Disclosure belangen spreker Prof. RJ Brummer

Geen (potentiële) belangenverstrengeling

Voor bijeenkomst mogelijk relevante relaties: Member Scientific Advisory Board Chr Hansen A/S, Danmark

Sponsoring of onderzoeksgeld:	geen
Honorarium of andere (financiële)vergoeding	geen
Aandeelhouder	geen
Andere relatie, namelijk	geen

Hersen-microbiota-darm as –

Van theorie naar praktijk

Robert-J M Brummer MD PhD

Professor of Gastroenterology and Clinical Nutrition. Director Nutrition-Gut-Brain Interactions Research Centre

Pro-Vice-Chancellor, Örebro University, Sweden

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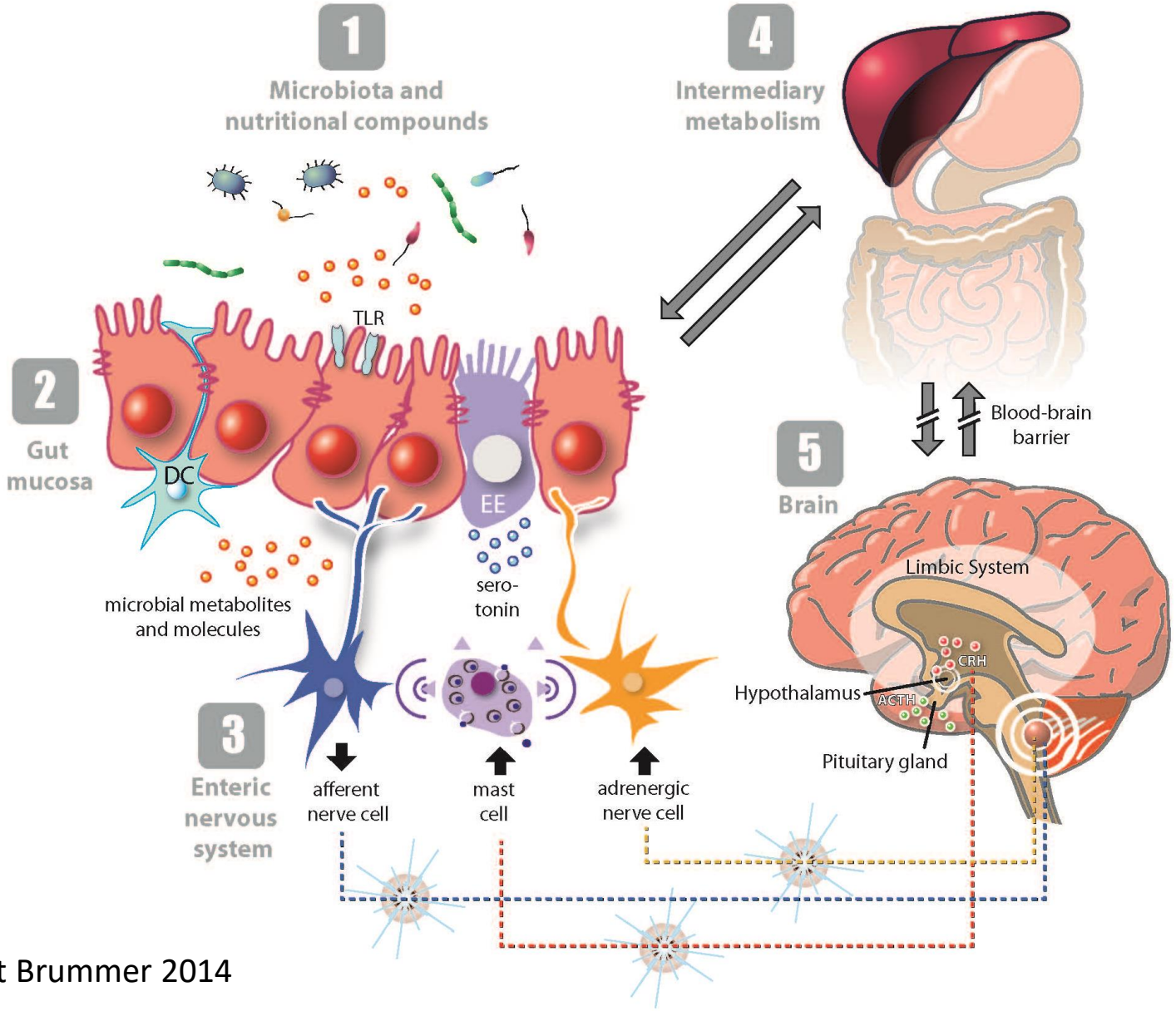
Gut-Brain axis

Components of the gut-brain axis



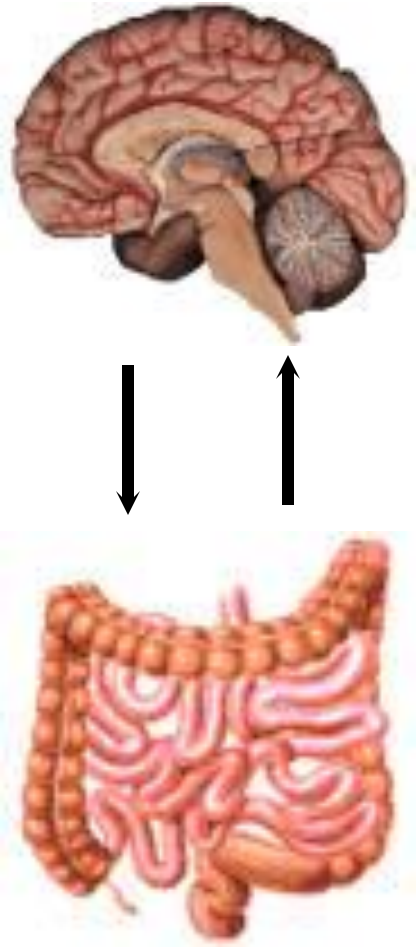
Vraag:

Ik gebruik het concept ”darm-hersen as”:

-nooit
-ongeveer 1 keer per jaar
-tussen 1 keer per maand en 1 keer per jaar
-vrijwel elke maand
-vrijwel elke week

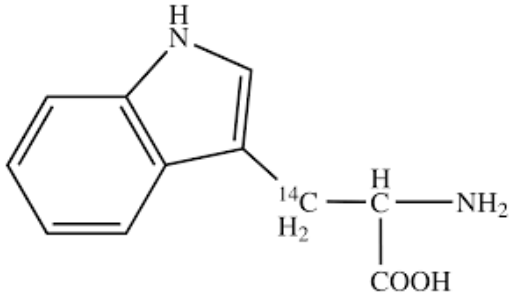
Mediators of bidirectional signalling

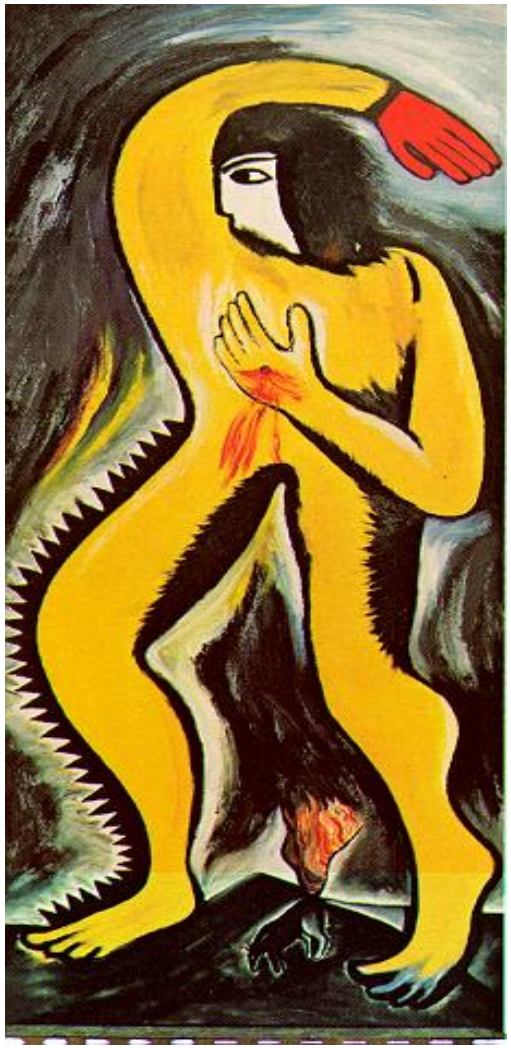
- Serotinin (5-HT)
- Mono-aminergic, opoid and endocannabinoid compounds
- Autonomic Nervous System (*N.X*)
- HPA-axis
- Gut hormones
- Cytokines
- Gut-derived (metabolic) signalling molecules (metabolites/ growth factors, etc.)
- Fatty acids
- ……

