Pro- and Prebiotics and the Gut-Brain Axis – *Knowledge and knowledge gaps*

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

Pro-Vice-Chancellor, Örebro University, Sweden

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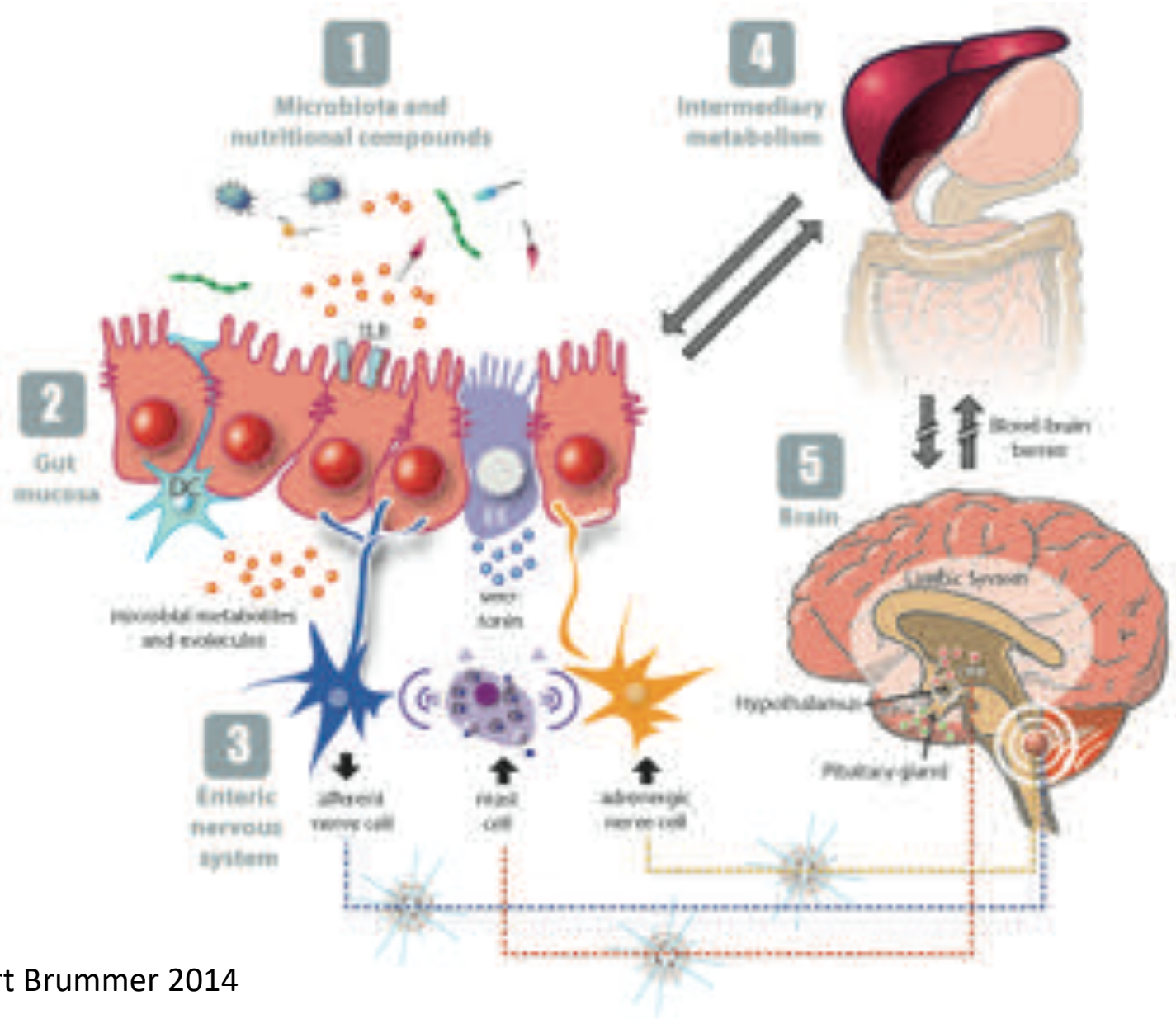
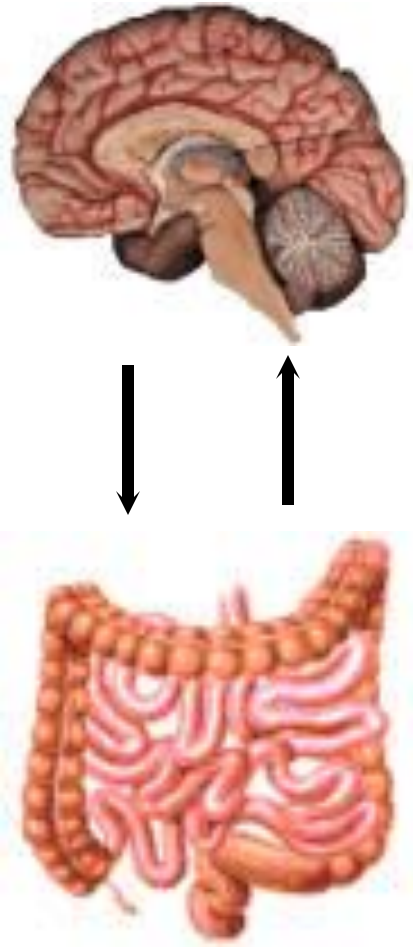
Gut-Brain axis

Components of the gut-brain axis



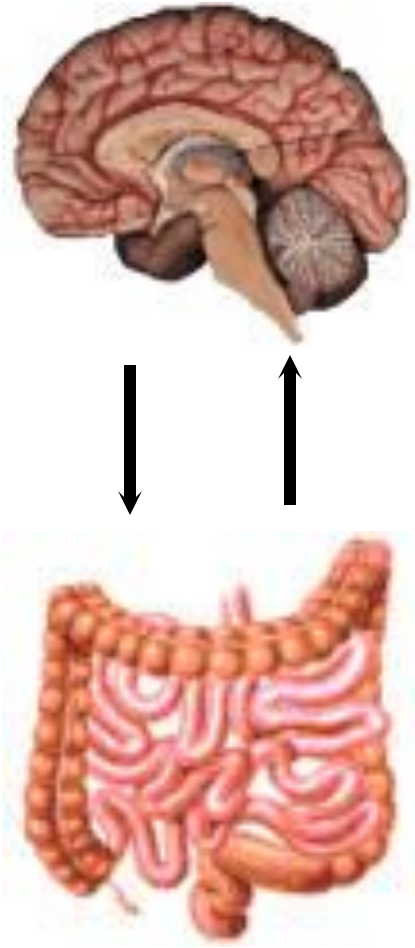
Mediators of bidirectional signalling

- 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
- ……



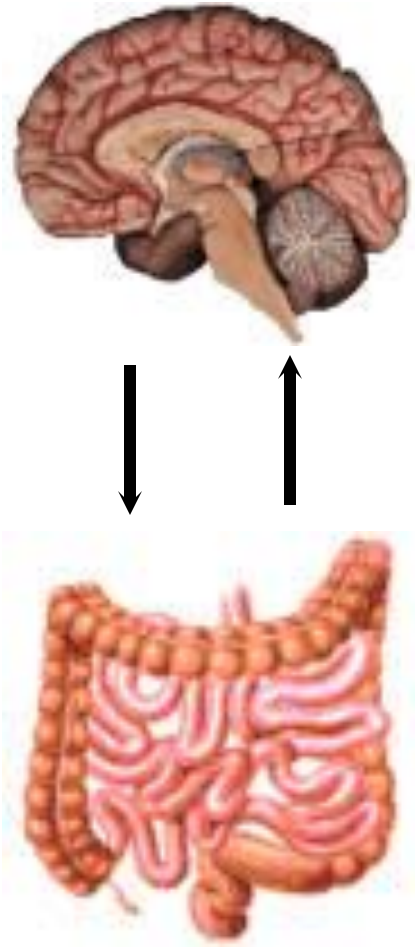
Gut microbiota ➔Brain
mechanistic pathways

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



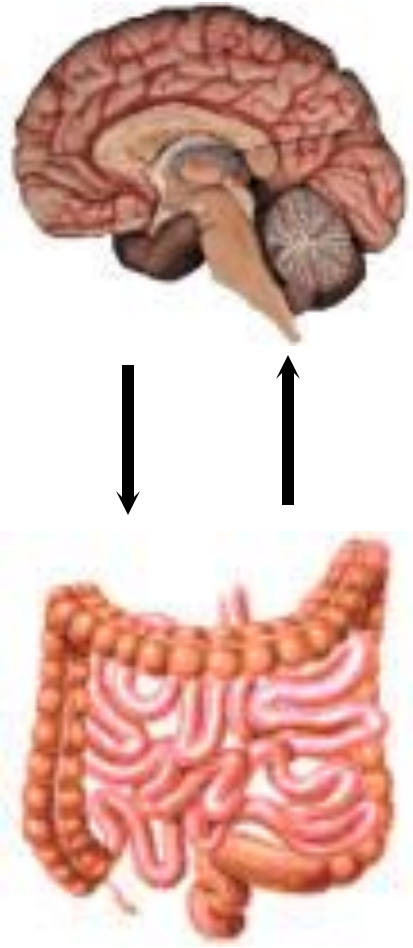
Examples of *direct* microbe-host signalling

