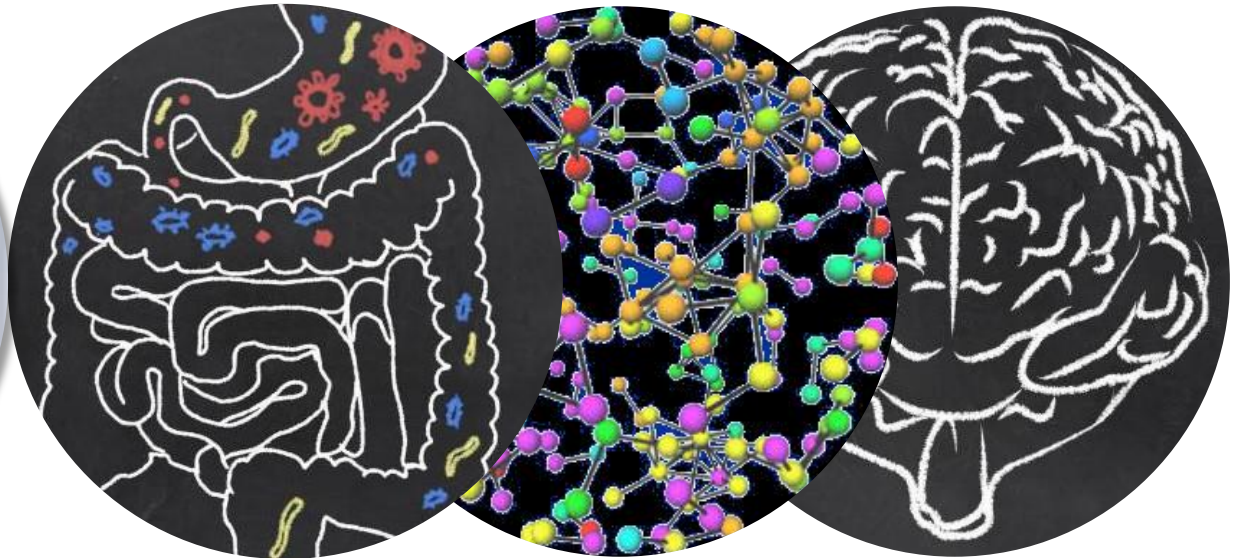


Microbiome-Gut-Brain communication

Mini-symposium “*Gut to Brain*”
informal farewell to Mari Smits

May 15, 2017
Impulse



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Wageningen University
Host Microbe Interactomics Group
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Microbiome-Gut-Brain communication

