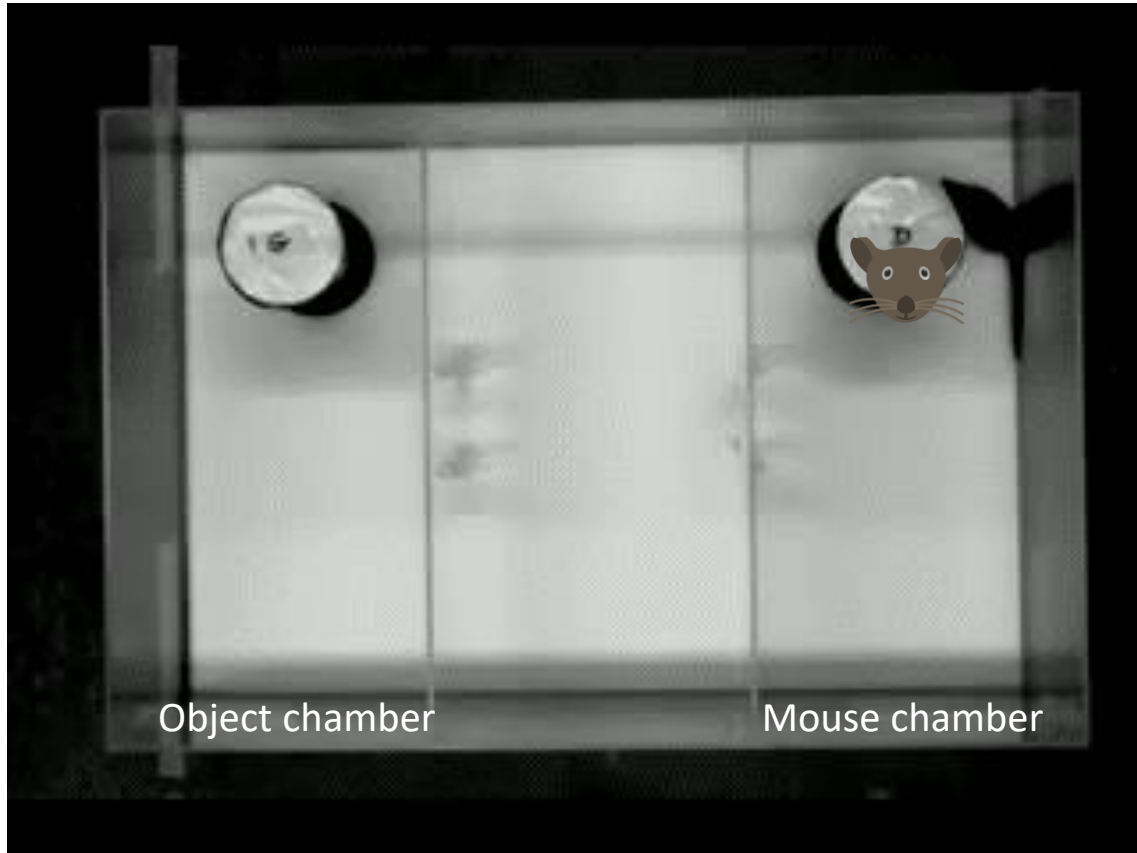
Fecal microbiota transplantation (FMT)



Aims

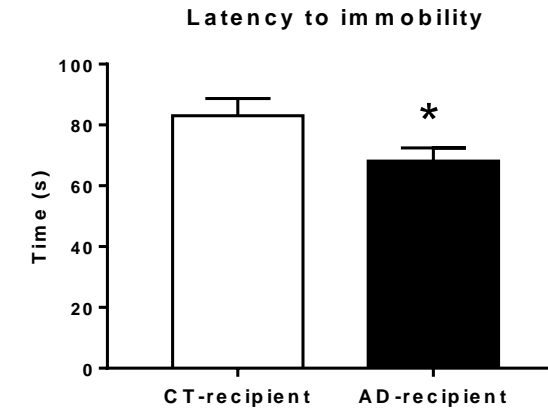
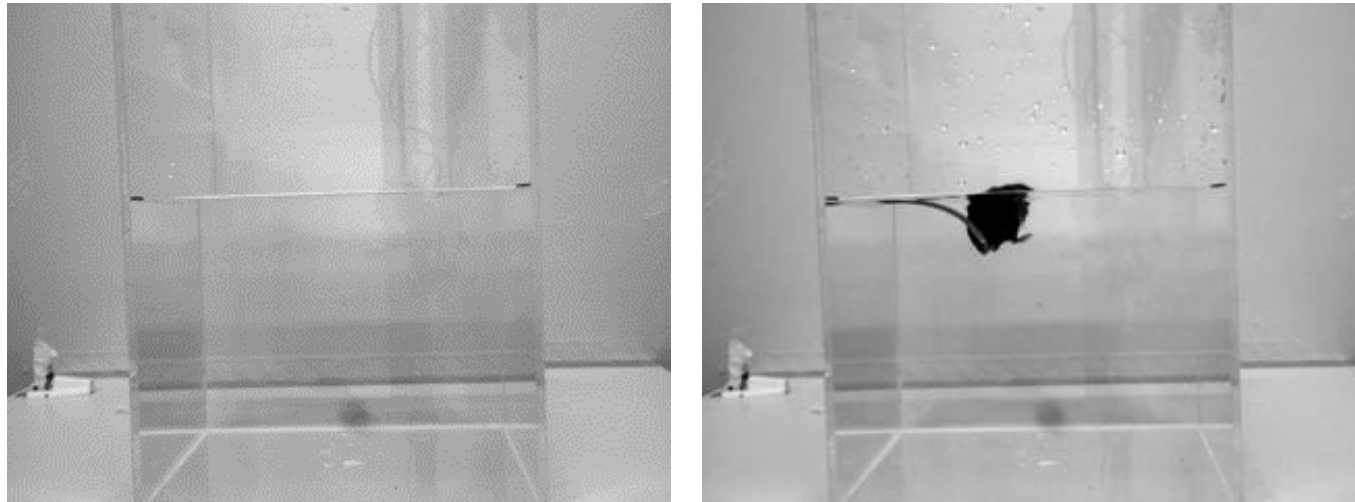


Social behavior



Reduced sociability in AD recipient mice

Depression-like behavior (Forced Swim Test)



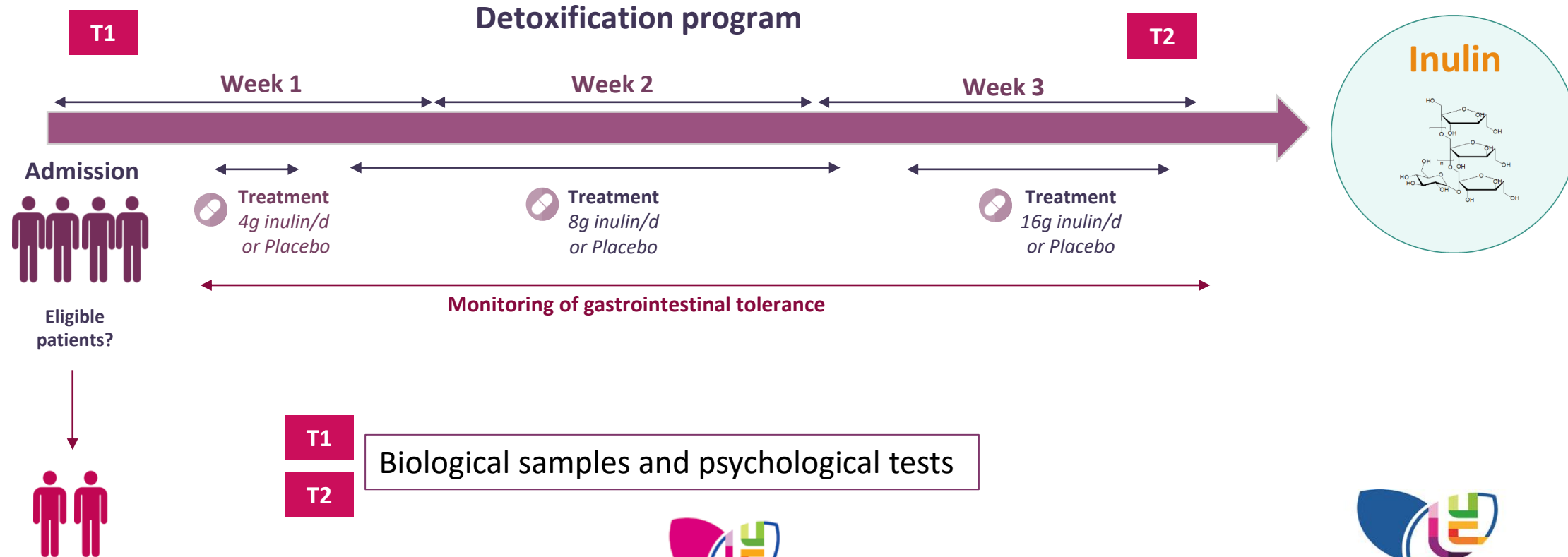
Increased depression-like behavior in AD recipient mice

The gut microbiota of AUD patient may play a causal role in the induction of some AUD symptoms, including decrease in social proneness

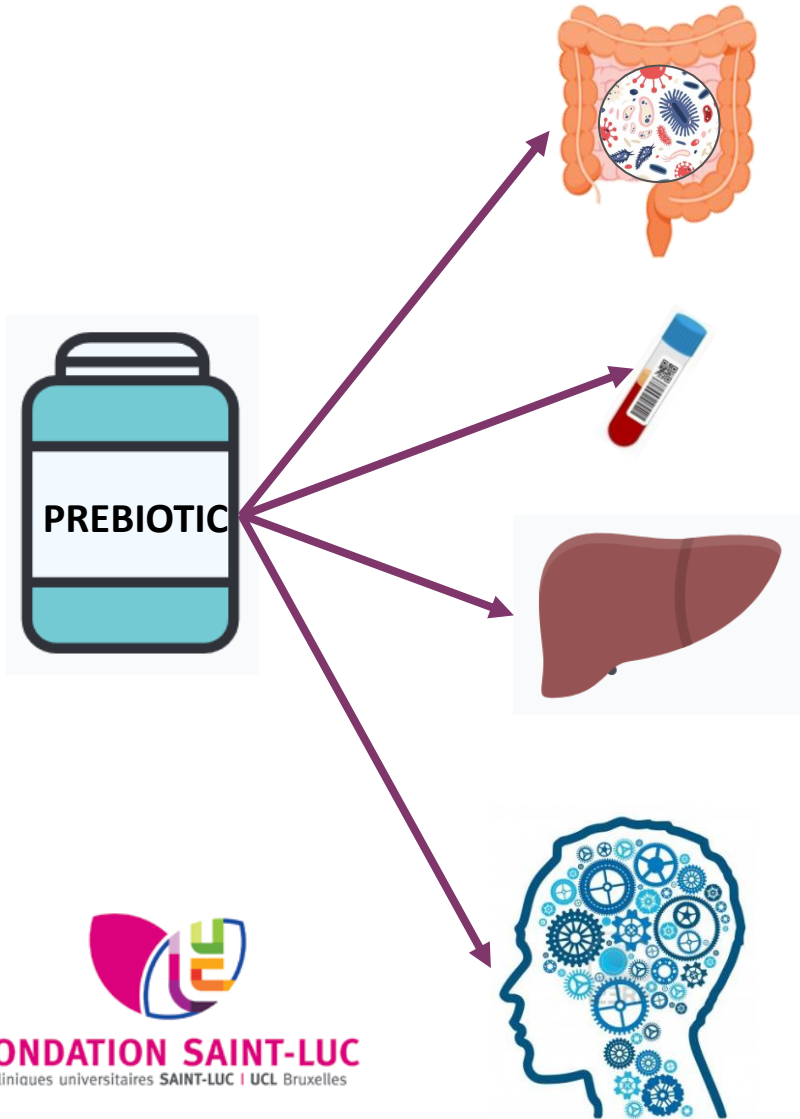
- Randomized, double blind, placebo controlled clinical study
- Supplementation of AD patients with prebiotic fiber (inulin) or placebo
- 50 patients included



Camille Amadiou



Main and secondary endpoints



Effect on gut microbiota composition and function

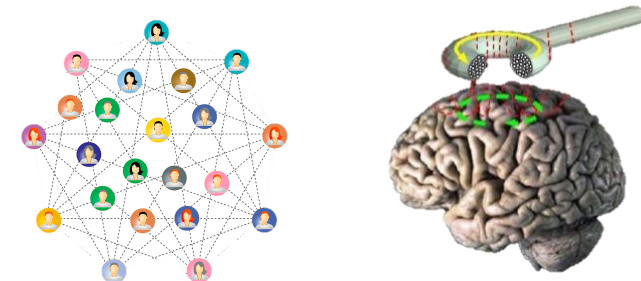
16S rDNA sequencing → results expected Oct 15th

Effect on metabolic profile and inflammation

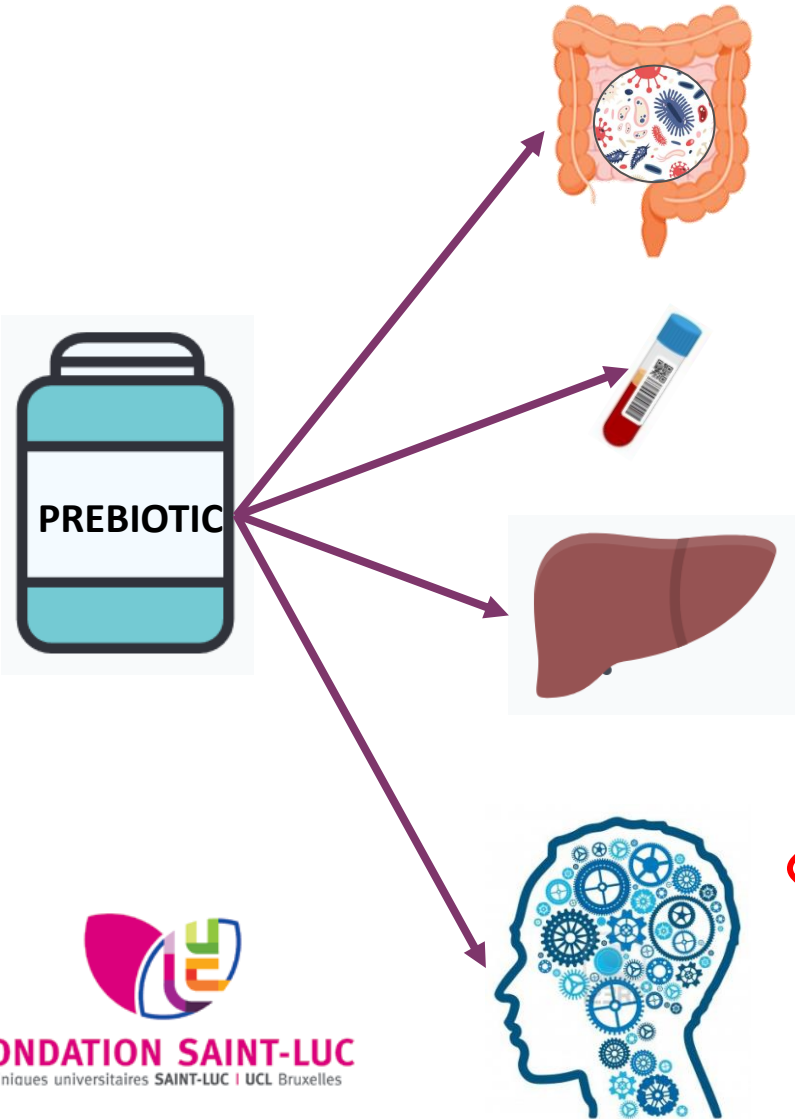
Metabolomics → results expected in December 2020