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



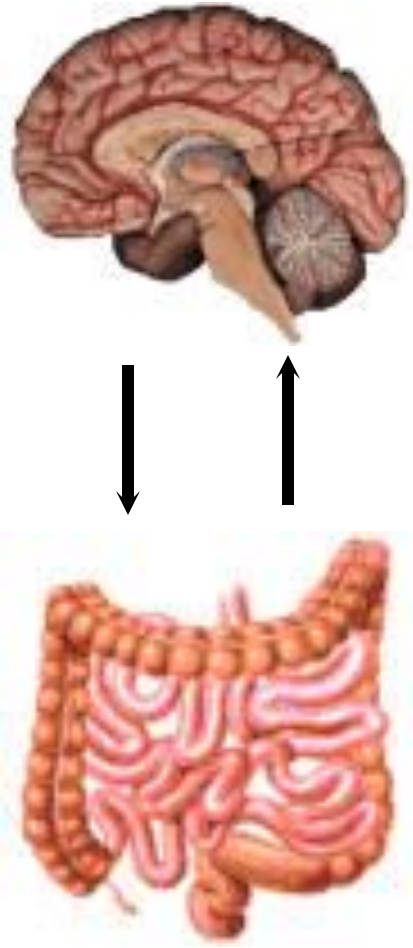
Examples of microbial metabolites that affect gut-brain signalling

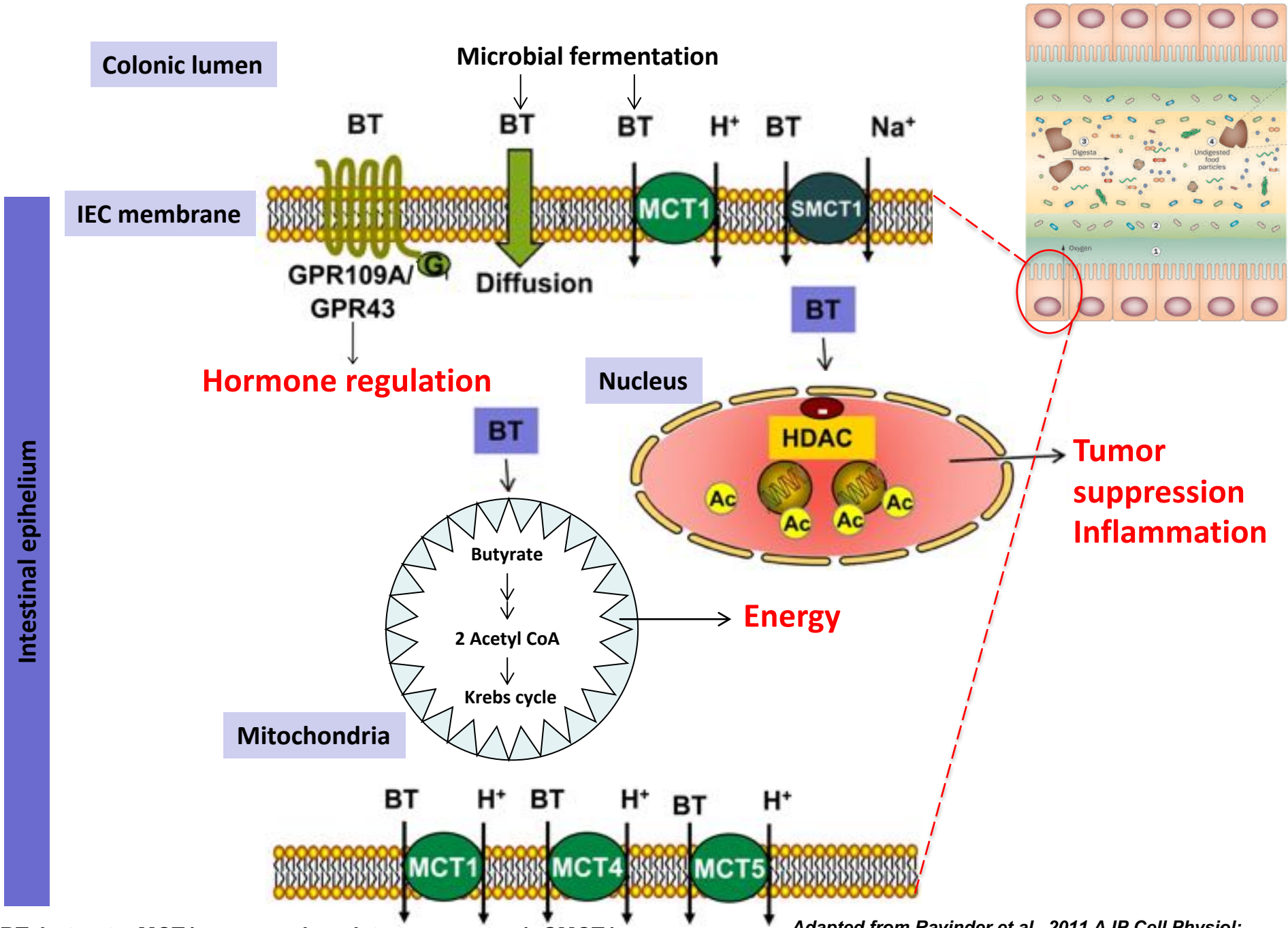
- SCFAs including iso-
- Hydrogen
- Methane
- Carbon dioxide
- Ammonia
- Hydrogen sulfide
- *!! Nutrition and metabolic cross-feeding*



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





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

Bacterial metabolites and visceral perception/ gut health

The effects of butyrate enemas on visceral perception in healthy volunteers

S. A. L. W. VANHOUTVIN,*,†, F. J. TROOST,*,† T. O. C. KILKENS,† P. J. LINDSEY,‡ H. M. HAMER,*,† D. M. A. E. JONKERS,*,† K. VENEMA*,§ & R.-J. M. BRUMMER*,†,¶

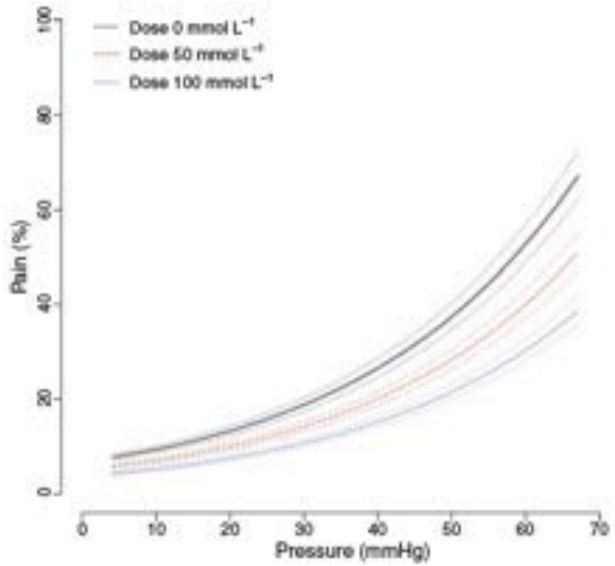


Figure 2 The effect of daily administration of enemas containing 0, 50 or 100 mmol L^{-1} butyrate for 7 days on pain scores (100 mm VAS) at the consecutive pressure steps of the barostat protocol. Ninety per cent confidence intervals of the pain scores are shown in grey.