Host-Microbe
Interactomics

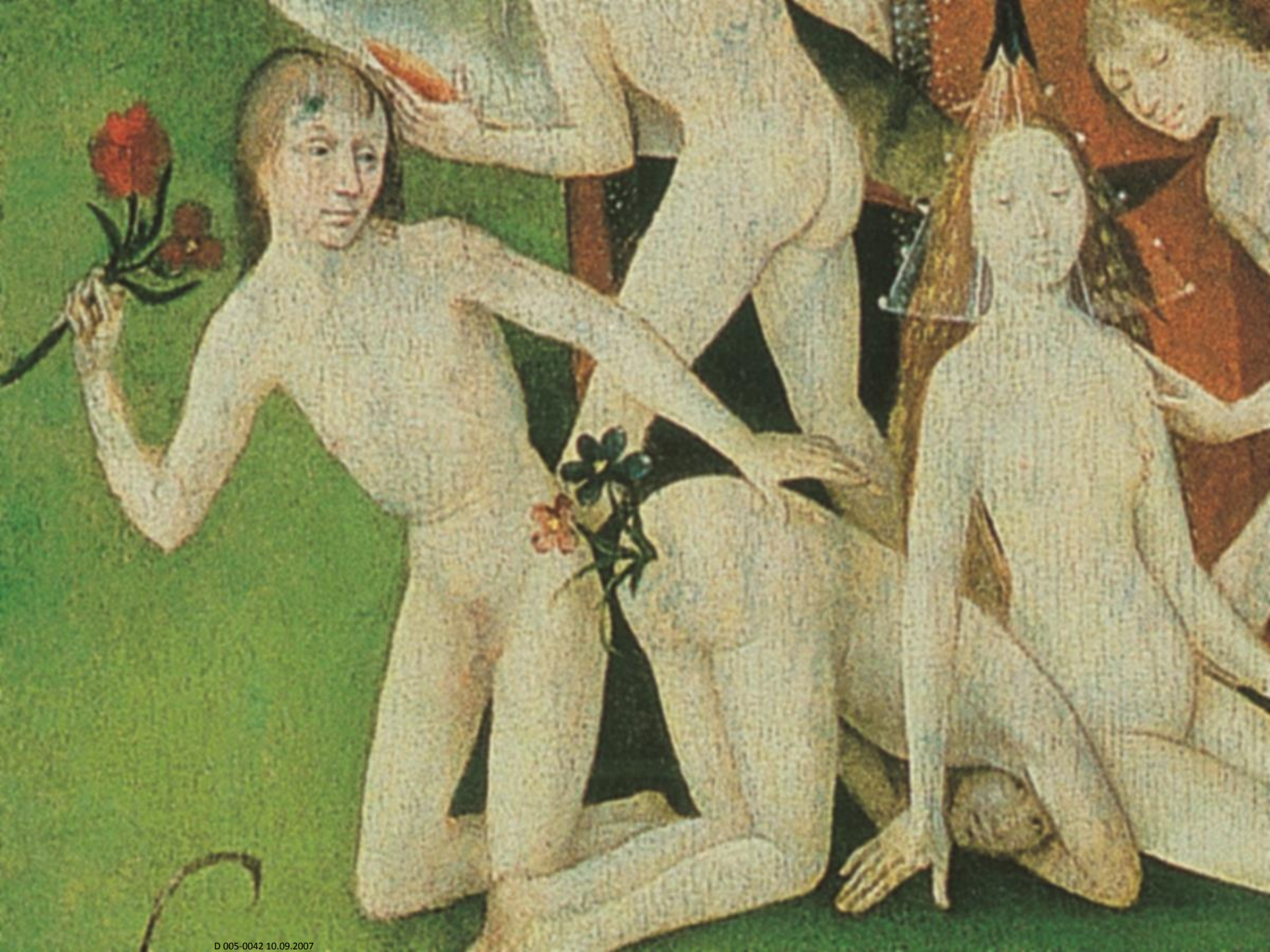




Intestine Microbiota or Intestinal flora







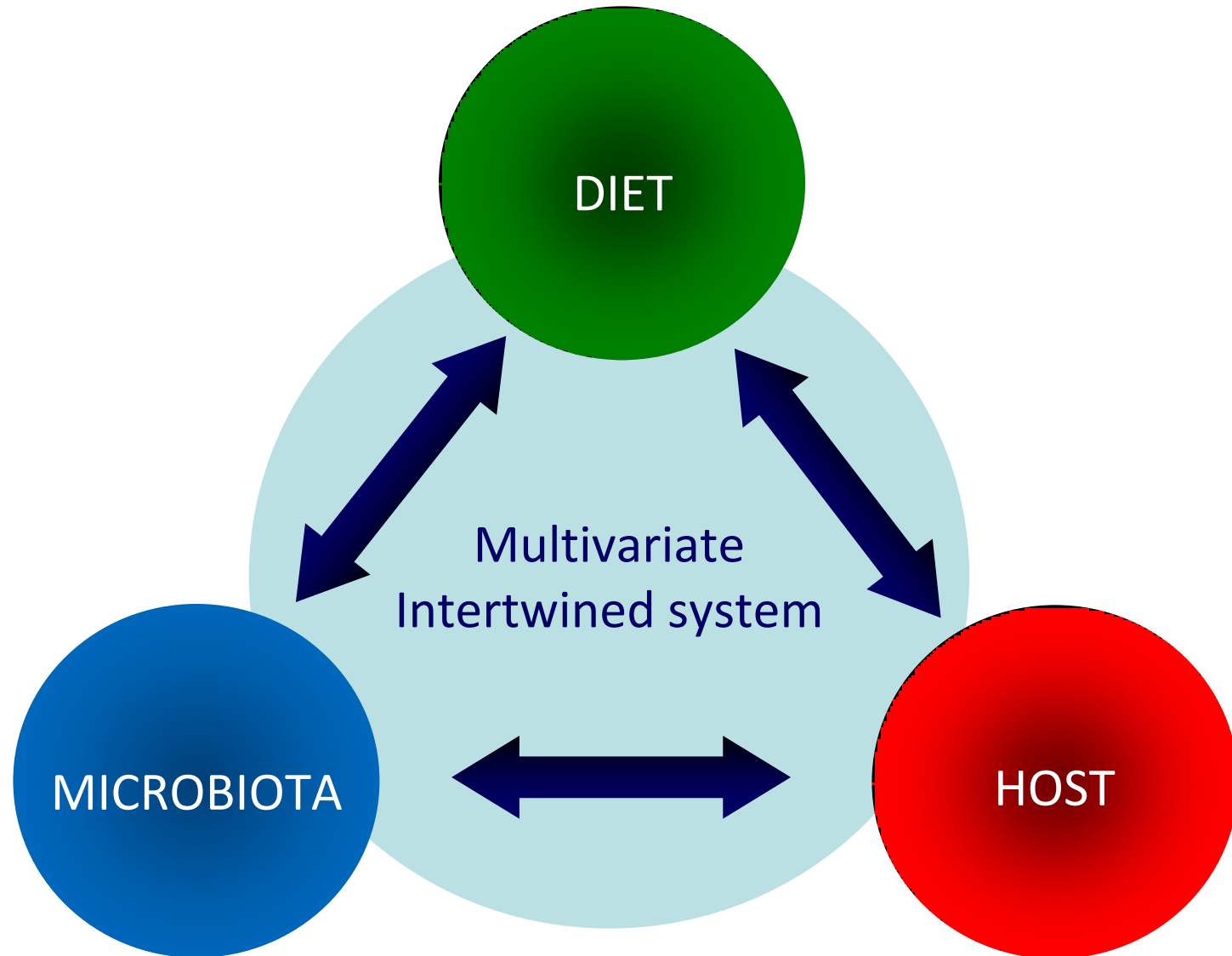


Intestine Microbiota

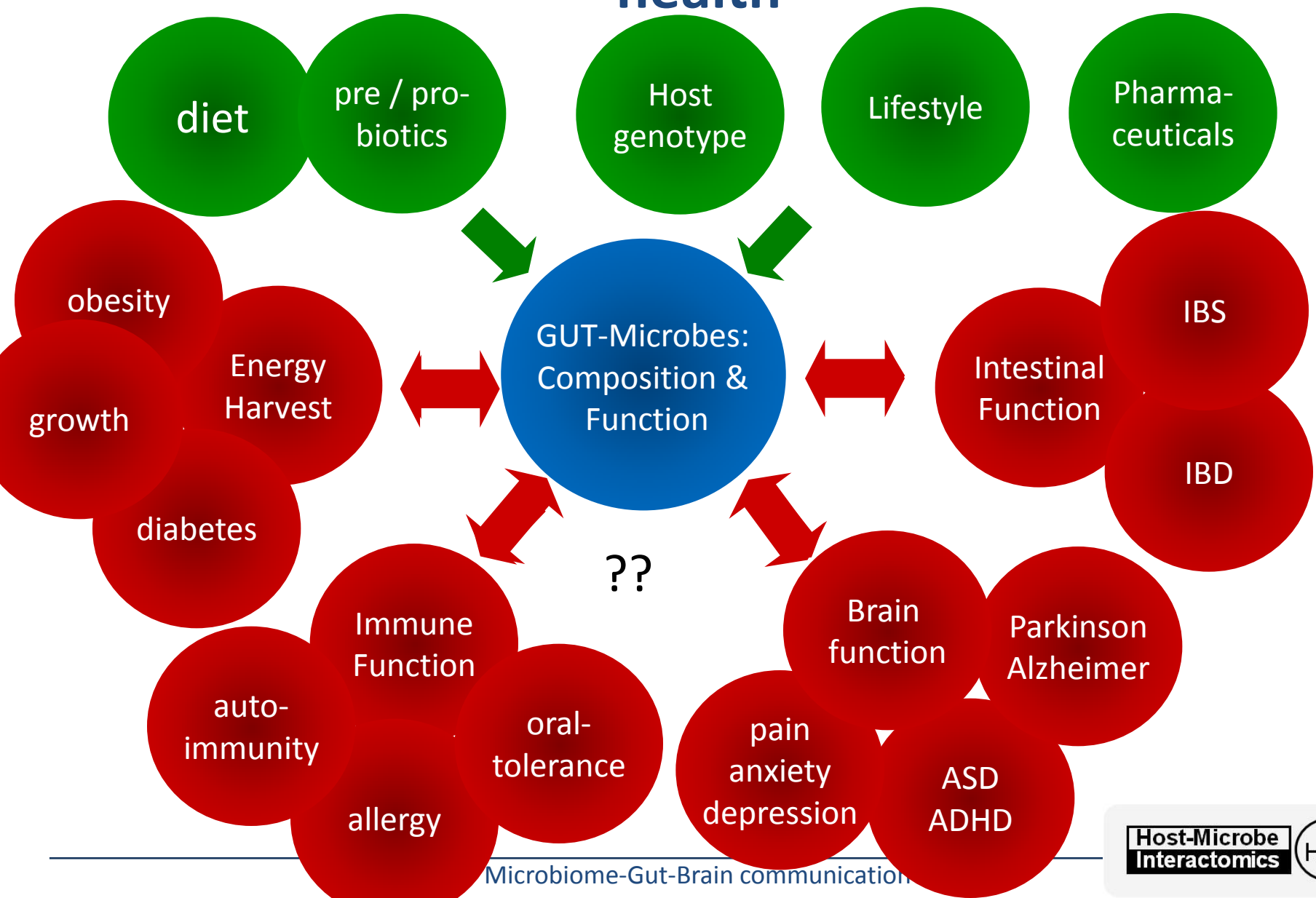
~~Intestinal flora~~