Effect on liver steatosis and stiffness

Effect on psychological symptoms / sociability / cognitive processes



Main and secondary endpoints



Effect on gut microbiota composition and function

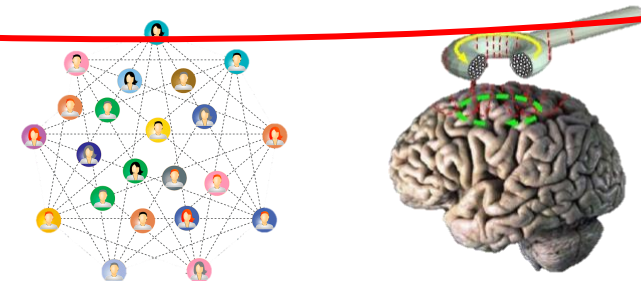
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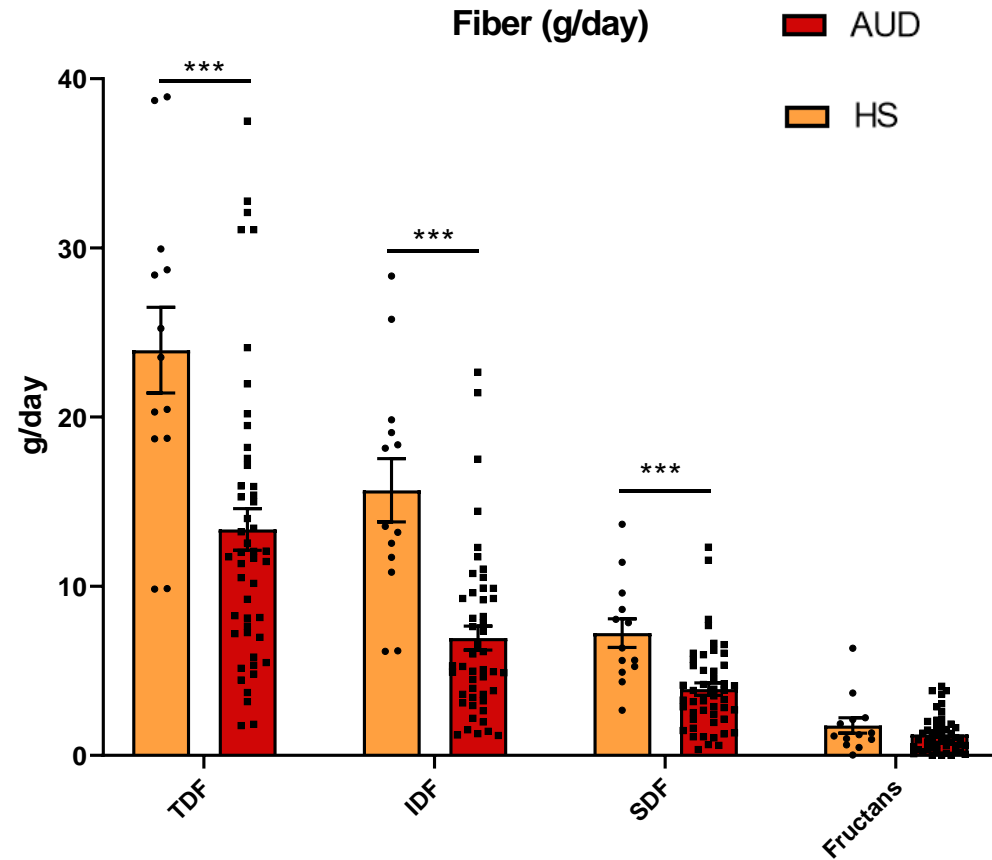
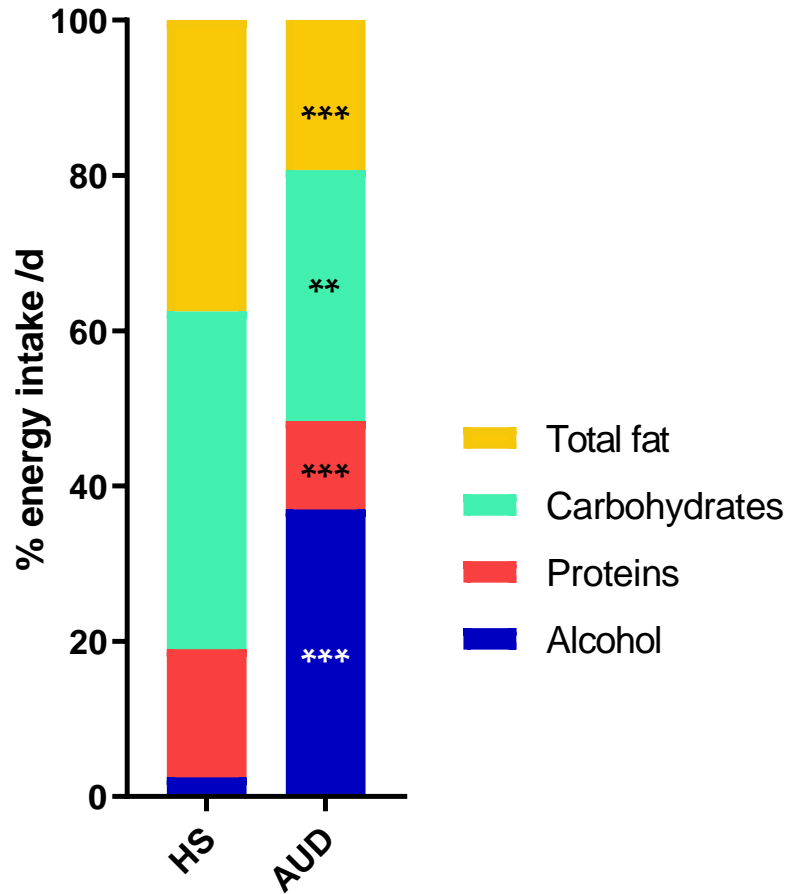
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Effect on liver steatosis and stiffness

Effect on psychological symptoms / sociability / cognitive processes



Macronutrients (% EI)



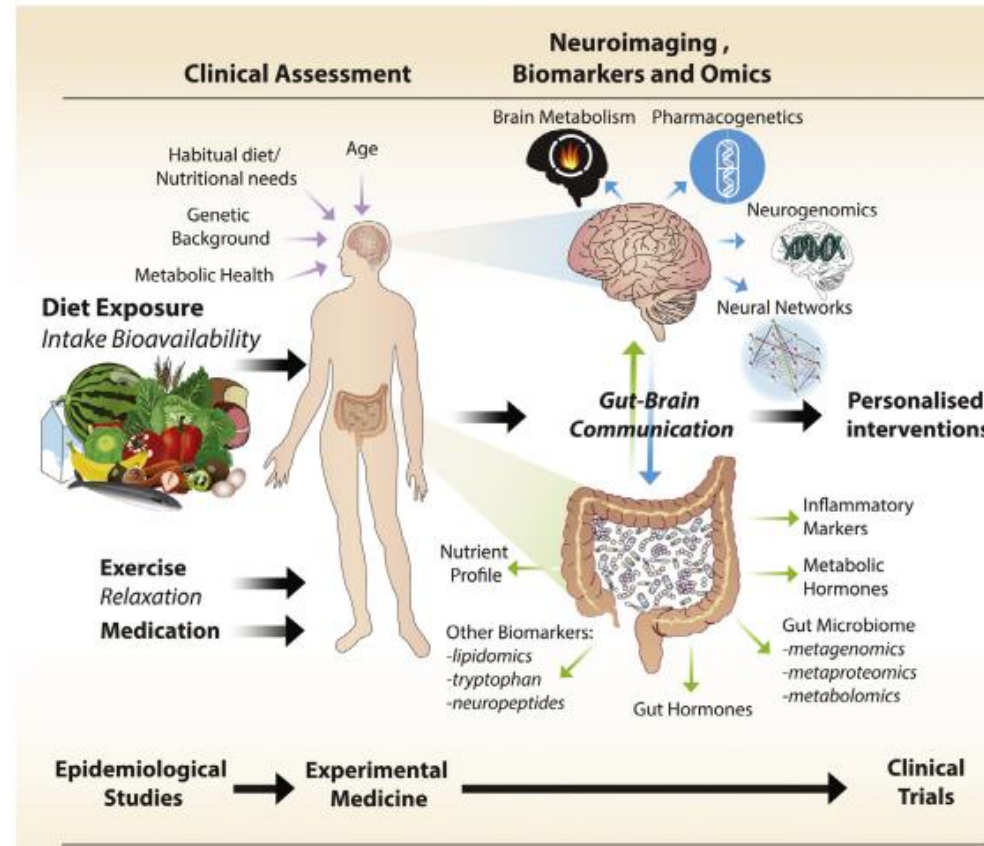
➔ Non-alcoholic energy intakes are lower in actively drinking AUD subjects compared to healthy subjects, especially for proteins, fats, carbohydrates and fibers



Is there a link between dietary intakes and psychological symptoms developed by AUD patients ?

Nutritional psychiatry: Towards improving mental health by what you eat

Roger A.H. Adan^{a,b,*}, Eline M. van der Beek^{c,d},
Jan K. Buitelaar^{e,f}, John F. Cryan^g, Johannes Hebebrand^h,
Suzanne Higgsⁱ, Harriet Schellekens^g, Suzanne L. Dickson^{b,**}



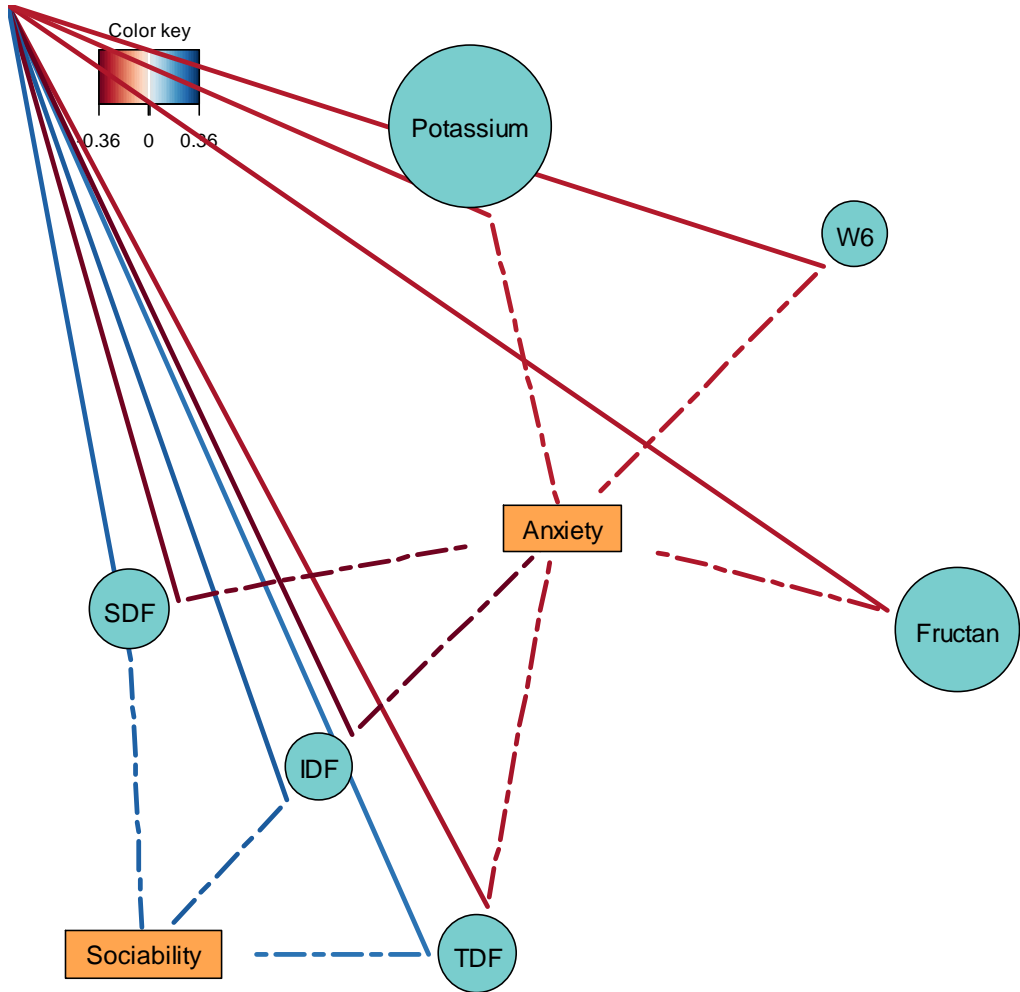
FONDATION SAINT-LUC
Cliniques universitaires SAINT-LUC | UCL Bruxelles



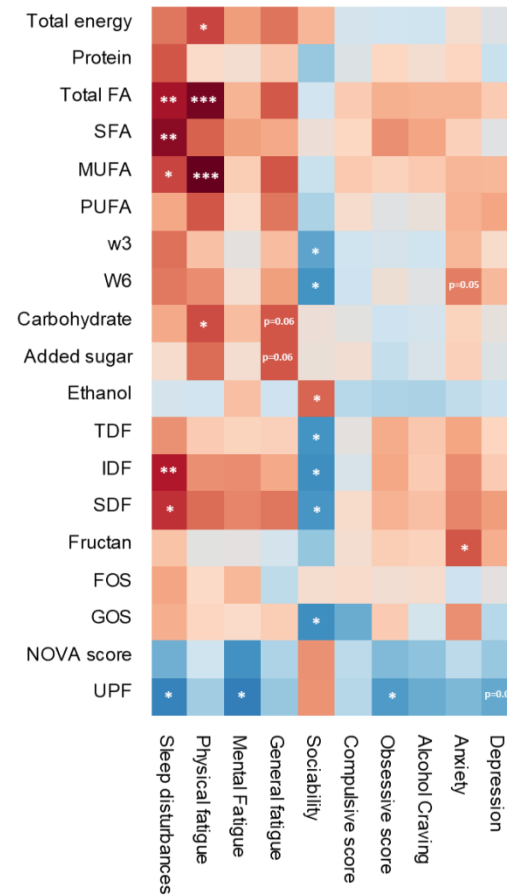
Cliniques universitaires
SAINT-LUC
UCL BRUXELLES