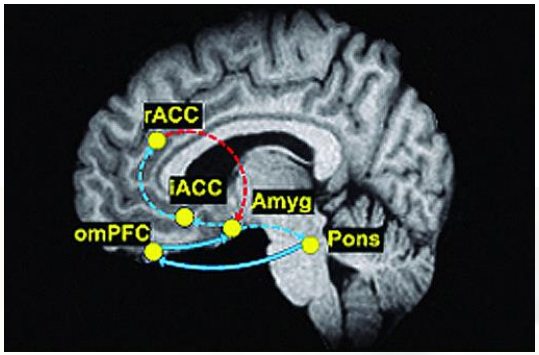


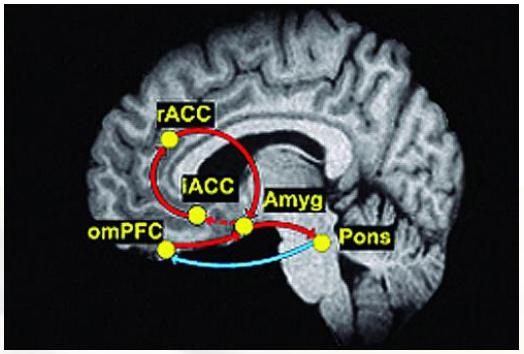
Serotonin (5-HT) as an example:

- 3% in the brain and …
- 95% in the gut, …
- but does not pass BBB
- Tryptophan is the substrate
- Synthesis of 5-HT is affected by inflammation and stress



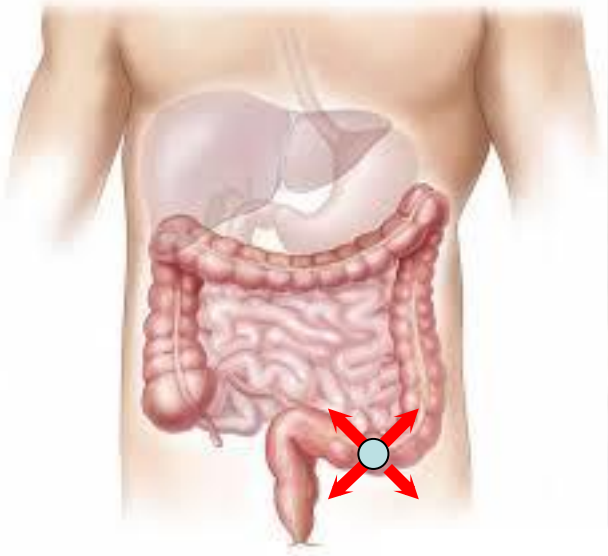


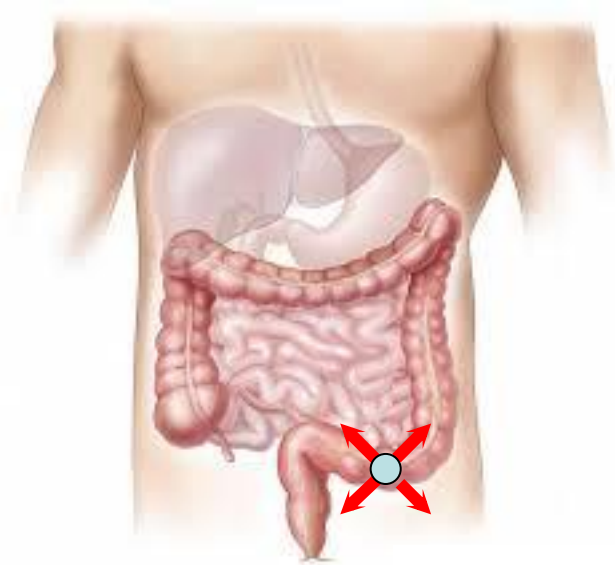




Plac.

↓5-HT





Labus et al Gut 2011;60:1196-203

Serotonin - ATD study

Acute tryptophan depletion affects brain-gut responses in irritable bowel syndrome patients and controls

T O C Kilkens, A Honig, M A van Nieuwenhoven, W J Riedel, R-J M Brummer

Gut 2004;**53**:1794–1800. doi: 10.1136/gut.2004.041657

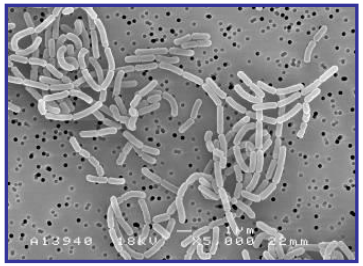
Table 3 Influence of acute tryptophan depletion (ATD) on affective memory performance in diarrhoea predominant irritable bowel syndrome (d-IBS) patients and control subjects

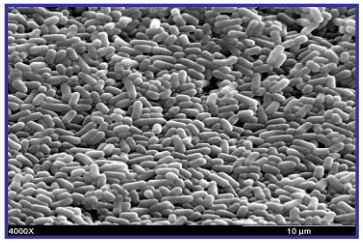
		d-IBS patients	Controls	ATD *v* placebo (p value)
Total immediate recall				
Positive words	ATD	38.4 (4.1)	42.4 (4.2)	0.06
	Placebo	45.3 (3.7)	48.9 (4.4)	
Negative words	ATD	41.7 (2.2)	44.4 (3.3)	0.86
	Placebo	42.0 (4.2)	43.4 (4.3)	
Neutral words	ATD	44.8 (4.3)	50.1 (5.2)	0.20
	Placebo	46.9 (4.4)	56.6 (3.8)	
Delayed recall				
Positive words	ATD	31.6 (5.6)	43.5 (7.4)	<0.005*
	Placebo	46.1 (5.6)	52.9 (7.0)	
Negative words	ATD	41.4 (4.7)	45.3 (6.1)	0.40
	Placebo	44.0 (6.8)	48.2 (7.3)	
Neutral words	ATD	34.6 (5.9)	57.5 (8.4)	0.31
	Placebo	48.6 (7.4)	57.9 (8.7)	

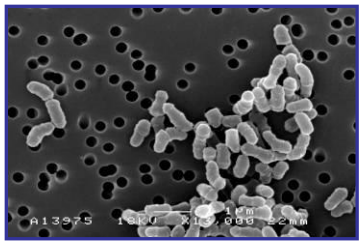
Mean (SEM) percentages of positive, negative, and neutral words recalled immediately (total immediate recall) and recalled after a delay of 30 minutes (delayed recall).
*Significant after Bonferroni correction.