A World of great complexity

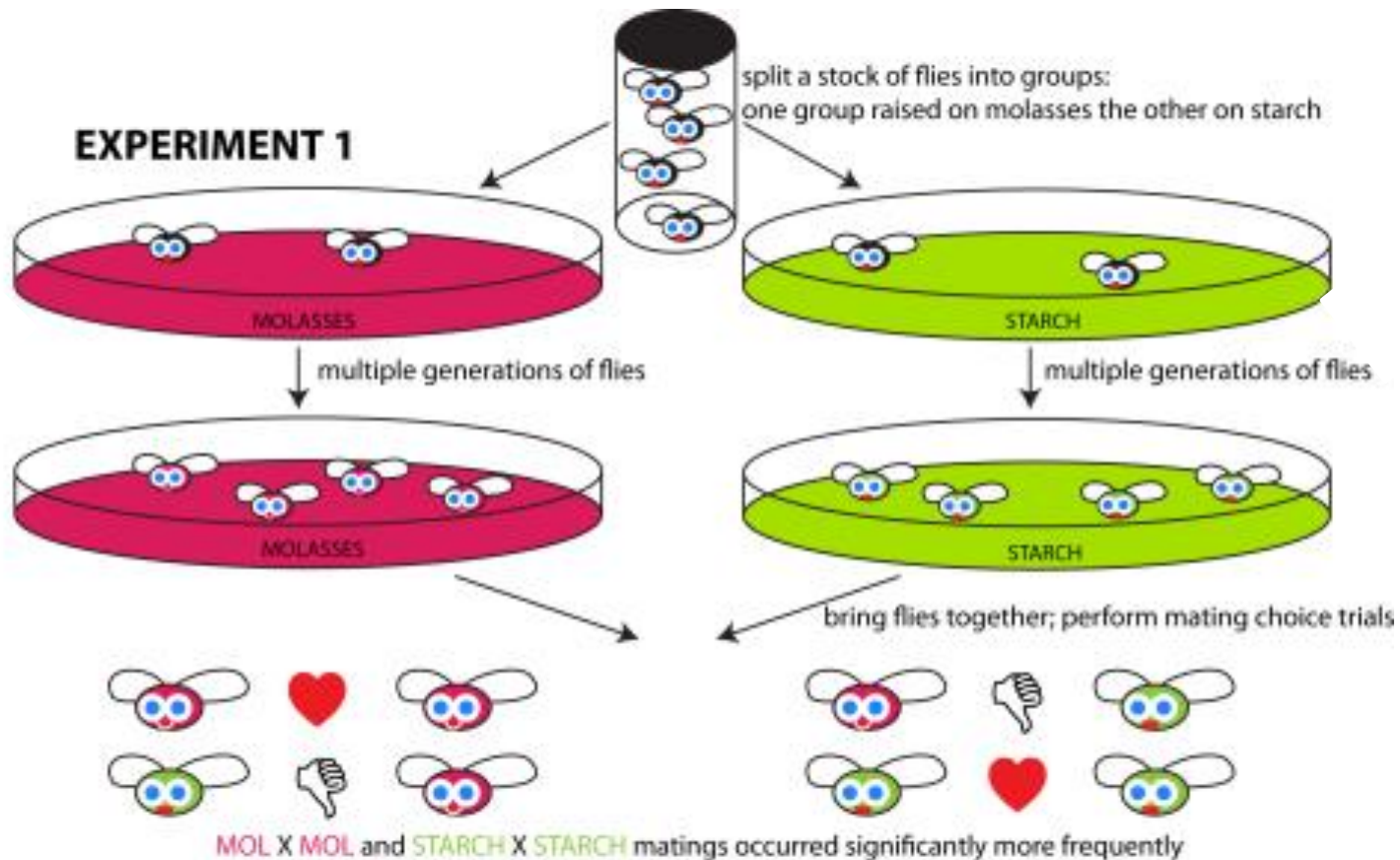


The interrelations of diet, microbiota and host-health



Who is in control.....

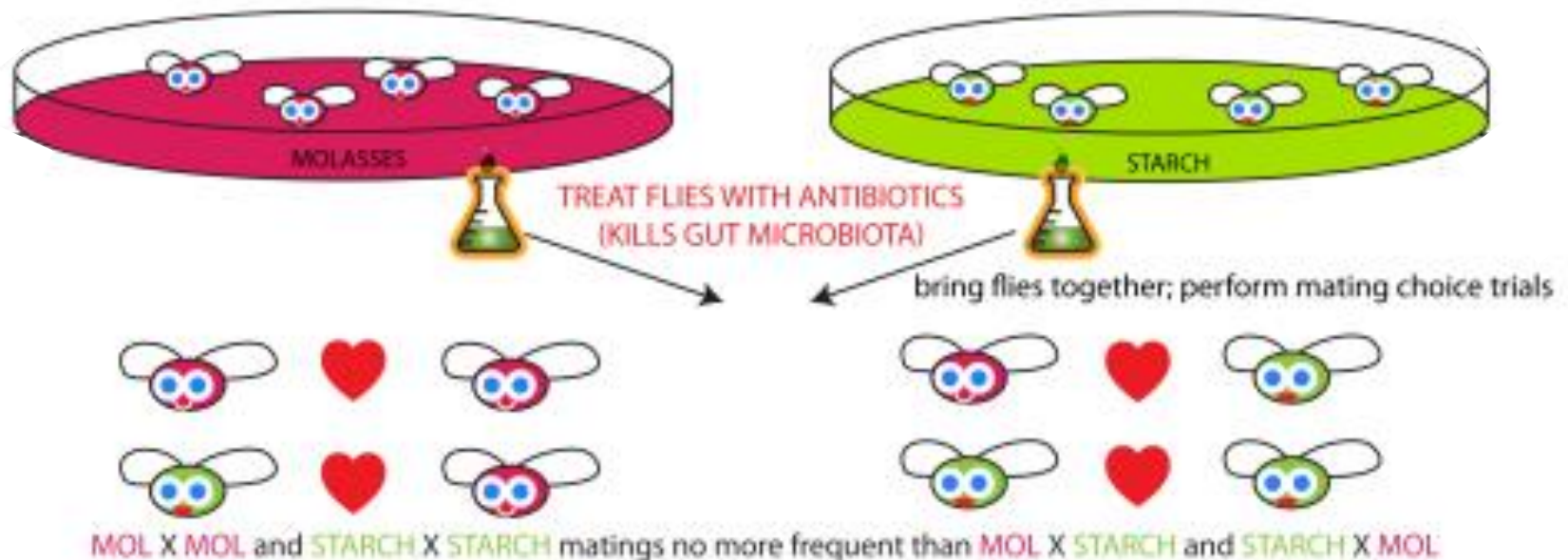
We may learn from *Drosophila* ?