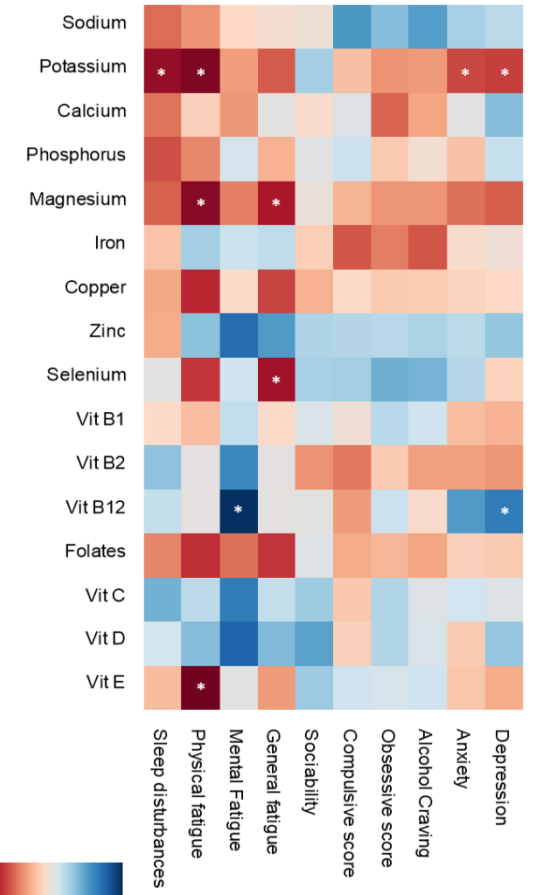
Link between nutrients and psychological symptoms in AUD patients



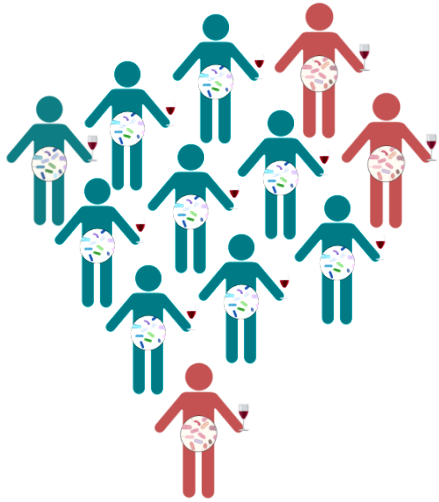
A. Energy, Macronutrients, UPF



B. Micronutrients



What are the characteristics of dysbiotic AUD patients?

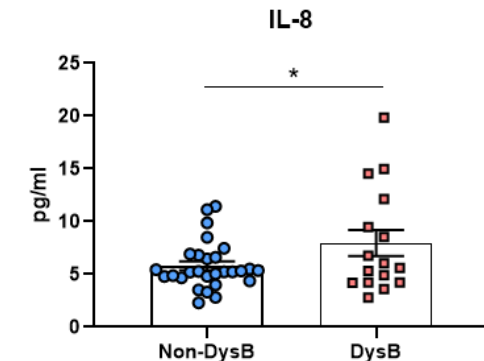


	Dysbiotic n=16	Non Dysbiotic n=30	p
Sociodemographic characteristics			
Age (y)	43.6 ± 7.3	50.7 ± 9.2	0.01
Gender (woman)	7 (43.8)	9 (30.0)	0.35
Family status, n (%)			0.08
Single	9 (56.2)	10 (33.3)	
Couple / married	3 (18.8)	16 (53.3)	
Separated/divorced	4 (25.0)	4 (13.4)	
Clinical examination			
BMI	22.3 ± 3.3	24.8 ± 3.0	0.01
Alcohol history			
Numbers of withdrawal	2.6 ± 2.2	2.1 ± 2.3	0.07
Duration of drinking habit (y)	14.2 ± 7.6	17.7 ± 11.9	0.56
Alcohol consumption (g/d)	135.8 ± 63.9	127.1 ± 50.7	0.65
Mood			
Anxiety	48.2 ± 16.7	46.7 ± 13.8	0.67
Depression	27.4 ± 14.1	25.1 ± 11.0	0.63
Craving			
Total score	27.3 ± 4.6	23.2 ± 5.7	0.03
Compulsive score	15.6 ± 2.2	13.2 ± 2.8	0.007
Sociability (TEIque)			
	3.5 ± 1.0	4.3 ± 1.1	0.03

Dysbiotic patients are:

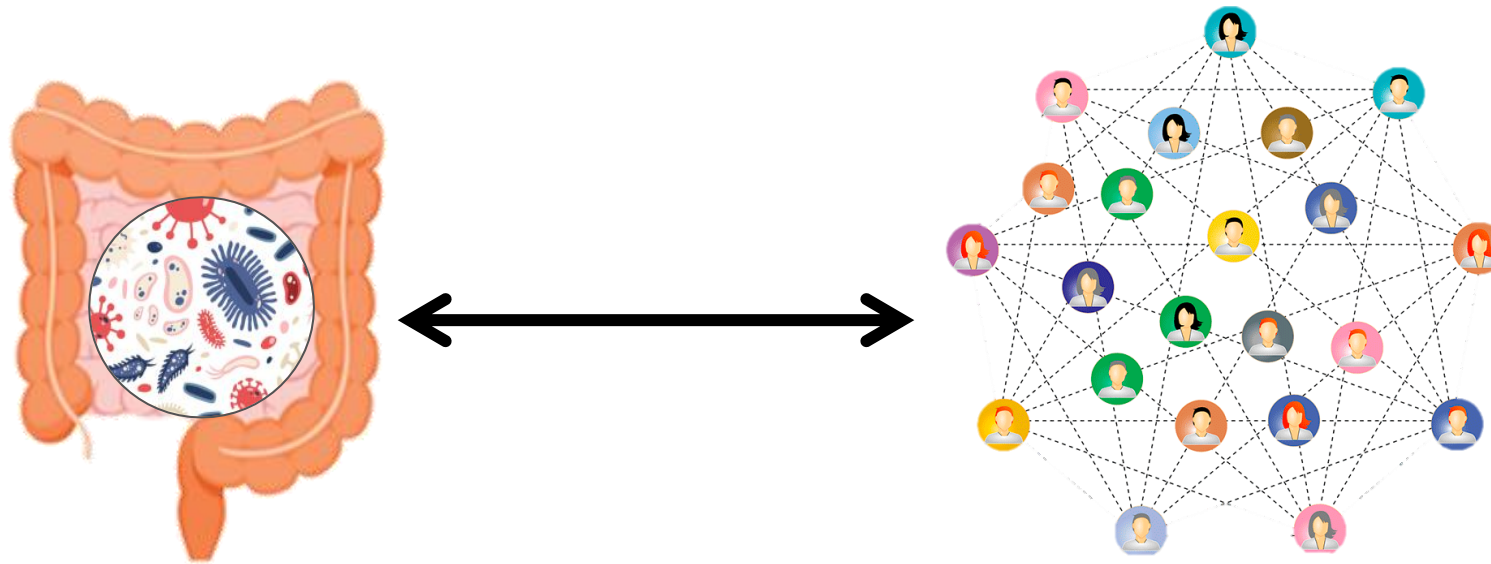
- Younger
- Thinner
- Have a higher craving score
- Have a lower sociability score

-There is no difference for biological parameters except IL-8 (higher in dysbiotic patients)



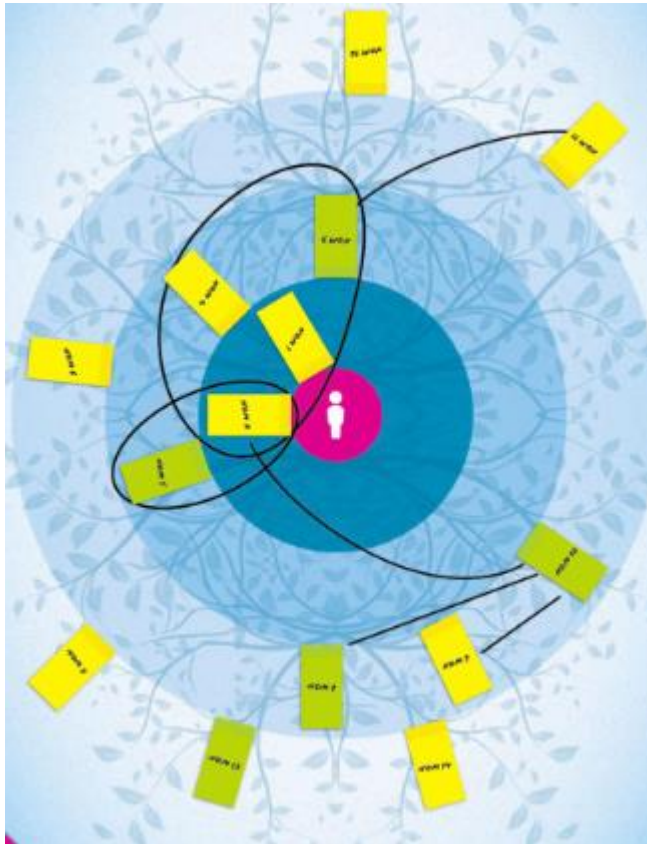


Pr. Vincent Lorant



▪ Is the social network of dysbiotics comparable to non-dysbiotics?

Sociogramme



Indexes:

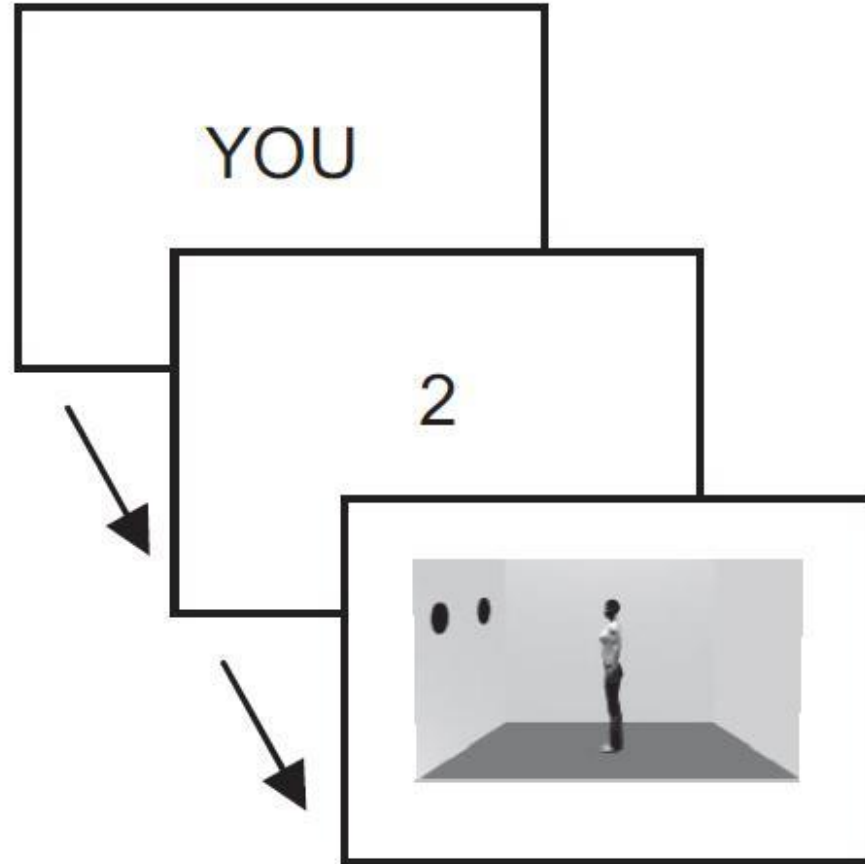
- Network size ↓
- Density
- Number of community ↓
- Professional proportion
- Number of isolated alters
- Number of cliques ↓
- Transitivity ↓
- Modularity ↓
-



→ Dysbiotic patients have a smaller, less connected social network than non-dybiotics

Who are the people who support you in your daily life?

Visual Perspective task

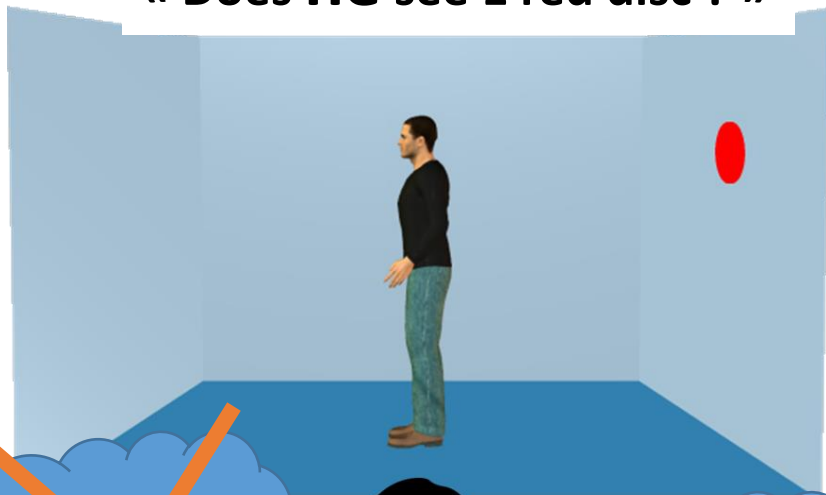


Measure of BIAS using and the visual perspective taking task

Egocentric bias :

- Erroneous response : « he sees one disc »
- Slowing down of the response : « heu... »

« Does **he** see 1 red disc ? »



~~1 disc~~

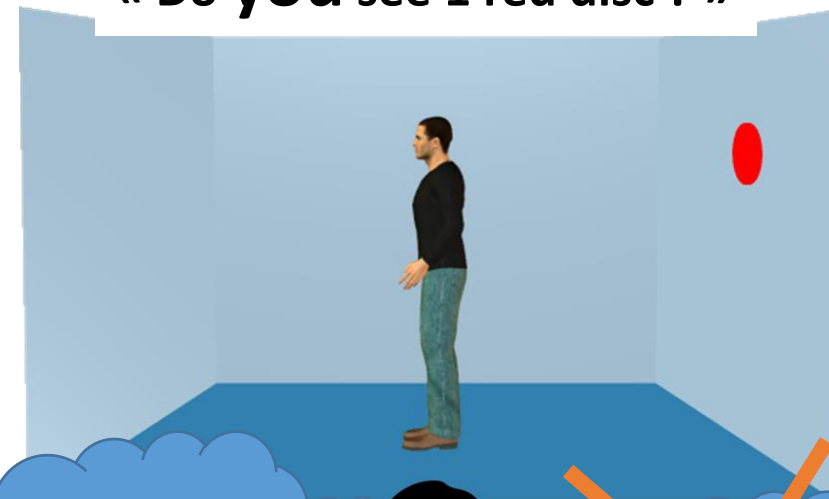
0 disc

me

Altercentric bias :

- Erroneous response : « I see 0 disc »
- Slowing down of the response : « heu... »

« Do **you** see 1 red disc ? »