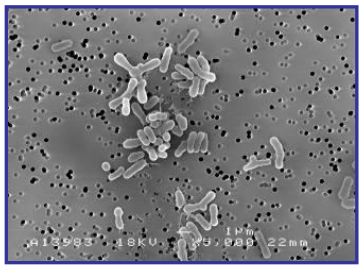
Gut microbiota

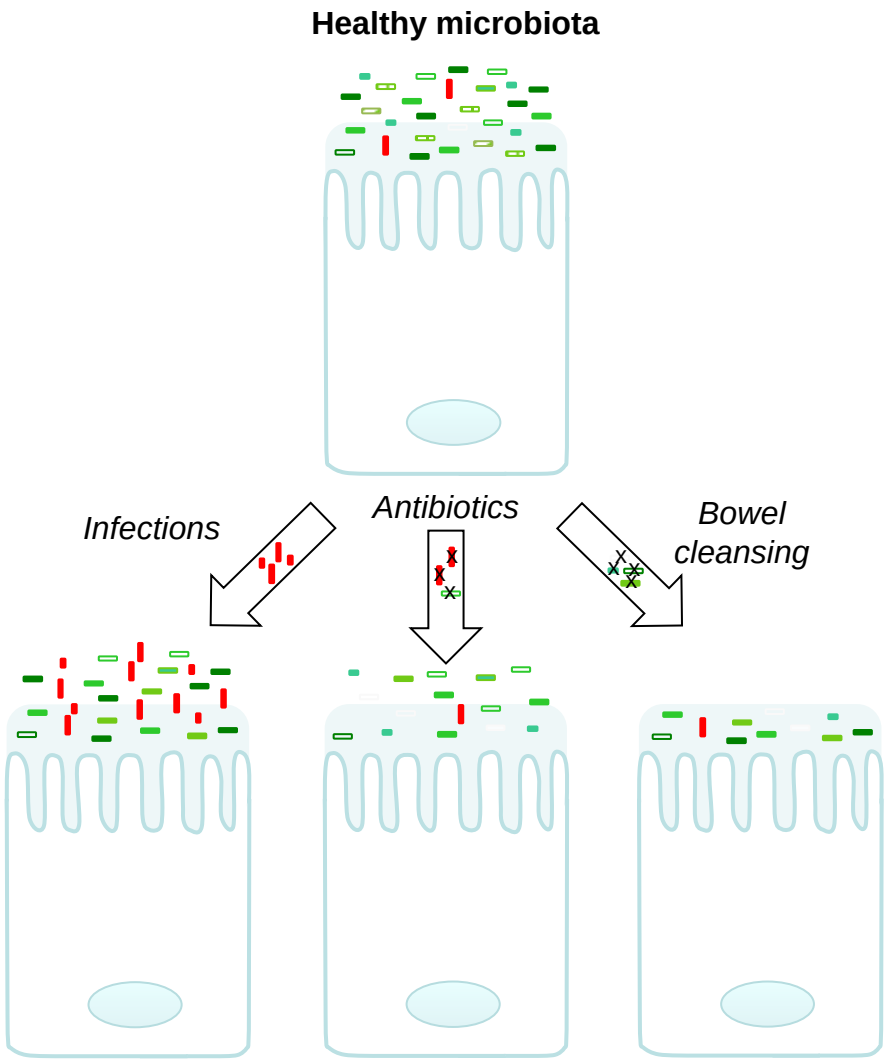
- As many microbes as somatic nucleated cells
- Separate genome
- Most microbes hard to culture
- ‘Ecosystem’
- First years of life are pivotal
- Aberrant composition in many disorders
- Effect on brain function?







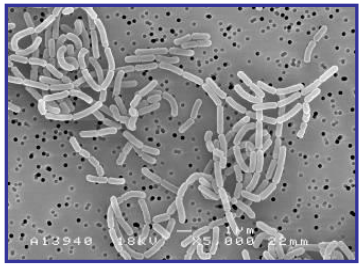


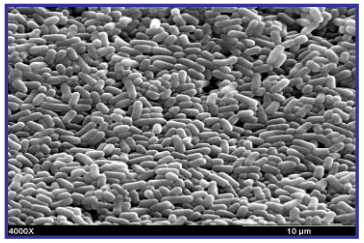


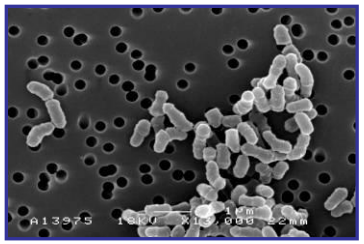
König and Brummer, *Benef Microbes* 2014;5(3) 247-261

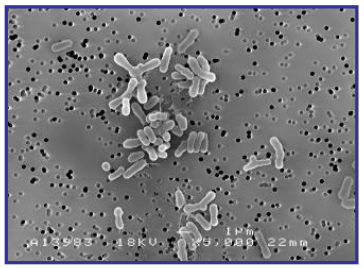
Gut microbiota diversity

- Compositional diversity
- Functional diversity
- Richness
- Metabolic networking
- Resilience
- “catastrophic event”



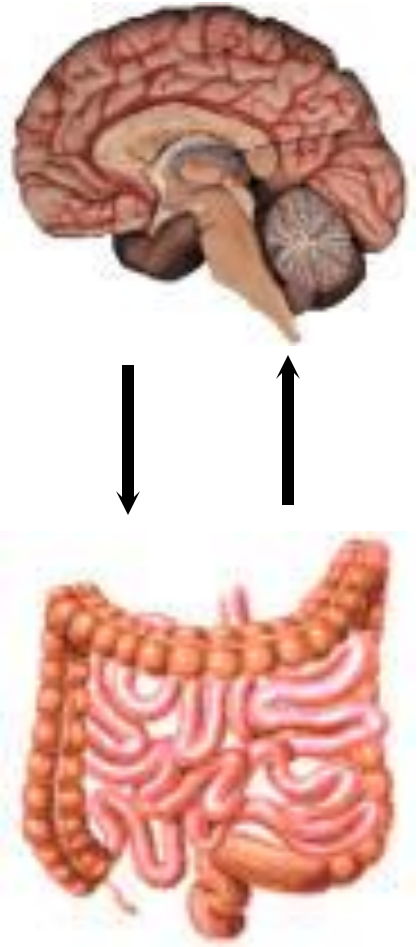






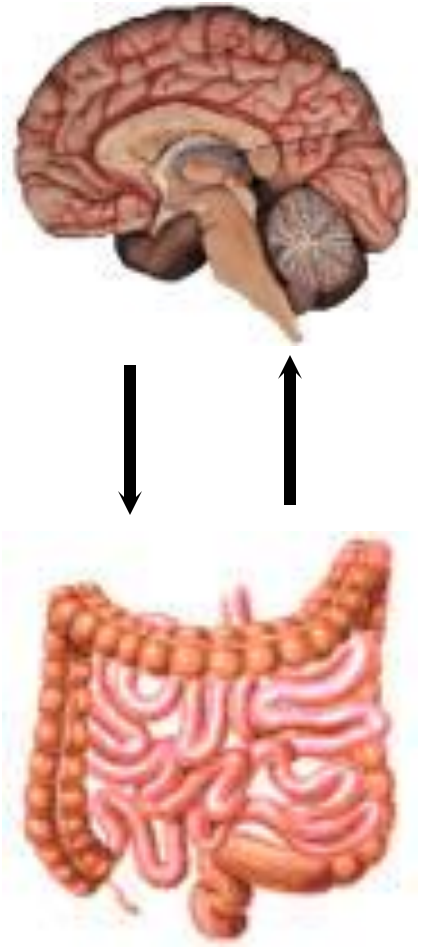
Gut microbiota ➔Brain
mechanistic pathways

- *Direct* microbe-host interactions
- *Indirect* actions mediated by microbial metabolites



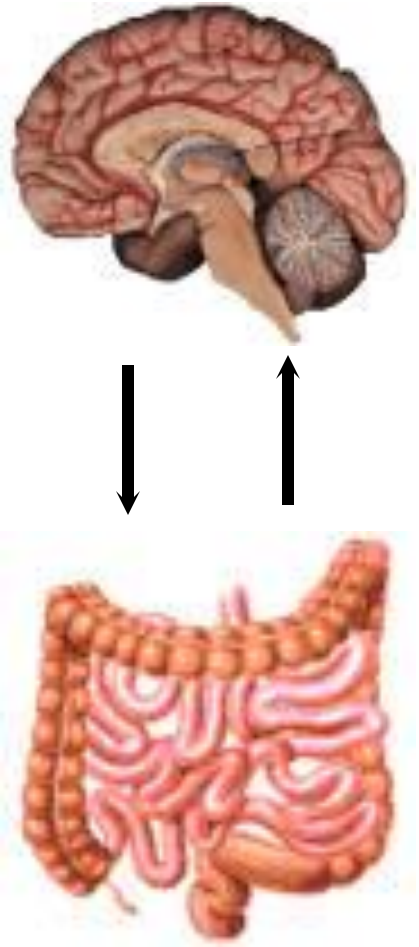
Examples of *direct* microbe-host signalling

- Activation of vagus nerve
- Activation of ENS
- Production of GABA
- Production of 5-HT
- Shift of “eCB tone”
- Modulation of epithelial cytokine production