We may learn from *Drosophila* ?

Diet or microbiota ?

EXPERIMENT 2 (same as EXPERIMENT 1, except...)



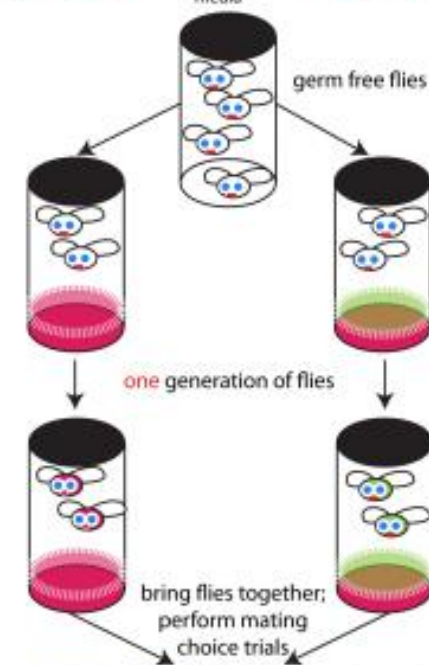
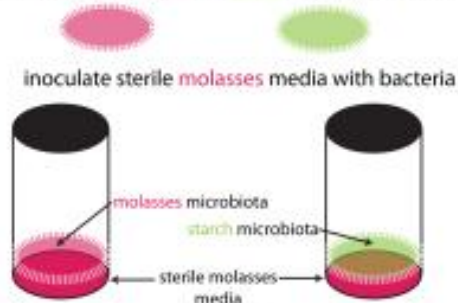
“removing” microbiota eliminates mate choice preference

Is the microbiota a causal factor in mate choice ??

We may learn from *Drosophila* ?

Microbiota determines mate-choice.....

isolate bacteria from molasses and starch media flies were reared on



MOL X MOL and STARCH X STARCH matings occurred significantly more frequently



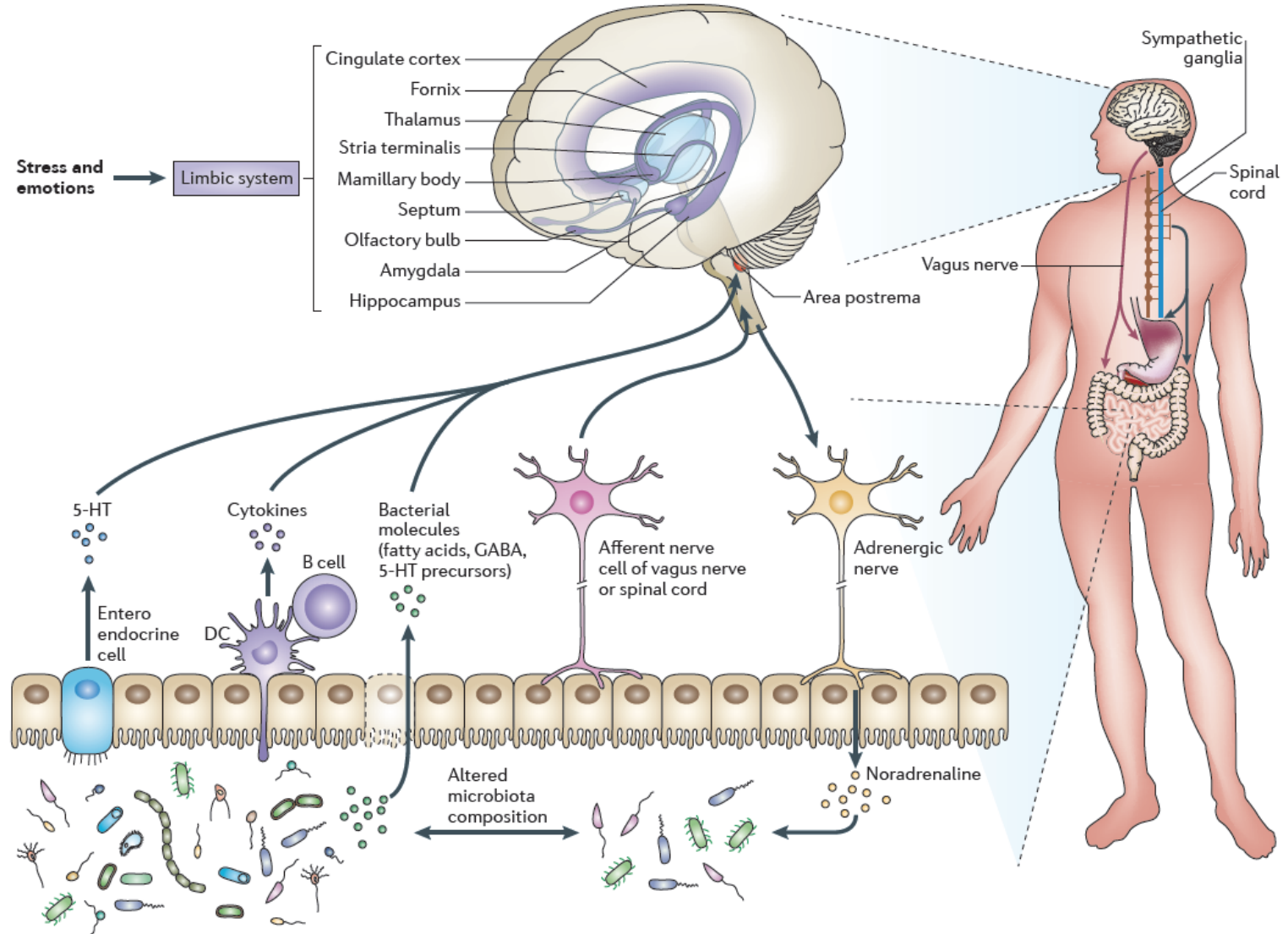
- Microbiota from molasses and starch media isolated
 - Inoculated in sterile molasses media
 - Germ free flies grown on molasses media, with distinct microbiotas ('fecal transplantation')
 - Mating preference, similar to distinct media culture; driven by the distinct microbiota.....
-
- Many comments in editorials of journals:
 - What if this would also work in human ?
-
- Rob Knight in Cell editorial:
"I consider storing my fecal material to transplant into myself after my next antibiotic treatment, it may prevent me wishing to leave my partner"

Rapidly emerging association of microbiota dysbiosis and brain function

‘Altered’ microbiota composition observed in people with:

- Alzheimers disease
- Parkinson’s disease
- Depression
- Cognitive performance in elderly
- Schizophrenia
- Attention Deficit Hyperactivity Disorder (ADHD)
- Autism spectrum disorder (ASD)
-