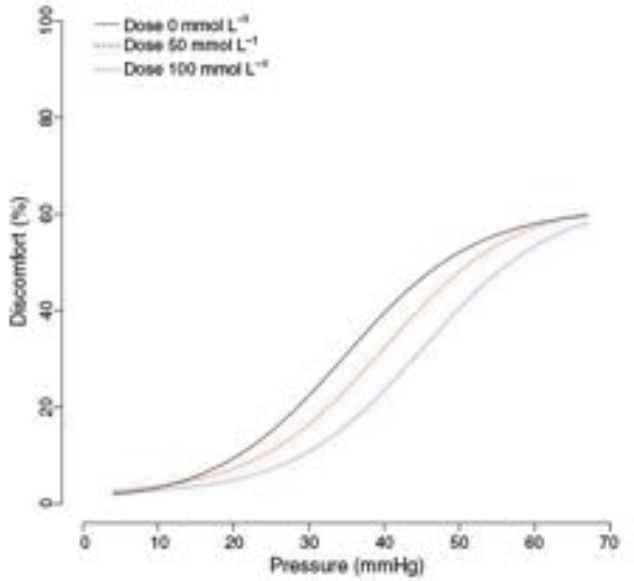
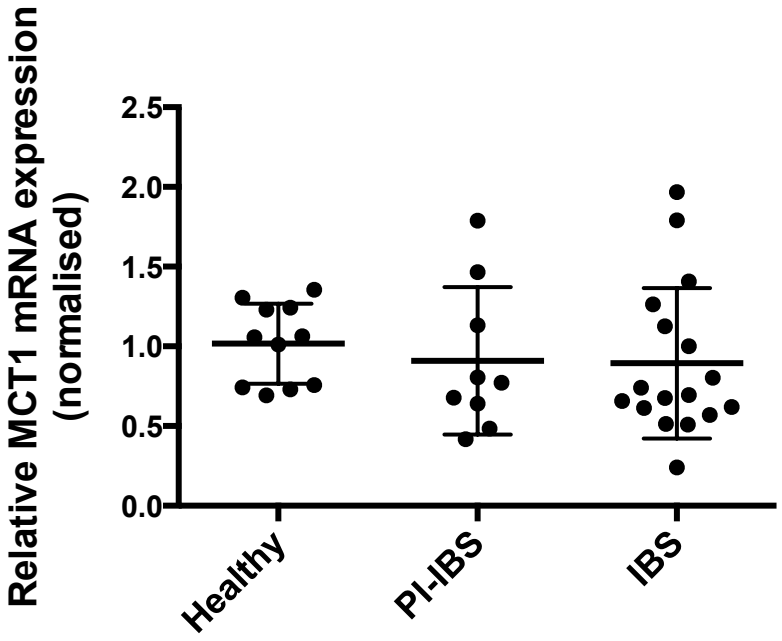
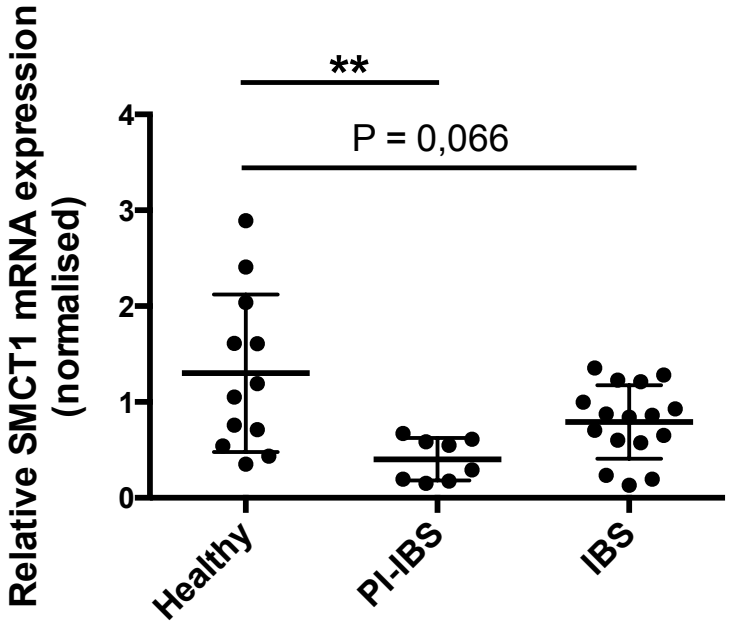


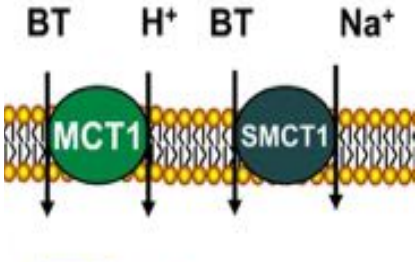
Figure 3 The effect of daily administration of enemas containing 0, 50 and 100 mmol L^{-1} butyrate for 7 days on discomfort scores (100 mm VAS) at the consecutive pressure steps of the barostat protocol.

Neurogastroenterol Motil (2009)

SMCT1 and MCT1 expression in IBS mucosal biopsies

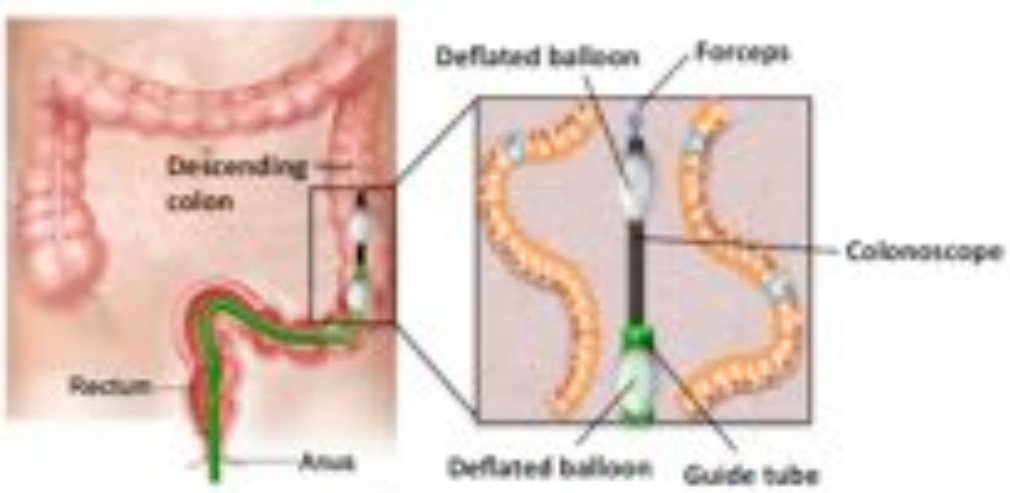






Butyrate – Mode of Action

A)



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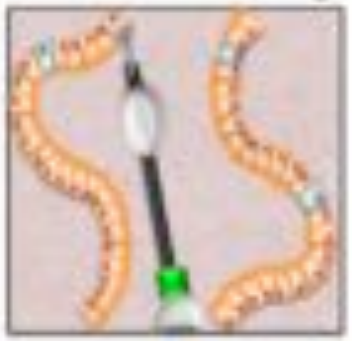

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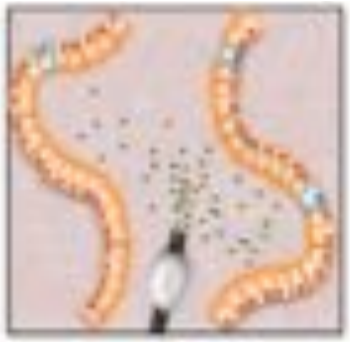

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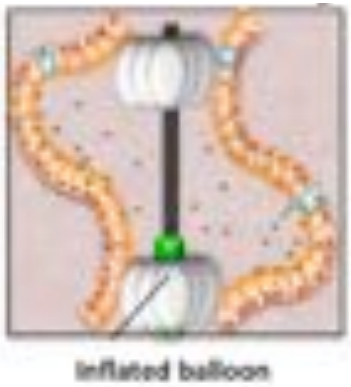
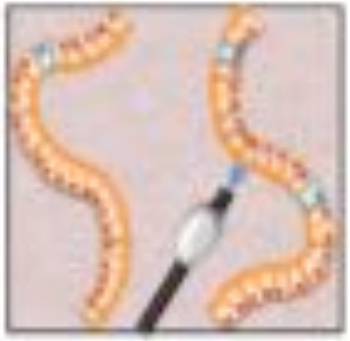
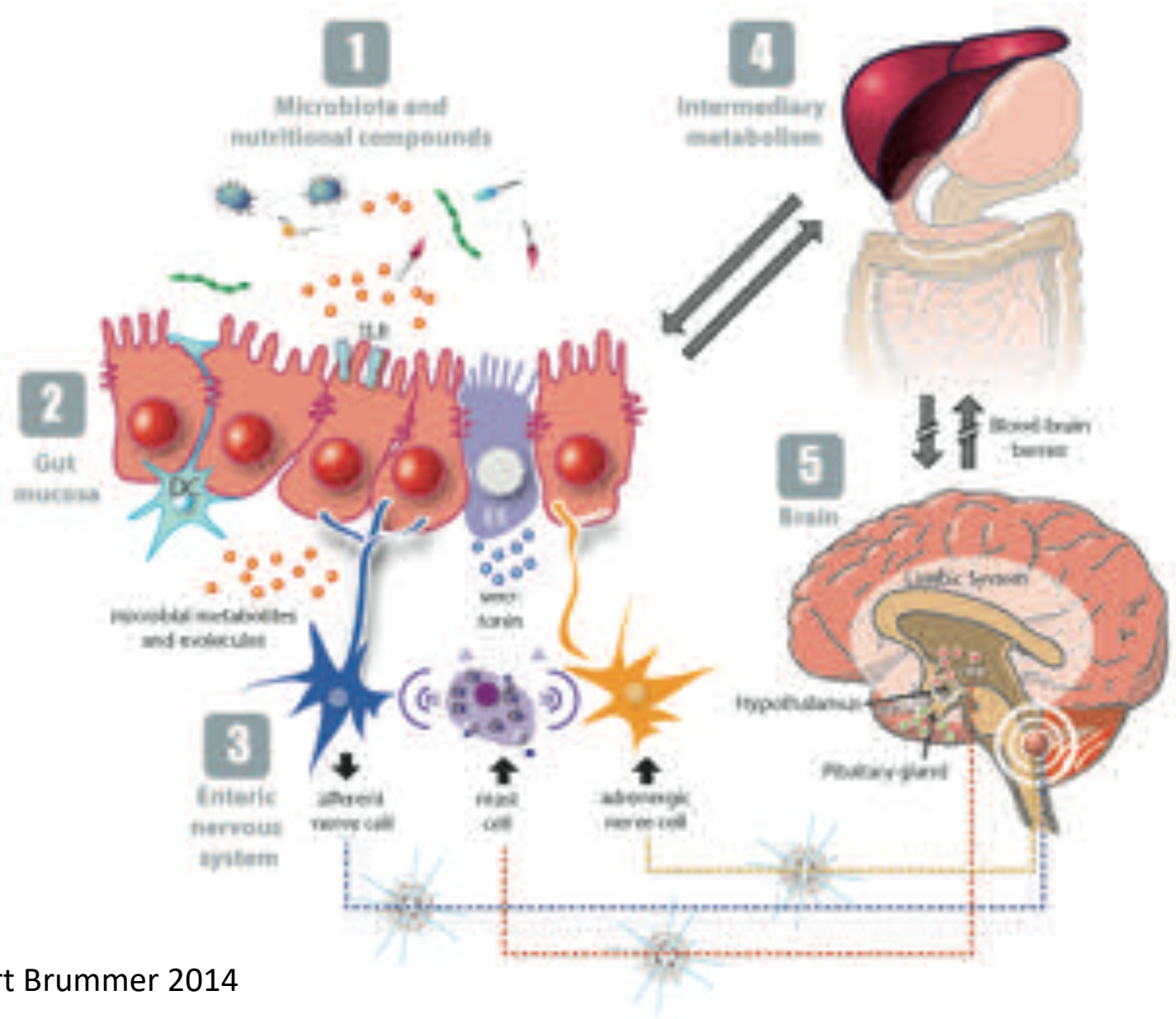