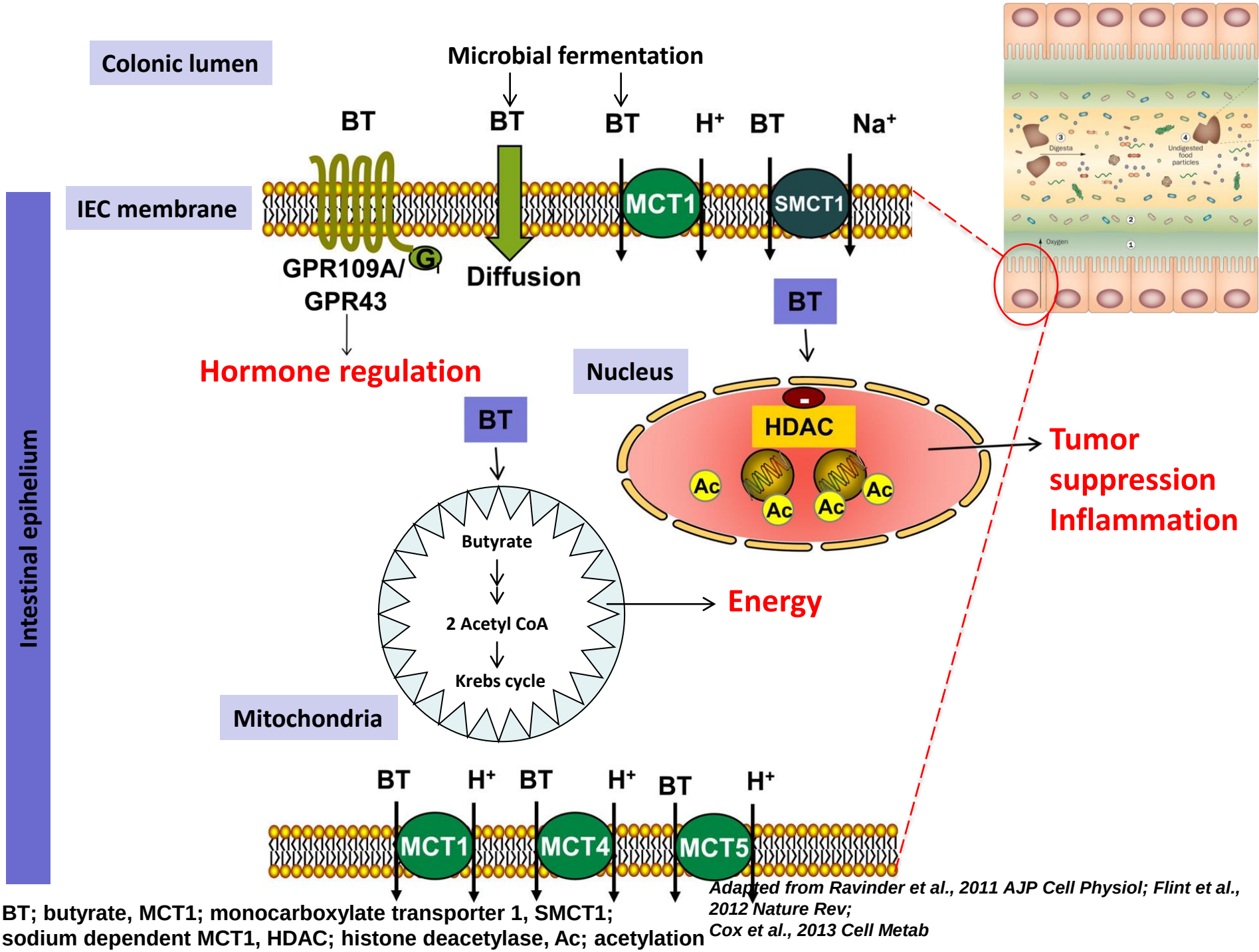
Examples of microbial metabolites that affect gut-brain signalling

- SCFAs including iso-
- Hydrogen
- Methane
- Carbon dioxide
- Ammonia
- Hydrogen sulfide
- *!! Nutrition and metabolic cross-feeding*



Short chain fatty acids

- Activation of GPR41 and GPR43 in e.g. macrophages, dendritic cells and mast cells
- Direct interaction with ENS and vagus nerve
- Release of 5-HT
- Transfer across BBB
- (CLA production)

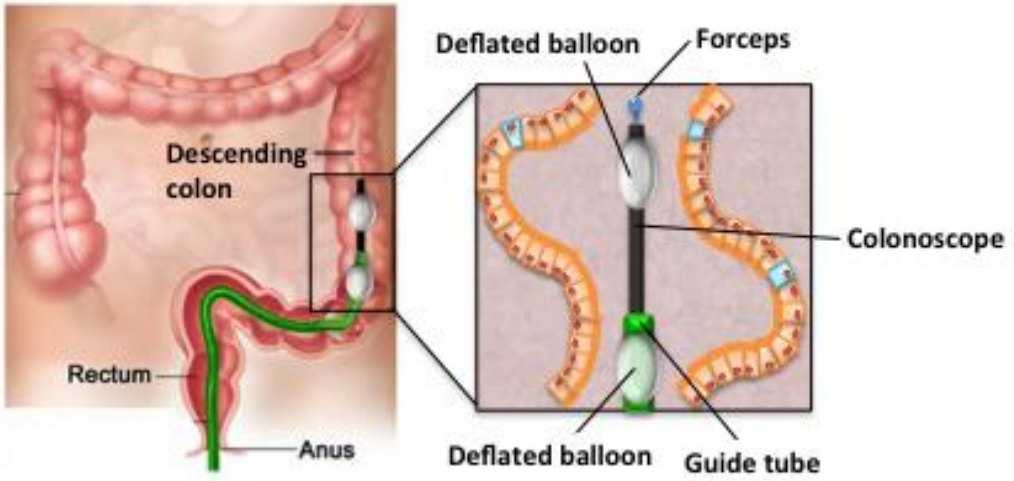


BT; butyrate, MCT1; monocarboxylate transporter 1, SMCT1; sodium dependent MCT1, HDAC; histone deacetylase, Ac; acetylation

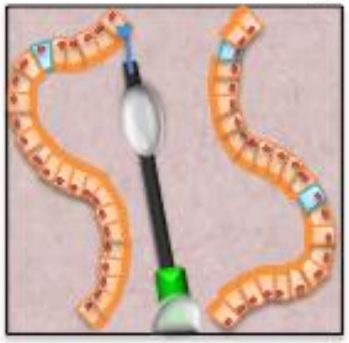
Adapted from Ravinder et al., 2011 AJP Cell Physiol; Flint et al., 2012 Nature Rev; Cox et al., 2013 Cell Metab

Butyrate – Mode of Action

A)

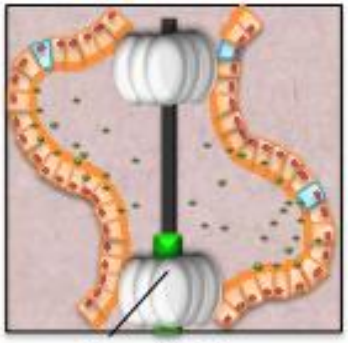


B)