Communication along the gut-brain axis

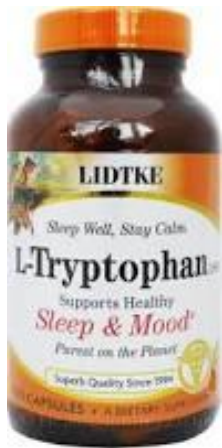


Chemical communication, food derived neurotransmitter (precursors)

Neurotransmitter molecules or their precursors are present in our diets
They can also be produced / converted by the microbiota

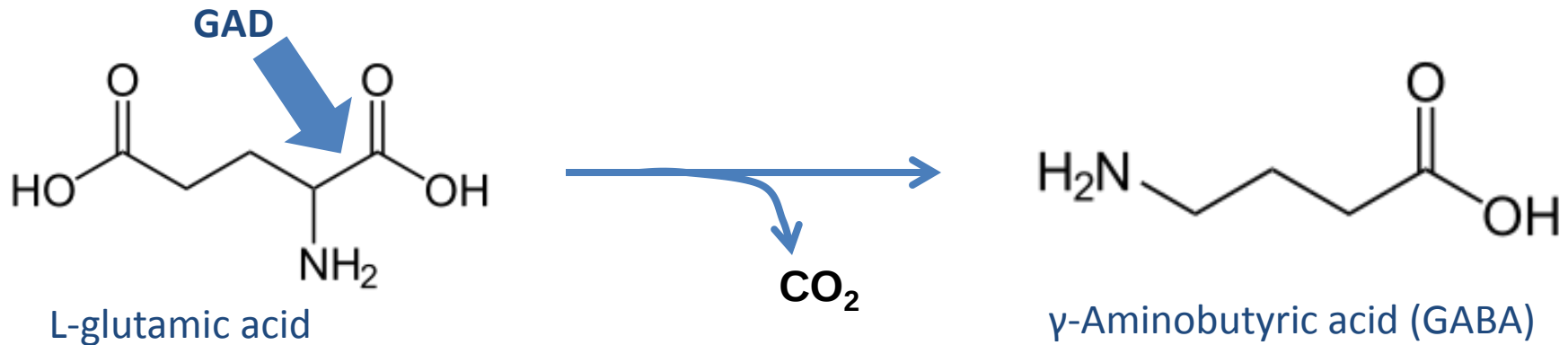
Key examples are Tryptophan metabolism derived products and glutamic acid derived GABA

Basis for so-called MOOD-FOODs & supplements



The importance of chemistry !

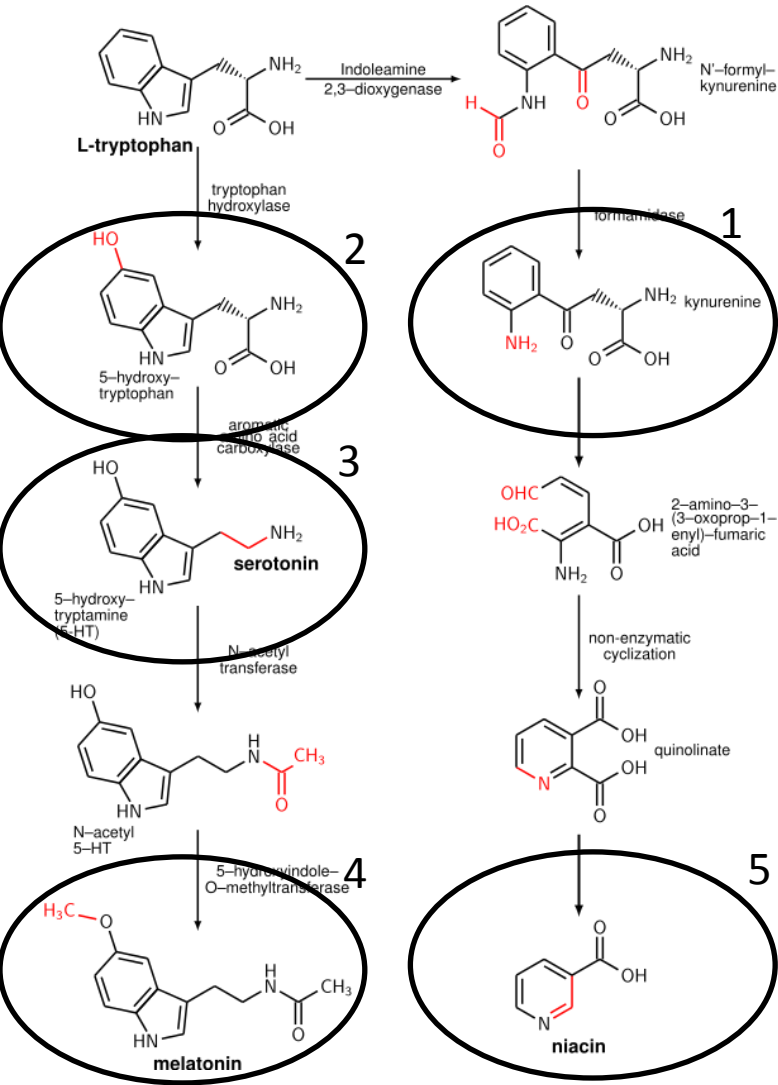
GABA & Tryptophan



- GABA is the predominant inhibitory neurotransmitter in the mammalian central nervous system; GABA reduces neuronal excitability.
- Many bacteria produce GAD activity, and make GABA.

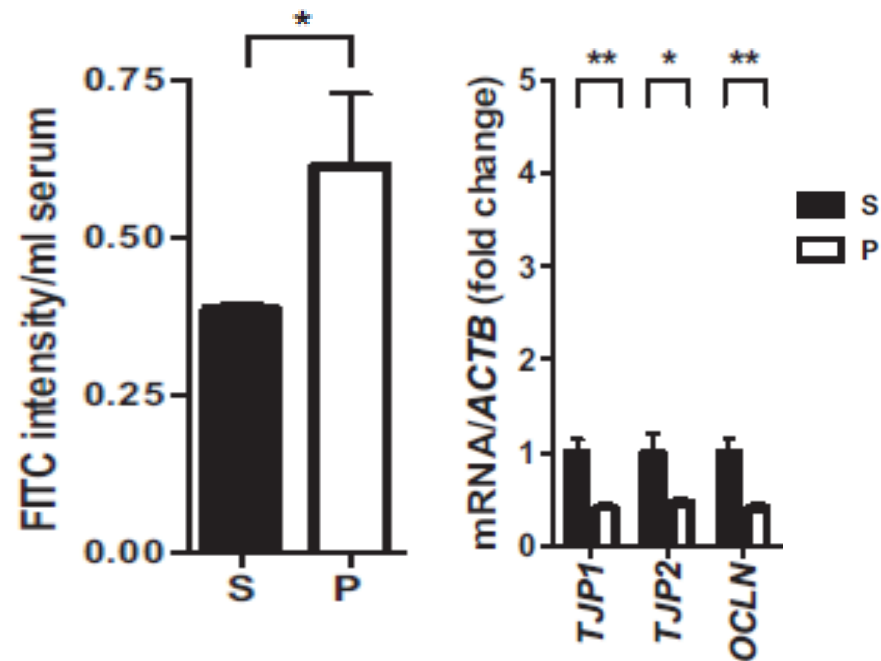
The importance of chemistry !

