Microbiota Gut Brain Axis : at the command of our health and well being

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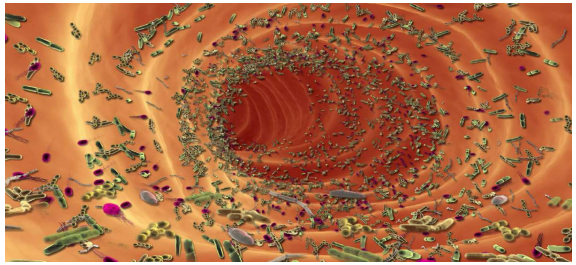
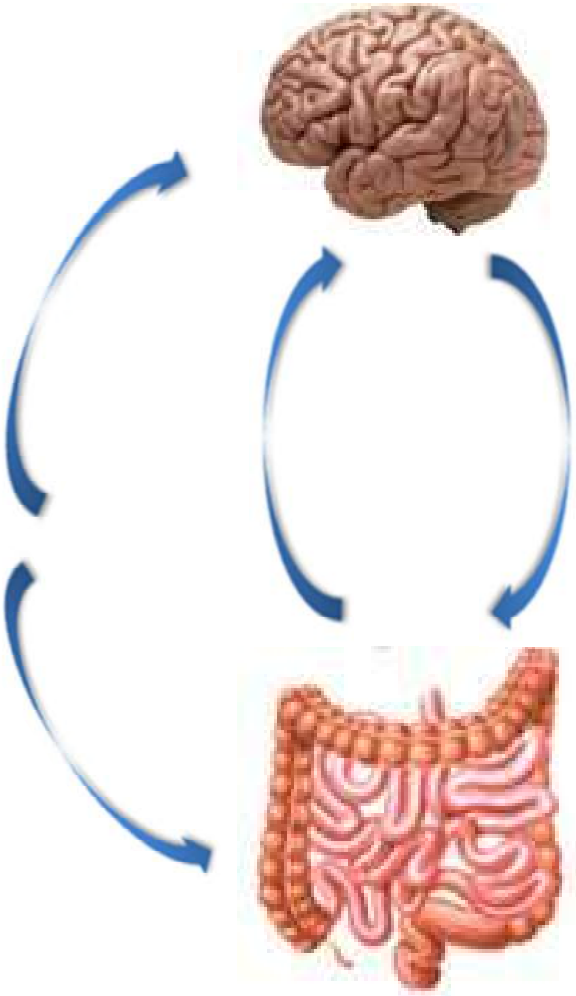
TENS - Inserm U1235 – The enteric nervous system in gut and brain disorders
Institut des Maladies de l'Appareil Digestif, Nantes

olmix Group
Instituts thématiques Inserm Institut national de la santé et de la recherche médicale
UNIVERSITÉ DE NANTES
DHU 2020 médecine personnalisée des maladies chroniques
IMAD L'Institut des Maladies de l'Appareil Digestif CHU de Nantes





Talk outlines

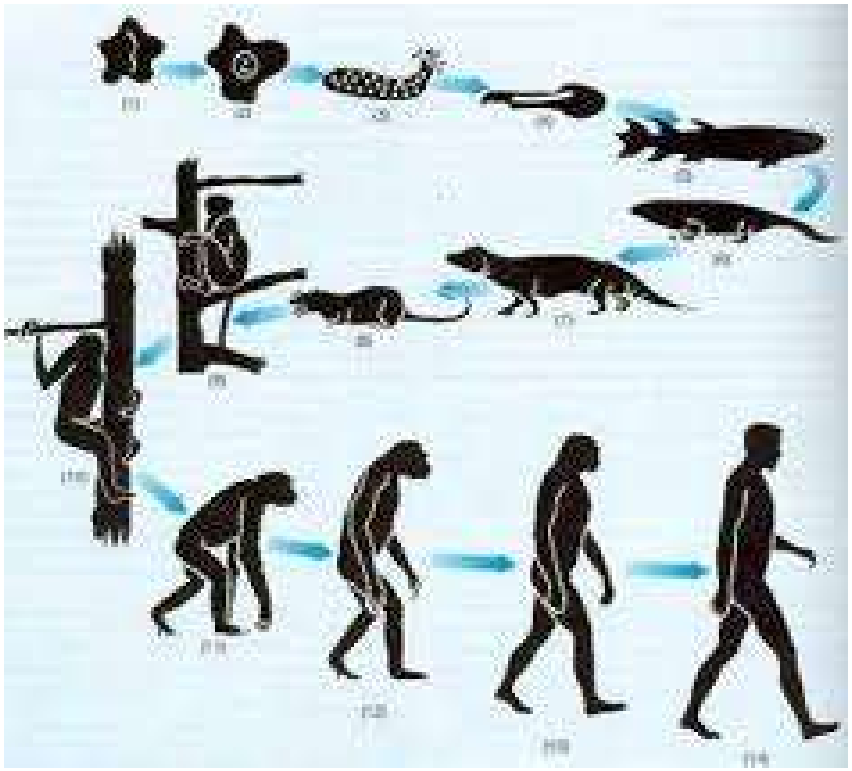
I. **The gut-brain axis**

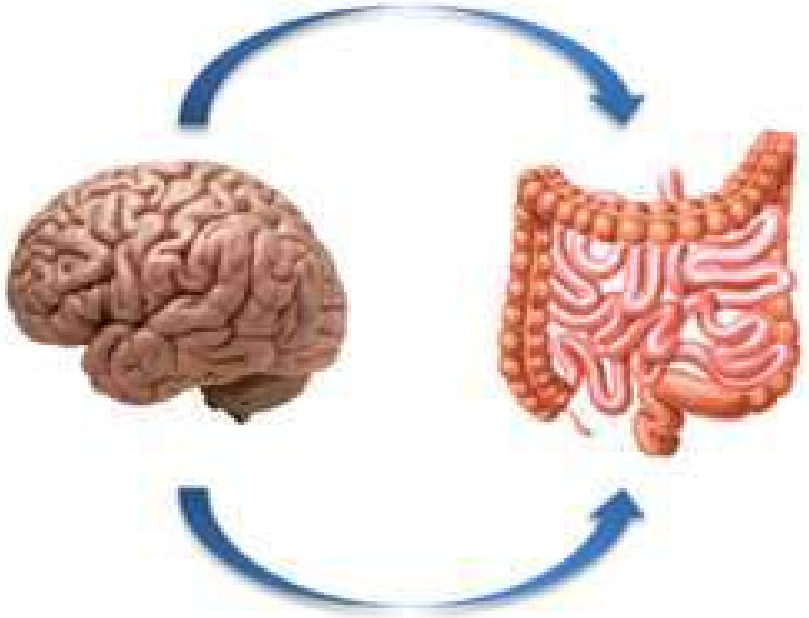
II. The microbiota: a forgotten organ

III. The crosstalk between the microbiota and the gut nervous system

IV. The impact of the microbiota upon the brain health and diseases

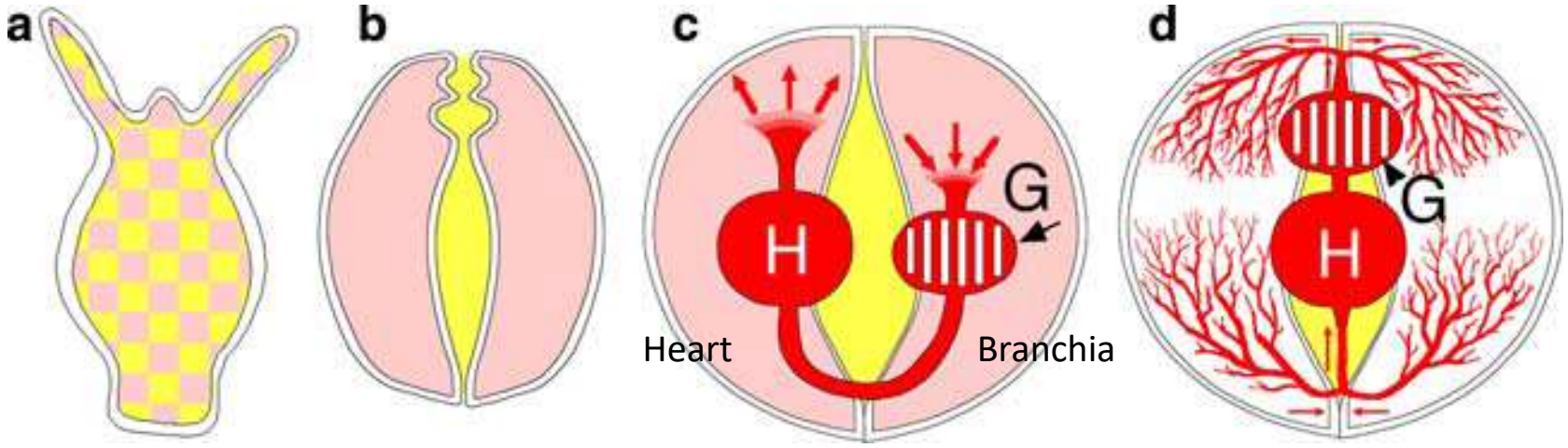
Two organ at the center of evolution and our lives…





Survival (reproduction) and adaptation of organisms to their environment

The gut : the first organ in evolution



Hydra (cnidaire) Nematode Mollusk Fish

The gut : the first organ in evolution

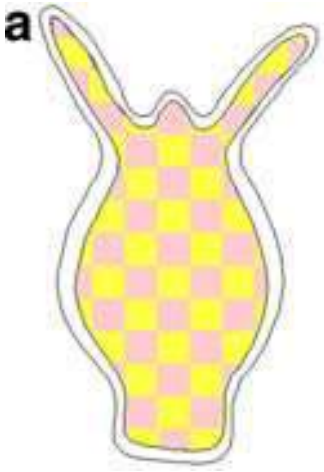
LETTER

doi:10.1038/nature21072

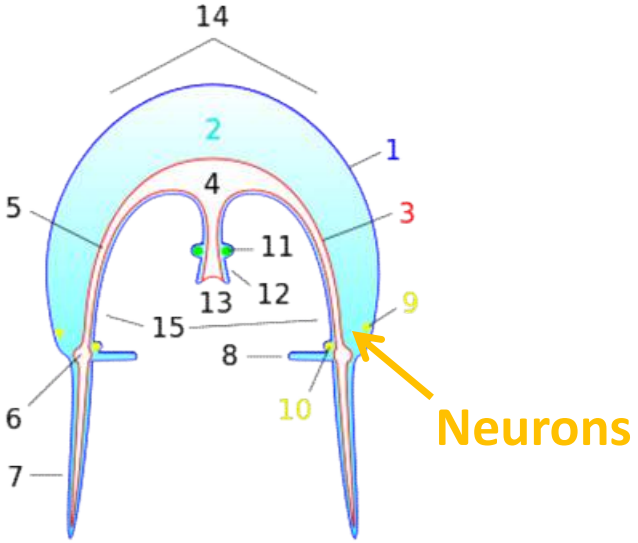
Meiofaunal deuterostomes from the basal Cambrian of Shaanxi (China)

Jian Han[1], Simon Conway Morris[2], Qiang Ou[3,4], Degan Shu[1] & Hai Huang[5]

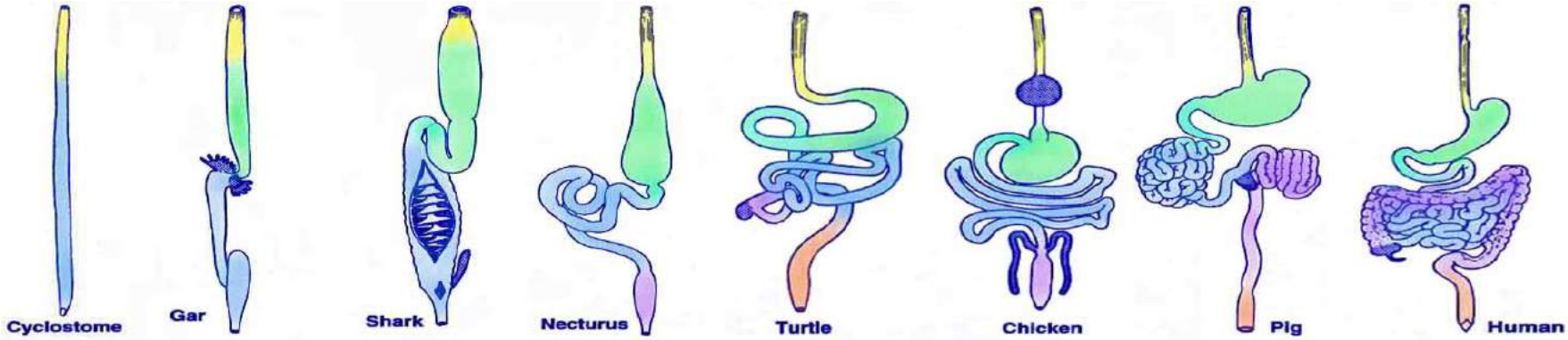
The gut : the first neurological organ in evolution

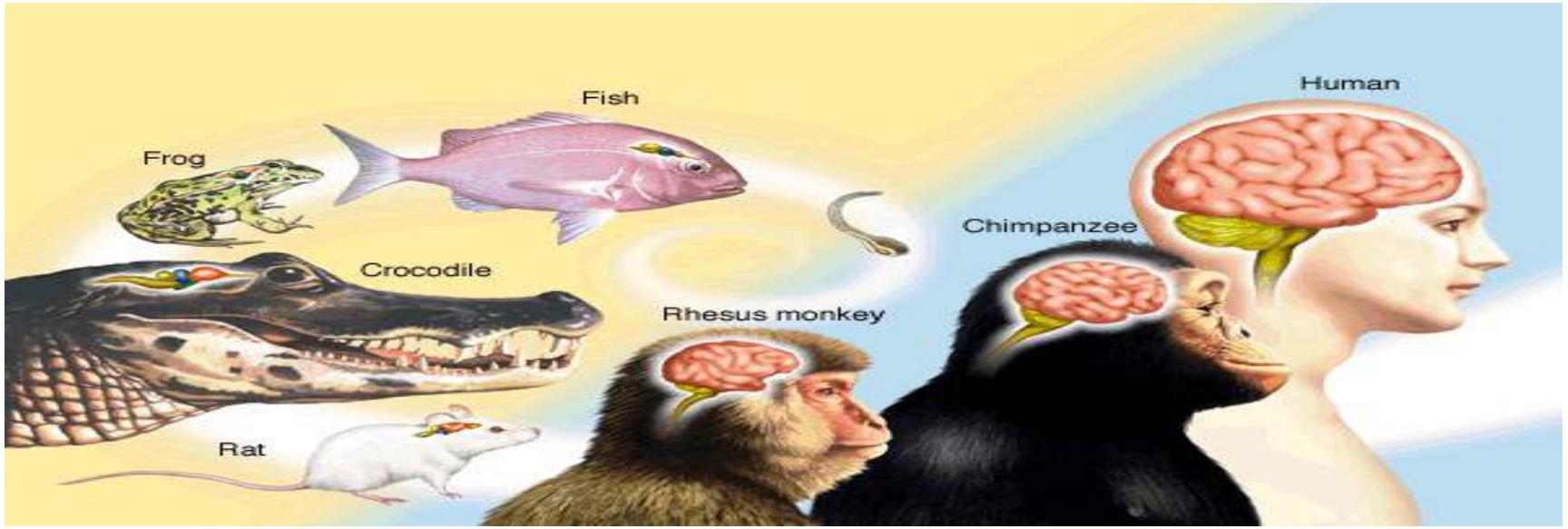


Hydra (cnidaire)

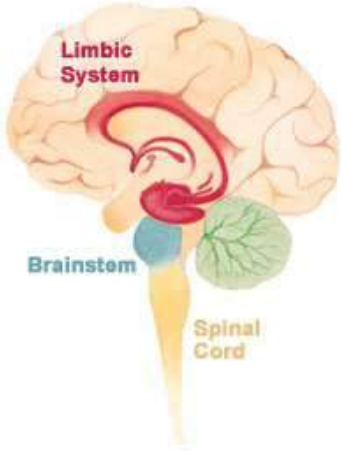


Co-evolution between gut and brain





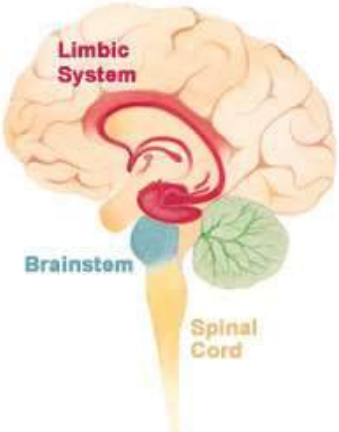
The gut and brain: two connected organs…