E)



Components of the gut-brain axis



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]

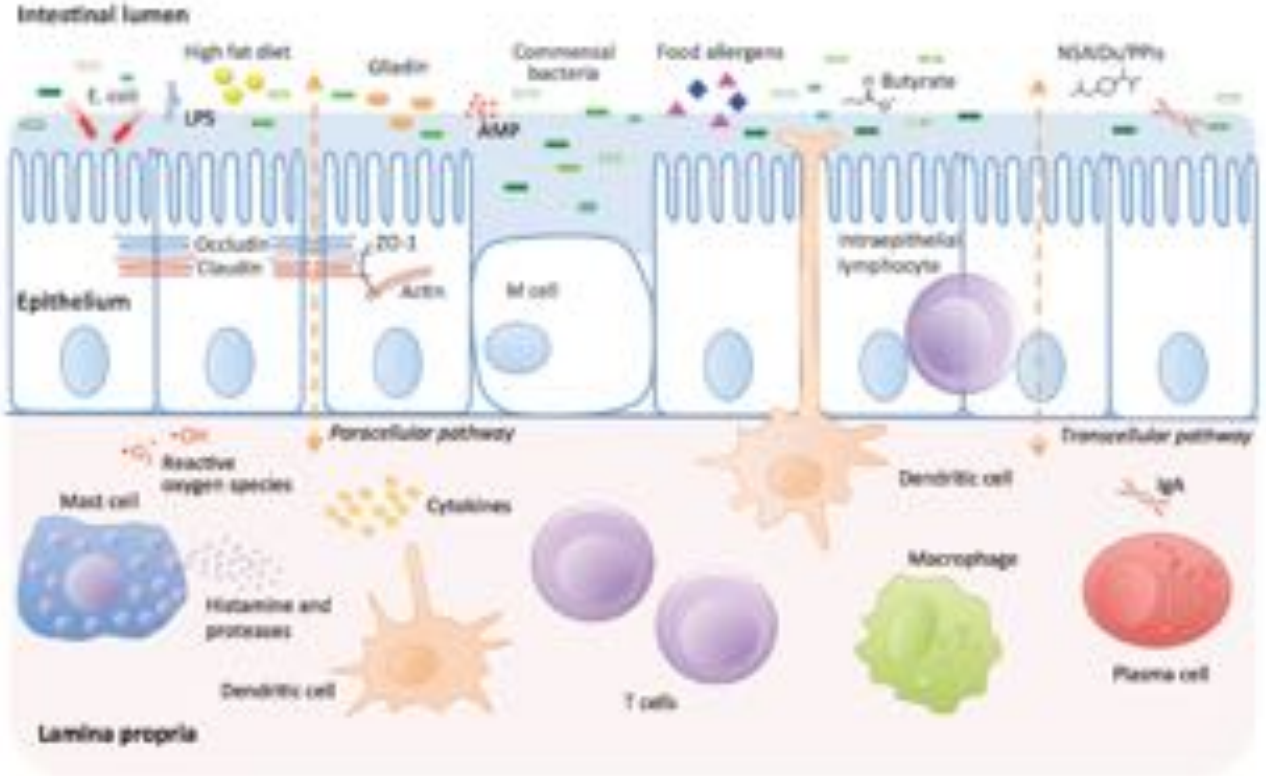


Figure 1 Schematic figure of the intestinal barrier and affecting factors. The intestinal barrier is composed of several layers providing protection against microbial invasion. The intestinal lumen contains anti-microbial peptides (AMPs), secreted immunoglobulin A (IgA), and commensal bacteria, which 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

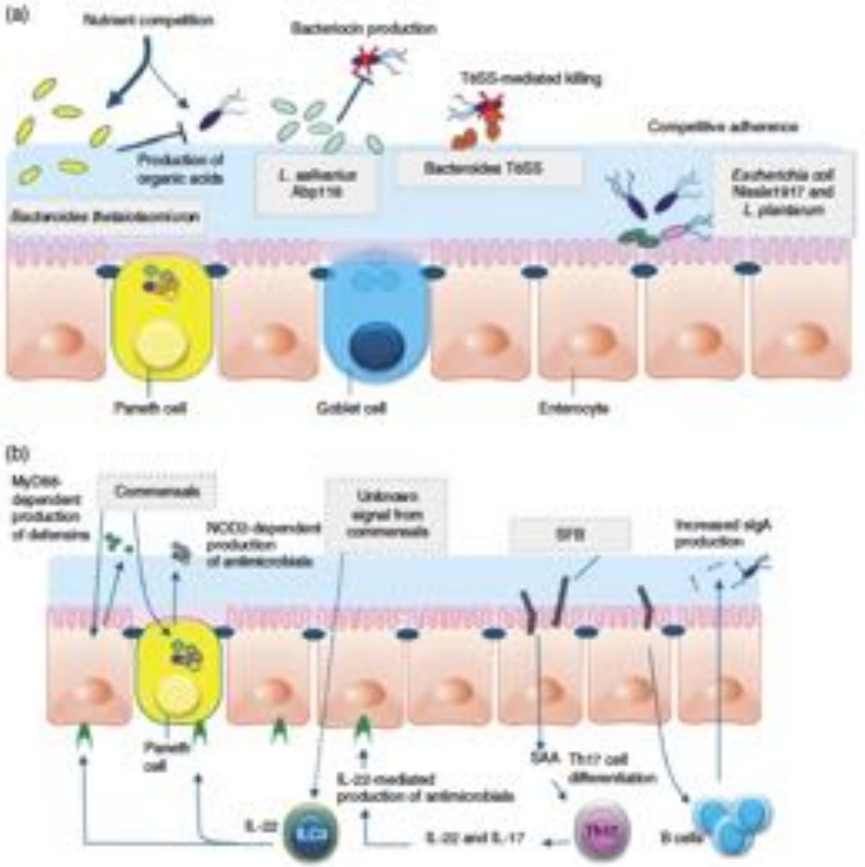
Gut microbiota, intestinal barrier and brain function