GABA & Tryptophan

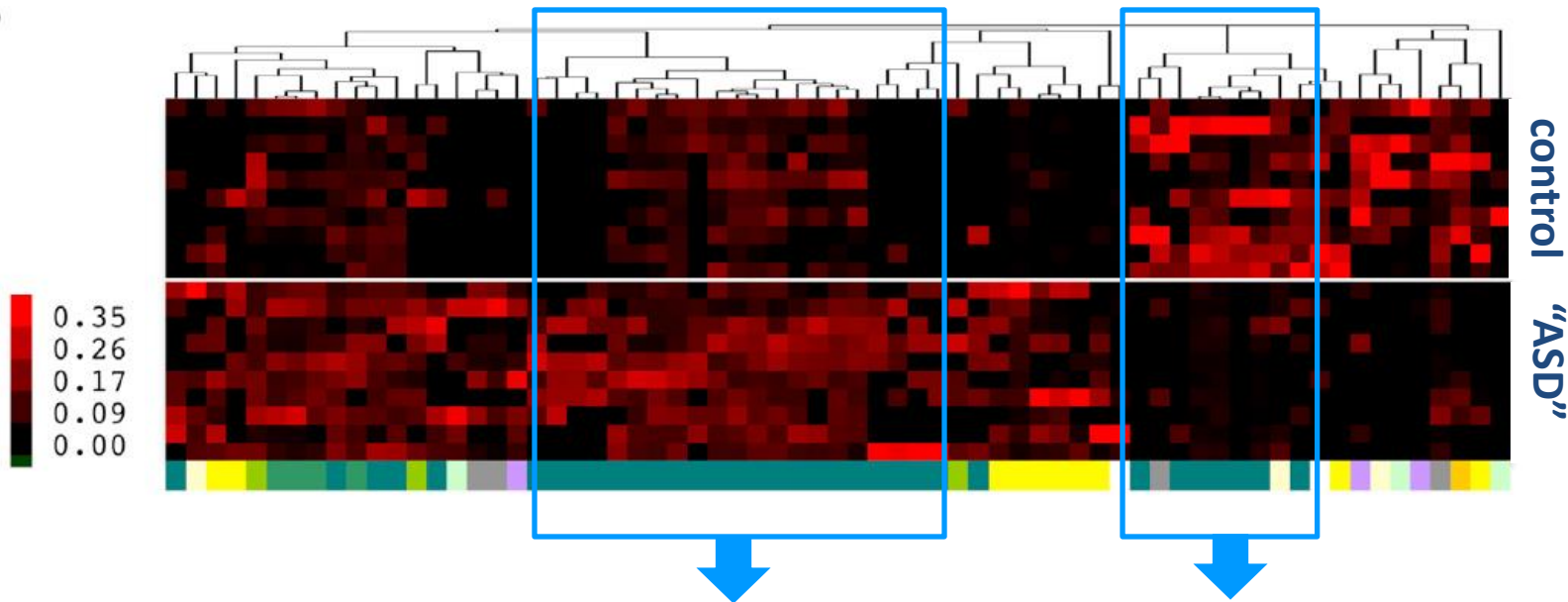


Murine model for Autism Spectrum Disorder

- ASD is associated with enhanced gut-permeability
- ASD children have reduced tight junction expression
- Mouse models based on maternal immune-challenge by poly-IC
- Offspring displays enhanced gut permeability
- Due to decreased tight junction expression



Microbiota dysbiosis in ASD mice



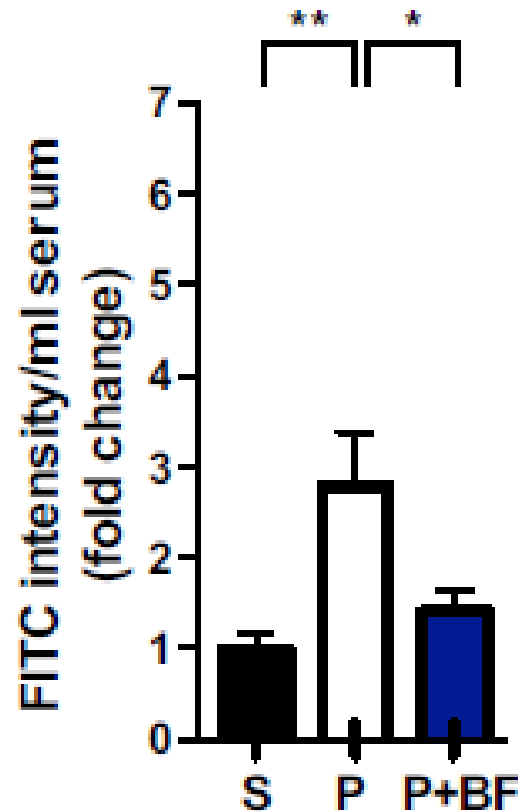
Prominent changes in subgroups of *Bacteroides* spp.
Specific species increase / decrease in this group.
Including 'absense' of *Bacteroides fragilis* / *thetaiotamicron*

Experiment: impact of *Bacteroides* supplement in ASD-mice ?



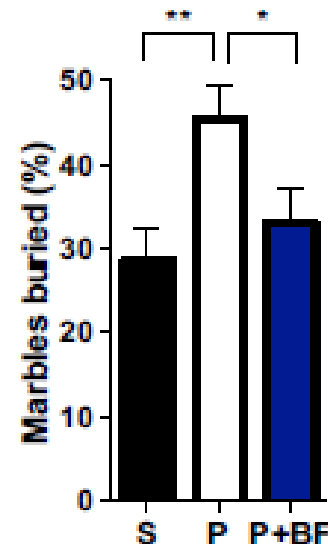
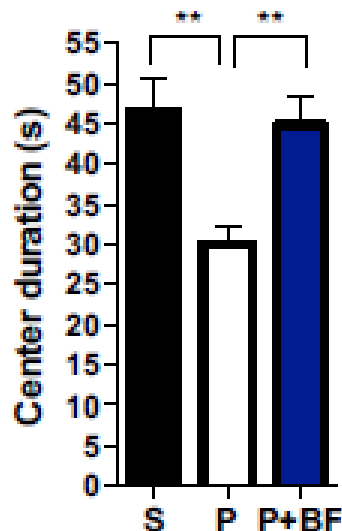
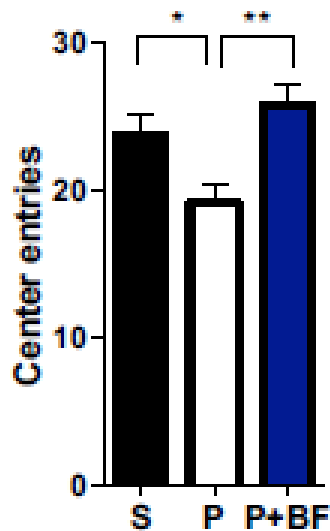
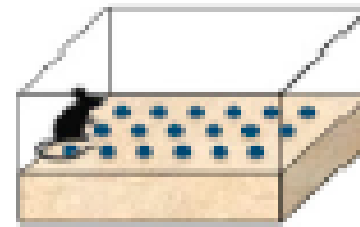
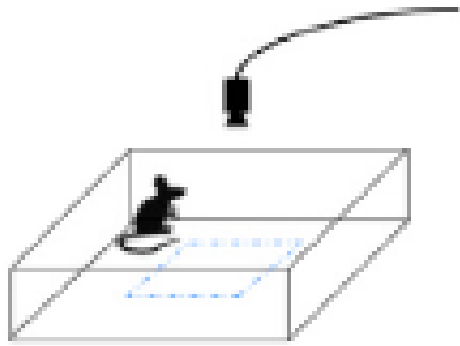
Bacteroides fragilis supplementation in ASD mice