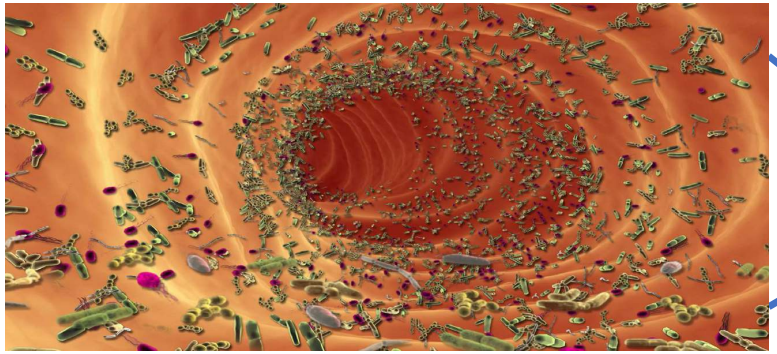
Hypothalamus (satiety ; food uptake)
Hippocampe (memory) ;
Amygdala (agressivity ; fear)

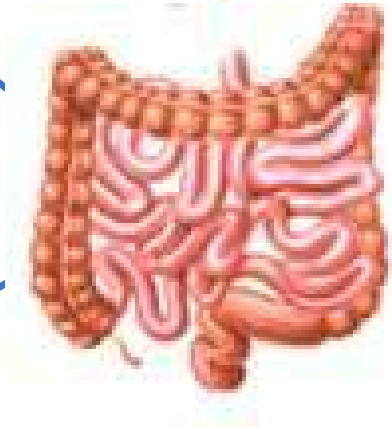
Direct connection :
via nerve (Vagus,..)
Indirect connexion:
via blood

The gut and brain : two organs connected to… our environment



Environment (microbiota ; nutrients ; polluants,……)





We are at the image of our food, microbiota…

Talk outlines

I. The gut-brain axis

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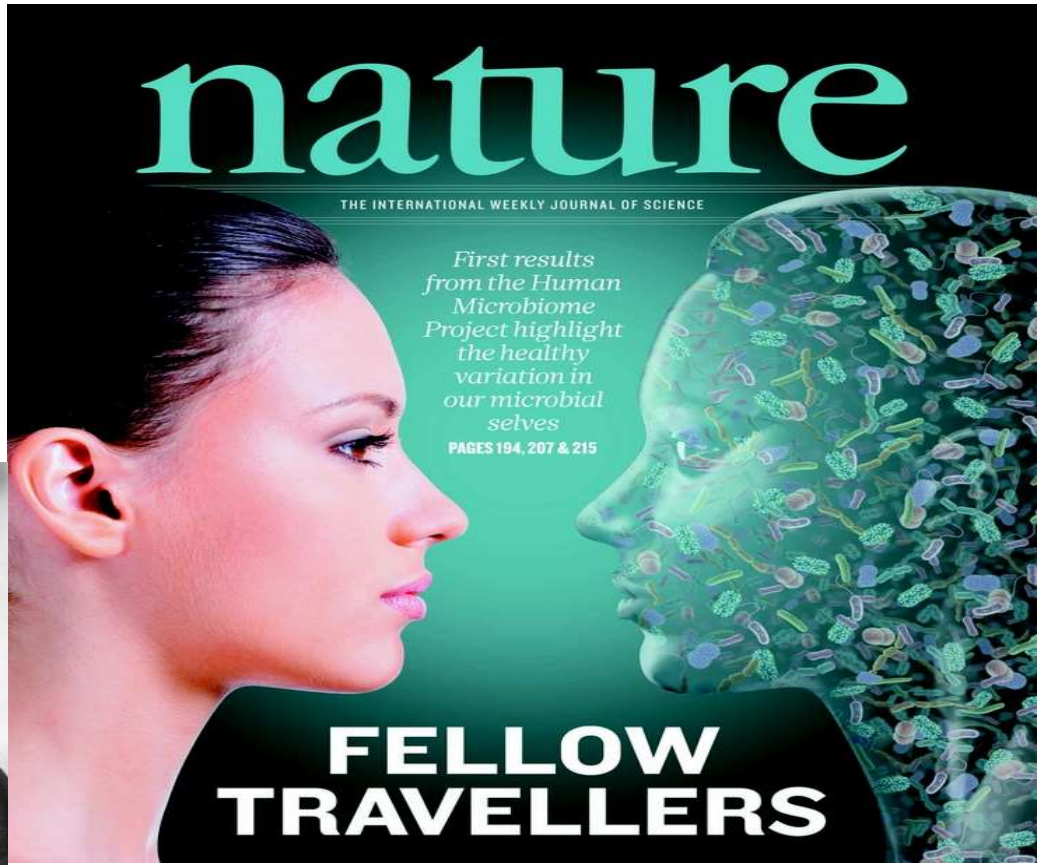
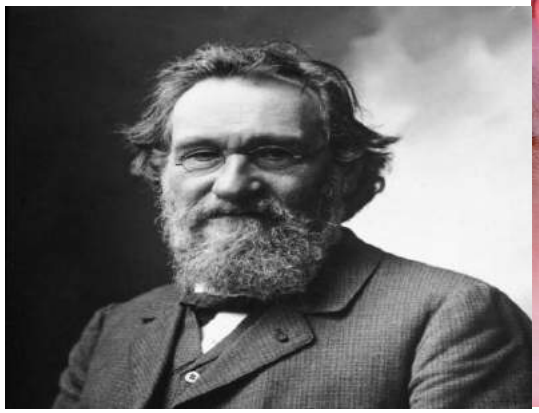
Microbes : contributors of health and diseases…

Charles-Emmanuel Sédillot
(1804-1883)



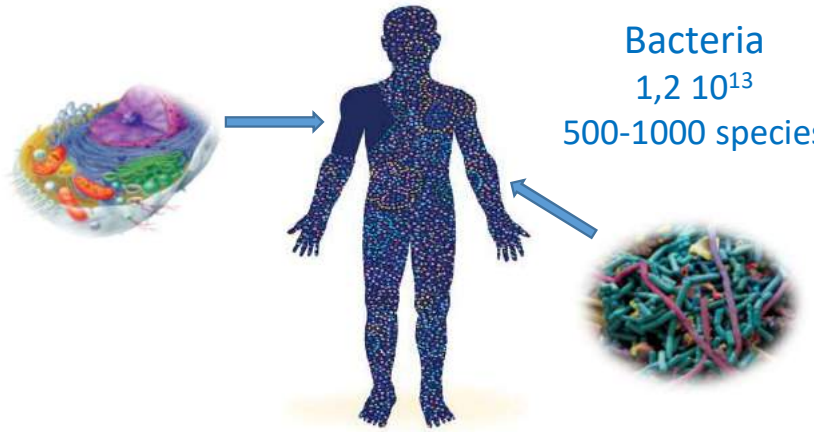
Louis Pasteur
(1825-1885)



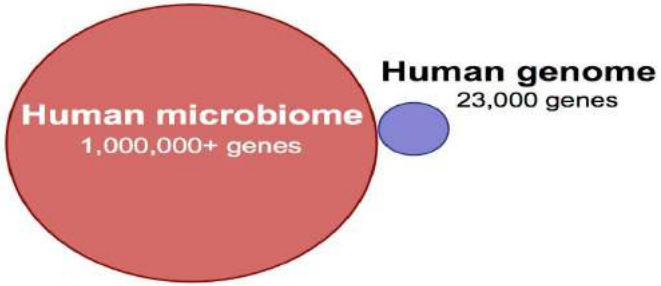
Elya Metchnikov
(1845-1916)

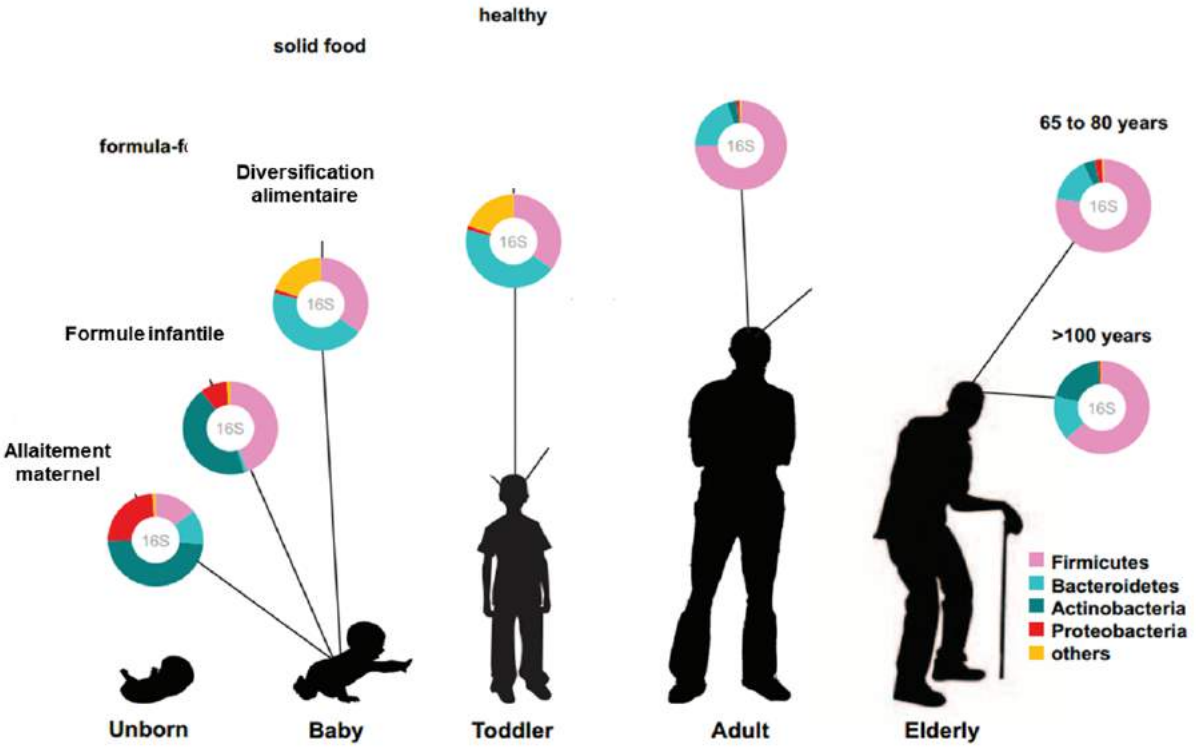
The gut microbiota and its evolution during life