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

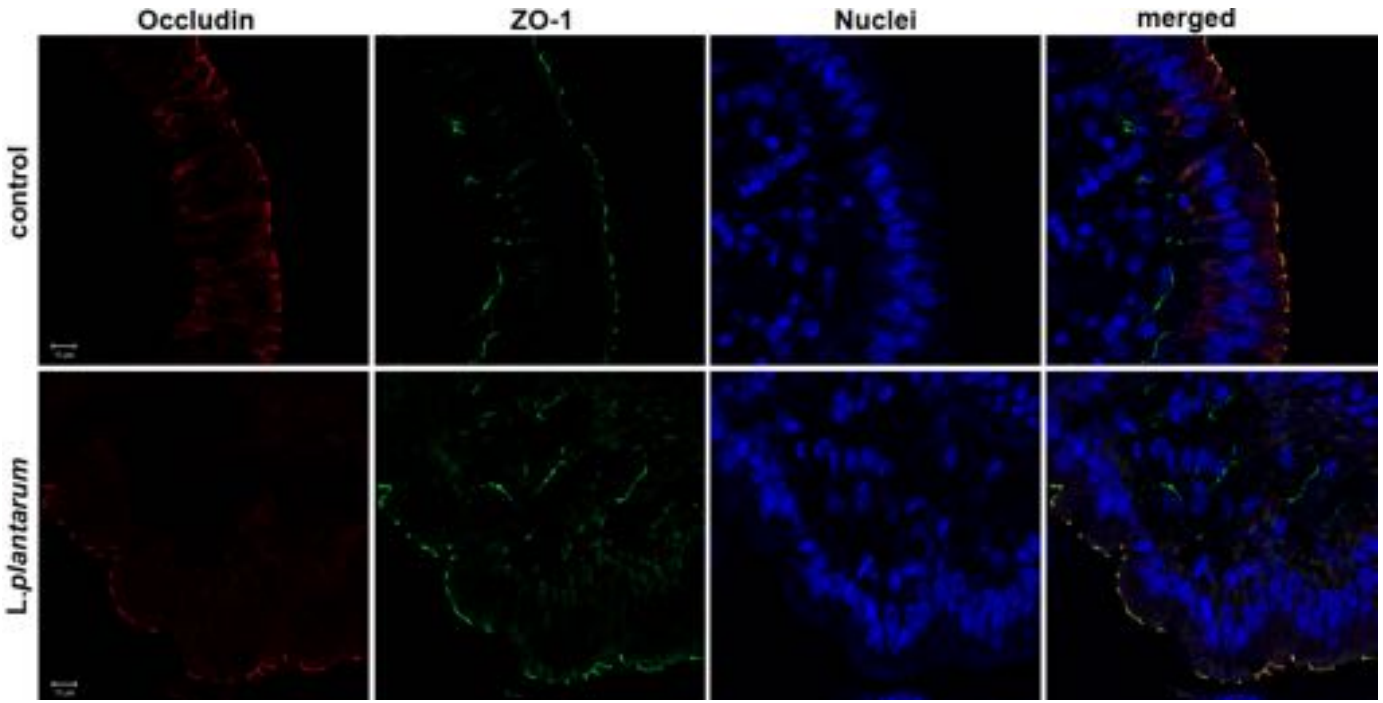
Can probiotics modulate human disease by impacting intestinal barrier function?

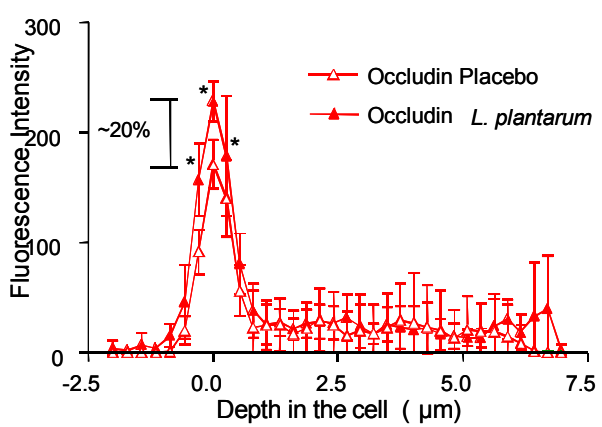
Peter A. Bron[1]*†, Michiel Kleerebezem[2]†, Robert-Jan Brummer[3], Patrice D. Cani[4], Annick Mercenier[5], Thomas T. MacDonald[6], Clara L. Garcia-Ródenas[5] and Jerry M. Wells[2]

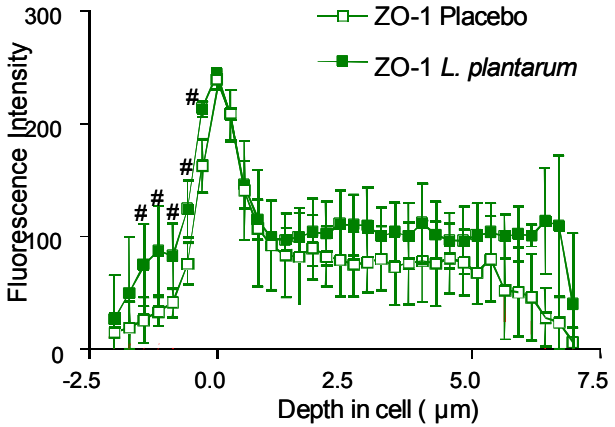
British Journal of Nutrition (2017), **117**, 93–107



Lactobacillus and tight junctions



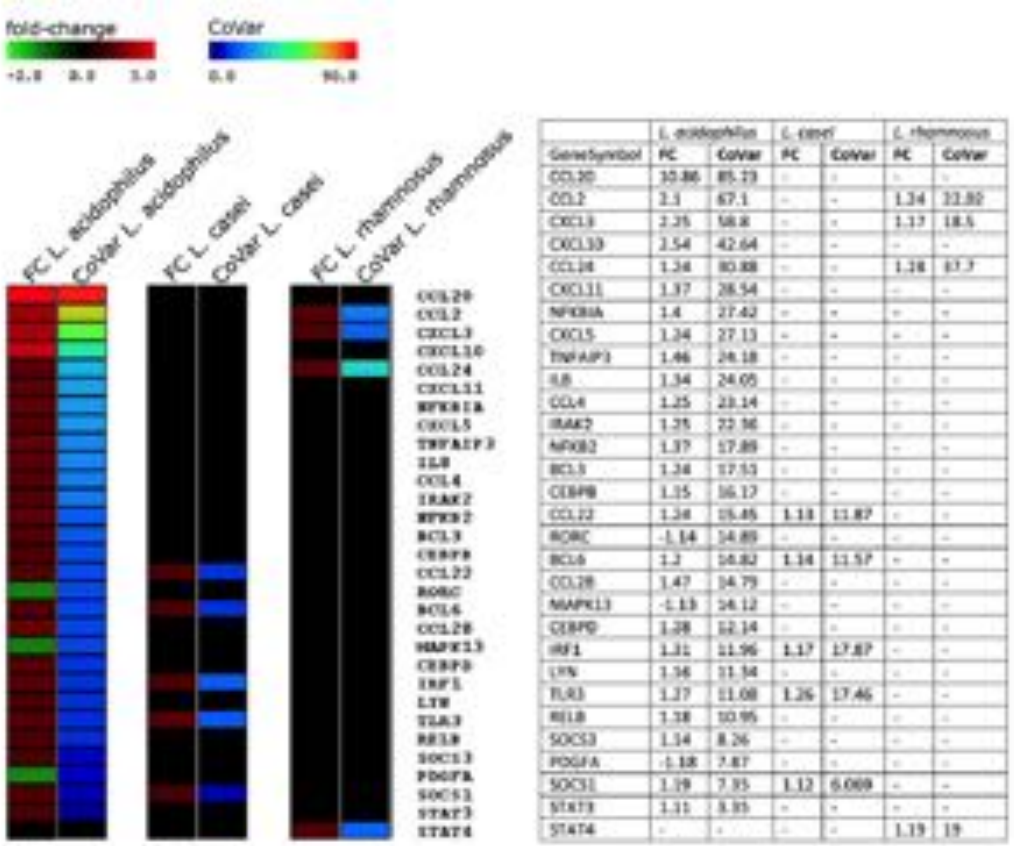




Am J Phys 2010

Human mucosal in vivo transcriptome responses to three lactobacilli indicate how probiotics may modulate human cellular pathways

Peter van Baarlen[a,b,1,2], Freddy Troost[a,c,2], Cindy van der Meer[a,d], Guido Hooiveld[a,e], Mark Boekschoten[a,e], Robert J. M. Brummer[a,c,3], and Michiel Kleerebezem[a,d,f,4]



	L. acidophilus		L. casei		L. rhamnosus	
GeneSymbol	FC	CoVar	FC	CoVar	FC	CoVar
CCL20	10.86	85.23	-	-	-	-
CCL2	2.1	67.1	-	-	1.34	22.82
CXCL3	2.35	58.8	-	-	1.17	18.5
CXCL10	2.54	42.64	-	-	-	-
CCL24	1.24	80.88	-	-	1.18	67.7
CXCL11	1.37	28.54	-	-	-	-
NFKBIA	1.4	27.42	-	-	-	-
CXCL5	1.24	27.13	-	-	-	-
TNFAIP3	1.46	24.18	-	-	-	-
IL8	1.34	24.05	-	-	-	-
CCL4	1.25	23.14	-	-	-	-
IRAK2	1.25	22.56	-	-	-	-
NFKB2	1.37	17.89	-	-	-	-
BCL3	1.24	17.53	-	-	-	-
CEBPB	1.15	16.17	-	-	-	-
CCL22	1.24	15.45	1.18	11.87	-	-
RORC	-1.14	14.89	-	-	-	-
BCL6	1.2	14.82	1.14	11.57	-	-
CCL28	1.47	14.79	-	-	-	-
MAPK13	-1.13	14.12	-	-	-	-
CEBPD	1.28	12.14	-	-	-	-
IRF1	1.31	11.96	1.17	17.87	-	-
LTF	1.16	11.54	-	-	-	-
TLR3	1.27	11.08	1.26	17.46	-	-
RELB	1.18	10.95	-	-	-	-
SOCS3	1.14	8.26	-	-	-	-
PDGFA	-1.18	7.87	-	-	-	-
SOCS1	1.19	7.35	1.12	6.009	-	-
STAT3	1.11	3.35	-	-	-	-
STAT4	-	-	-	-	1.19	19

PNAS 2011;108:4562-9

Fig. 3. Heat map visualization of transcriptional change (fold change) and coefficients of variation (CoVars) for those genes that encode the proteins that are represented in the interaction network depicted in Fig. 2. The values listed in the table correspond with the heat-map colors. An expression value represented in black indicates that the respective gene was not differentially expressed. From this, it can be seen that genes with functional annotations relating to the immune response are mainly regulated on consumption of *L. acidophilus*, not on consumption of the other two lactobacilli. Note that genes encoding proteins that occupy more central regulatory functions in the network of Fig. 2 tend to have lower CoVars compared with genes that encode proteins with more acute functions such as chemokines. This trend is also apparent in the responses to the other two lactobacilli (*SI Appendix*, *SI Results*, Figs. S8 and S9, and Tables S11 and S12).