- *Bacteroides fragilis* supplemented by gavage (3/week, 3 weeks)
- Complementation of gut permeability defect
- Complementation of the reduced Tight Junction protein expression



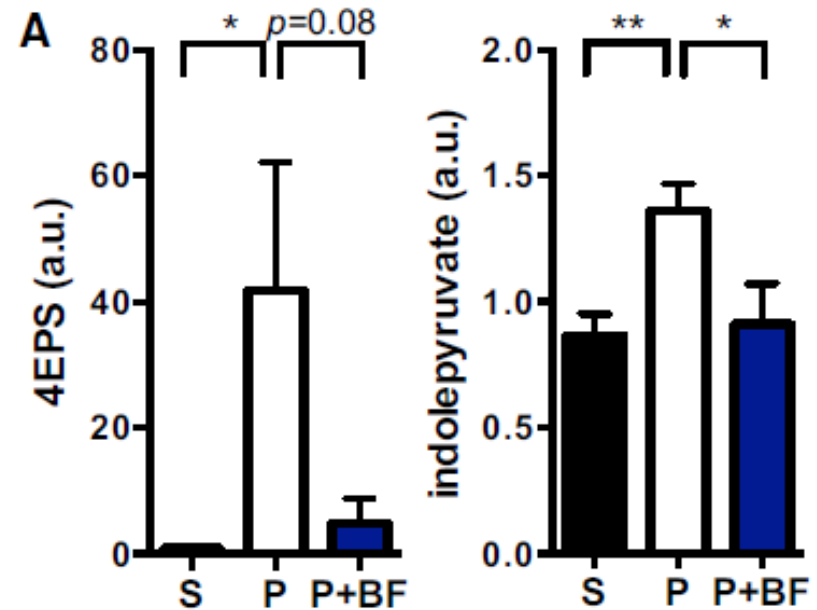
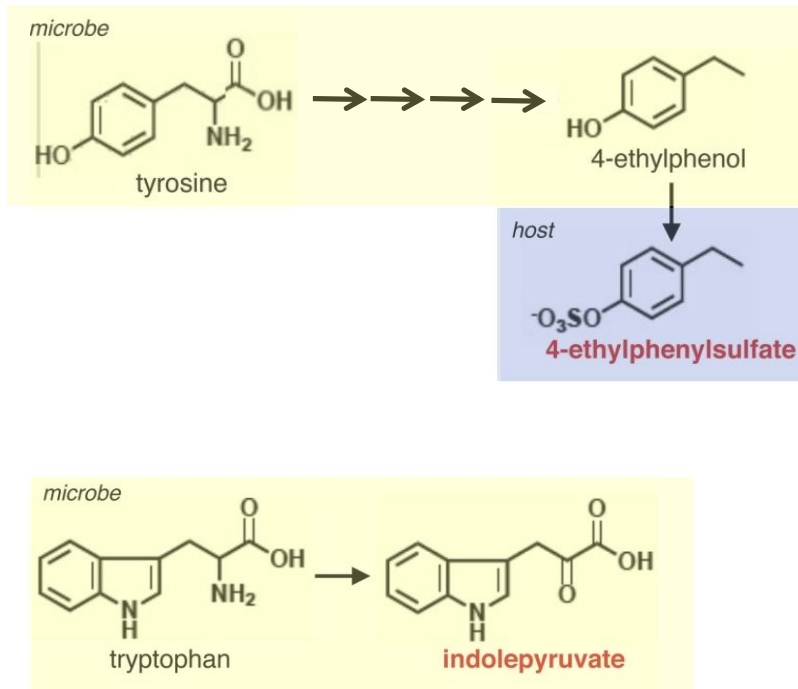
Bacteroides fragilis supplementation in ASD mice

- *Bacteroides fragilis* supplements also complement behavior defects in ASD mice: (1) open-field anxiety test & (2) Marble burying, stereotype behavior test

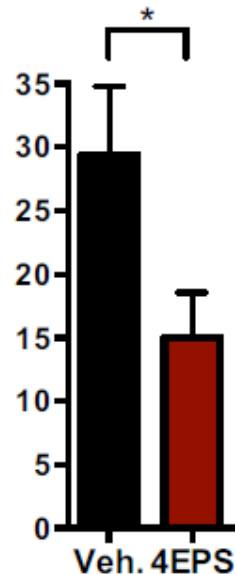
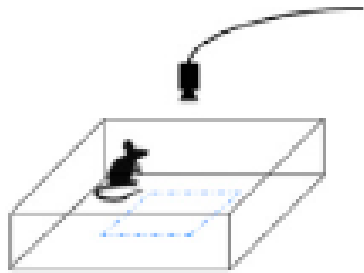


Bacteroides fragilis supplementation in ASD mice

- *Bacteroides fragilis* affects the host's neurotransmitter biochemistry
- Relevance for behavior phenotype ?