Eucaryotes **10^{13}**

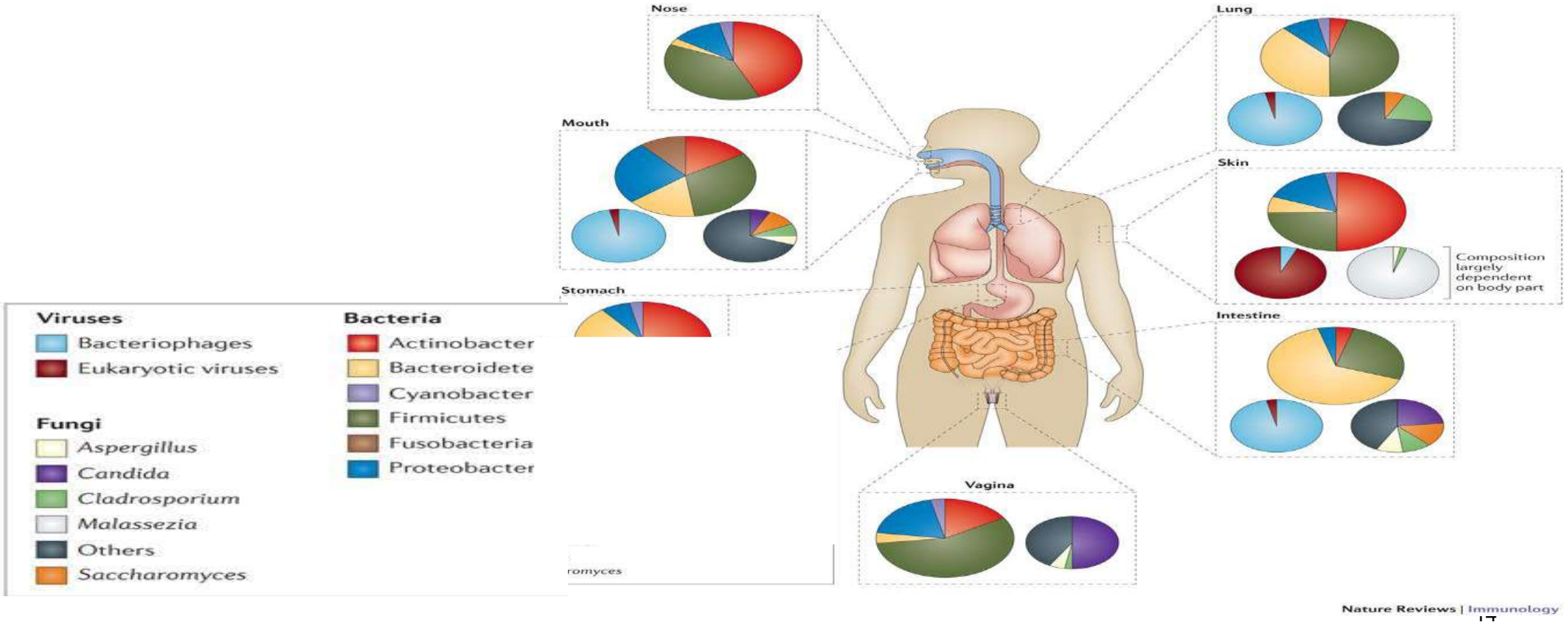


Bacteria
$1,2\ 10^{13}$
500-1000 species

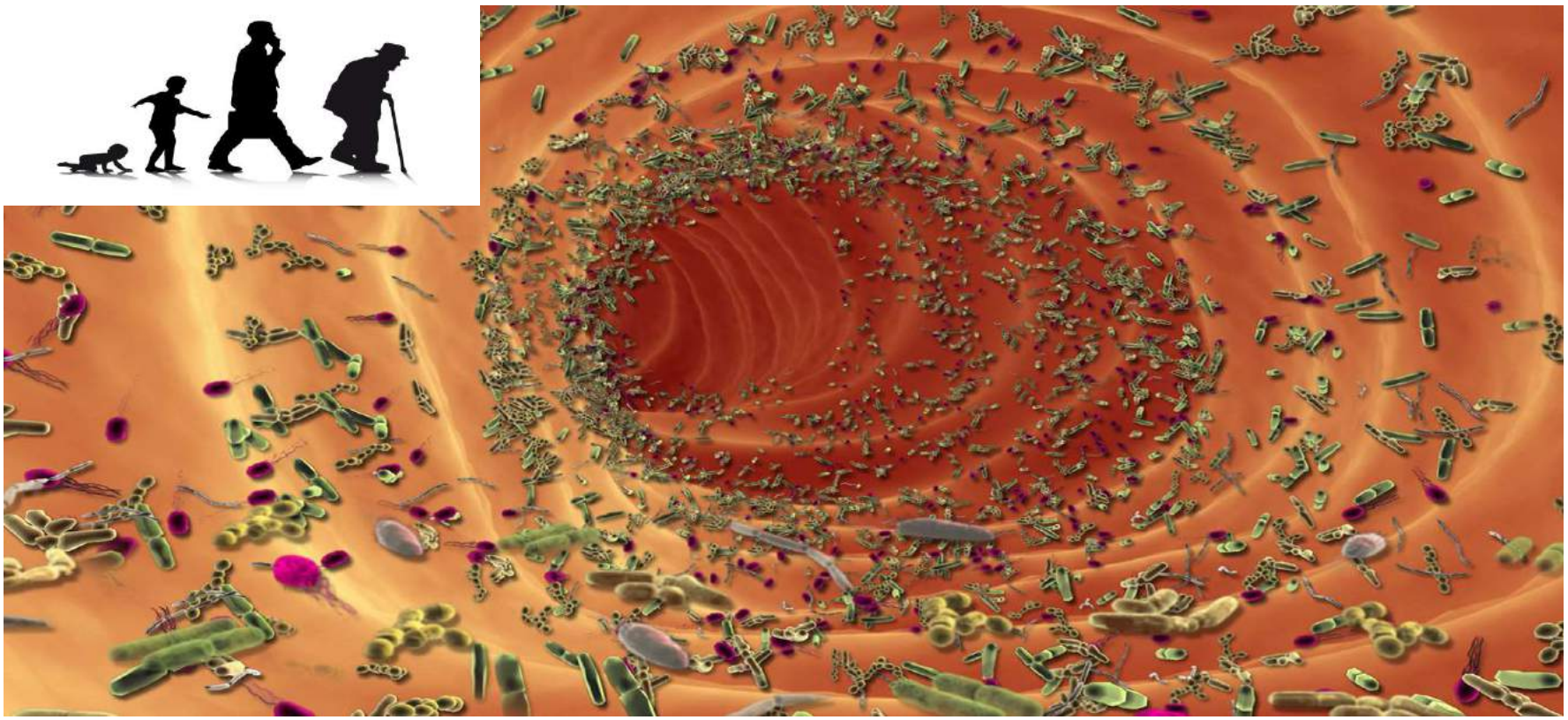




The microbiota of our organs



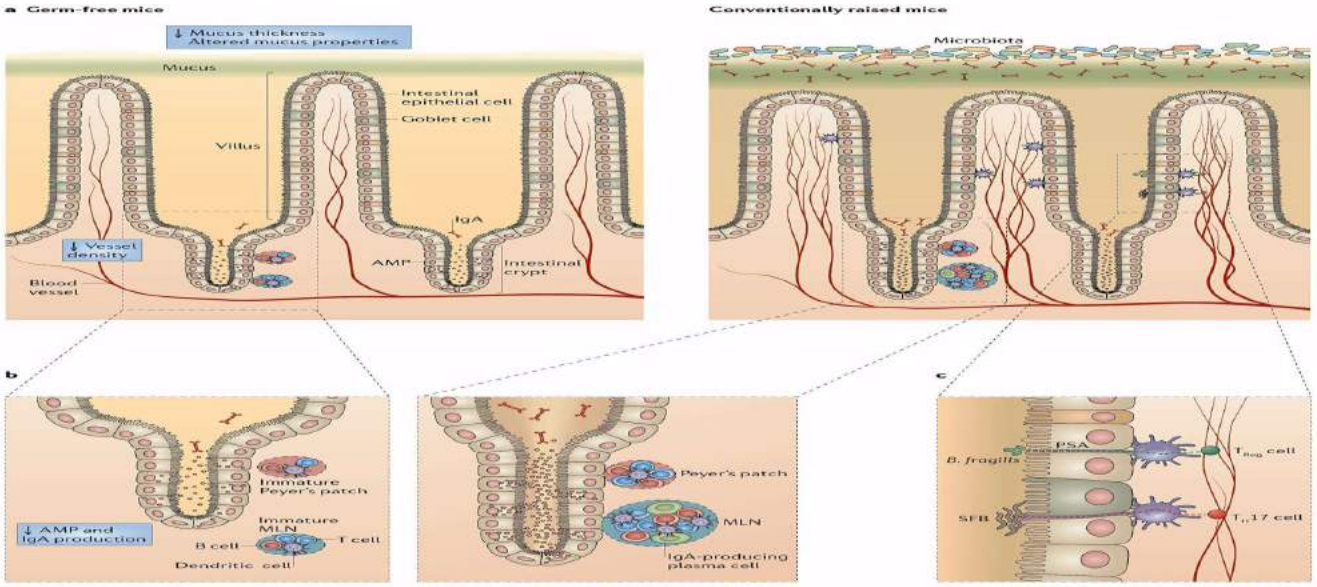
Microbiota : actors of our health during life



Without microbiota the beginning of life is harder

Intestin without microbiota

Intestin with microbiota



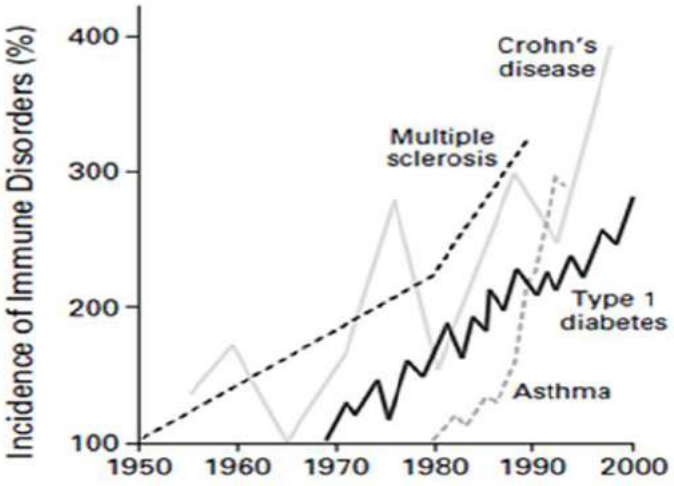
Macpherson and Harris, *Nat rev Immunol*., 2004

but without microbiota we also live longer…

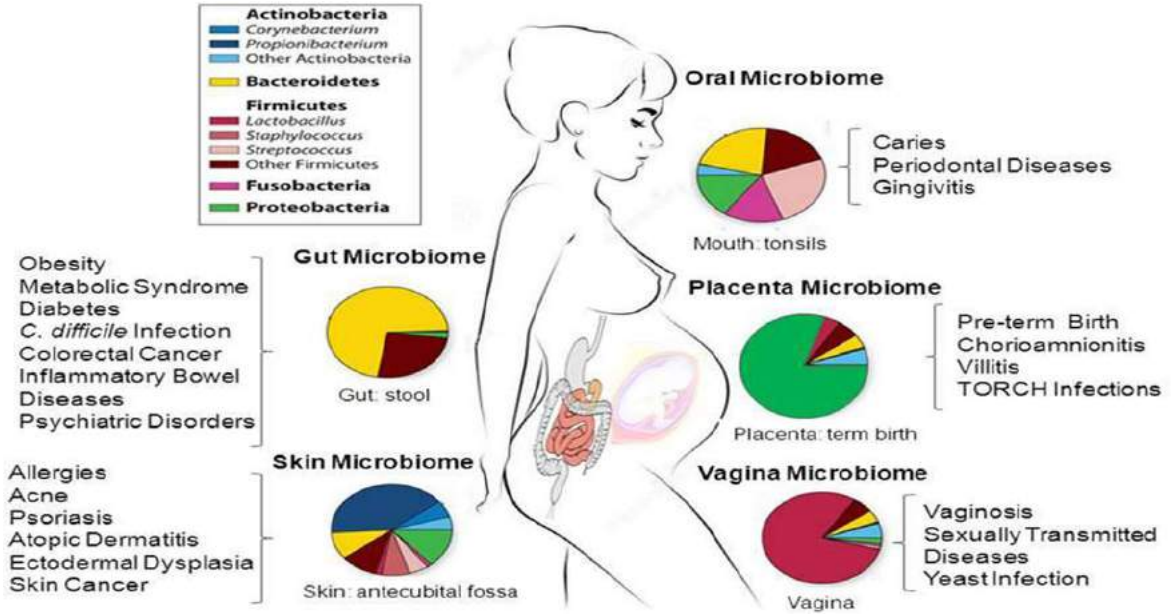
- Germ free mice have longer life expectancy (protected from inflammation associated ageing)
- Cohabitation of germ free mice with aged mice (but not young mice…) increases systemic inflammation associated with ageing….
- Age asscіated alteration in microbiota composition can be reduced by inhibiting host synthesis of TNF-a

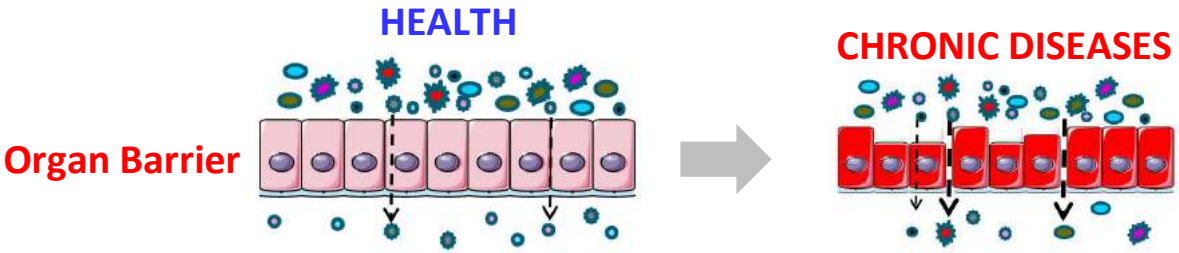
Thevarajan et al.,, Cell Host Microbes, 2017

The microbiota: actor of the development of chronic diseases



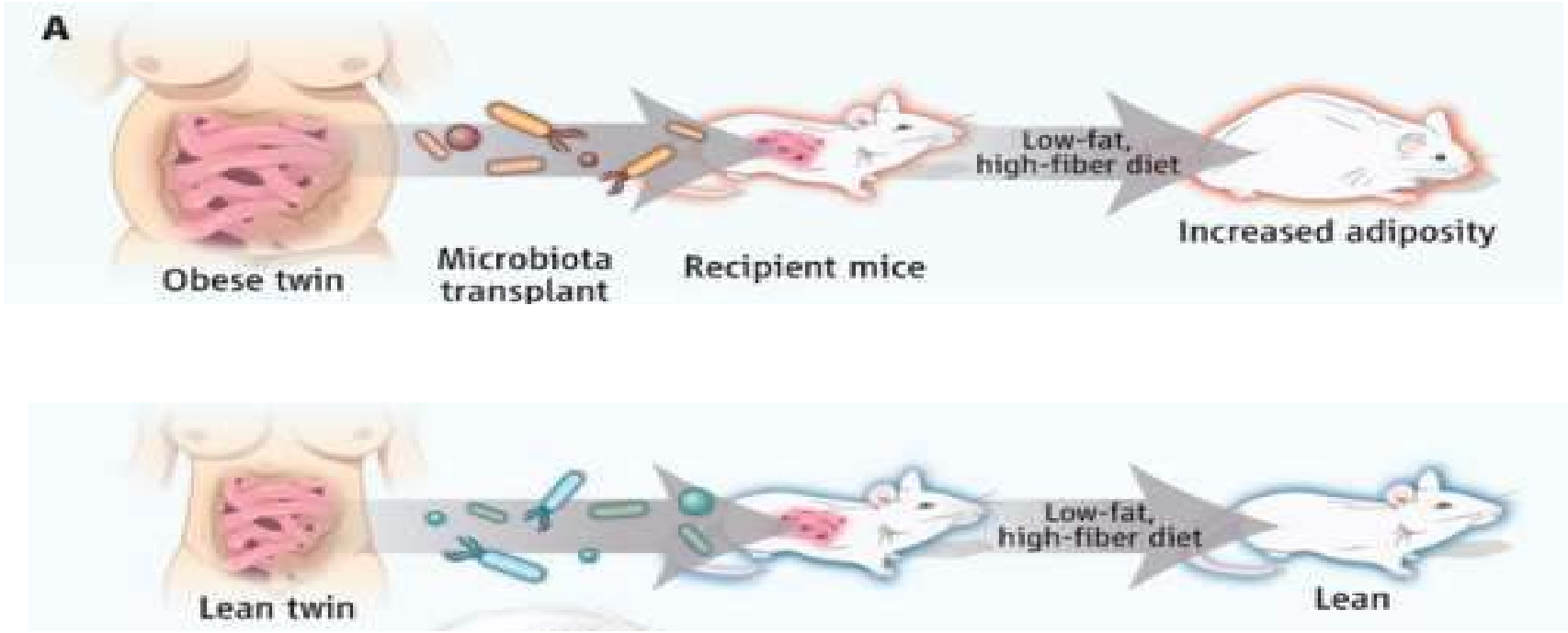
Bach et al.,*N Eng J Med*, 2000





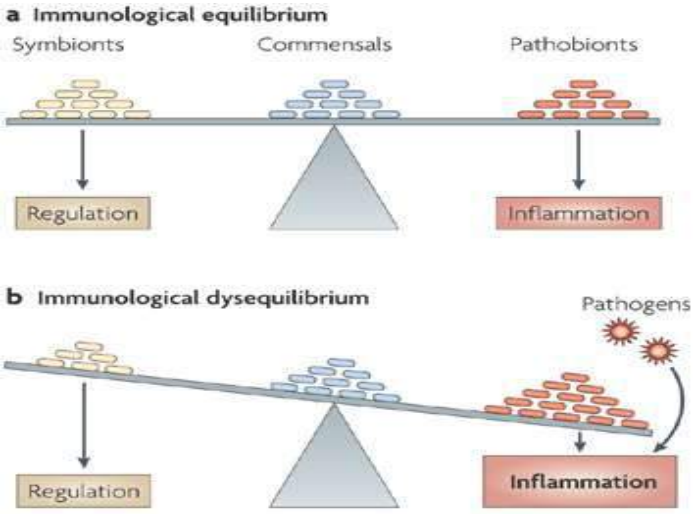
Belizarios and Napolitano, *Front Microbiol*, 2015

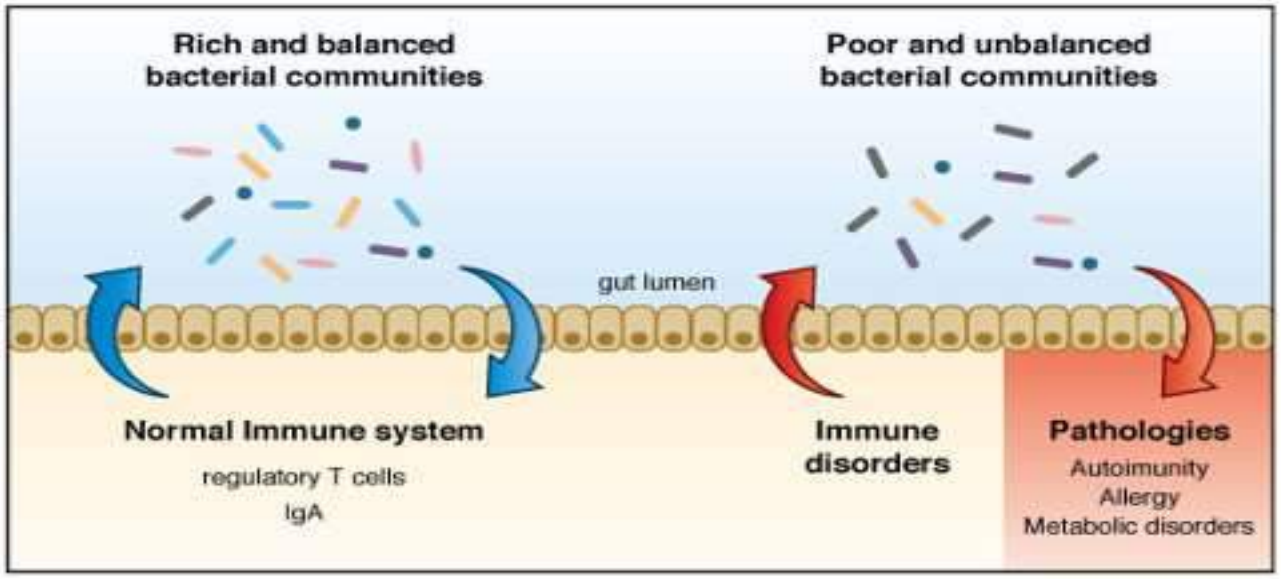
Chronic diseases: are they also (in part) transmissible / infectious diseases?



Ridaura et al Science 2013

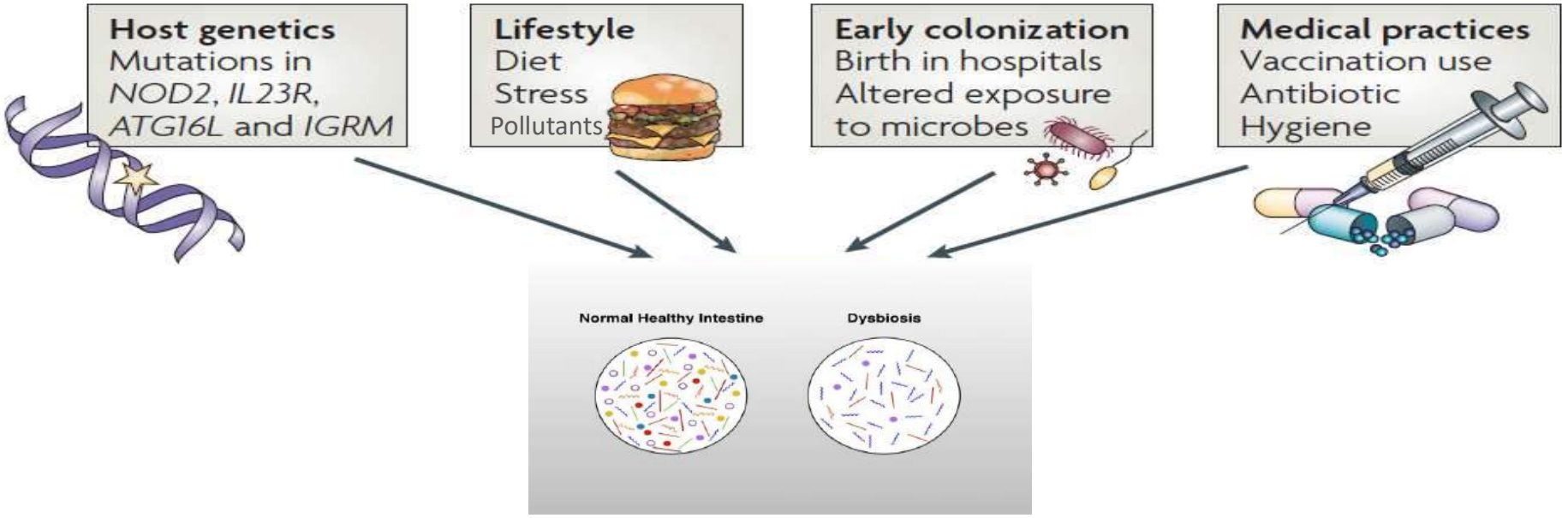
Dysbiosis vs eubyosis: loss of diversity/richness of the microbiota at the center of chronic diseases?