Prebiotics and intestinal permeability

A β-Glucan-Based Dietary Fiber Reduces Mast Cell-Induced Hyperpermeability in Ileum From Patients With Crohn's Disease and Control Subjects

John-Peter Ganda Mall, MSc, Maite Casado-Bedmar, MSc†, Martin E. Winberg, PhD†, Robert J. Brummer, MD, PhD.*, Ida Schoultz, PhD*, and Åsa V. Keita, PhD†,**

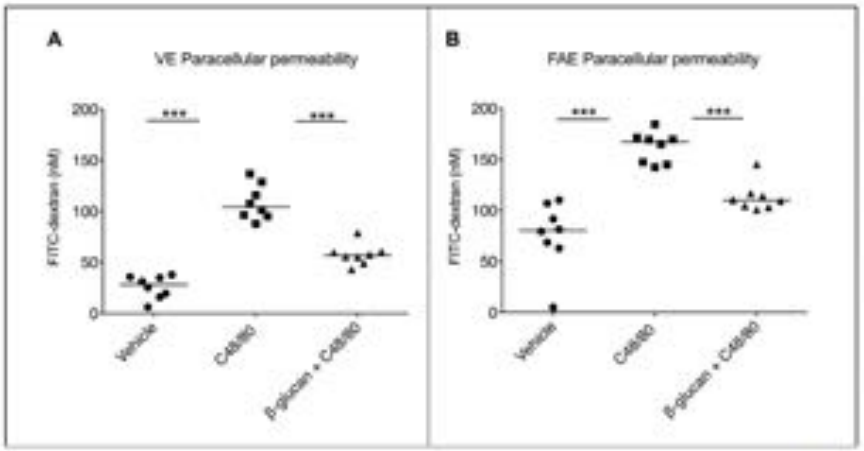


FIGURE 1. Effects of yeast-derived β-glucan on compound 48/80 (C48/80)-induced paracellular hyperpermeability in VE and FAE of 8 control subjects mounted in Ussing chambers. (A-B) Control subjects displayed an increased FITC-dextran passage in VE and FAE after stimulation with the mast cell degranulator C48/80 compared to unstimulated tissues (vehicles). Costimulation with β-glucan attenuated C48/80 effects to levels close to vehicles. A similar pattern was seen for CD patients (Suppl Fig. 1). Data (Δ90—0 min) are presented as a line intersecting the median and each dot representing one patient, ***$P < 0.001$

Inflamm Bowel Dis • Volume 24, Number 1, January 2018

Prebiotics and intestinal permeability

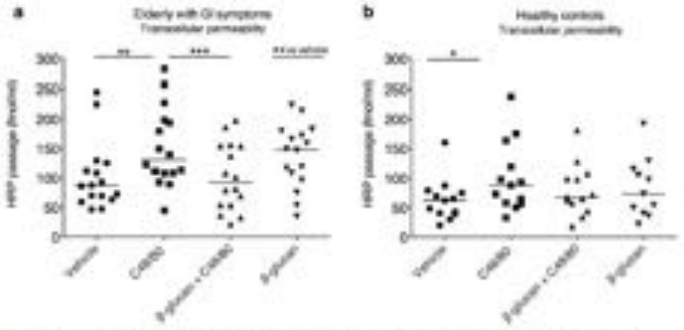


Figure 2. Effects of yeast-derived β-glucan on colonic transcellular permeability in biopsies mounted in Ussing chambers. Stimulation with Compound (C) 48/80 significantly increased the transcellular permeability compared to vehicle in both elderly with gastrointestinal (GI) symptoms (**a**, n = 16) and healthy controls (**b**, n = 13). Co-stimulation with β-glucan attenuated C48/80 induced transcellular hyperpermeability in elderly with GI symptoms but not healthy controls. Stimulation with β-glucan only displayed significantly increased transcellular permeability compared to vehicle in elderly with GI symptoms but not healthy controls (n = 11). Data (Δ 90–0 min) is presented as a line intersecting the median and each dot represents one participant. *p < 0.05, **p < 0.01, ***p < 0.001, ns = non-significant. Two elderly had to be excluded from horseradish peroxidase (HRP)-analysis due to technical problems, hence total number 16 instead of 18.

Differential effects of dietary fibres on colonic barrier function in elderly individuals with gastrointestinal symptoms

J. P. Ganda Mall[1,2], L. Löfvendahl[1], C. M. Lindqvist[1], R. J. Brummer[1], Å. V. Keita[1] & I. Schoultz[1,2]

SCIENTIFIC REPORTS | (2018) 8:13404 | DOI:10.1038/s41598-018-31492-5

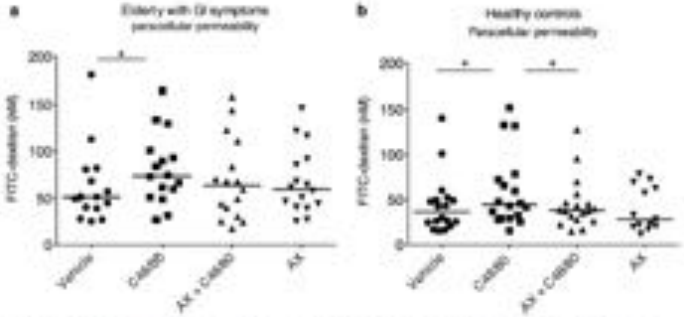


Figure 3. Effects of the wheat-derived arabinoxylan (AX) on colonic paracellular permeability in biopsies mounted in Ussing chambers. Stimulation with Compound (C) 48/80 (10 ng/ml) resulted in a significantly higher paracellular permeability compared to vehicle (**a**,**b**). Co-stimulation with AX (0.1 mg/ml) showed a significant decrease of C48/80-induced hyperpermeability on paracellular passage in only the healthy controls (**b**). Stimulation with AX only had no significant effect on neither paracellular nor transcellular permeability compared to vehicle. *p < 0.05, **p < 0.01, ***p < 0.001, ns = non-significant. Two elderly with GI symptoms and 3 healthy controls had to be excluded from the FITC-analysis due to technical problems, hence elderly with GI symptoms; n = 16 and healthy controls; n = 18 (AX only, n = 13).