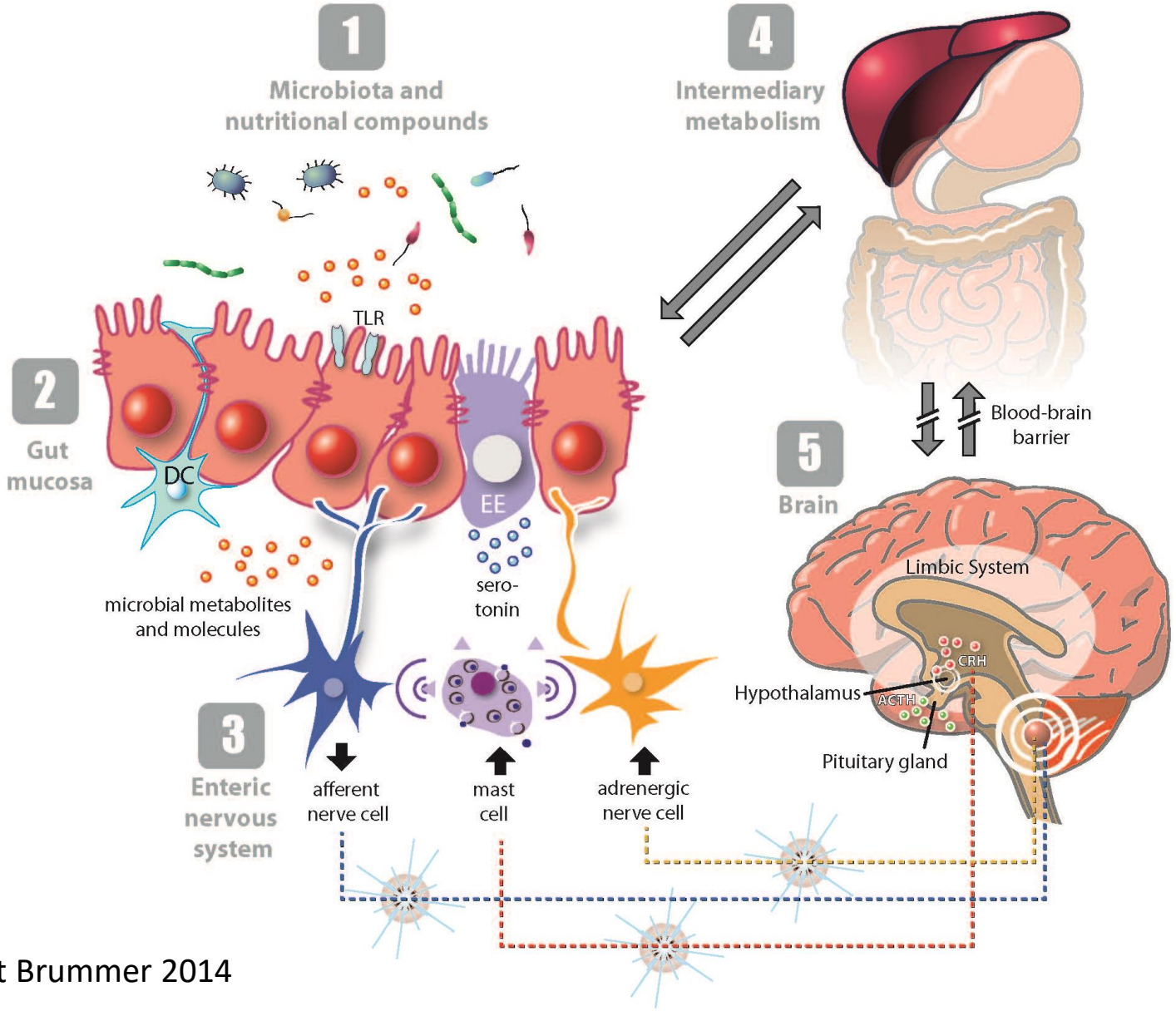
C)

D)



E)

Components of the gut-brain axis



Vraag:

Darmdoorlaatbaarheid (i.e. permeabiliteit) wordt wel als een maat voor darmbarriere functie gebruikt.
Verhoogde doorlaatbaarheid duidt op:

-**verbetering** van darmbarriere functie
-**verslechtering** van darmbarriere functie

Intestinal barrier function

Julia König, PhD[1], Jerry Wells[2], Patrice D. Cani[3], Clara L. García-Ródenas, PhD[4], Tom MacDonald[5], Annick Mercenier, PhD[4], Jacqueline Whyte, PhD[6], Freddy Troost[7] and Robert-Jan Brummer[1]

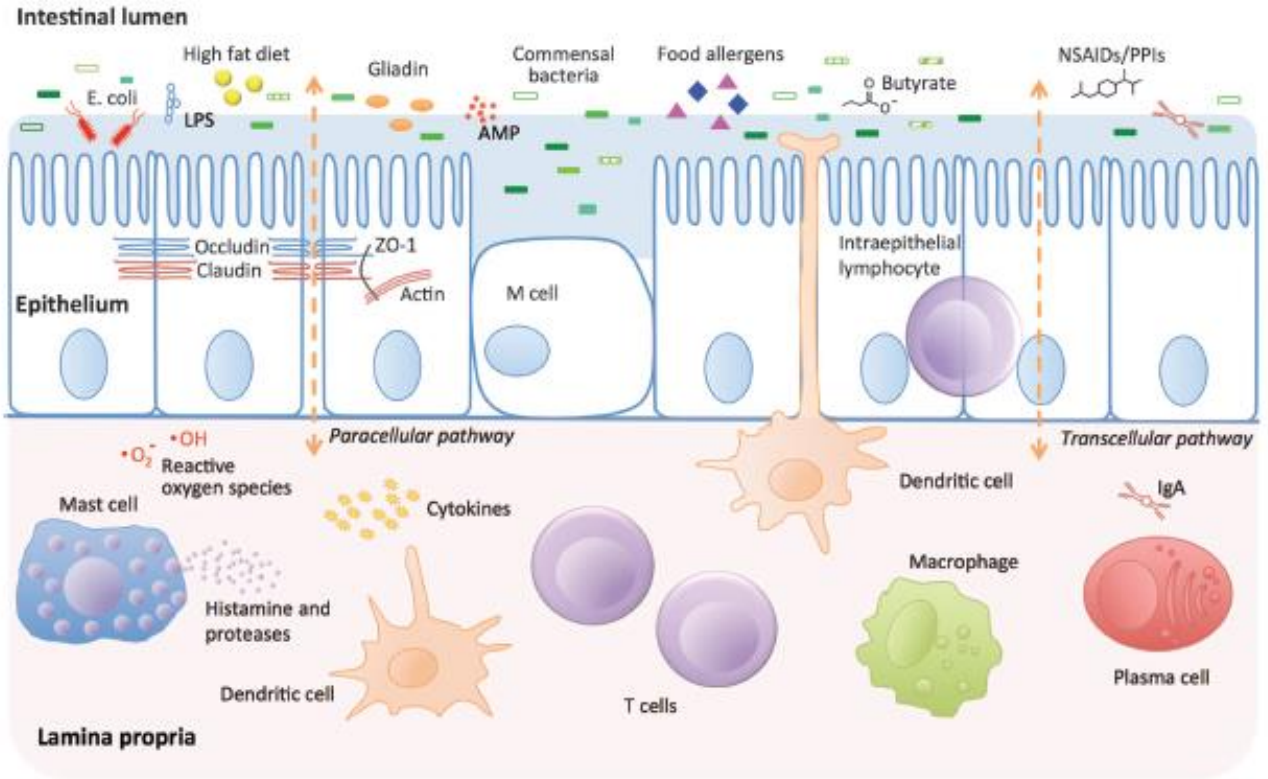
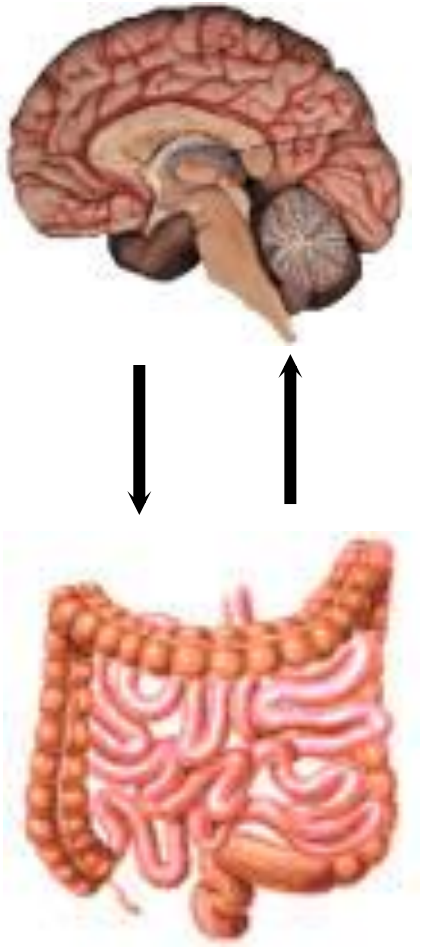


Figure 1 Schematic figure of the intestinal barrier and affecting factors. The intestinal barrier is composed of several layers providing protection against microbial invasion. The intestinal lumen contains anti-microbial peptides (AMPs), secreted immunoglobulin A (IgA), and commensal bacteria, which inhibit the colonization of pathogens by competitive inhibition and by production of, e.g., butyrate, which has barrier-protective properties. A mucus layer covers the intestinal surface providing a physical barrier. The epithelial layer consists of a single layer of epithelial cells that are sealed by tight junction proteins such as occludin, claudin, and zonulin-1 preventing paracellular passage. This layer also harbors intraepithelial lymphocytes, M cells (overlying Peyer's patches and lymphoid follicles), mucus-producing Goblet cells and bacteriocin-producing Paneth cells (not shown). The lamina propria contains a large amount of immune cells, both of the innate immune system (e.g., macrophages, dendritic cells, mast cells) and the adaptive immune system (e.g., T cells, IgA producing plasma cells). In addition, cells of the central and enteric nervous system innervate in the lamina propria (not shown). Factors affecting the intestinal barrier function include pathogenic bacteria such as enteropathogenic *E. coli*, high-fat diet, lipopolysaccharides (LPS), drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), and proton pump inhibitors (PPIs), as well as various food allergens and the gluten component gliadin.