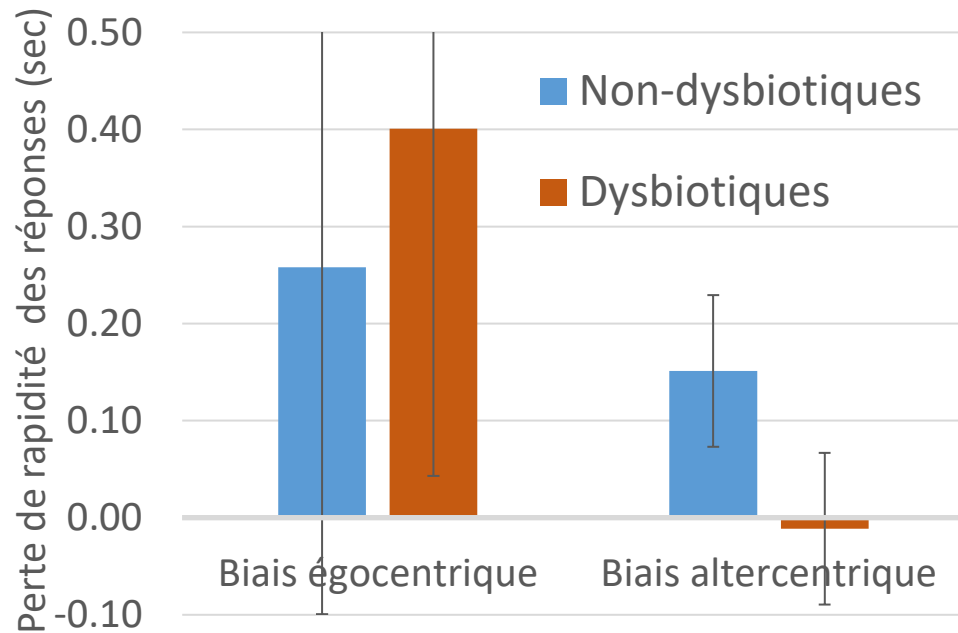
1 disc

~~0 disc~~

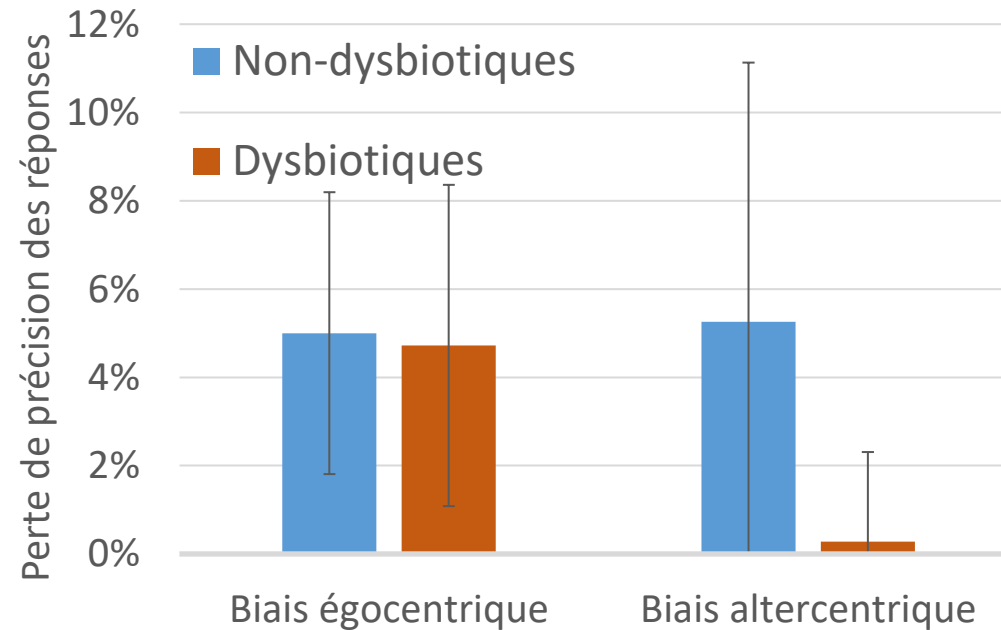
me

AUD: 16 dysbiotic versus 30 non-dysbiotic patients

Etendue de l'interférence sur la rapidité des réponses



Etendue de l'interférence sur la précision des réponses

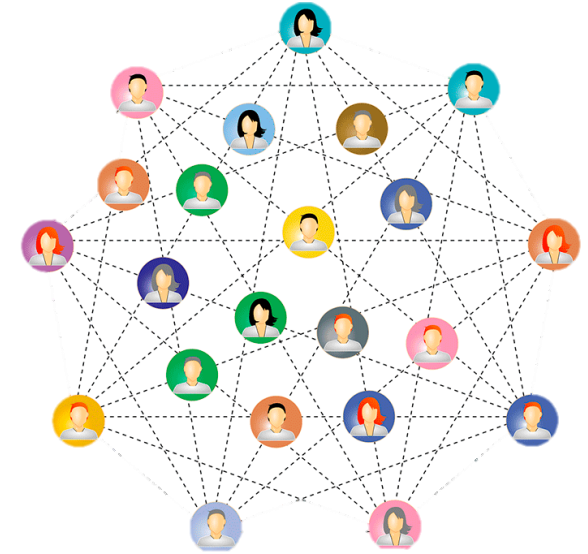
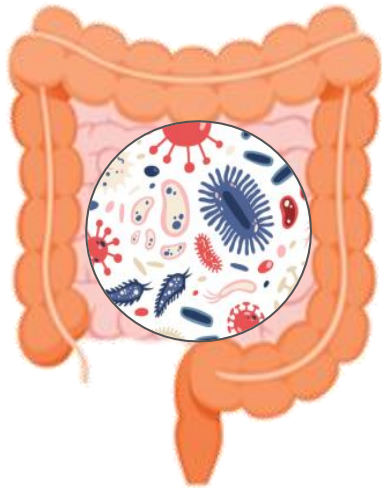


Amongst AUD patients, the altercentric is absent only in the dysbiotic subpopulation

Several studies support that there is a deficit in perspective taking in AUD patients and that it is related to the lack of paying attention to others.

Here we show that this difficulty to pay attention to others is related to abnormal gut microbiota

Is this the social brain?



REVIEW

MICROBIOLOGY

Microbiota and the social brain

Eoin Sherwin¹, Seth R. Bordenstein², John L. Quinn³, Timothy G. Dinan^{1,4}, John F. Cryan^{1,5*}



Anterior cingulate cortex (ACC)

This brain region functions in the detection and valuation of social processes such as interactions with dominant males and females in primates, and decision-making games in humans.

Prefrontal cortex (PFC)

In humans, this brain region is activated in response to various social cognitive tasks such as empathy, moral decision making, and judging the mental states of others. In rodents, stimulation of excitatory neurons abolishes social exploration and preference.

Paraventricular nucleus of the hypothalamus (PVN)

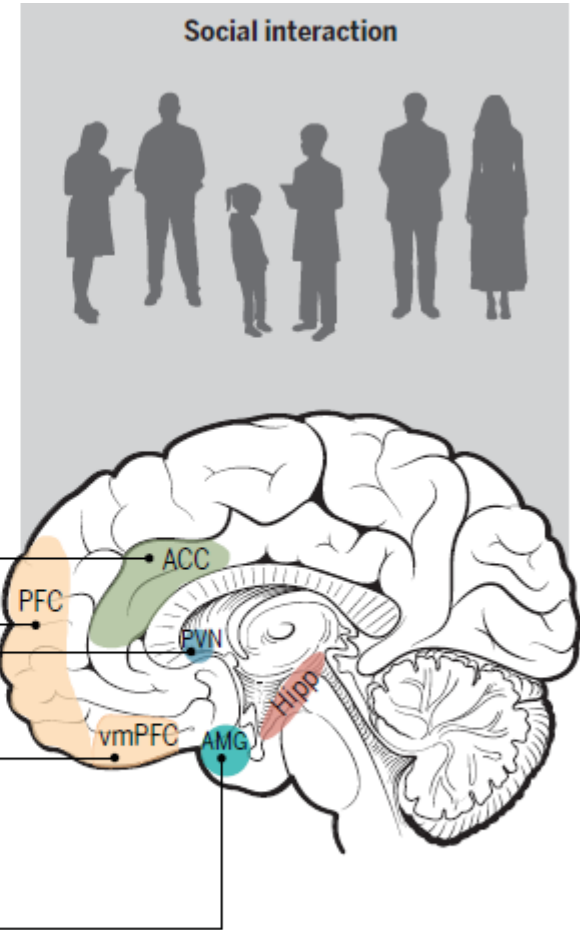
Magnocellular neurons of the PVN produce the neuropeptide oxytocin. Oxytocin is secreted to brain regions involved in sociability and social cognition, such as the ventral tegmental area and PFC. Reduced levels of oxytocin are documented in autism.

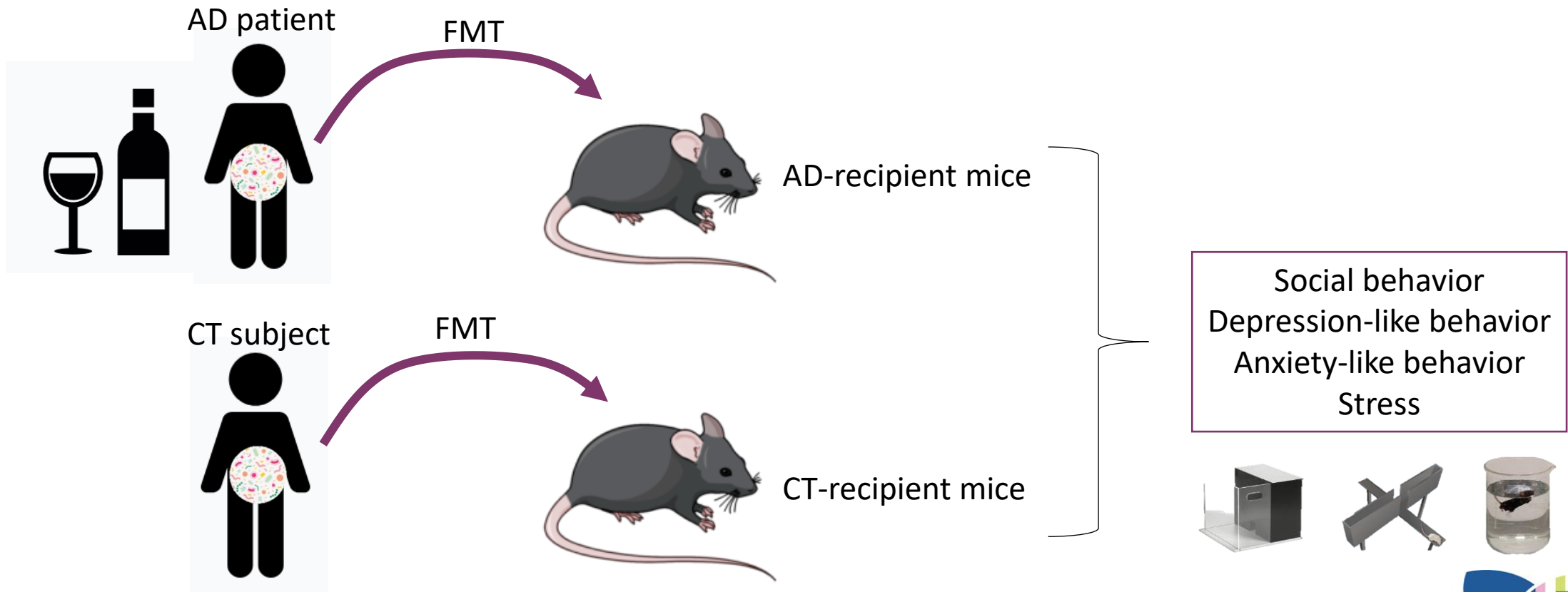
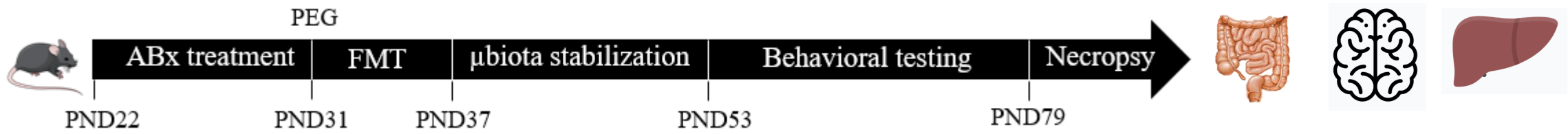
Ventromedial prefrontal cortex (vmPFC)

Lesions to this part of PFC result in social isolation and apathy in humans. The vmPFC is also important in the learning of cues that predict social reward. Children with ASD display reduced vmPFC activation in response to social reward.

Amygdala (AMG)

Amygdalar volume correlates with the size and complexity of social networks in humans. This brain region functions in the analysis of social situations. Individuals with autism demonstrate reduced activation of this brain region in response to social judgment tasks.

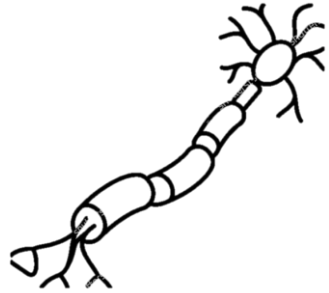




Which brain genes are modified by AD microbiota transplantation?