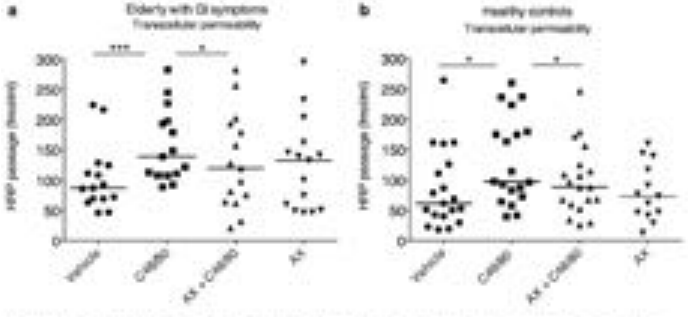
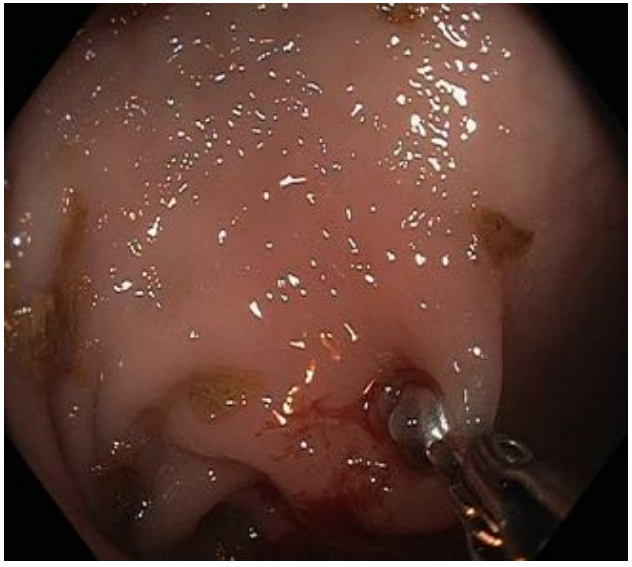
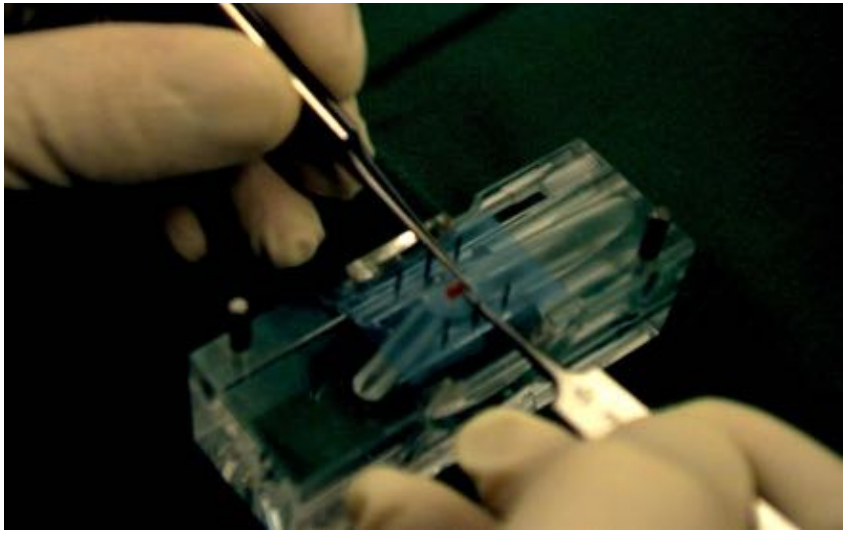
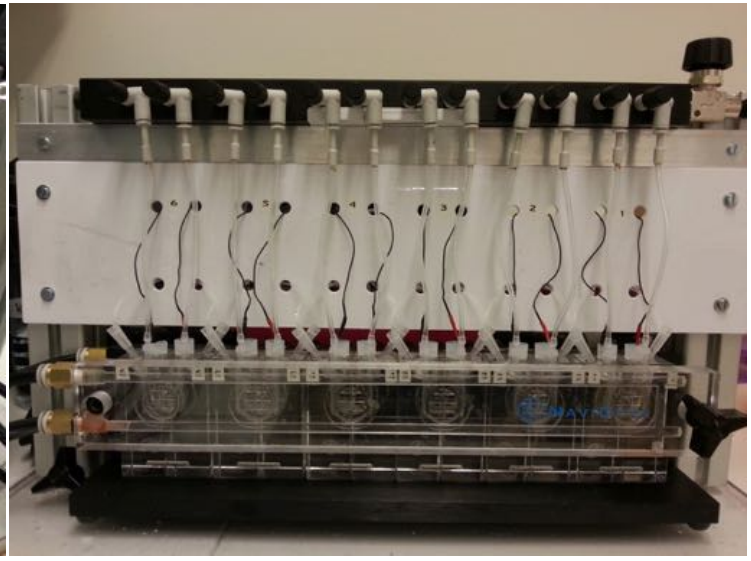


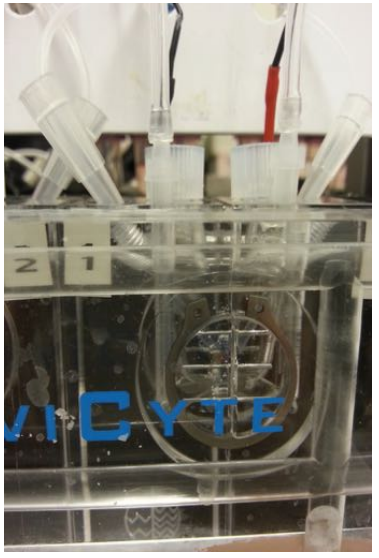
Figure 4. Effects of the wheat-derived arabinoxylan (AX) on colonic transcellular permeability in biopsies mounted in Ussing chambers. Stimulation with Compound (C) 48/80 (10 ng/ml) resulted in a significantly higher transcellular passage of horseradish peroxidase (HRP) compared to vehicle (**a**,**b**). Co-stimulation with AX (0.1 mg/ml) showed a significant decrease of C48/80-induced transcellular permeability in both elderly with GI symptoms and healthy controls (**b**). Stimulation with AX only had no significant effect on neither paracellular nor transcellular permeability compared to vehicle. *p < 0.05, **p < 0.01, ***p < 0.001, ns = non-significant. Three elderly with gastrointestinal (GI) symptoms and 2 healthy controls had to be excluded from the FITC-analysis due to technical problems, hence elderly with GI symptoms; n = 15 and healthy controls; n = 19 (AX only, n = 13).