Citation: Clinical and Translational Gastroenterology (2016) 7, e196; doi:10.1038/ctg.2016.54

Examples of aberration in intestinal barrier function

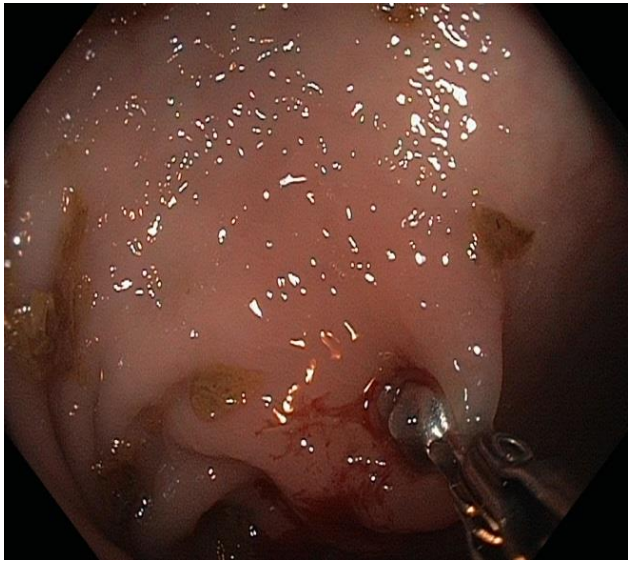
- Inflammatory Bowel Disease
- Irritable Bowel Syndrome
- Metabolic Syndrome
- Ageing
- Stress
- Strenous exercise
- Dehydration
- Etcetera..

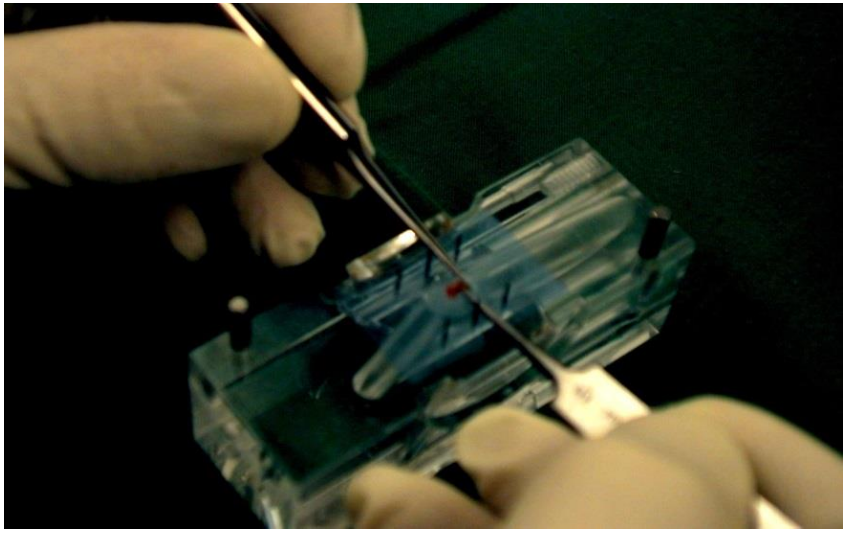


Gut microbiota, intestinal barrier and brain function

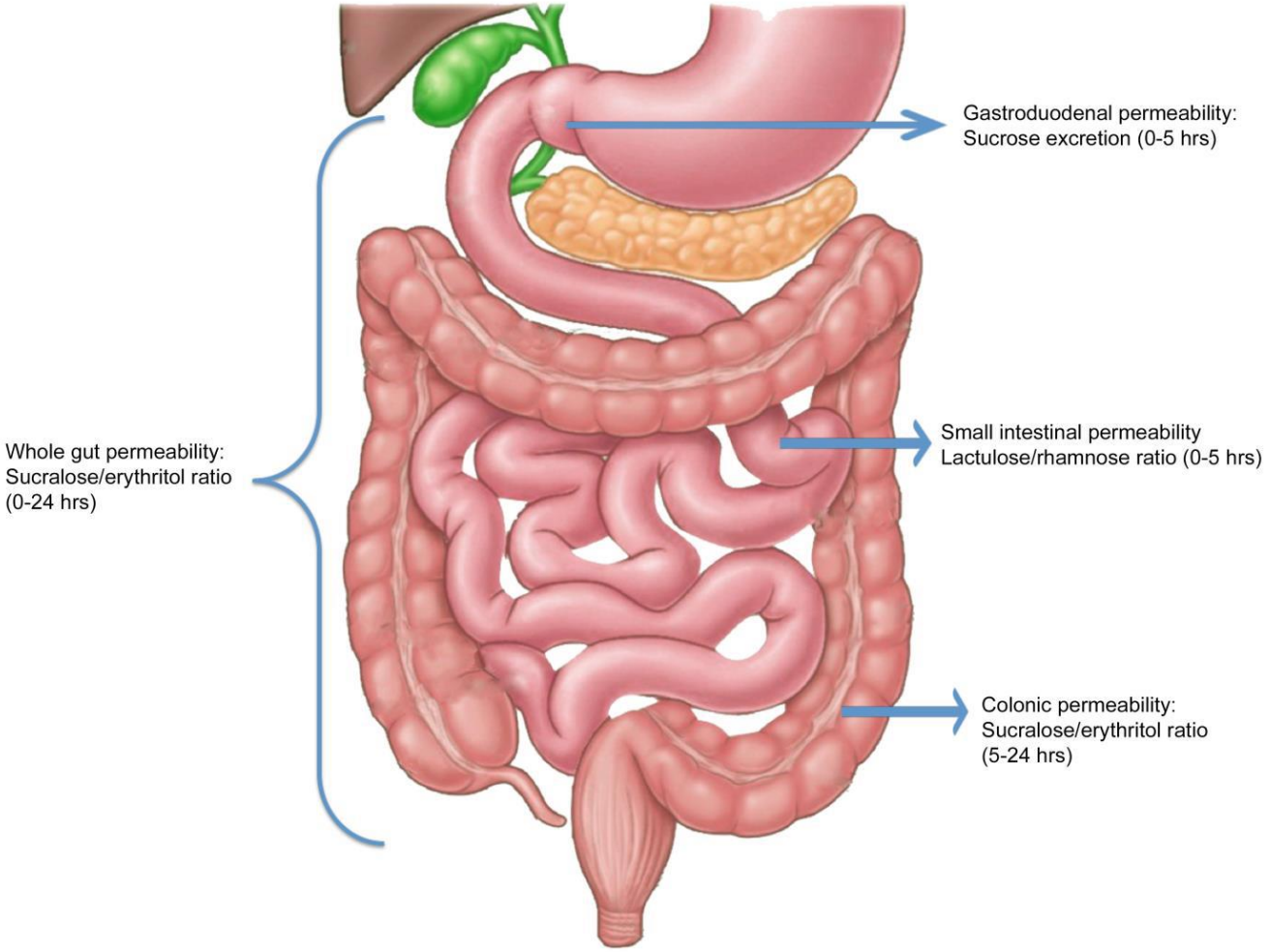
- Impaired intestinal barrier function will cause:
  - local/systemic immune responses
  - mast cell degranulation/ VIP release
  - Neuroinflammation/ ENS
  - afferent vagus nerve activation
- Enteric glia cells