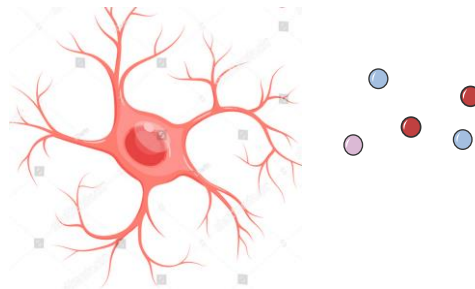
Myelination



Inhibition/excitation neurotransmissions

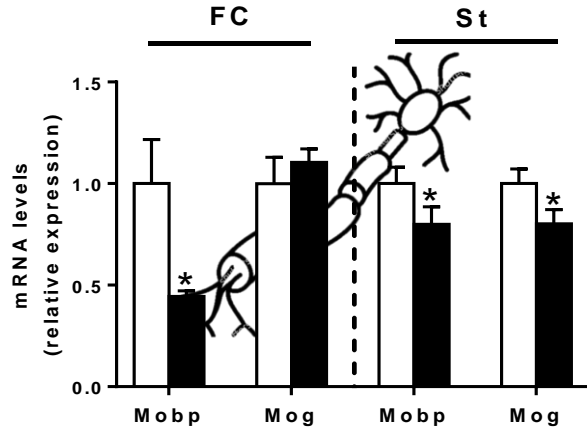


Inflammation and microglial activation

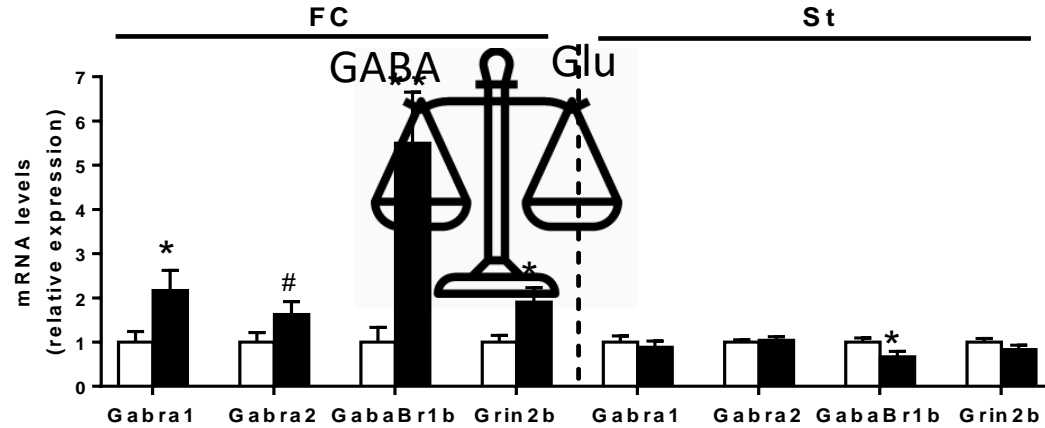


Results

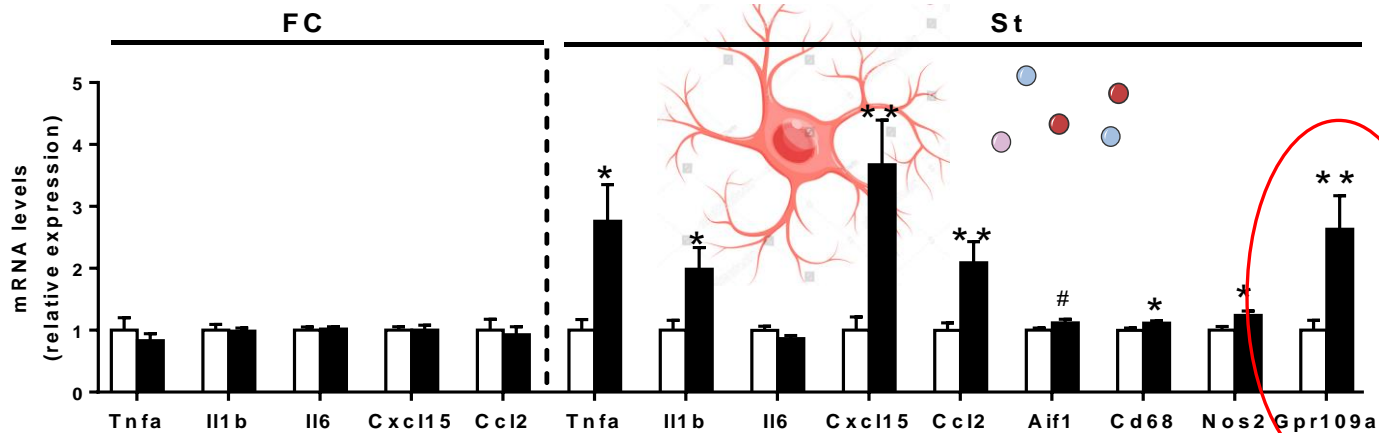
Myelination



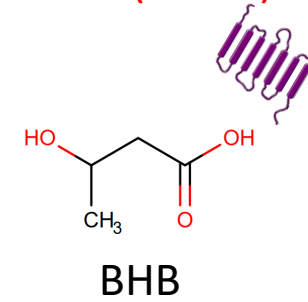
Inhibition/excitation neurotransmissions



Inflammation and microglial activation



GPR109A (Hcar2)

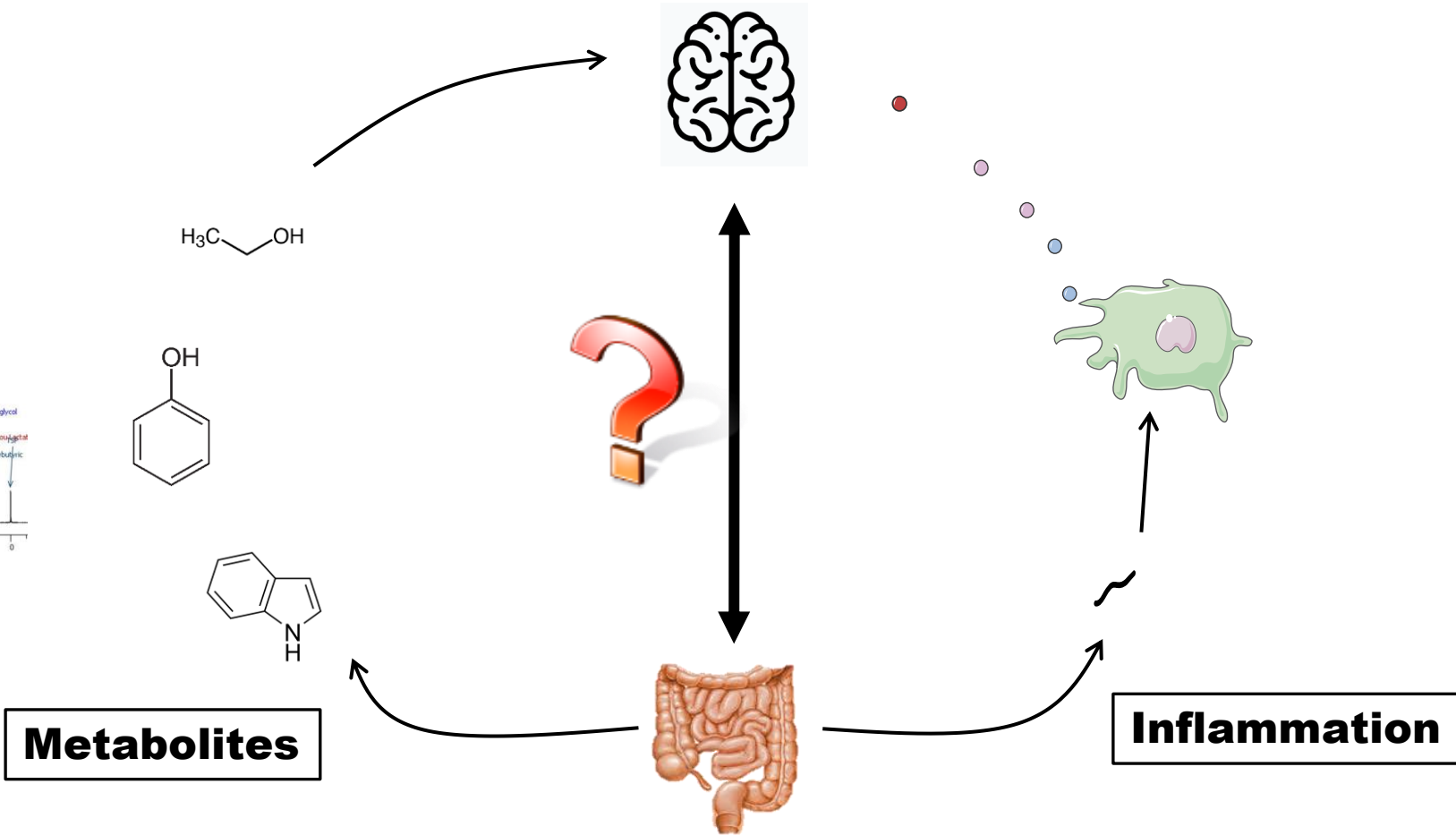
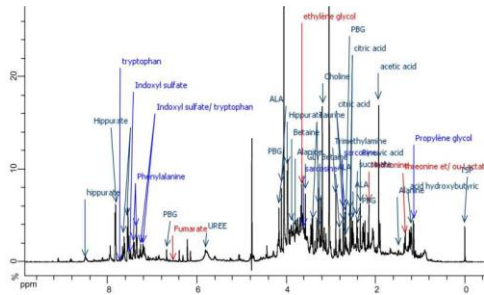


□ CT-recipient
 ■ AD-recipient

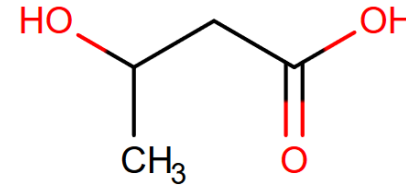
What is driving alterations of myelination, neurotransmission and neuroinflammation?

Metabolomics

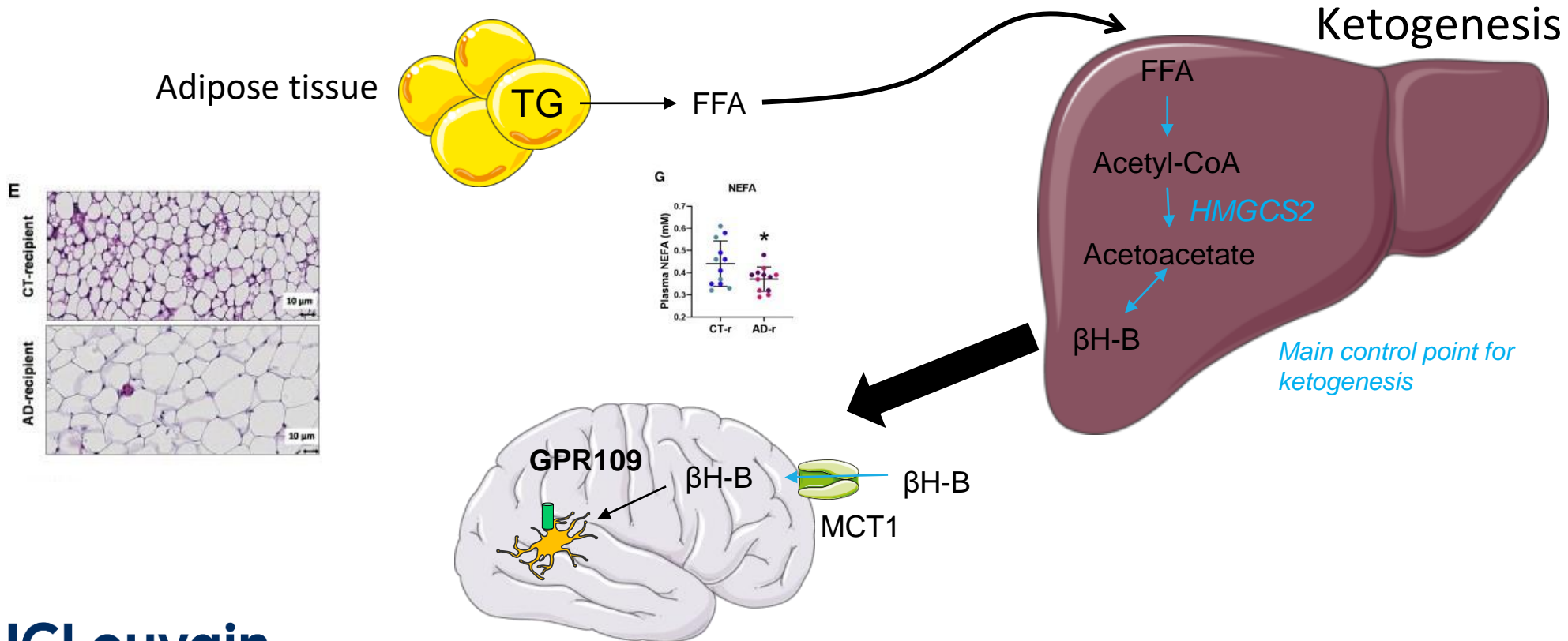
¹H-NMR spectrometry



β -hydroxybutyrate (BHB)

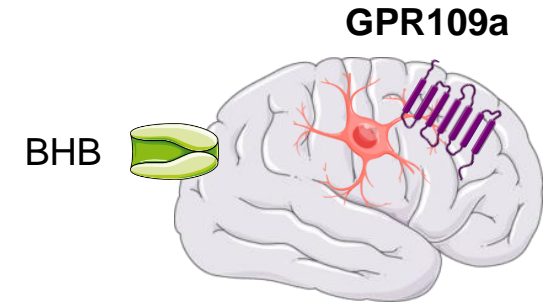
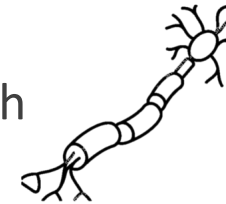


- Ketone body (acetone, acetoacetate)
- Produced by the liver (fasting, low glycemia, prolonged physical exercise)

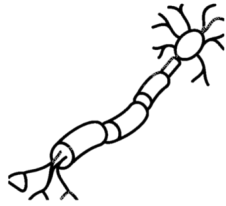
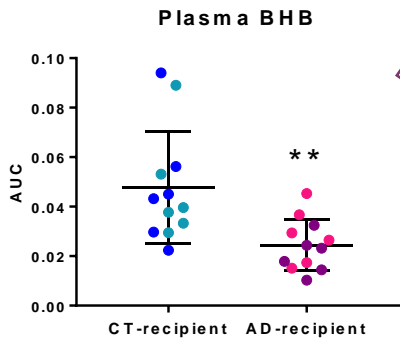


Roles of BHB

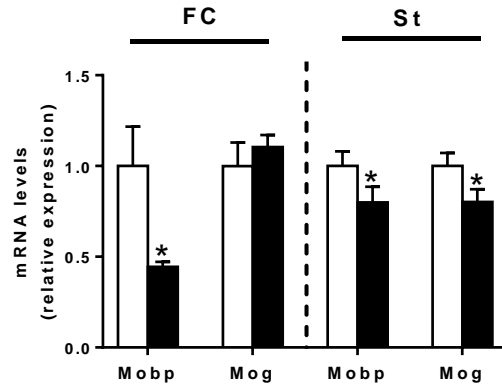
- ❑ Energy source for the brain
- ❑ Role in depression and social behavior
- ❑ Anti-inflammatory effect (GPR109a)
- ❑ Serves as glycosphingolipids synthesis → component of myelin sheath
- ❑ Regulation of GABA/glutamate balance