Round and Mazmanian *Nat Rev Immunol* 2009

What causes the shift from eubiosis to dysbiosis?



Round and Mazmanian *Nat Rev Immunol* 2009

The gut microbiota: novel source of therapeutical targets in the prevention/treatment of chronic diseases?

Lozupone et al Nature 2012

Microbiota transplant: regenerative medicine?

THE LANCET, OCTOBER 8, 1983

RELAPSING CLOSTRIDIUM DIFFICILE ENTEROCOLITIS CURED BY RECTAL INFUSION OF HOMOLOGOUS FAECES

SIR,—Recurrent *Clostridium difficile* associated enterocolitis is uncommon but troublesome for the patient. The patient described here received vancomycin treatment several times but always relapsed with *C difficile* enterocolitis 2–3 weeks after discontinuation of treatment.

A 65-year-old woman with a lifelong history of irritable colon also had diverticulosis of the colon and diverticulitis of increasing severity. A partial colectomy was done to remove the diseased

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial

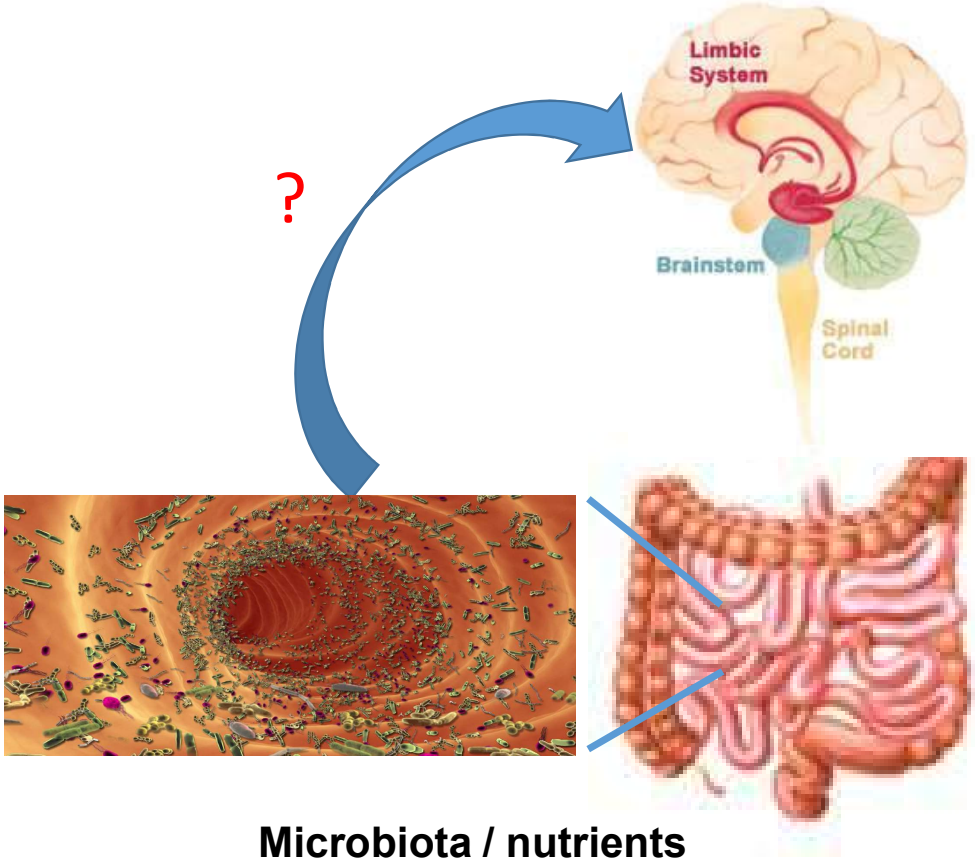
Sudarshan Paramsothy, Michael A Kamm, Nadeem O Kaakoush, Alissa J Walsh, Johan van den Bogaerde, Douglas Samuel, Rupert W L Leong, Susan Connor, Watson Ng, Ramesh Paramsothy, Wei Xuan, Enmoore Lin, Hazel M Mitchell, Thomas J Borody

Lancet 2017; 389: 1218–28
Published Online February 14, 2017
http://dx.doi.org/10.1016/S0140-6736(17)30182-4

Summary

Background The intestinal microbiota is implicated in the pathogenesis of ulcerative colitis. Faecal microbiota transplantation is a novel form of therapeutic microbial manipulation, but its efficacy in ulcerative colitis is uncertain. We aimed to establish the efficacy of intensive-dosing, multidonor, faecal microbiota transplantation in active ulcerative colitis.

The microbiota – gut – brain axis



We think with our microbiota…

Talk outlines

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The functions of the gastrointestinal tract

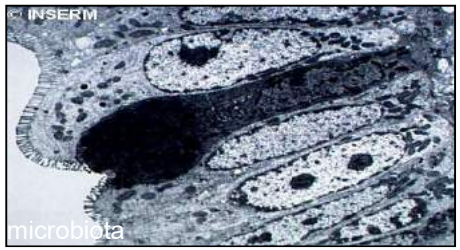
30 tons of food

50 tons liquids

1- Motility

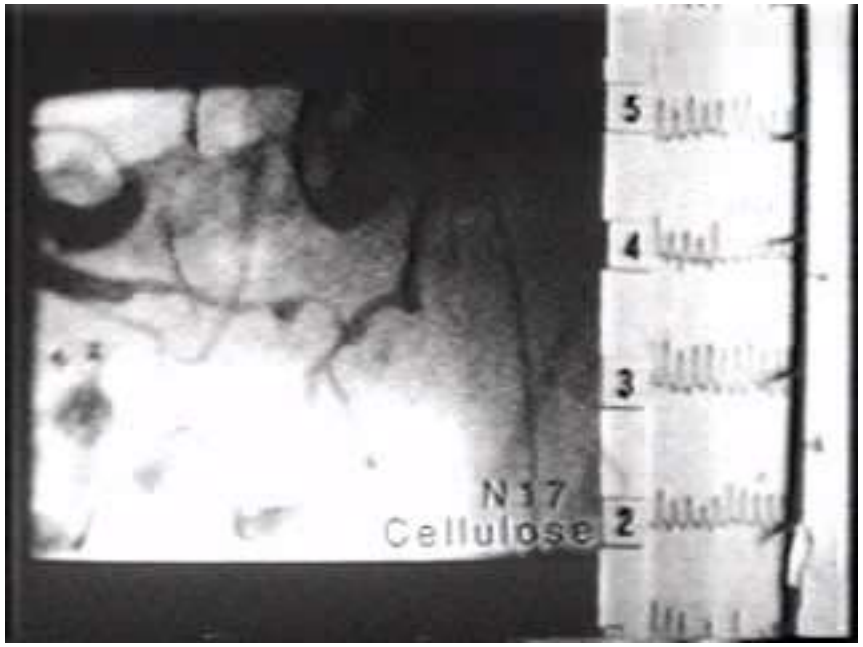
2- Absorption of nutrients/minerals/electrolytes

3- Barrier/immune functions

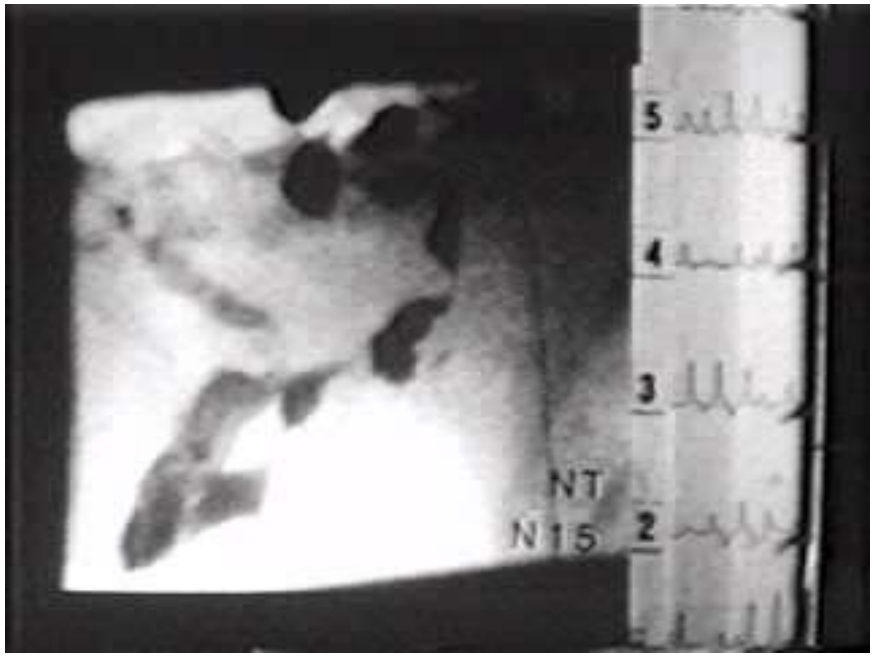


Our gut in motion…

Transport (peristaltism)

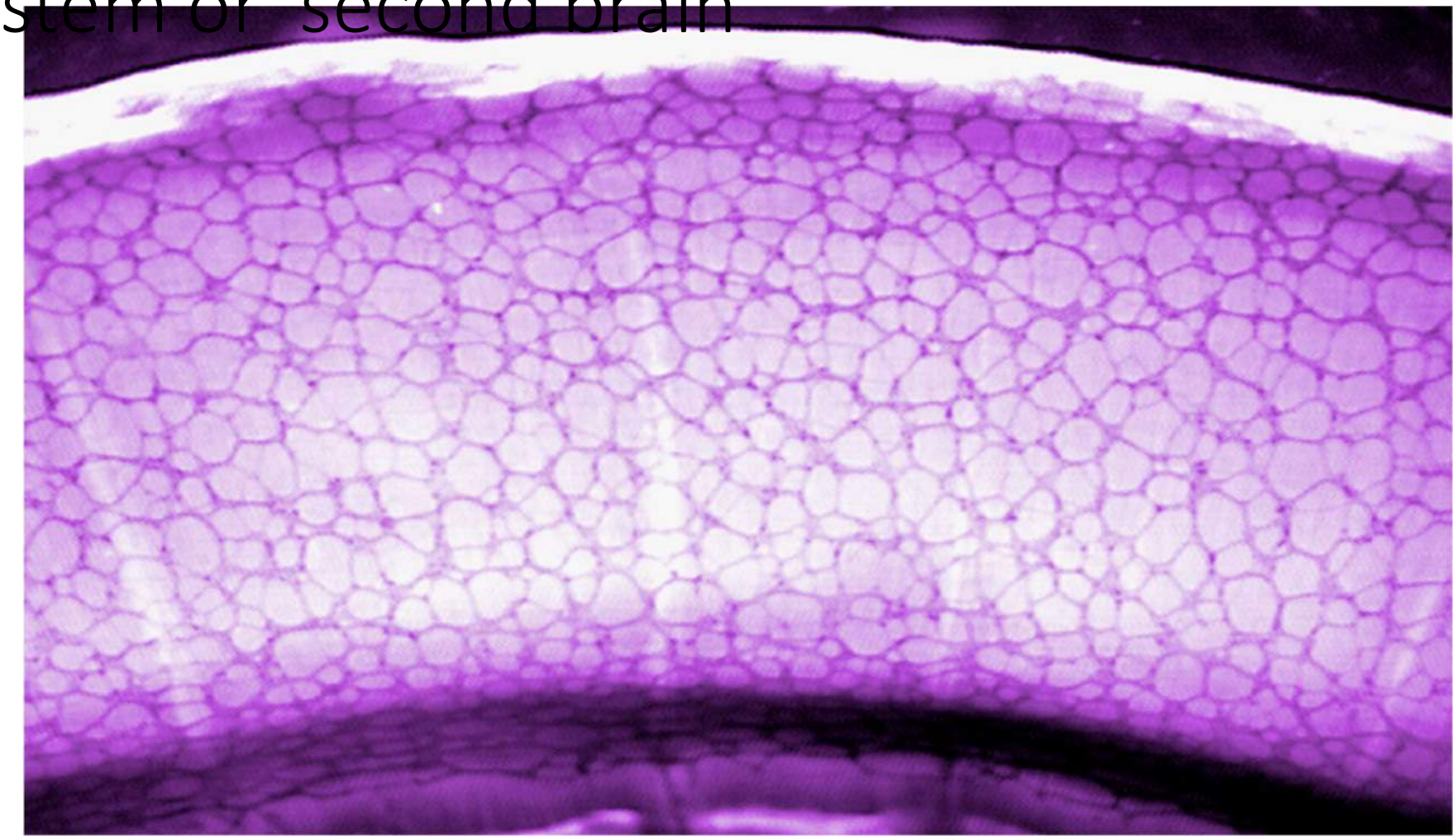


Segmentation



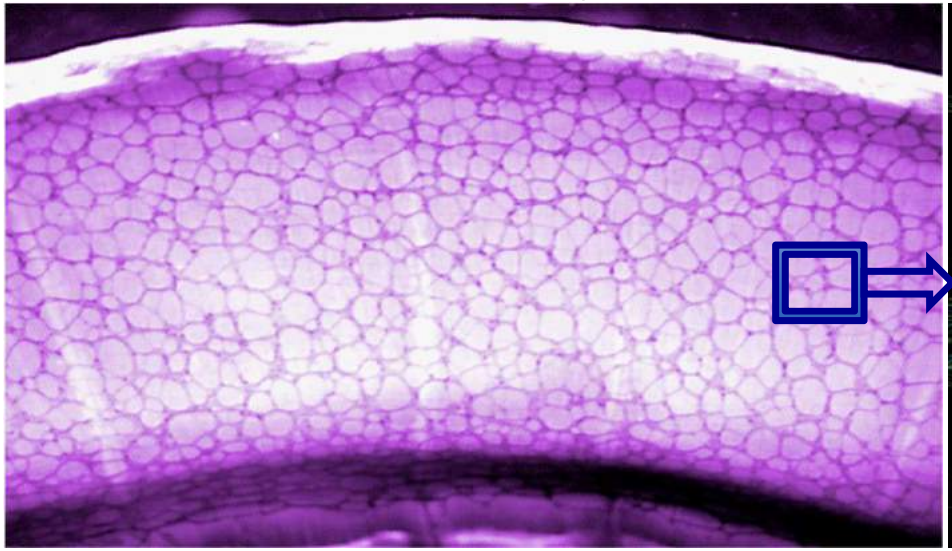
He can do it without the brain

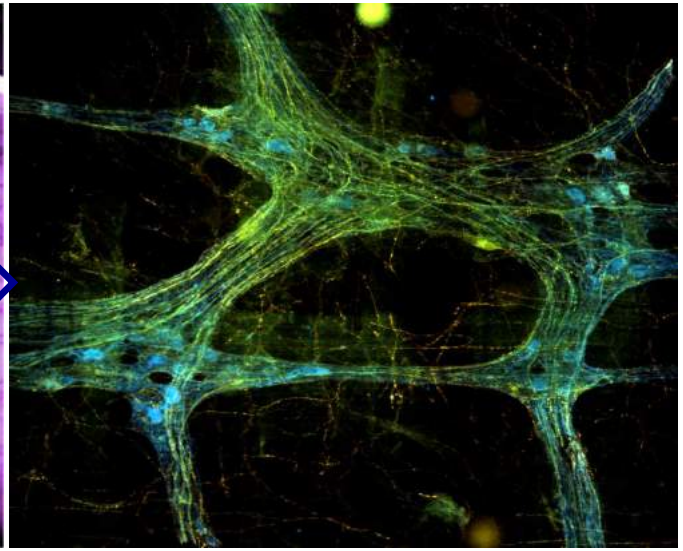
...without its own brain: the enteric nervous system or ‘second brain’