Ussing chamber/ intestinal permeability





Non-invasive multi-sugar test



Inflammatory mediators, 5-HT, and brain function

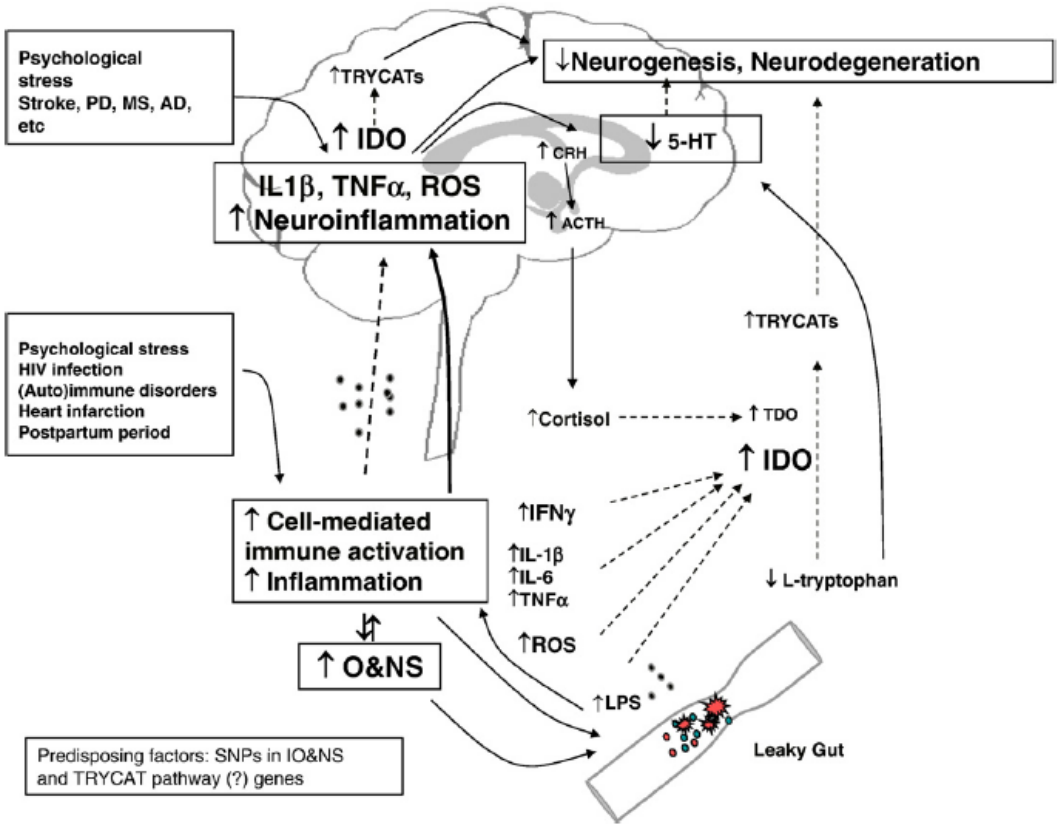


Fig. 4. The TRYCAT pathway and indoleamine 2,3-dioxygenase (IDO) and their interconnections with peripheral and central immune, inflammatory, oxidative and nitrosative stress (IO&NS) pathways. In depressive conditions, peripheral IDO activation may occur following induction by increased levels of cytokines, mainly interferon-γ (IFNγ), but also interleukin-1β (IL-1), tumor necrosis factor-α (TNF) and IL-6; reactive oxygen species (ROS); and increased lipopolysaccharide (LPS) caused by increased gut permeability, which itself is induced by inflammation and free radicals. Peripheral IDO activation contributes to lower plasma tryptophan and thus lowered brain 5-HT and increased levels of tryptophan catabolites (TRYCATs). Peripheral TRYCATs may pass the blood-brain-barrier to provoke depressogenic and anxiogenic effects. Inflammation may cause increased corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) secretion and thus increased cortisol levels, which may induce liver tryptophan 2,3-dioxygenase (TDO) thus further decreasing plasma tryptophan and increasing the production of TRYCATs. Peripheral cell-mediated immune activation and inflammation may cause microglial activation with increased levels of pro-inflammatory cytokines, e.g. IL-1β and TNFα, and free radicals, will all together induce brain IDO and thus increase TRYCAT formation in the brain. Consequently, increased TRYCAT production and neuroinflammation contribute to depressive symptoms. Peripheral IO&NS pathways are induced by a number of trigger factors that are known to cause depression, while central neuroinflammation may be induced by conditions that provoke microglial activation and depression, e.g. stroke and neurodegenerative disorders, such as Parkinson's disorder (PD), Alzheimer's disorder (AD) and multiple sclerosis (MS).

Vraag:

Inname van prebiotica heeft een biofunctioneel effect voornamelijk in de:

-dunne darm
-dikke darm

Pre-/probiotics and Gut-Brain Interaction – mechanistic pathways

- Small bowel vs. colon
- Direct microbe-host interaction vs. microbe-microbe and metabolites
- Enforcing intestinal barrier/ anti-inflammatory
- SCFA production/profile, uptake, utilisation
- Signalling compounds/ 5HT, immune and metabolic pathways

Pre-/probiotics and Gut-Brain Interaction – some potential functional applications

- Attenuating stress impact on gut function
- Improving affective symptoms/ disorders
- Modulating satiation and satiety
- Preventing/delaying neuro-degenerative disorders/ Parkinson's
- Precision nutrition

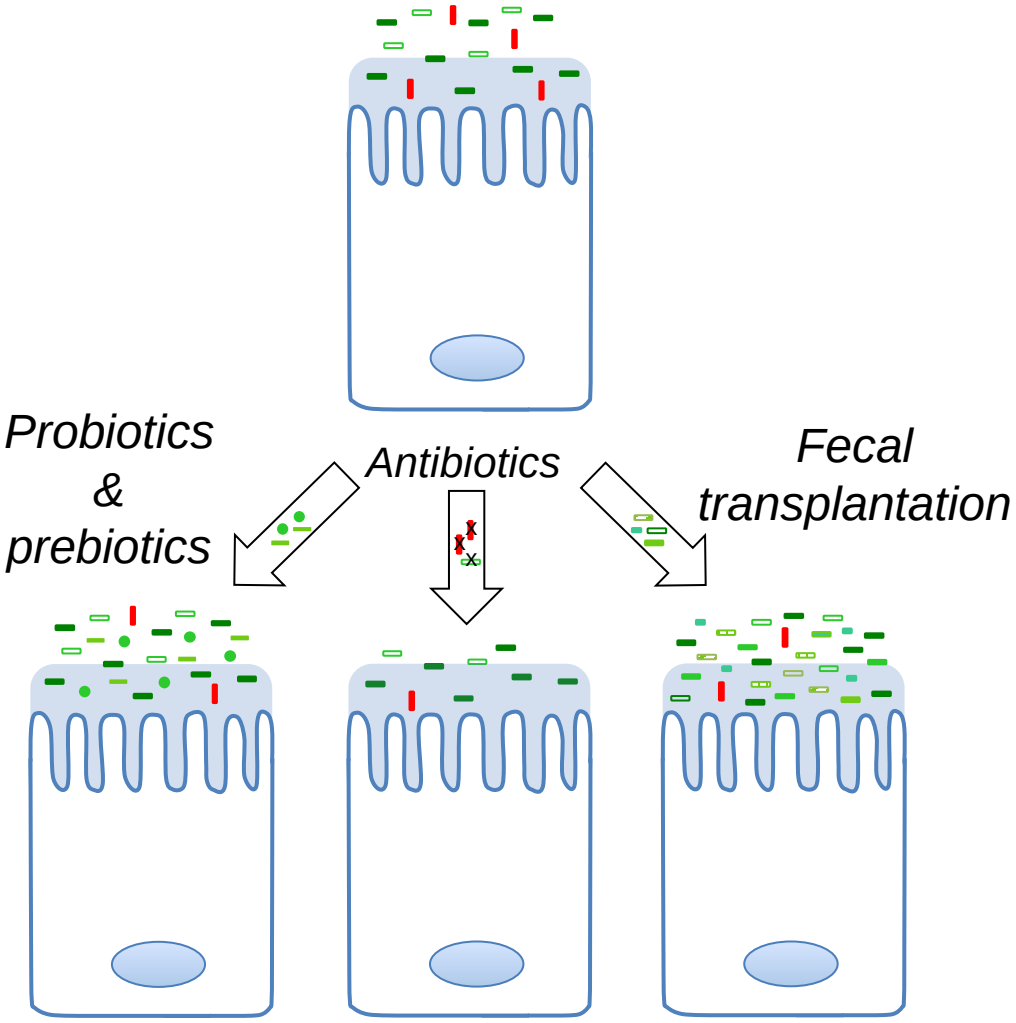
The importance of diet

- ‘Food’ for bacteria
- Direct impact on gut and brain function
- Affects the brain’s composition
- Affects intestinal barrier and immune function
- Effect on inflammation
- Production of bioactive compounds in the gut

What do we know on food and well-being?

- Animal studies give a hint
- Few human studies (placebo/control?)
- Gut health is important
- Gut ecosystem
- Anti-inflammatory diet
- Life style in general
- Personalised/ precision nutrition
- Effect markers?