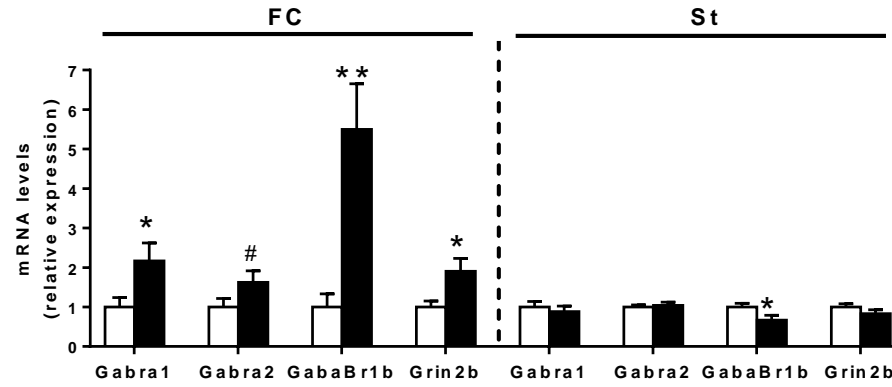
Deficit in β -hydroxybutyrate



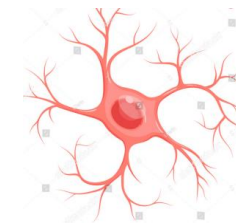
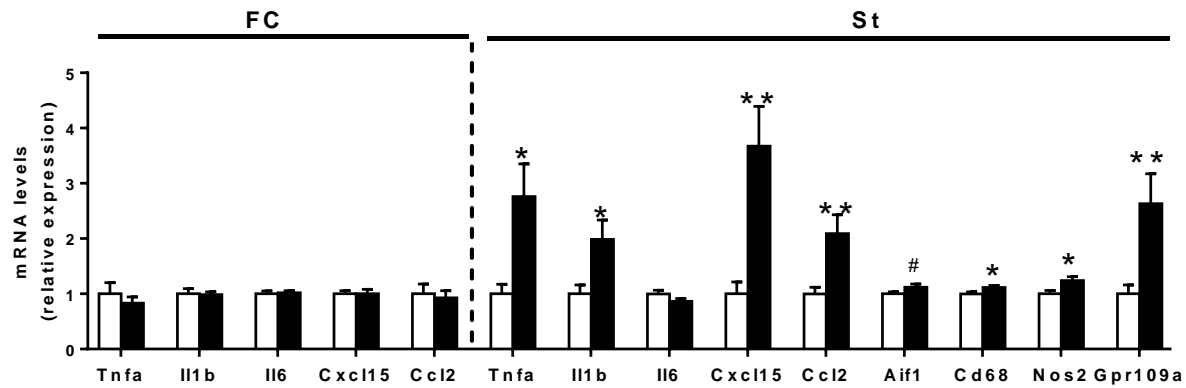
Myelination



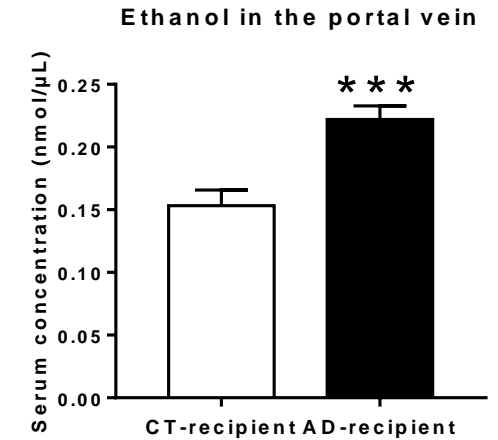
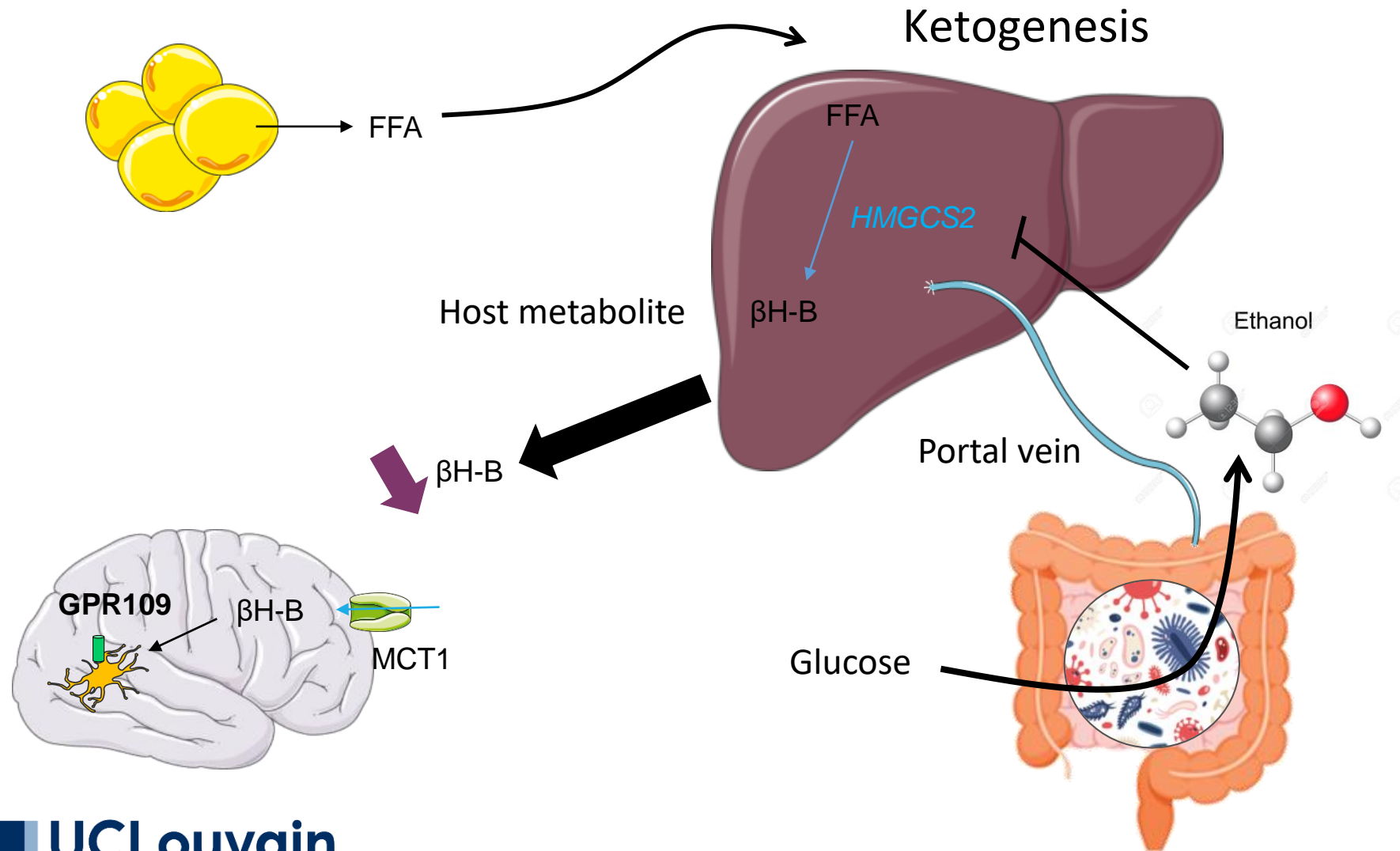
Inhibition/excitation neurotransmissions



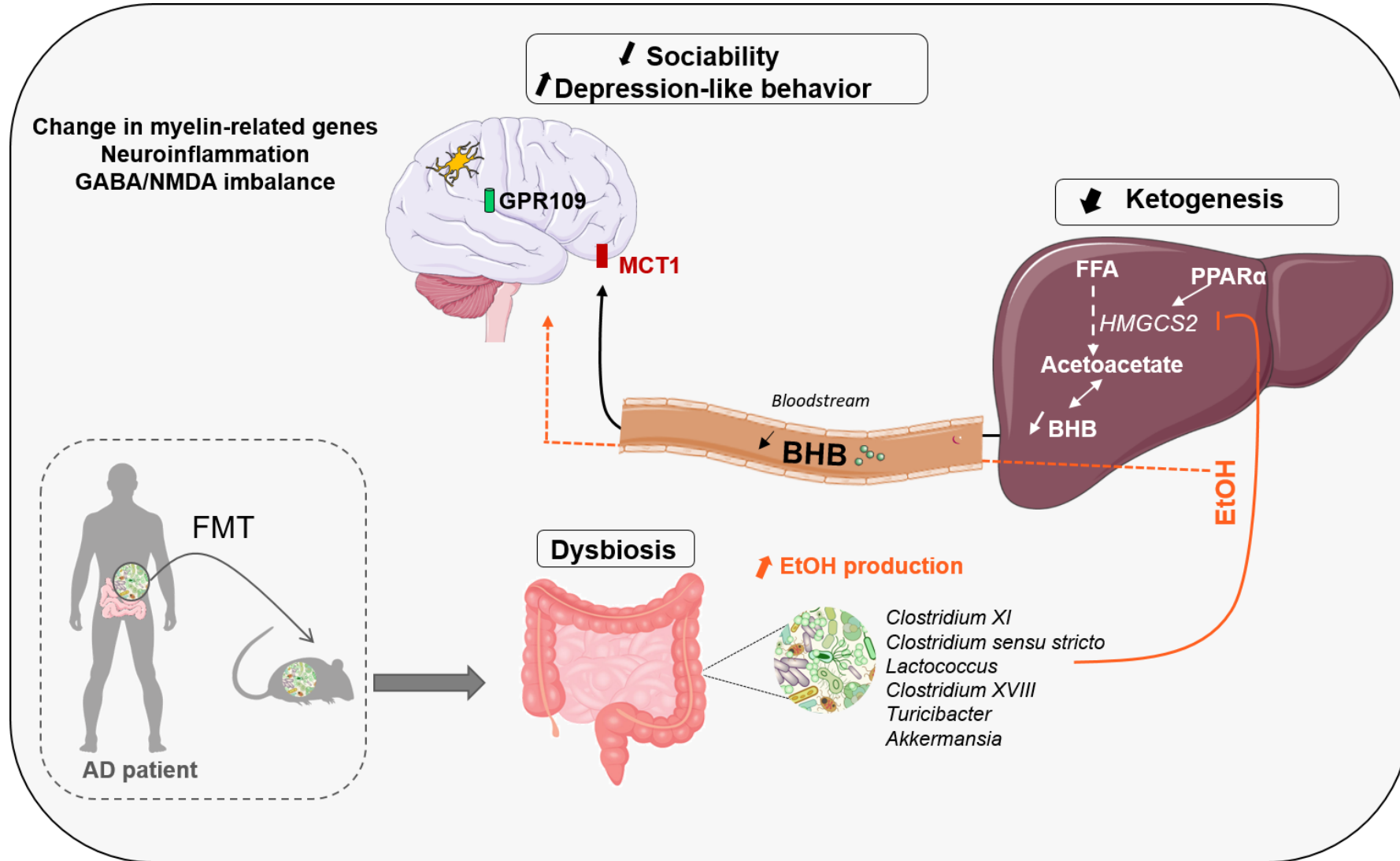
Inflammation and microglial activation



What is the microbial product driving ketogenesis inhibition ?