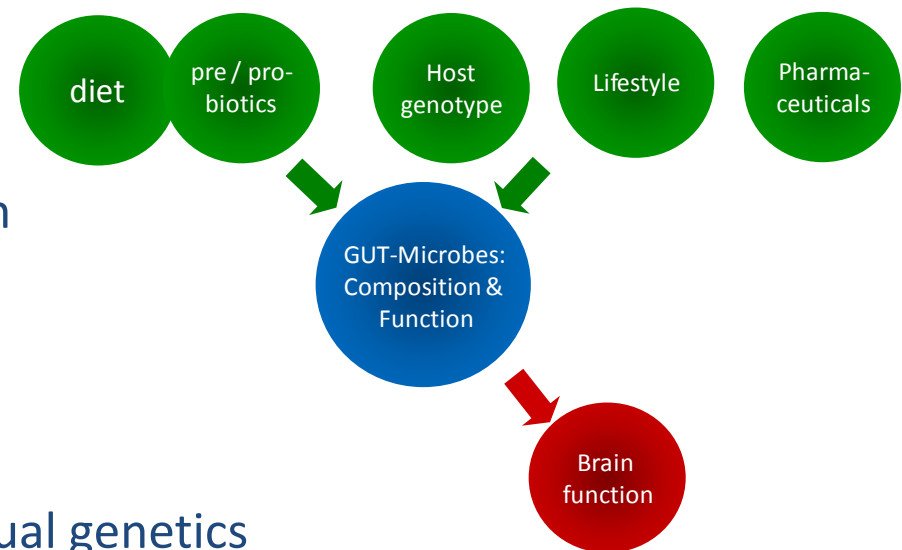
4-EPS injections lead to ASD-like behavior



- ASD mouse model
- Behavior phenotypes
- Microbiota dysbiosis
- Complemented by bacterial supplementation
- Behavior complementation
- Neurotransmitter complementation
- Neurotransmitter causal in behavior
- A single microbial group can make the difference !
- Microbiota impacts behavior
- In this model via neurotransmitter chemistry
- Other papers / models show modulation via:
 - nervus vagus
 - hormone household
 - immune system

What does it mean for domesticated animals ?

- Behavior problems in domesticated farm animals
 - especially in pigs and poultry
 - the most omnivorous among farm animals
- Pig: tail biting
- Poultry: feather picking
 - Detrimental for animal welfare
 - Mutilation measures are common
- Behavior affected by multiple factors
 - physical and social environment
 - diet
 - highly diverse phenotype, individual genetics
- To date, not much attention for the microbiota.....



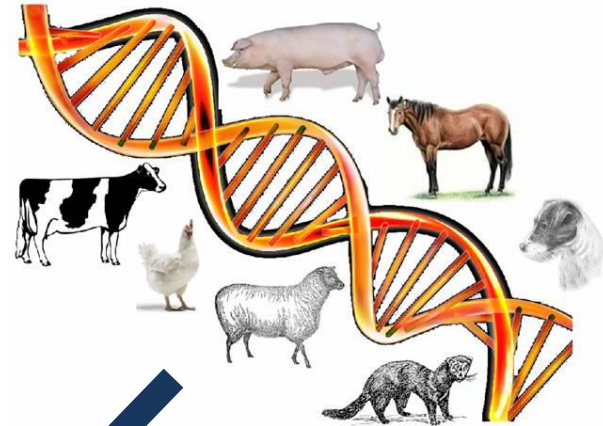
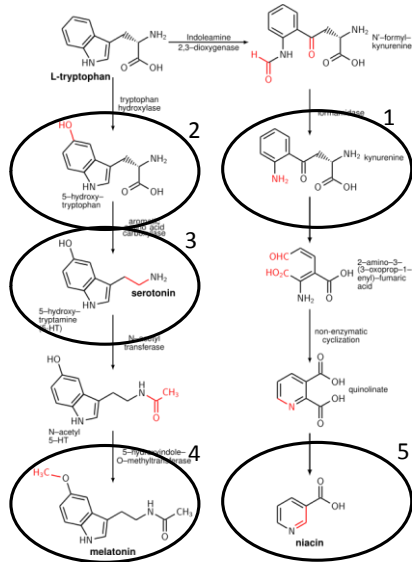
Targeting behavior, to improve animal welfare

- Behavior and intestine / neurotransmitters
 - mucosal morphometry (villus length, crypt depth)
 - absorptive capacity (reduced in jejunum)
 - altered brain development & neurotransmitter levels (various amines)
- Genetics
 - multiple SNPs associated with undesired behavior
 - selection for socially affected traits has been proposed
 - social genetic effects as a selection criterion holds promise
- Diet
 - protein and amino acids; (saturated) fats; refined carbohydrates
- Environment
 - low and high sanitation conditions
 - environmental enrichment

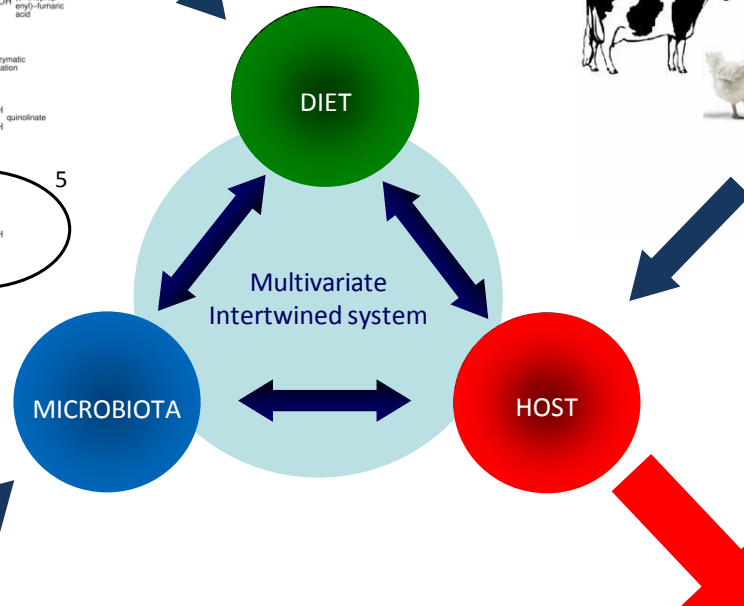
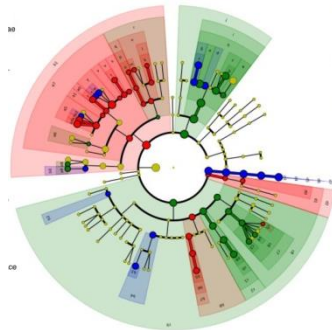
- Barely any information about the intestinal microbiota, or integrative studies

Palander et al. 2013, *Animal* 7:1523; Kops et al. 2017, *Behav. Brain Res.* 327:11; Birkel et al. 2017, *Physiology and Behavior* 175: 88; Grams et al. 2015, *Genet Sel Evol* 47: 77; Ellen et al. 2014, *Frontiers in Genetics* 5:377; Van der Meer et al. 2017, *PLoS One* 12:e0174688; Luo et al. 2017 *Animal* 6:1-8; Van der Meer et al. 2017, *PLoS One* 12:e0174688; van Dixhoorn et al. 2016, *PLoS One* 11:e0161832; Clouard et al. 2016, *PLoS One* 11:e0154698

Microbiome-Gut-Brain communication

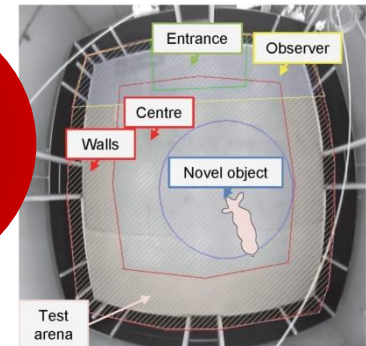


“psychobiotics”



**Behavior
Animal Welfare**

**Brain
function**



**Host-Microbe
Interactomics**