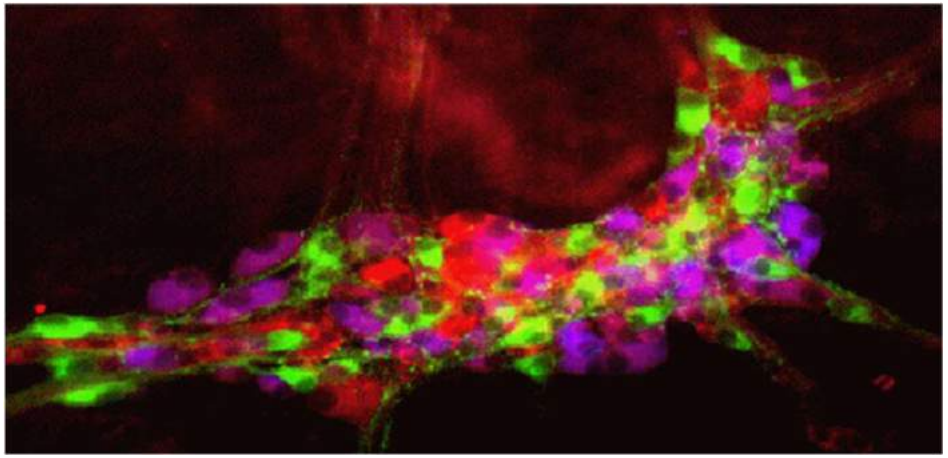


Inserm U913

The enteric nervous system







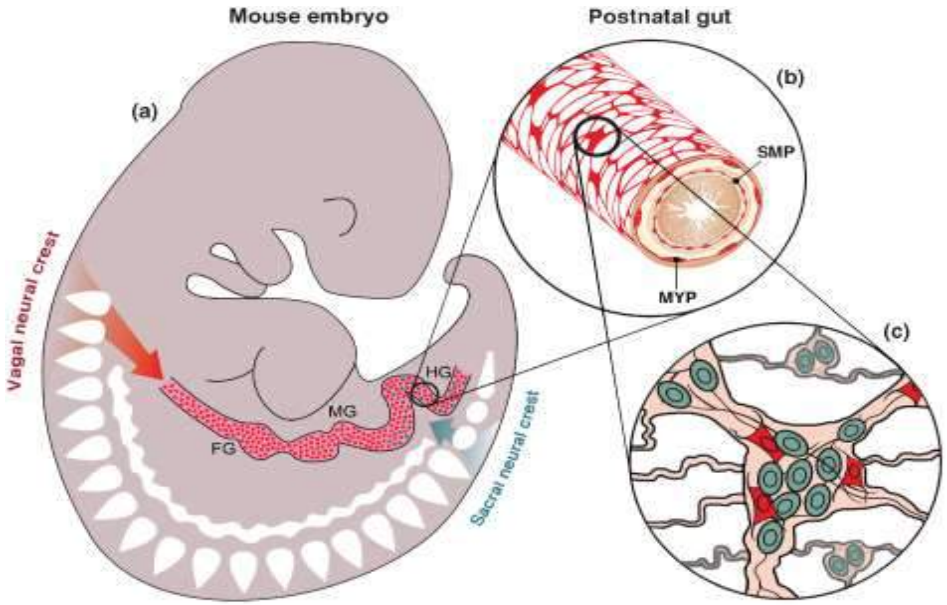
ChAT: choline acetyl Transferase

NOS : Nitric oxide synthase

VIP : Vasoactive intestinal peptide

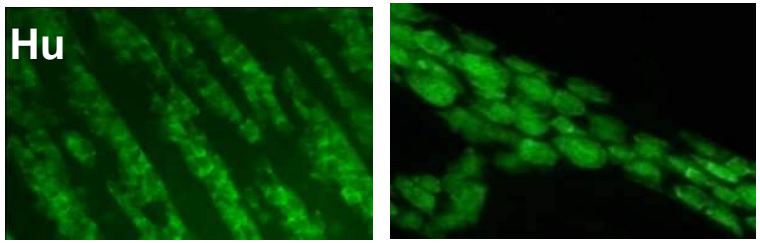
Origin and development of the ENS

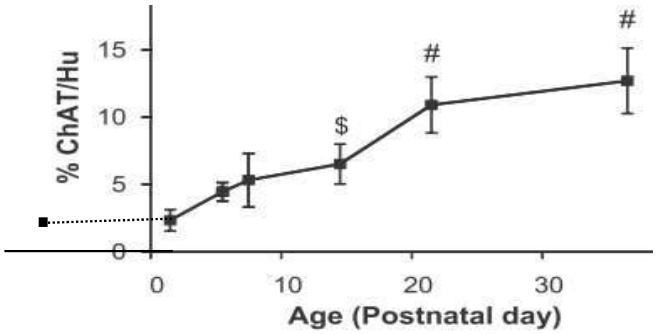
Nyshiyama et al., *Nat Neuroscience*, 2012



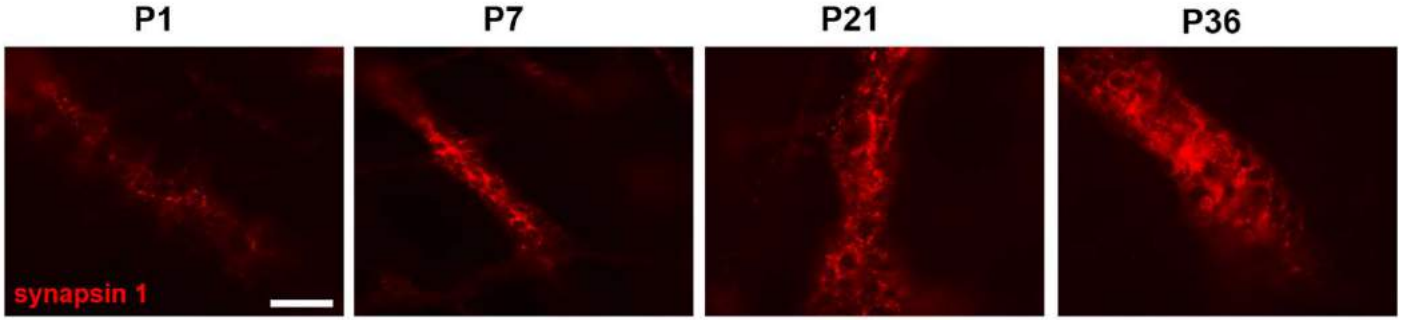
Goldstein and Burns, *Clinical Genetics*, 2012
Heanue TA, Pachnis V, *Nat. Rev. Neurosci.* 2007

The post natal period: a key period for building a brain in the gut…



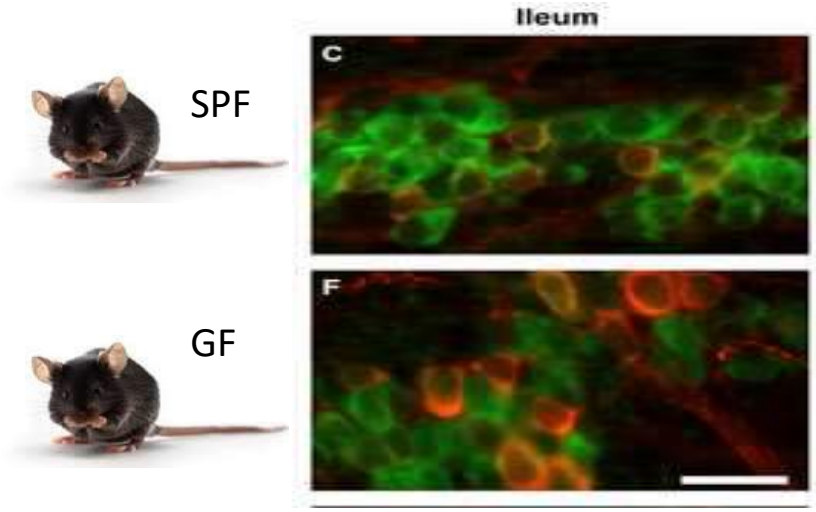


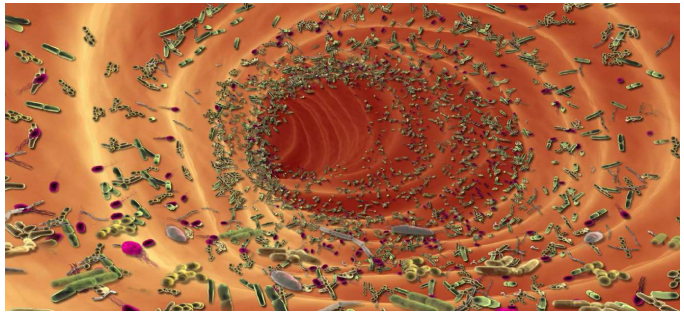
de Vries et al., *Am J Phys*, 2010

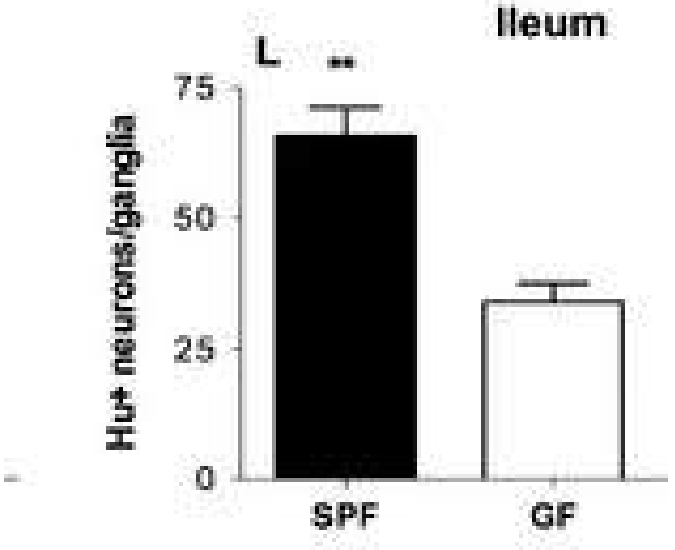


Le Berre Scoul et al., *J Phys*, 2016

Gut microbiota contributes to the building of the enteric nervous system...

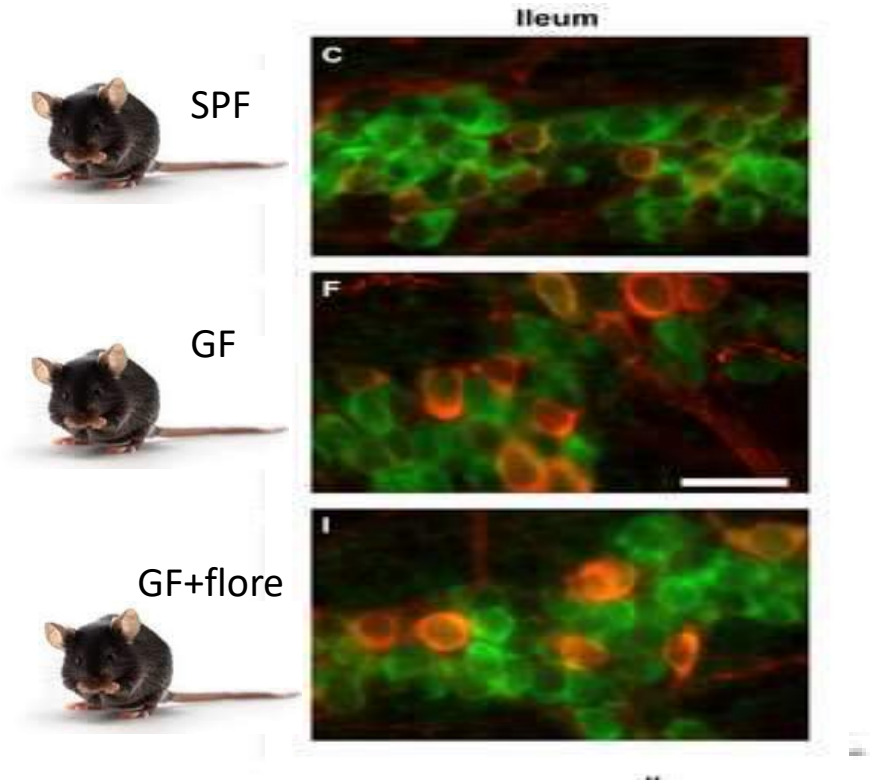


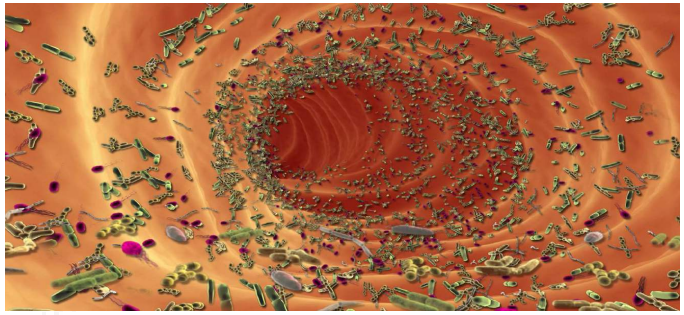


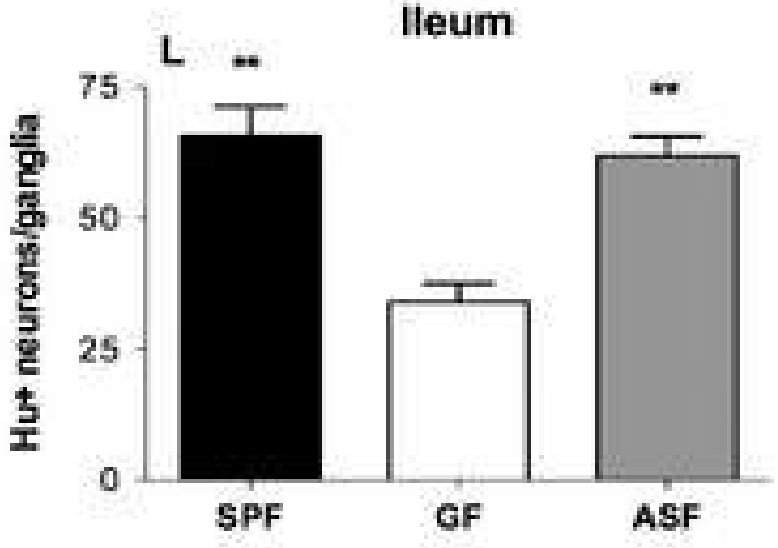


Collins et al., *Neurogastroenterology Mot,* 2013

Gut microbiota contributes to the building of the enteric nervous system...