Results



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UCLouvain

Leclercq et al, 2020, Cell Reports



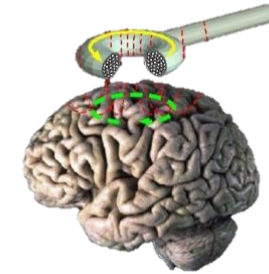
UCLouvain / Institute of Neuroscience

Dr. Sophie Leclercq

Dr. Caroline Quoilin

Dr. Laurence Dricot

Dr. Géraldine Petit



UCLouvain / LDRI / Metabolism and nutrition research group

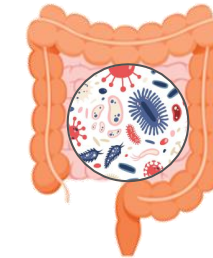
Pr. Nathalie Delzenne

Dr. Tiphaine Le Roy

Dr. Audrey Neyrinck

Camille Amadiou

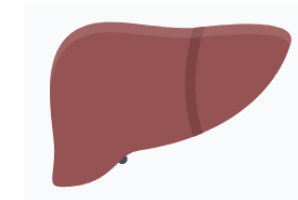
Valentin Coste



UCLouvain / IREC / Hepato-Gastro-enterology lab

Pr. Peter Stärkel

Luca Maccioni



UCLouvain / IRSS

Pr. Vincent Lorant

Dr. Pablo Nicaise

Hélène Garin



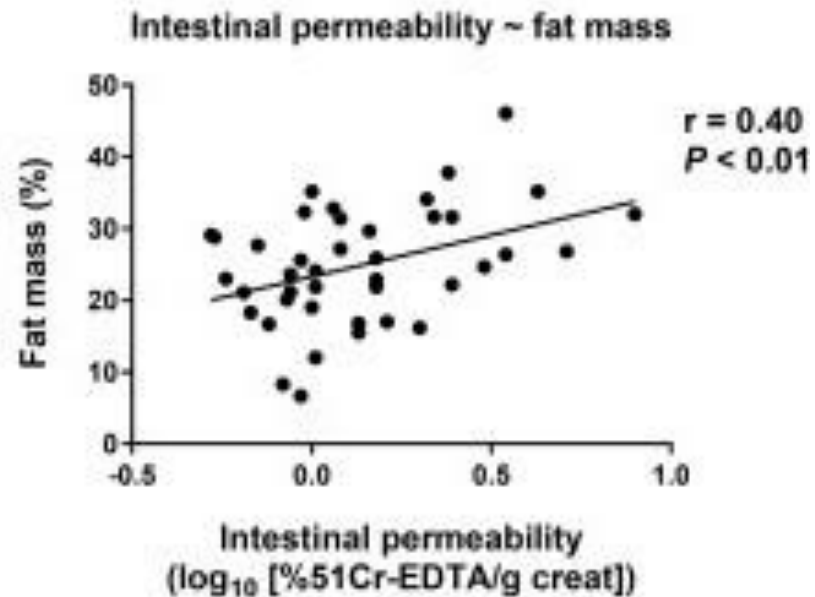
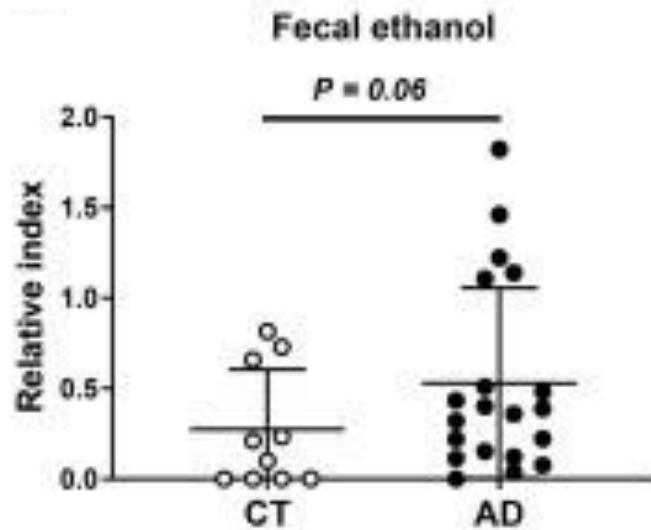
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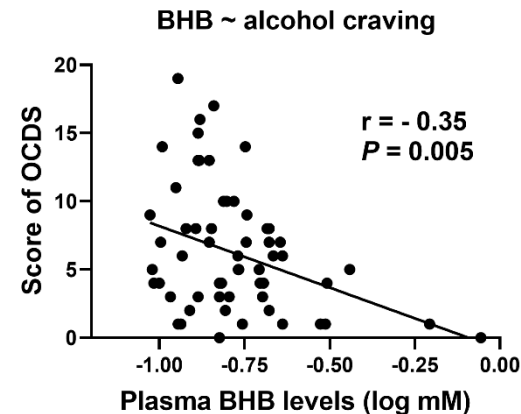
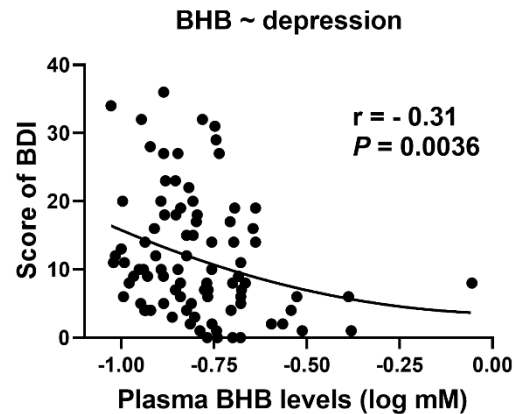
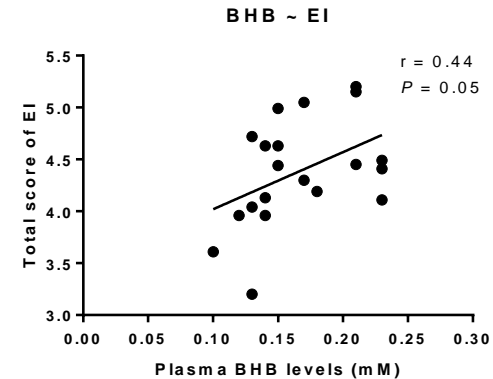
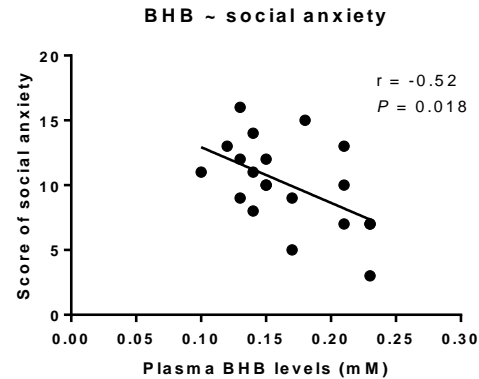
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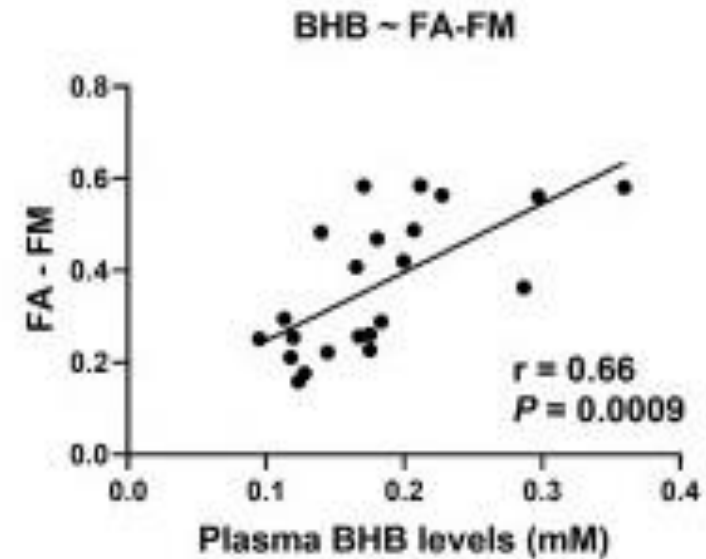
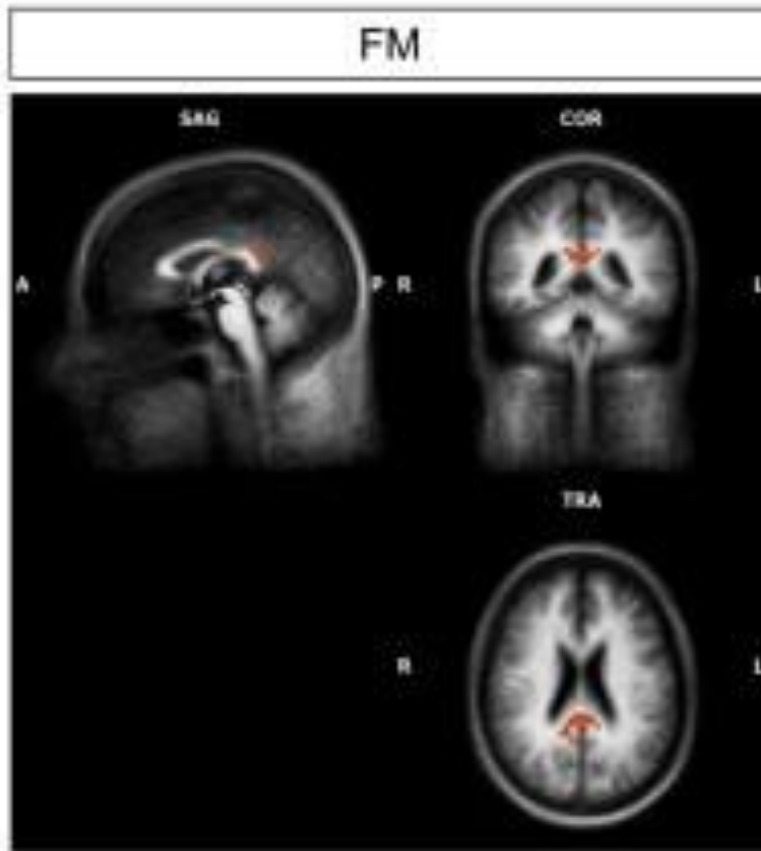
Is the model valid in AUD patients?

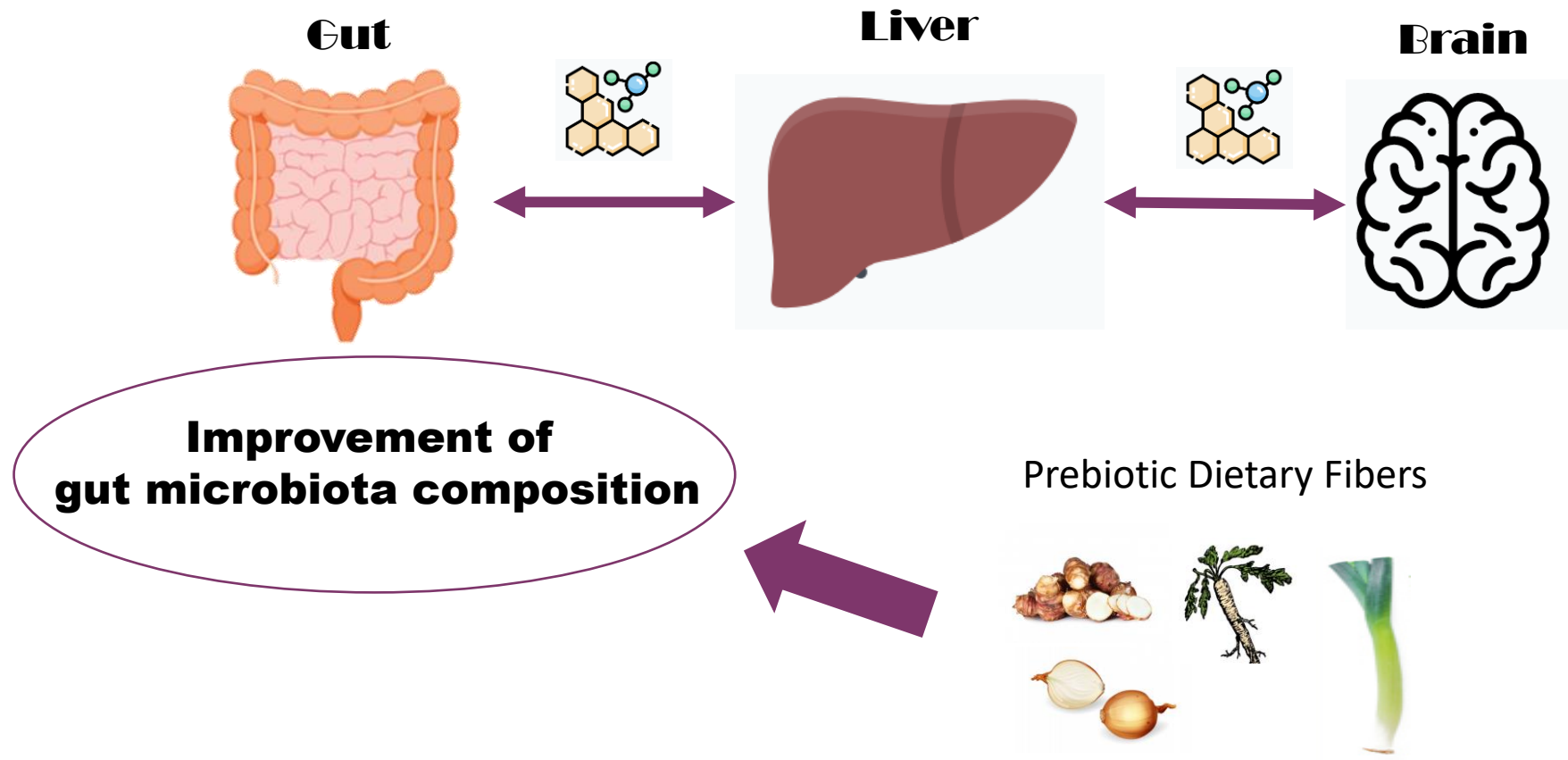


Is BHB associated with psychological symptoms in AD patients?

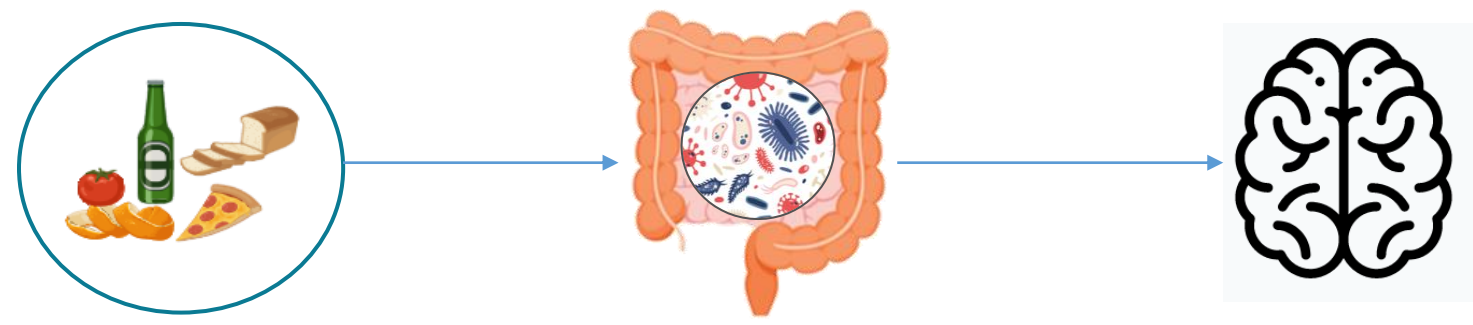


Is BHB associated with changes in white matter?





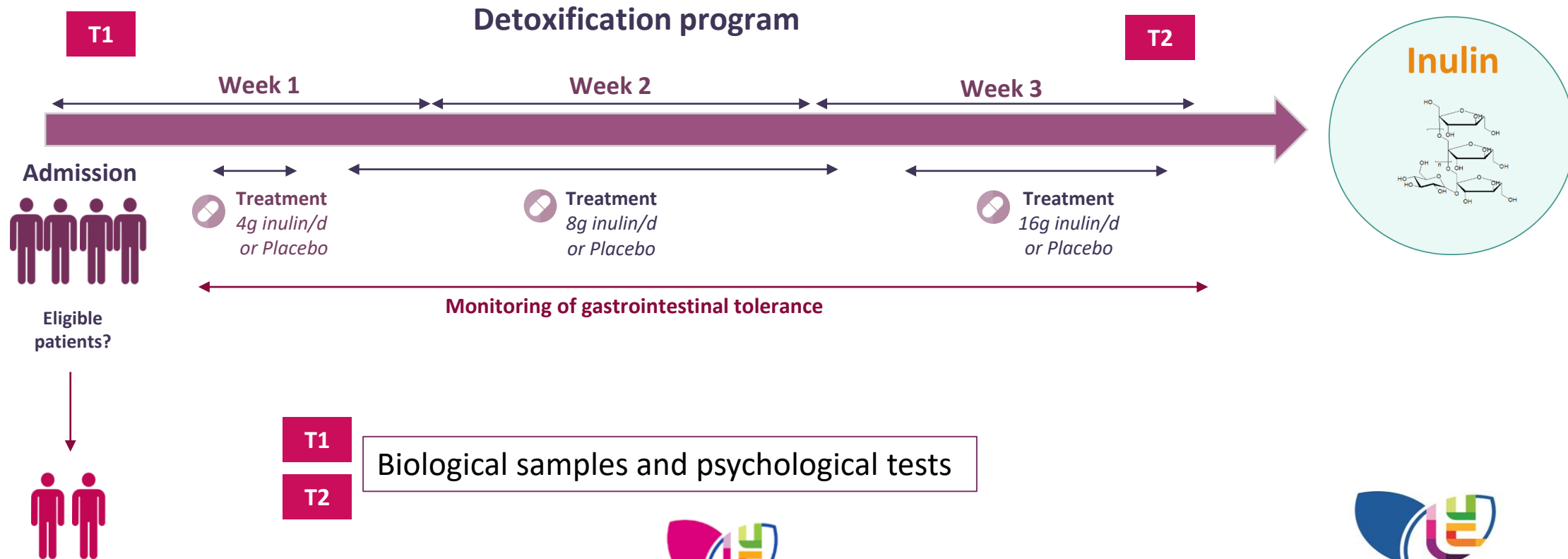
Implication de la Fondation Saint-Luc dans nos projets de recherche