“Microbial” therapy



König J, Brummer RJ, Ben Micr 2014;5(3):247-261

Probiotics in IBS

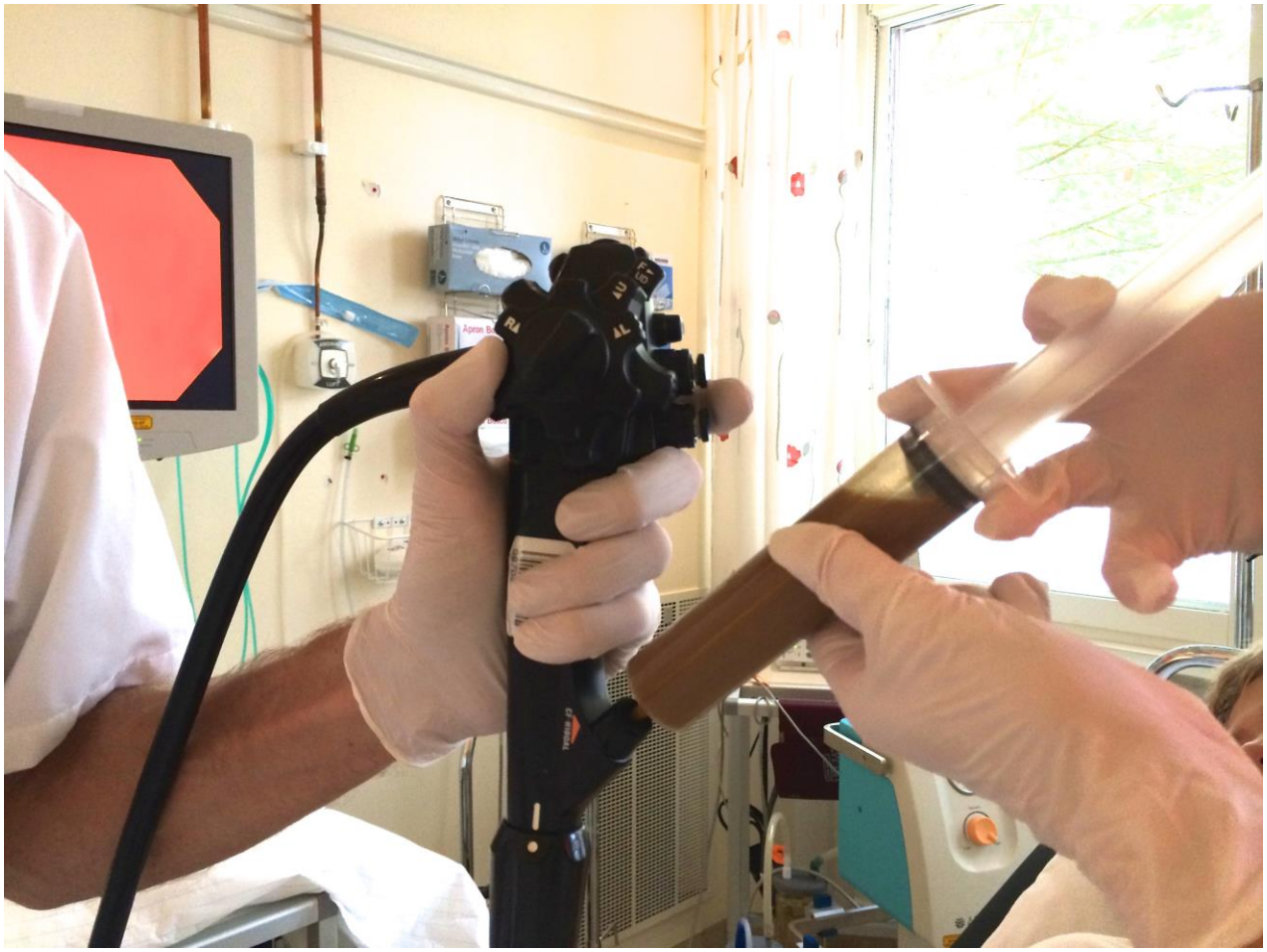
WILEY AP&T Alimentary Pharmacology & Therapeutics

Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome

Alexander C. Ford[1,2] | Lucinda A. Harris[3] | Brian E. Lacy[4] | Eamonn M. M. Quigley[5] | Paul Moayyedi[6]

Aliment Pharmacol Ther. 2018;48:1044–1060.

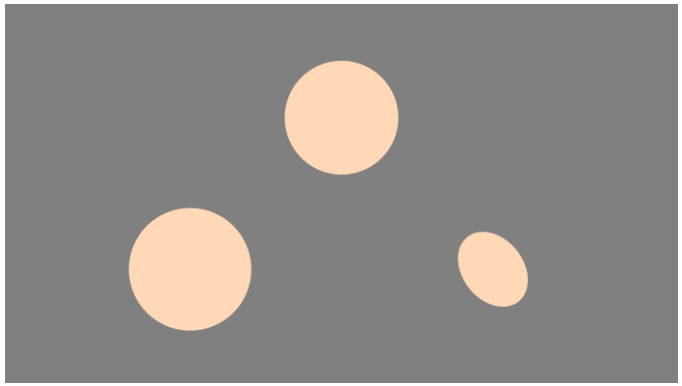
Condusions: Which particular combination, species or strains of probiotics are effective for IBS remains, for the most part, unclear. Rifaximin has modest efficacy in improving symptoms in non-constipated IBS.



fMRI paradigm

"EAT" paradigm = Emotional Attention Task

Liebermann et al., 2007



Match shapes (MS)

Match emotions (ME)

Analysis model: ME - MS

Results

Emotional Attention Task = EAT paradigm

Liebermann et al., 2007

Match shapes

Match emotions (fear or anger)

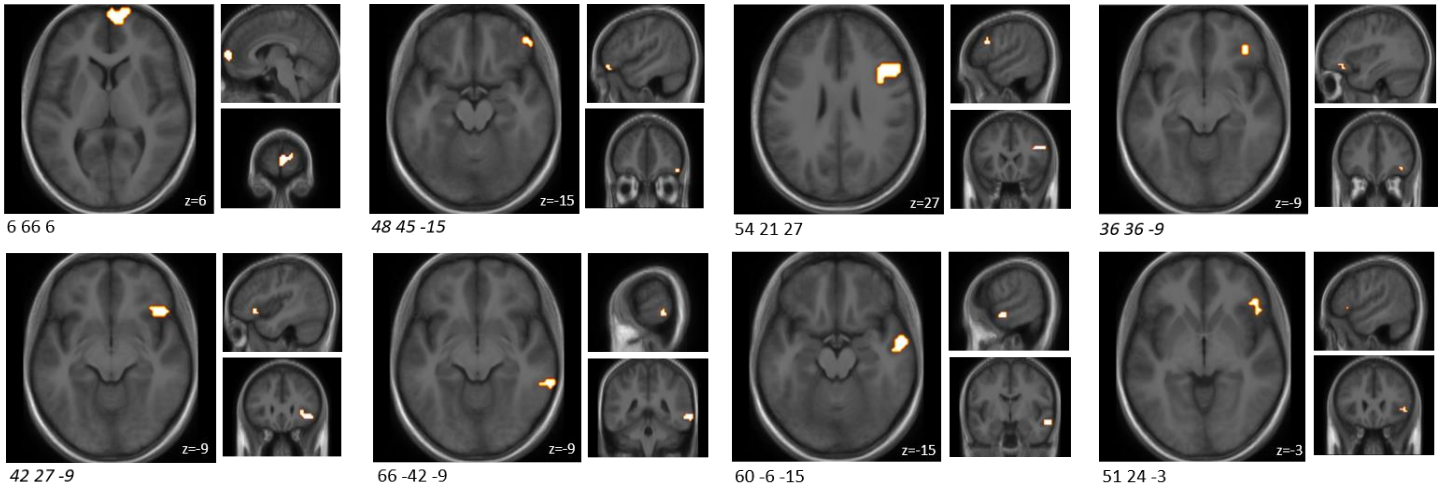


Figure 2. Sub-clusters that were found to be associated with significant ($p < 0.1$) changes in brain activity between both interventions (probiotic > placebo) before multiplicity correction, during the EAT paradigm.

Vraag:

Gezonde buik – beter brein?

-ja
-nee
-ik weet niet
-kan niet antwoorden i.v.m. sanitaire pauze

Hersen-microbiota-darm as –

Van theorie naar praktijk?

Robert-J M Brummer MD PhD

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April 22, 2021