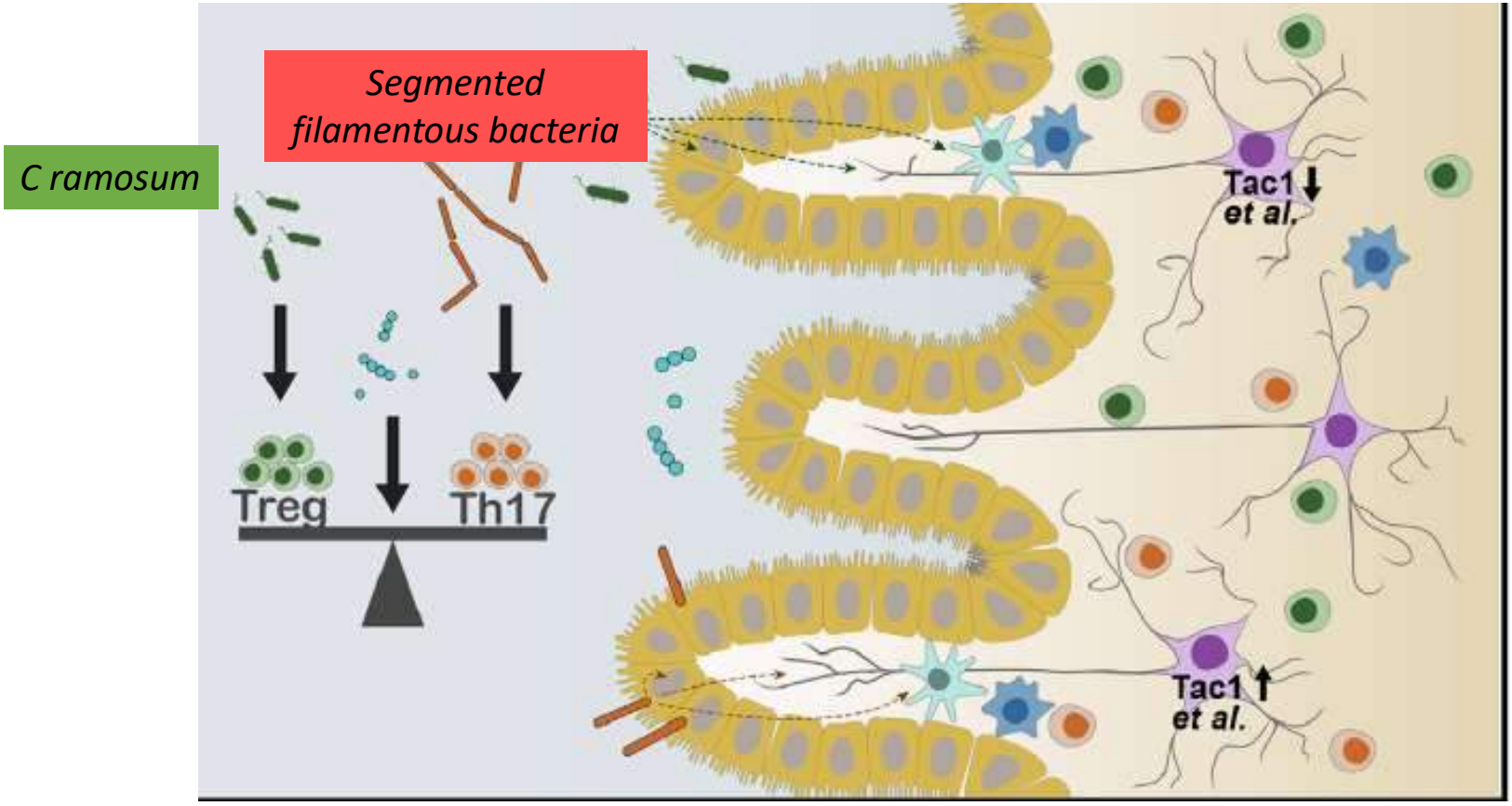






Collins et al., *Neurogastroenterology Mot,* 2013

The enteric nervous system helps bacteria to educate the gut immune system



Yiassachar et al., *Cell, 2017*

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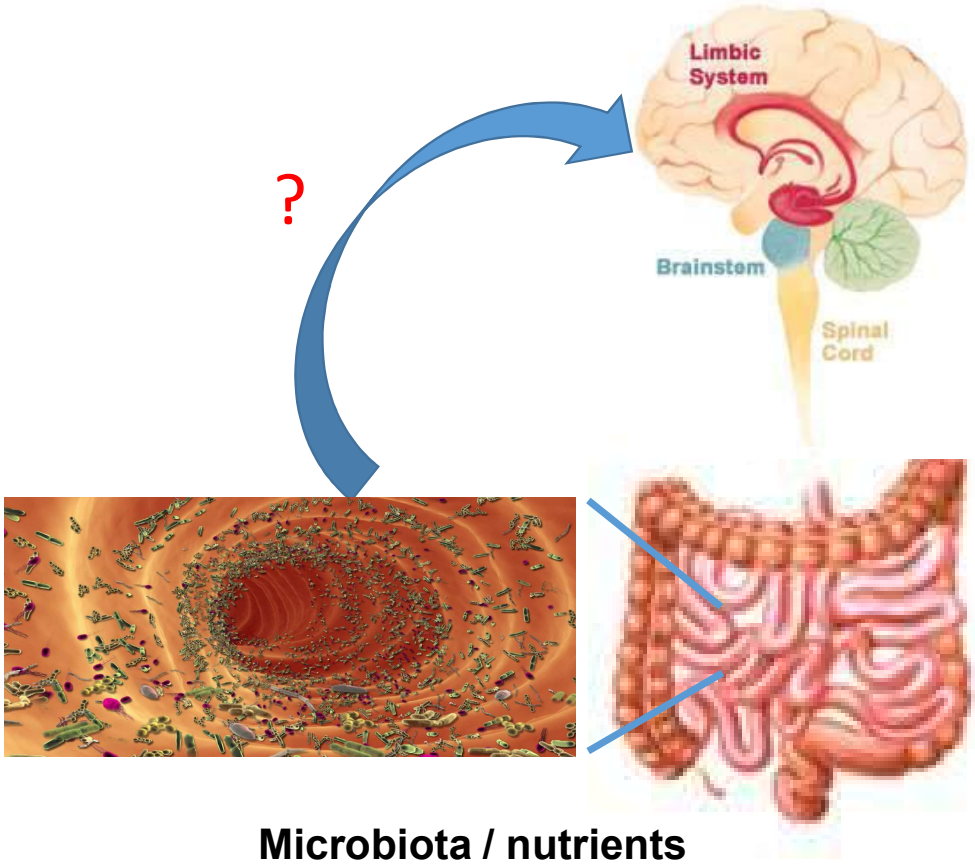
IV. The impact of the microbiota upon the brain health and diseases

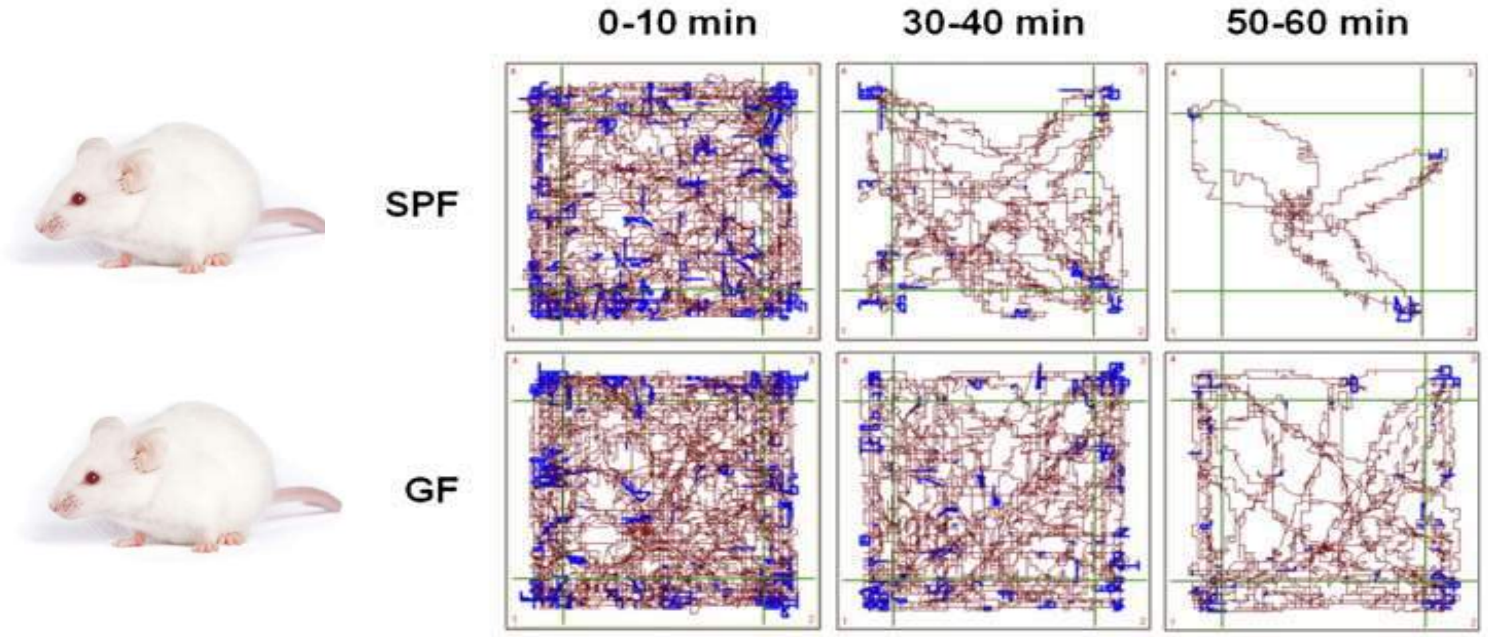
The microbiota – gut – brain axis



Microbiota / nutrients

We think with our microbiota…

The gut microbiota modulates our behaviour

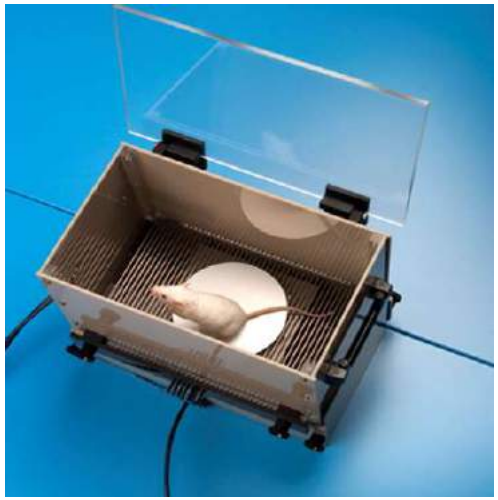


Lack of microbiota increases exploratory behavior

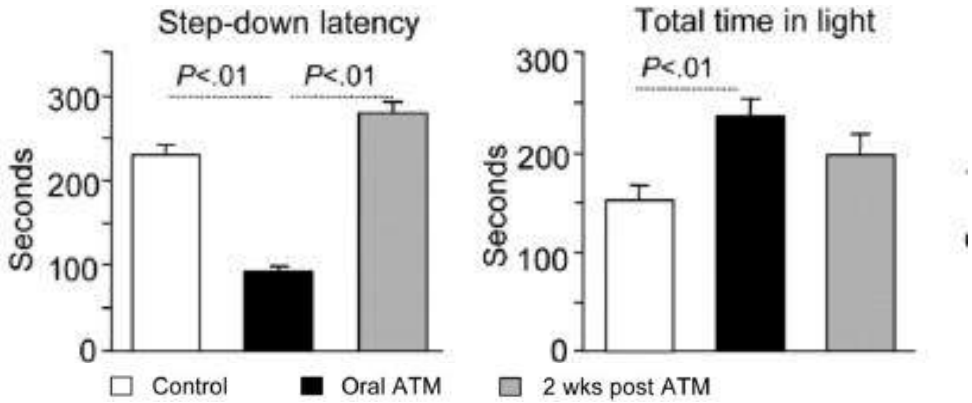
Diaz Heijtz et al. *PNAS* 2011

The gut microbiota modulates our behaviour

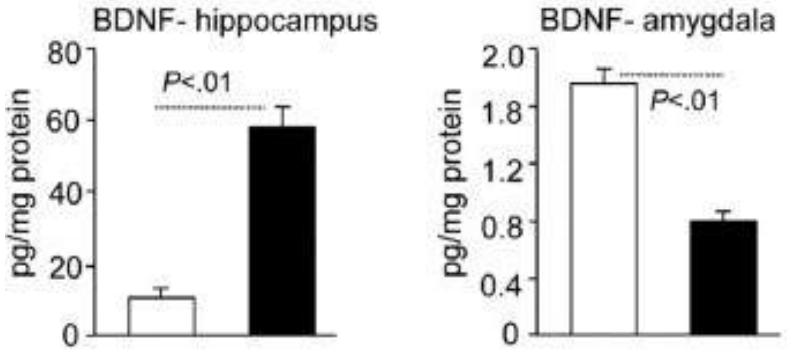
14j +/- antibiotiques



Step down test



Increase exploration and reduces anxiety



Bercik et al., *Gastroenterology*, 2011

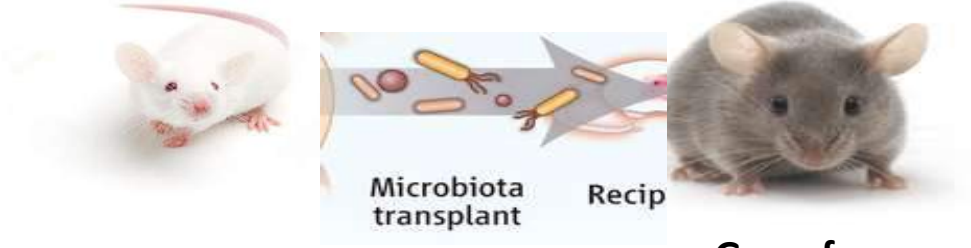
‘Transplantation’ of behaviour via feces.

BALB/c

Shy and anxious

NIH Swiss

Agressive



Germ free

Shy and anxious

Germ free

Agressive

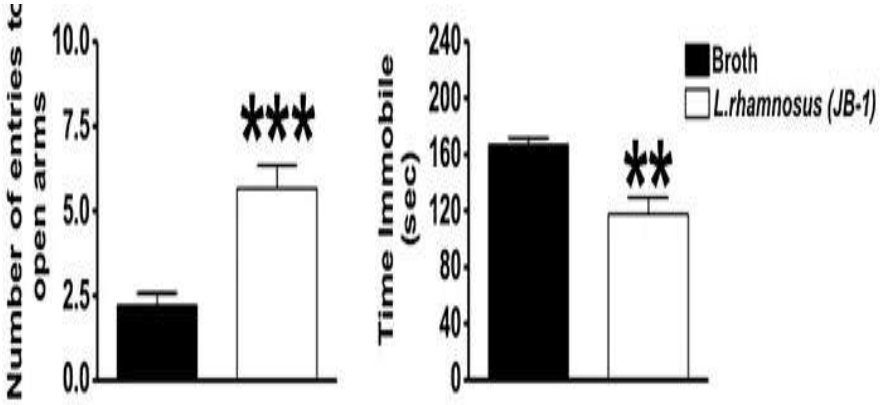
Bercik et al Gastroenterology 2016

A single bacterial strain can reduce anxiety and depression in mice

2 weeks +/- probiotic (L rhamnosus)

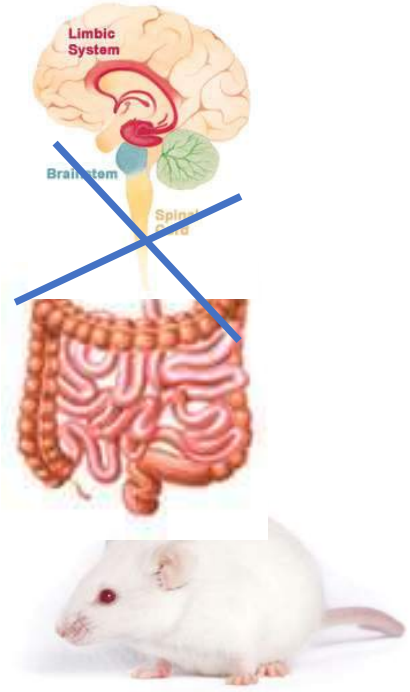
Open field (↘anxiété)

Forced swim test (↘dépression)

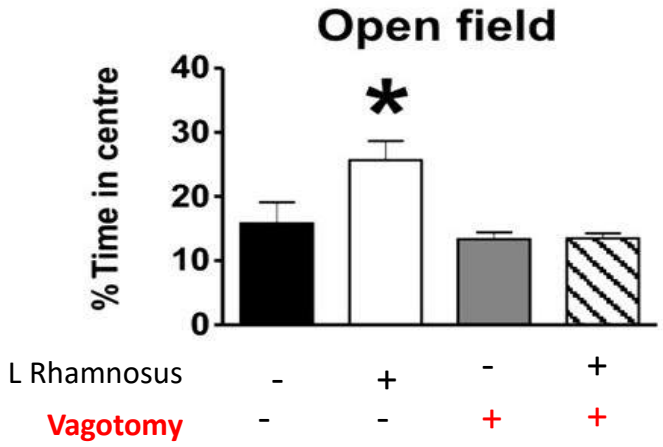


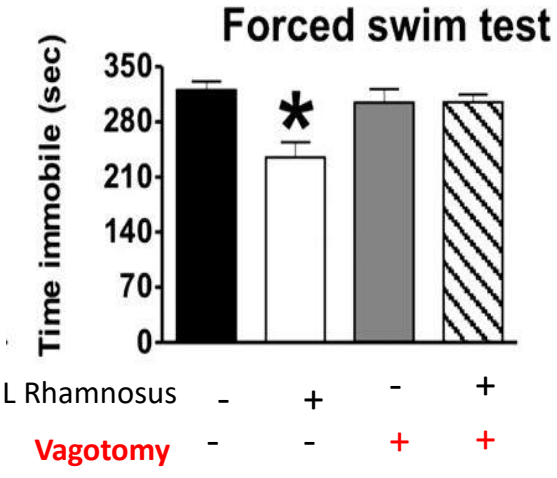
Bravo et al., *PNAS*, 2011

Effects of *L. rhamnosus* are mediated by vagus nerve



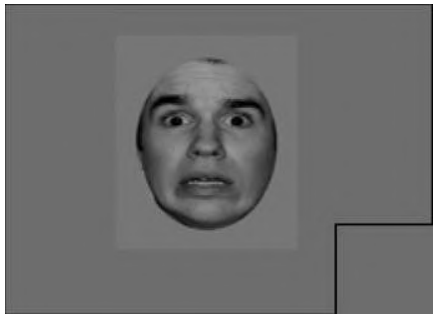
+/- probiotic
(L rhamnosus)
+/- vagotomy