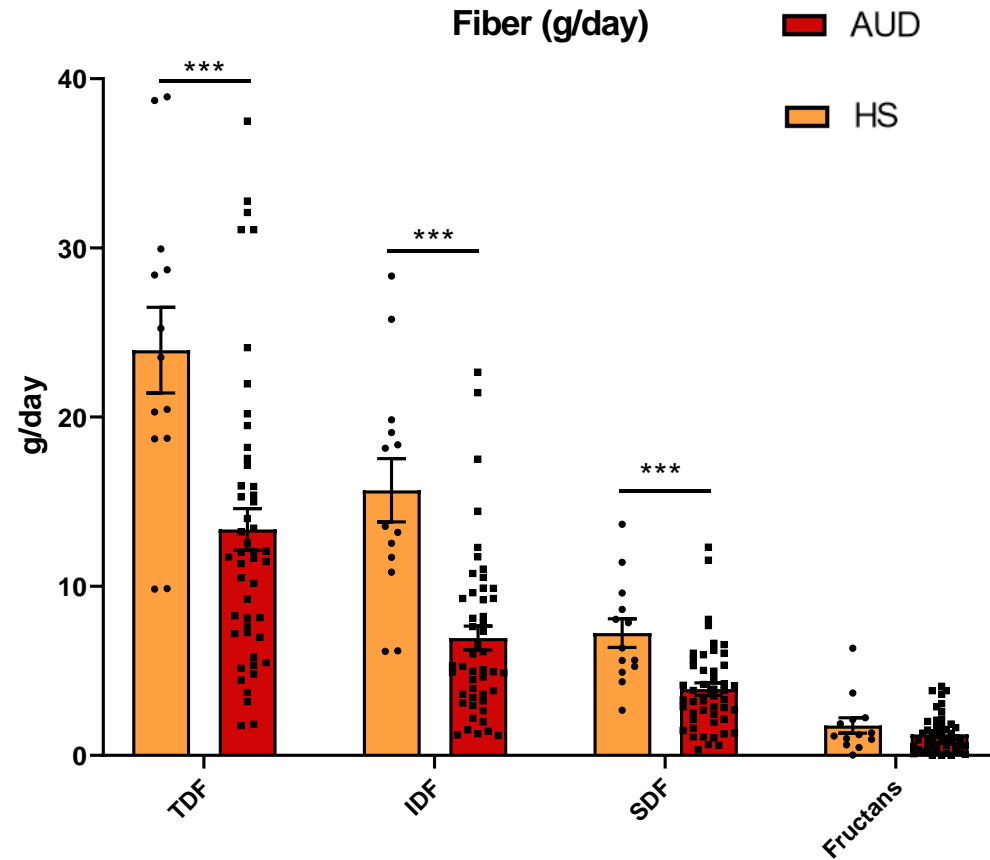
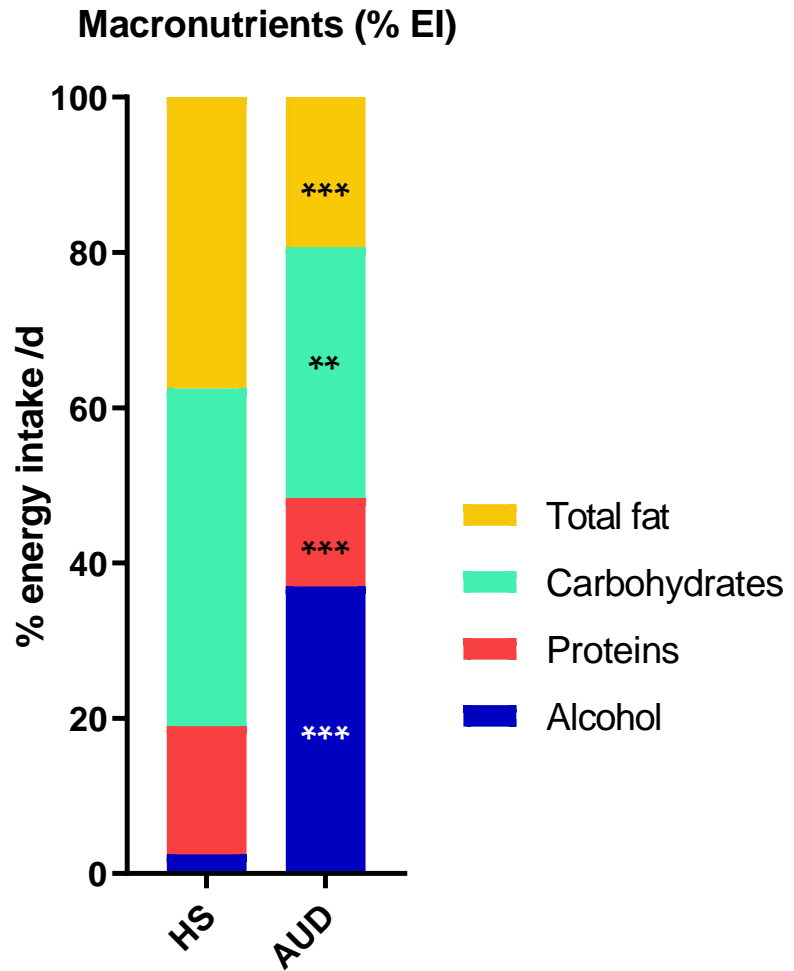


- Randomized, double blind, placebo controlled clinical study
- Supplementation of AD patients with prebiotic fiber (inulin) or placebo
- 50 patients included



Camille Amadiou





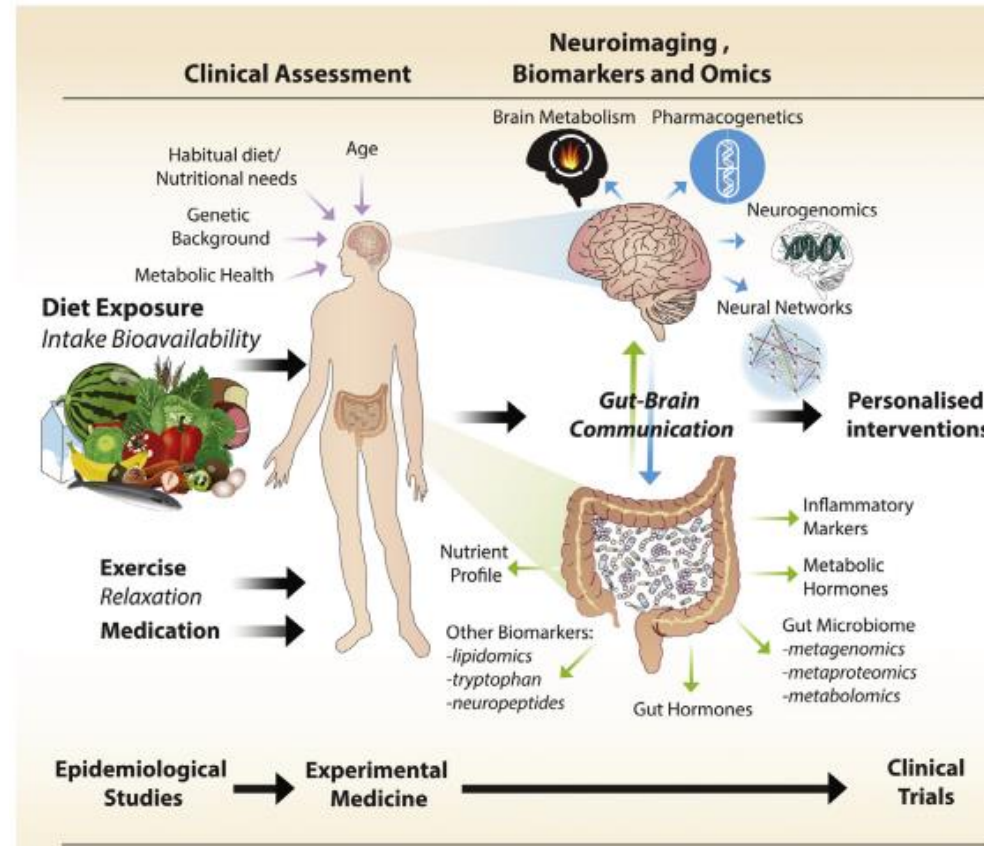
➔ Non-alcoholic energy intakes are lower in actively drinking AUD subjects compared to healthy subjects, especially for proteins, fats, carbohydrates and fibers



Is there a link between dietary intakes and psychological symptoms developed by AUD patients ?

Nutritional psychiatry: Towards improving mental health by what you eat

Roger A.H. Adan^{a,b,*}, Eline M. van der Beek^{c,d},
Jan K. Buitelaar^{e,f}, John F. Cryan^g, Johannes Hebebrand^h,
Suzanne Higgsⁱ, Harriet Schellekens^g, Suzanne L. Dickson^{b,**}



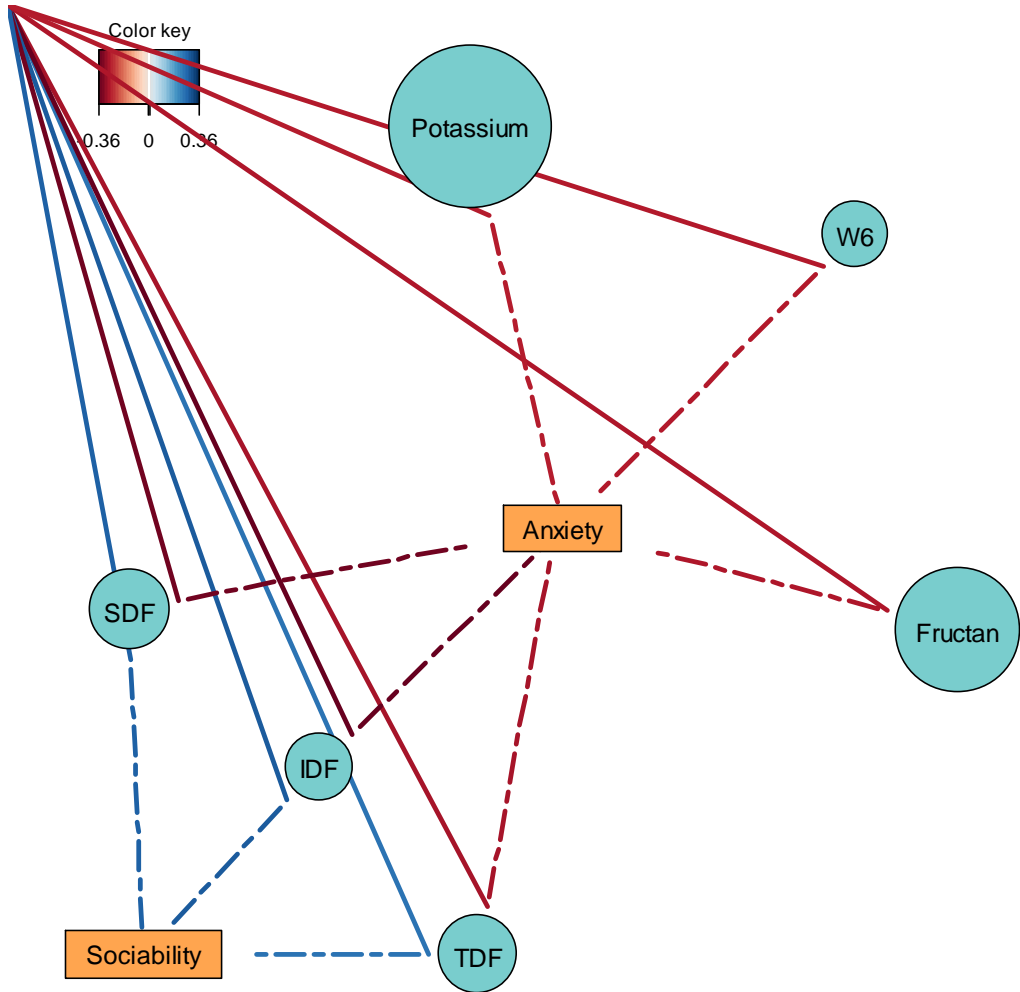
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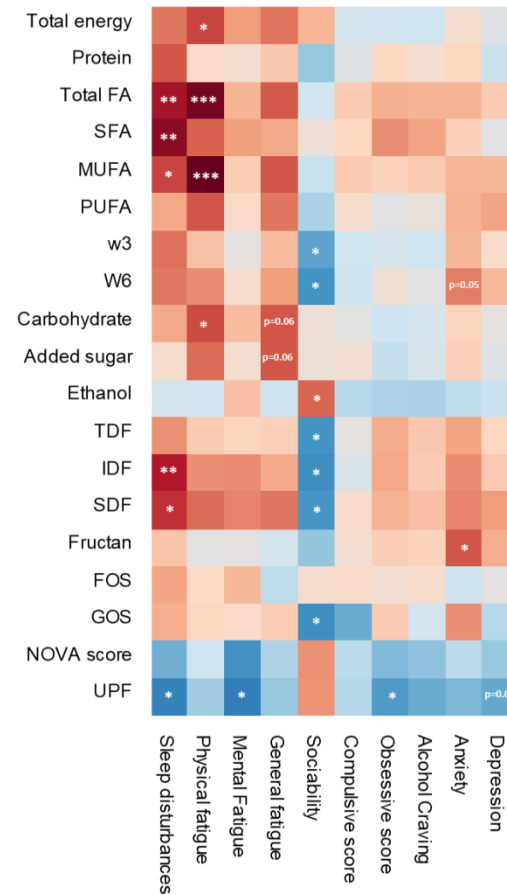
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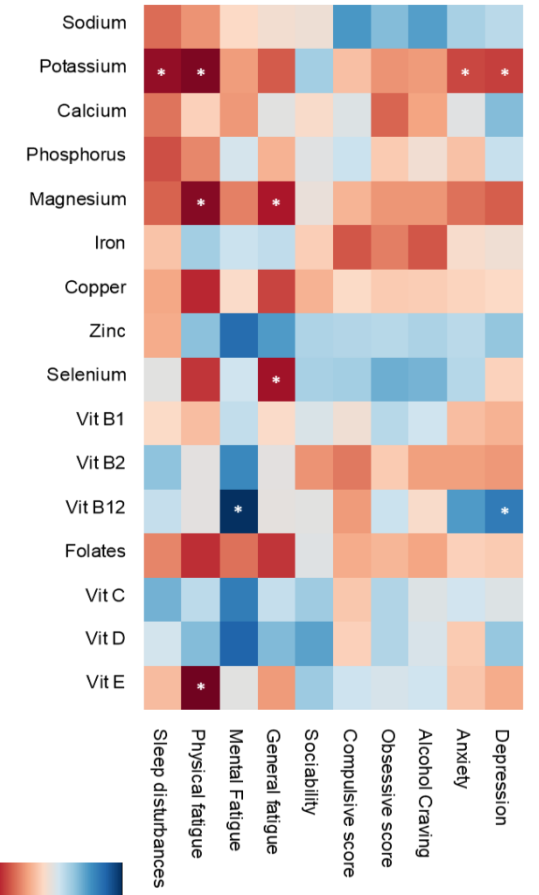
Link between nutrients and psychological symptoms in AUD patients



A. Energy, Macronutrients, UPF



B. Micronutrients



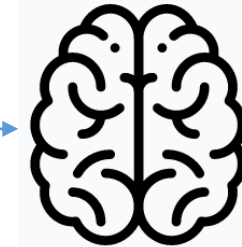
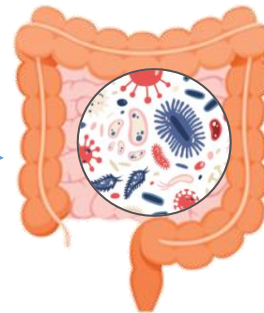
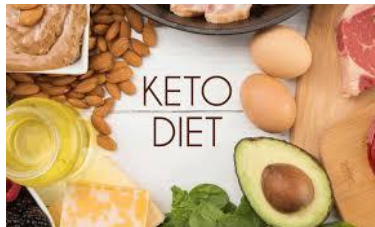
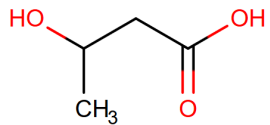
Etudes futures ???



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Prébiotiques (fibres)
Probiotiques (bactéries)
Post-biotiques (métabolites)
Régimes alimentaires



Etudes multicentriques (partenaires européens)



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