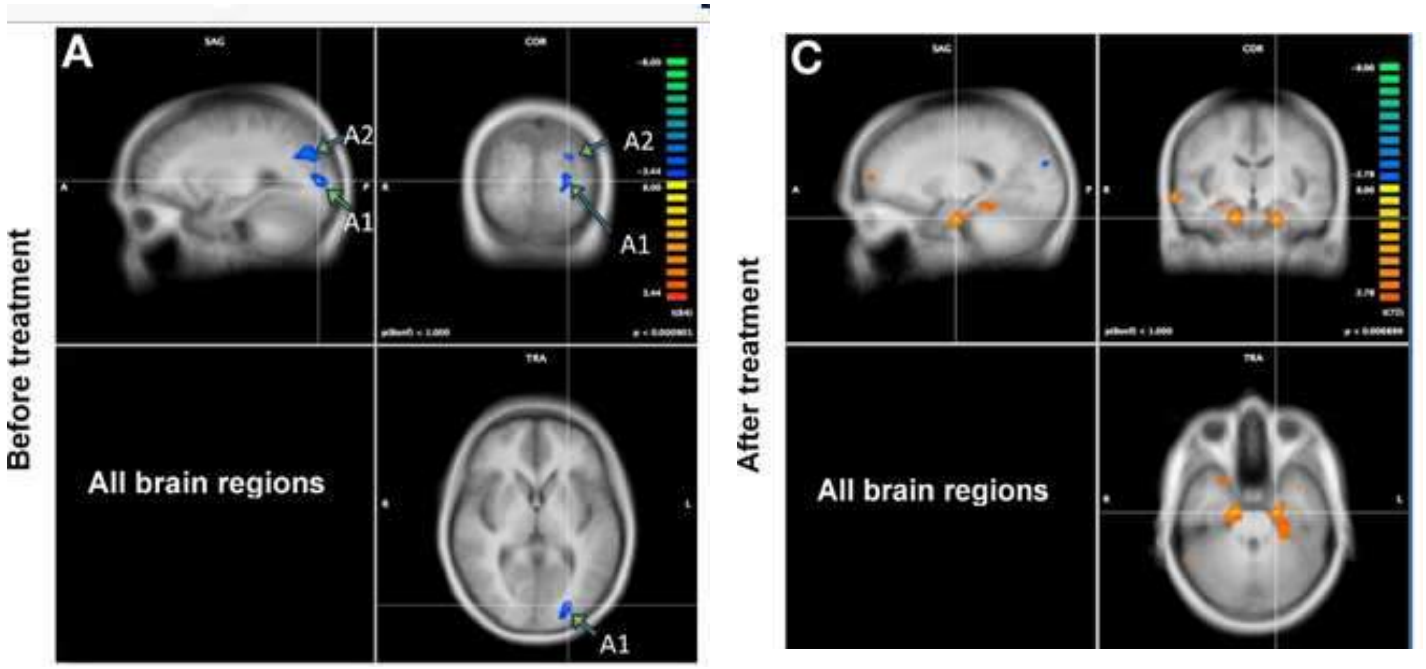




Bravo et al., *PNAS*, 2011

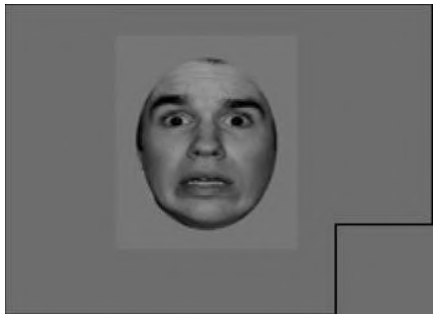
A single bacterial strain (*Bifidobacterium longum* NCC3001) administration reduces anxiety in humans

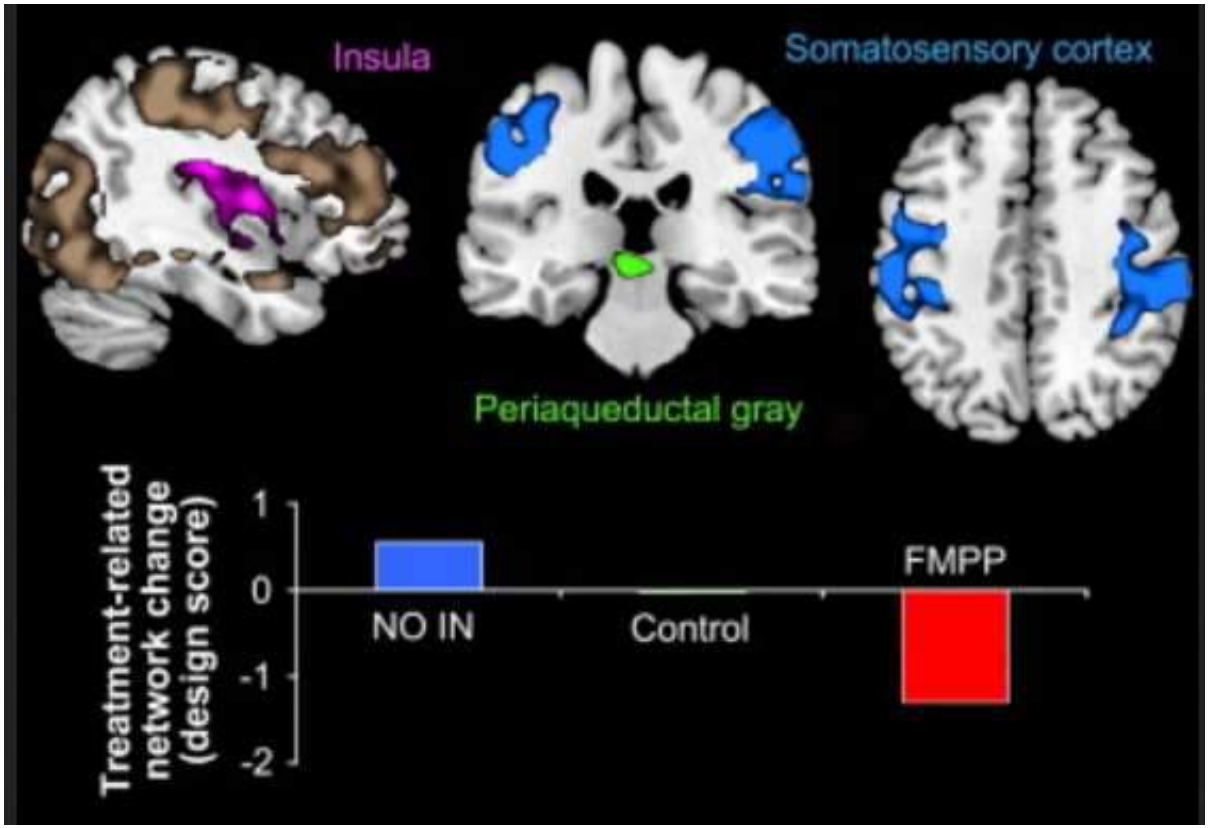




Pinto Sanchez et al., *Gastroenterology,* 2017

Fermented milk products reduces fear induced activation of brain regions

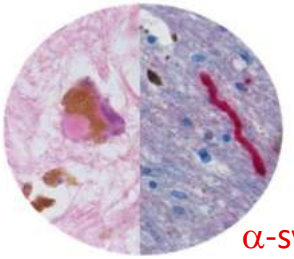




Tillisch et al., *Gastroenterology*, 2013

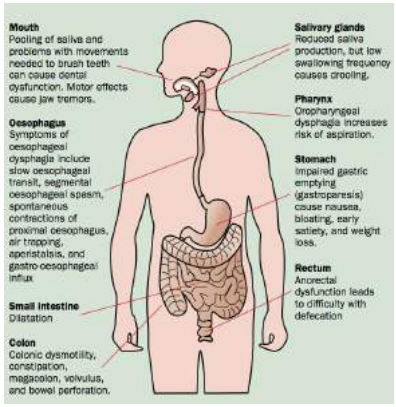
Are brain diseases also diseases of the gut (and microbiota)?
Example 1: neurodegenerative diseases (Parkinson's disease)

Substancia Nigra



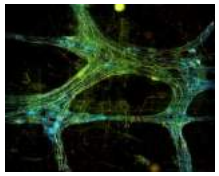
α-synuclein

➡ Motor symptoms
(rigidity; tremor; instability)

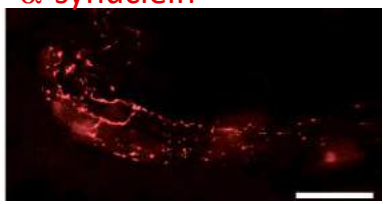


Pfeiffer, *Ann Neurol*, 2013

Enteric nervous system



α-synuclein



Lebouvier et al., *PlosOne,* 2010

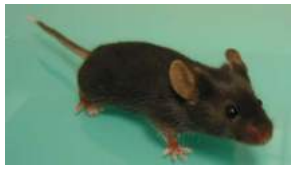
PD risk for patients with less than 1 stool/d

Nbre selles	1/j	2/j	>2/j
Risque relatif	2.7	4.1	4.5

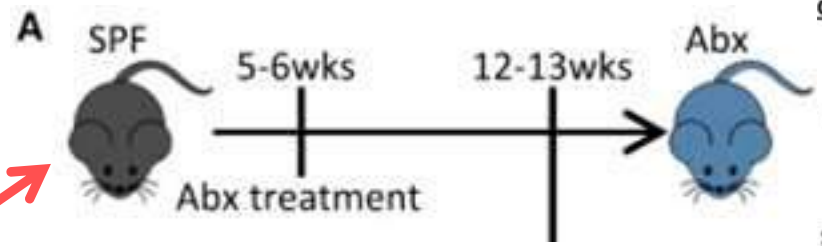
Abbott et al., Neurology 2001

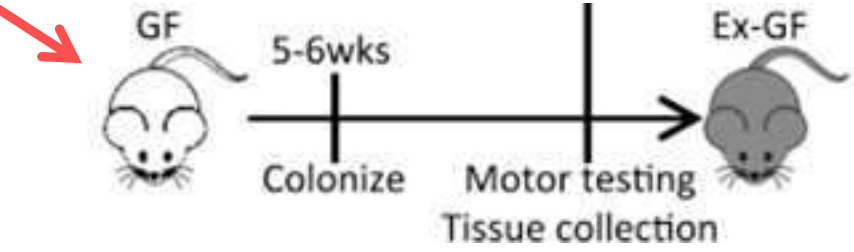
Gut microbiota enhances PD pathology

Thy1-haSyn

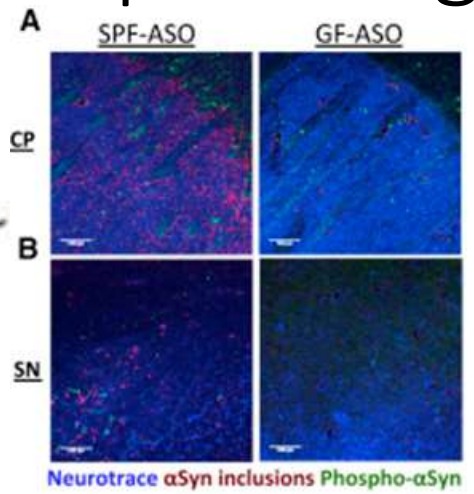


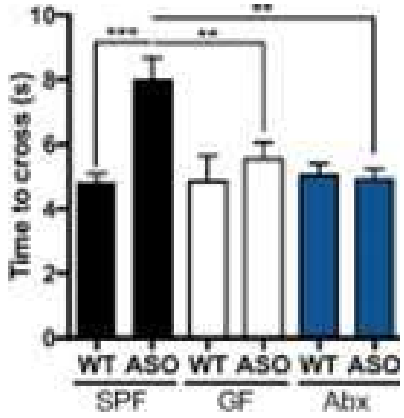
Parkinson mice

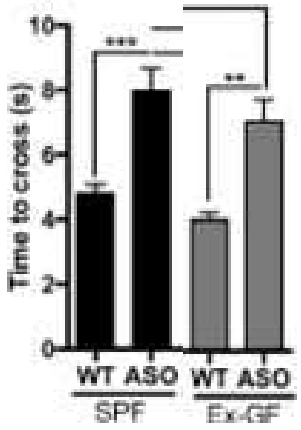




Feces PD patients



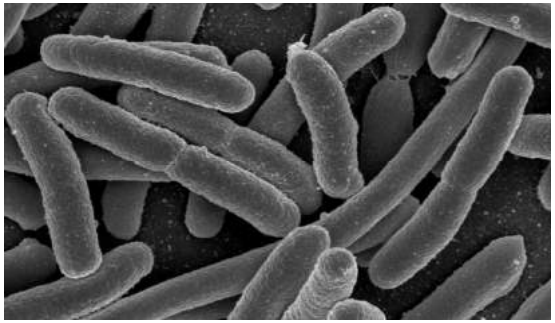




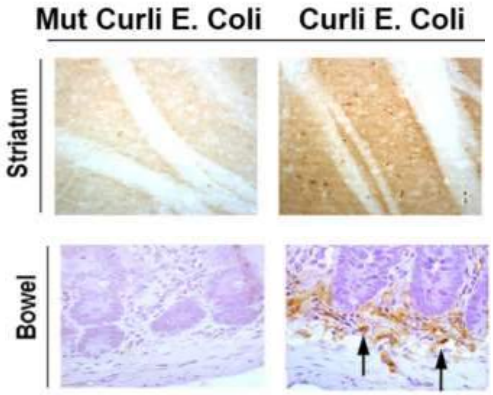
Sampson et al., *Cell* 2016

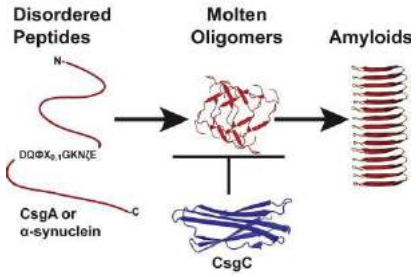
Bacteria producing amyloid peptides induces neuropathological hallmark of PD

E Coli



Extracellular functional amyloids: curli
Biofilm formation/host colonization



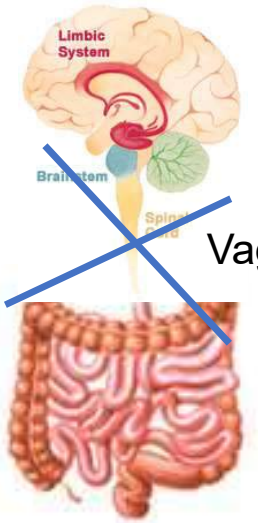


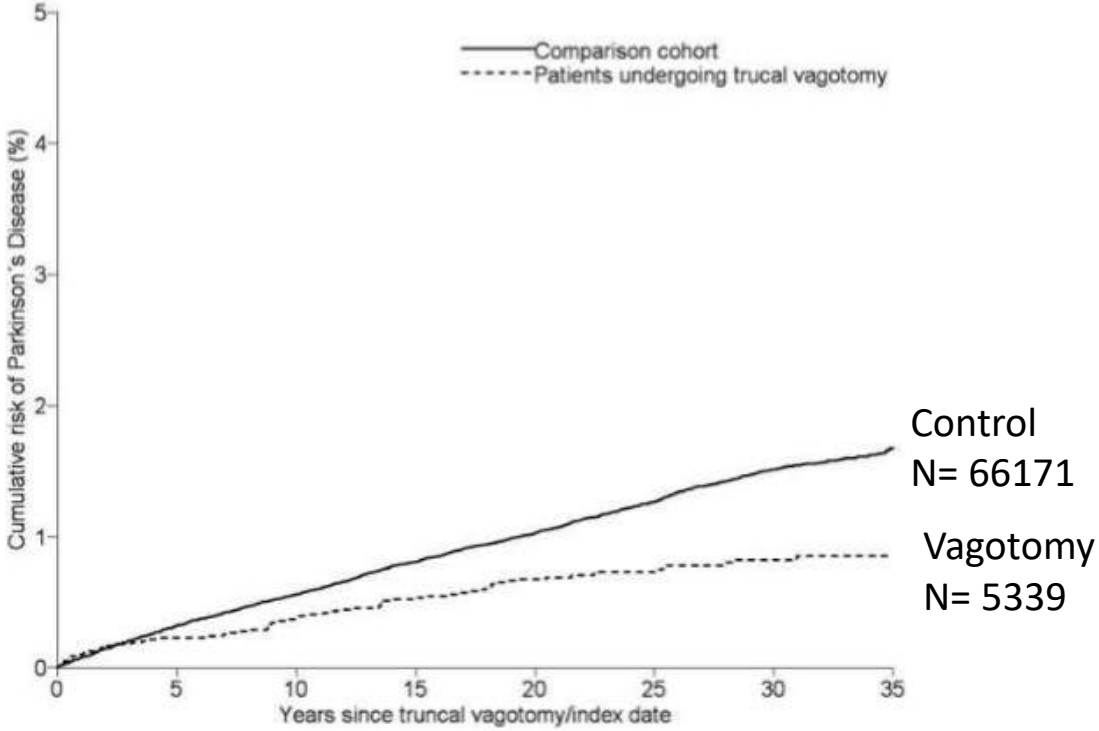
Evans et al., *Mol Cell* 2015

Gavage once weekly for 2-3 months with E Coli +/- curli

Chen et al., *Scient Rep.*, 2016

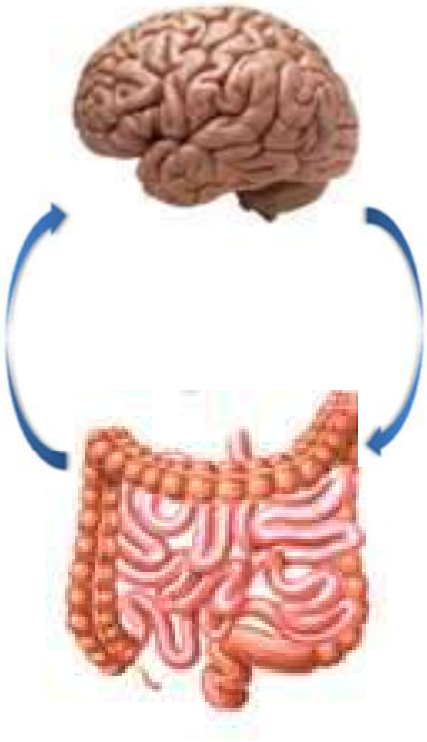
Isolating the gut from the brain reduces the risk of developping Parkinson's disease





Svensson et al.,*Annals of Neurol 2015*

Are psychiatric also diseases of the gut (and microbiota)?
Example 2 : Autism



Symptoms
- Diarrhea
- Bloating
- Constipation
- Abdominal pain
- Reflux

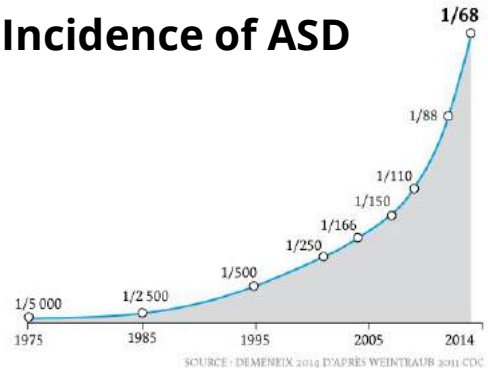
Nb of digestive symptoms*/ child	Children with ASD	Age-matched siblings
0	19.8	70.5
1	16.4	18.2
2	24.1	4.5
3	25	4.5
>=4	14.7	2.3

64 %

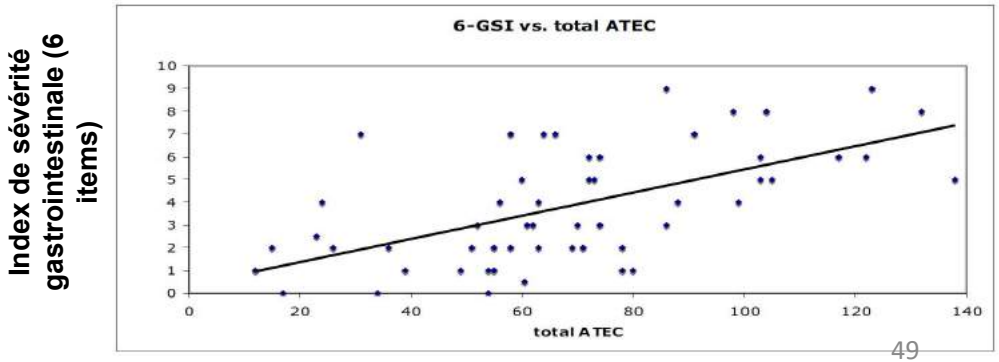
11%

Horvath and Perman, Current Opinion in Pediatrics (2012)

Incidence of ASD

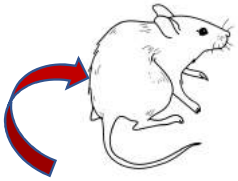


Adams et al. BMC Gastroenterology 2011

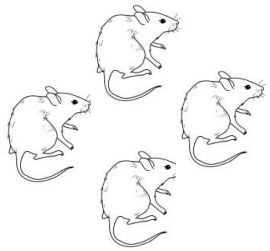


Autism is associated with altered gut permeability and microbiota composition

Pregnant mice



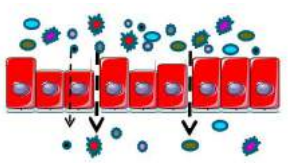
Immune activation
(viral mimic: poly (I:C))

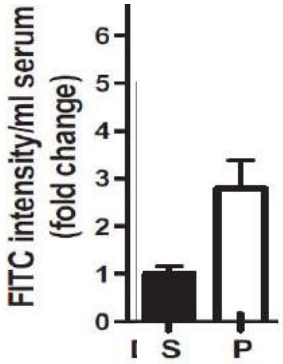


Progeny

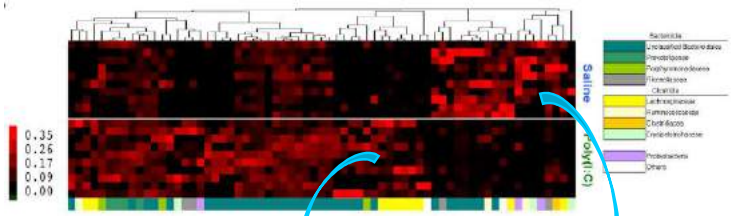
- **↗ stereotypic behavior**
- **↘ social interactions**

↗ gut permeability





Dysbiosis



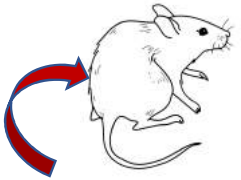
Bacteroidia et Clostridia

Proteobacteria

Hsia et al.,*Cell, 2013*

Reinforcing intestinal barrier with a probiotic prevents in part autistic symptoms

Pregnant mice



Immune activation
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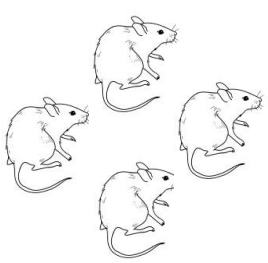
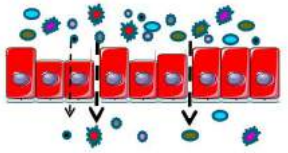
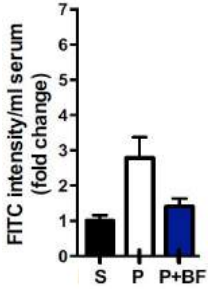


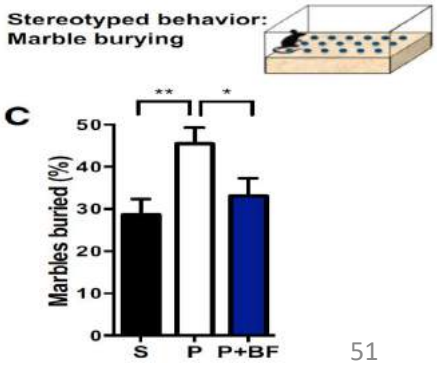
bacteroides fragilis
(anti-inflammatory effects)



Restauration of intestinal pemeability

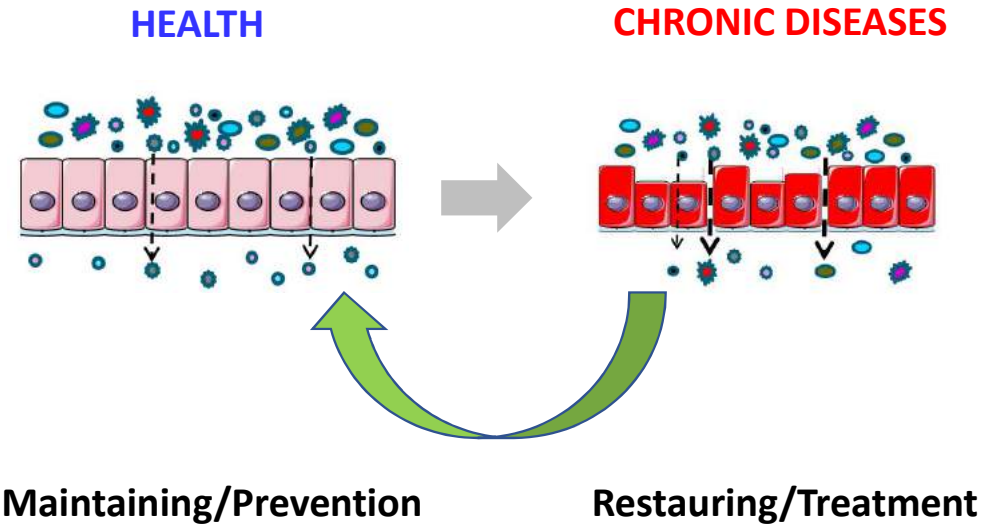


↘ stereotypic behavior

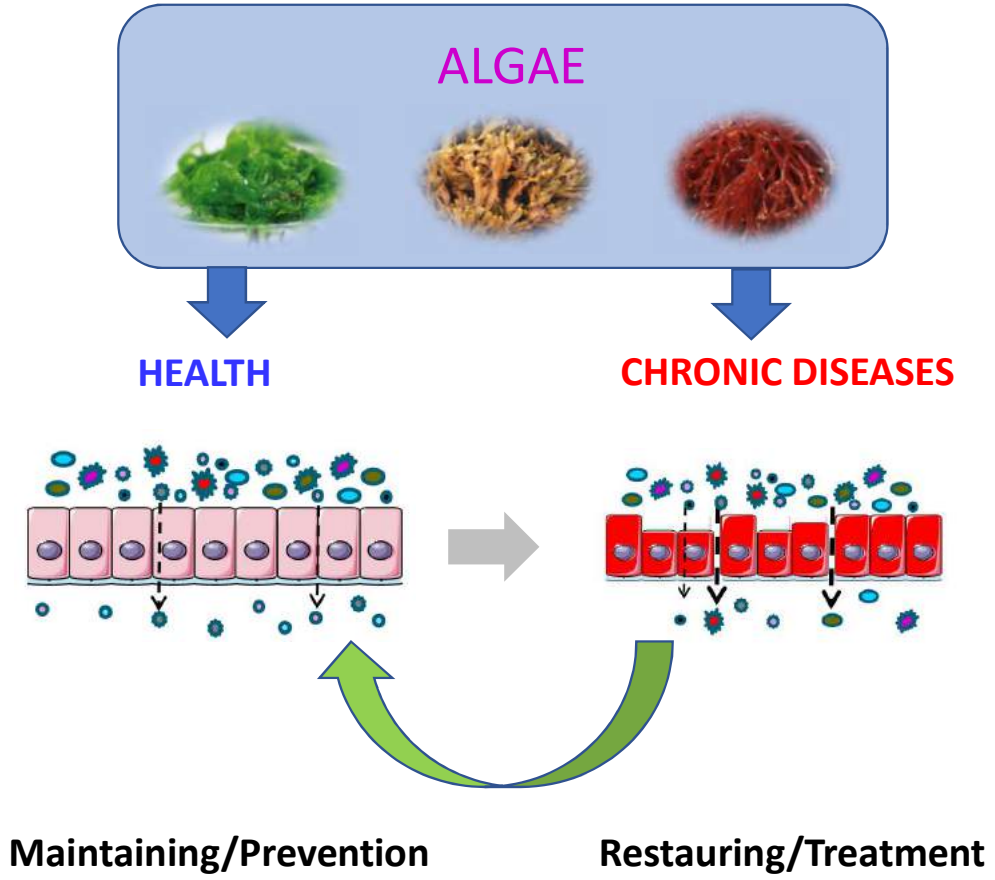


Hsia et al.,*Cell, 2013*

Conclusion Perspectives: Maintaining/restauring gut health to prevent and/or treat chronic diseases

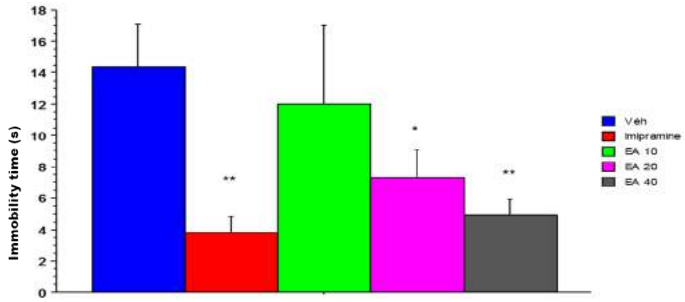


Conclusion Perspectives: Maintaining/restauring gut health to prevent and/or treat chronic diseases

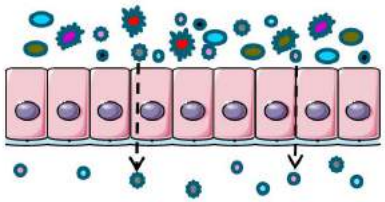


Conclusion Perspectives: Maintaining/restauring gut health to prevent and/or treat chronic diseases

Ulva armoricana



Violle et al. *Nut Neuroscience* 2017



- ↘ Gram-positive and Gram-negative bacteria growths
- ↗ intestinal epithelial cell innate response

Berri M *et al.*, *J Appl Phycol* 2016

TENS Inserm U1235

Inserm U1235 TENS

INRA UMR 1280 Phan
UMR Senah

JP Segain
G Boudry

Harvard Medical School

G Tearney
A Goldstein

Institut Pasteur

P Sansonetti

TECHNISCHE UNIVERSITÄT MÜNCHEN

M Schemann

ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA

G Barbara
R de Giorgio

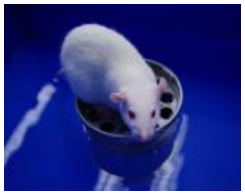
Single bacteria (*L. fermentum*) modulate gut brain axis response to stress

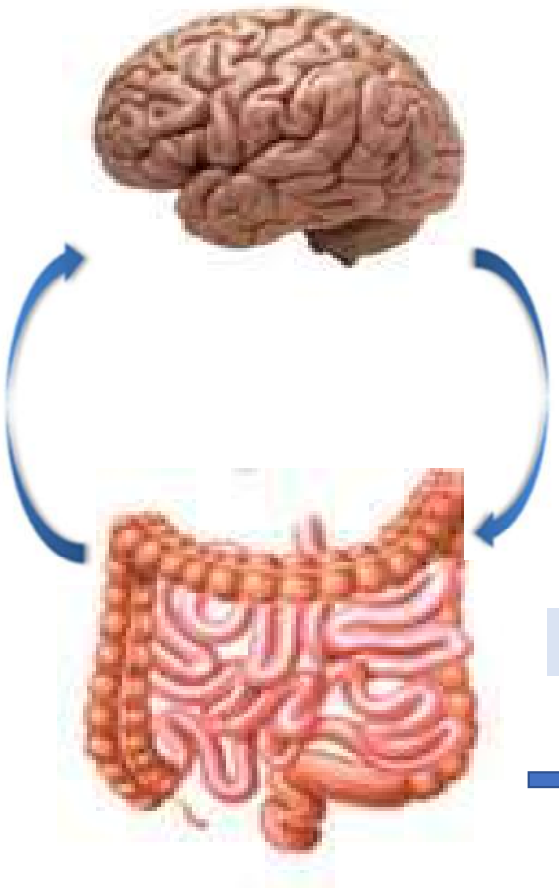
L fermentum

P1 P21 P36

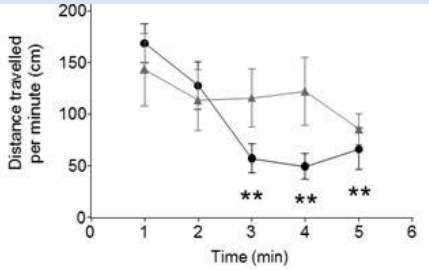
Weaning

± stress

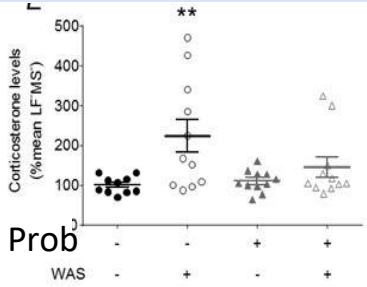




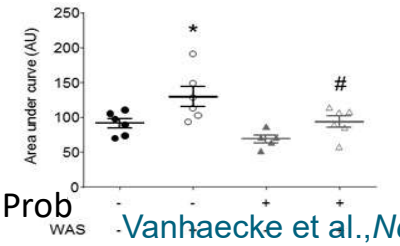
Bacteria increases exploration



Bacteria reduces stress induced HPA activation



Bacteria prevents stress induced barrier dysfunction



Vanhaecke et al., *Neurogastro Mot* In Press

Thank you
for your attention!

olmix Group