Ussing chamber/ intestinal permeability

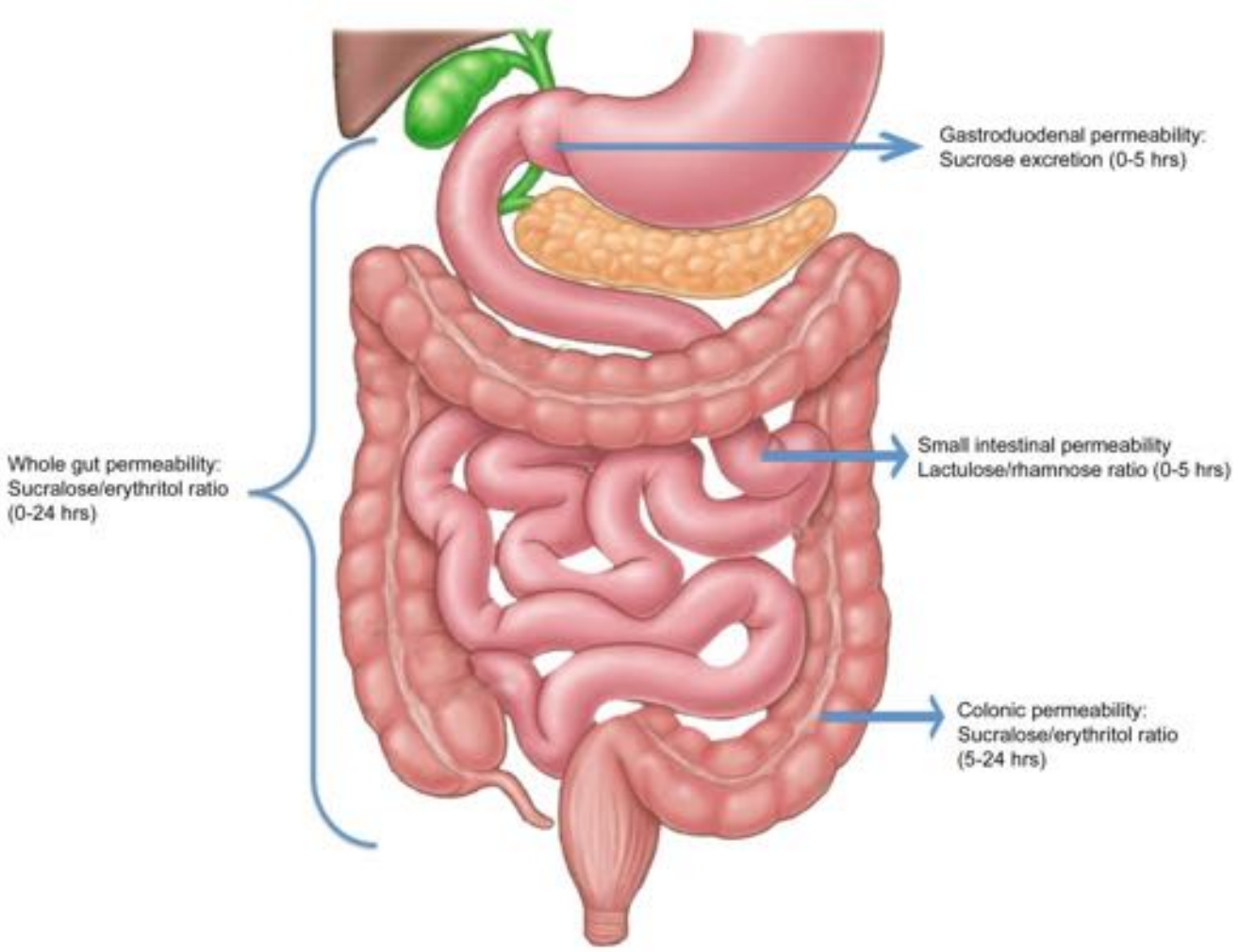




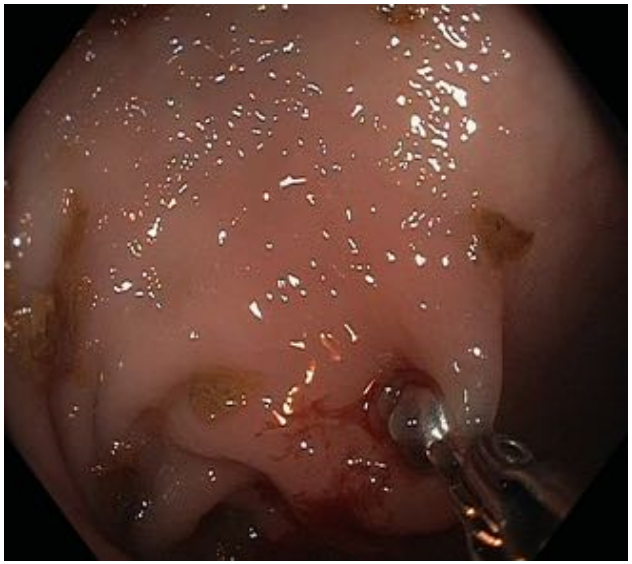


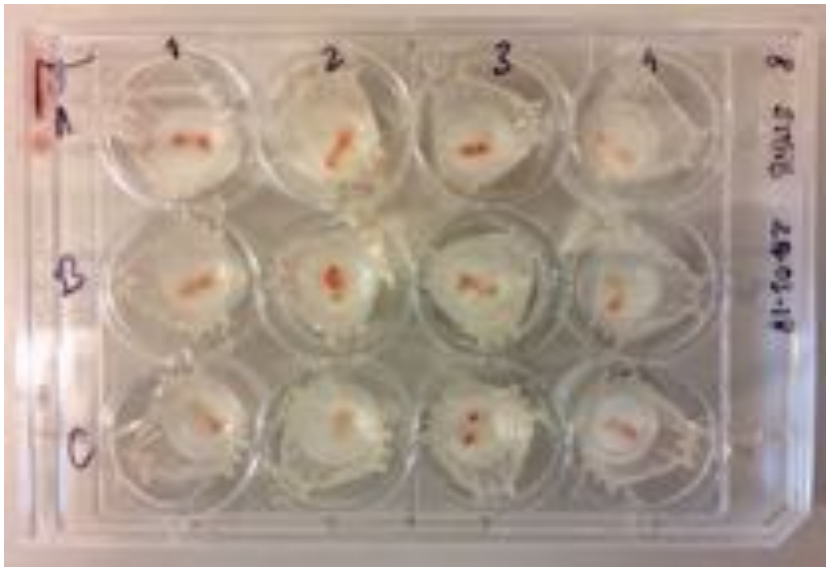


Non-invasive multi-sugar test



Ex-vivo stimulation of intestinal biopsies





Inflammatory mediators, 5-HT, and brain function

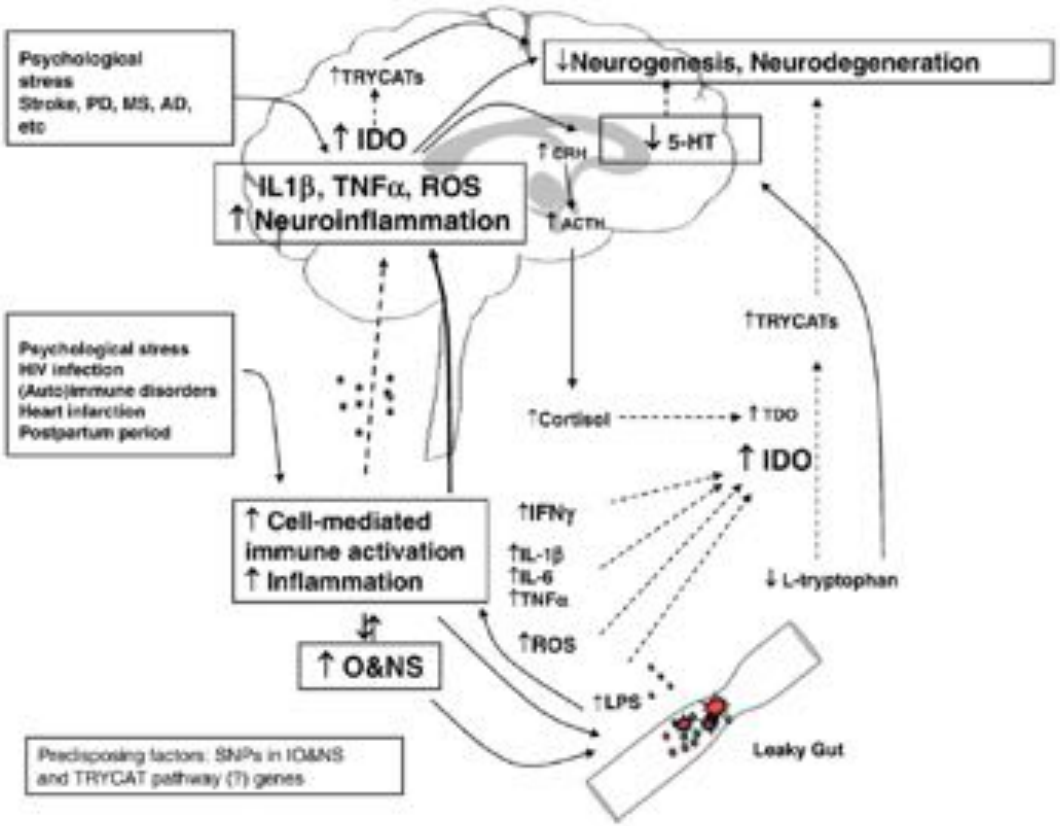
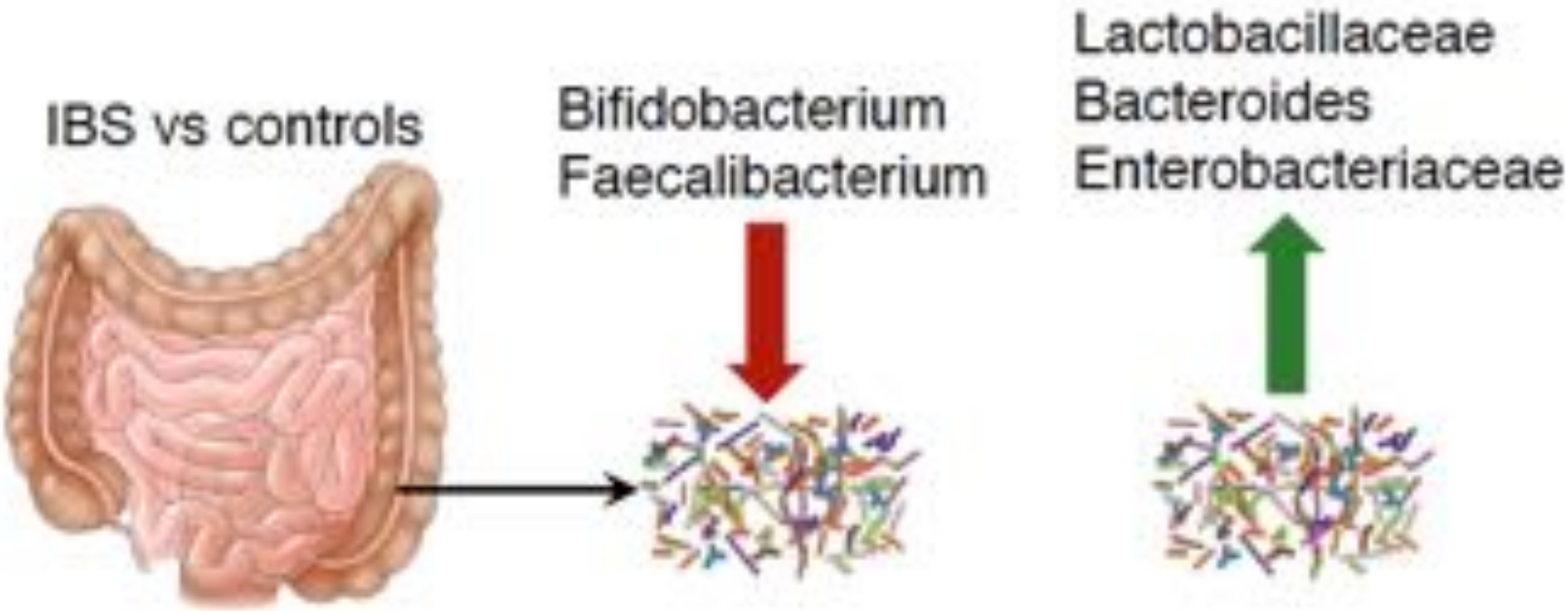


Fig. 4. The TRYCAT pathway and indoleamine 2,3-dioxygenase (IDO) and their interconnections with peripheral and central immune, inflammatory, oxidative and nitrosative stress (IO&NS) pathways. In depressive conditions, peripheral IDO activation may occur following induction by increased levels of cytokines, 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).

Knowledge Gaps in Gut-Brain Interaction

- The specificity of alterations in gut microbiota (disorders)

Microbial composition in IBS



Please cite this article as: Pittayanon R, Lau JT, Yuan Y, Leontiadis GI, Tse F, Surette M, Moayyedi P, Gut Microbiota in Patients With Irritable Bowel Syndrome—a Systematic Review, *Gastroenterology* (2019), doi: https://doi.org/10.1053/j.gastro.2019.03.049.

Microbial composition in IBS

Alterations of Gut Microbiota in Patients With Irritable Bowel Syndrome Based on 16S rRNA-Targeted Sequencing: A Systematic Review

Ruqiao Duan, MD[2], Shiwei Zhu, MD[1], Ben Wang, MD[2] and Liping Duan, MD[1]

INTRODUCTION: Alterations of gut microbiota have been thought to be associated with irritable bowel syndrome (IBS). Many studies have reported significant alterations of gut microbiota in patients with IBS based on 16S ribosomal RNA-targeted sequencing. However, results from these studies are inconsistent or even contradictory. We performed a systematic review to explore the alterations of gut microbiota in patients with IBS compared with healthy controls (HCs).

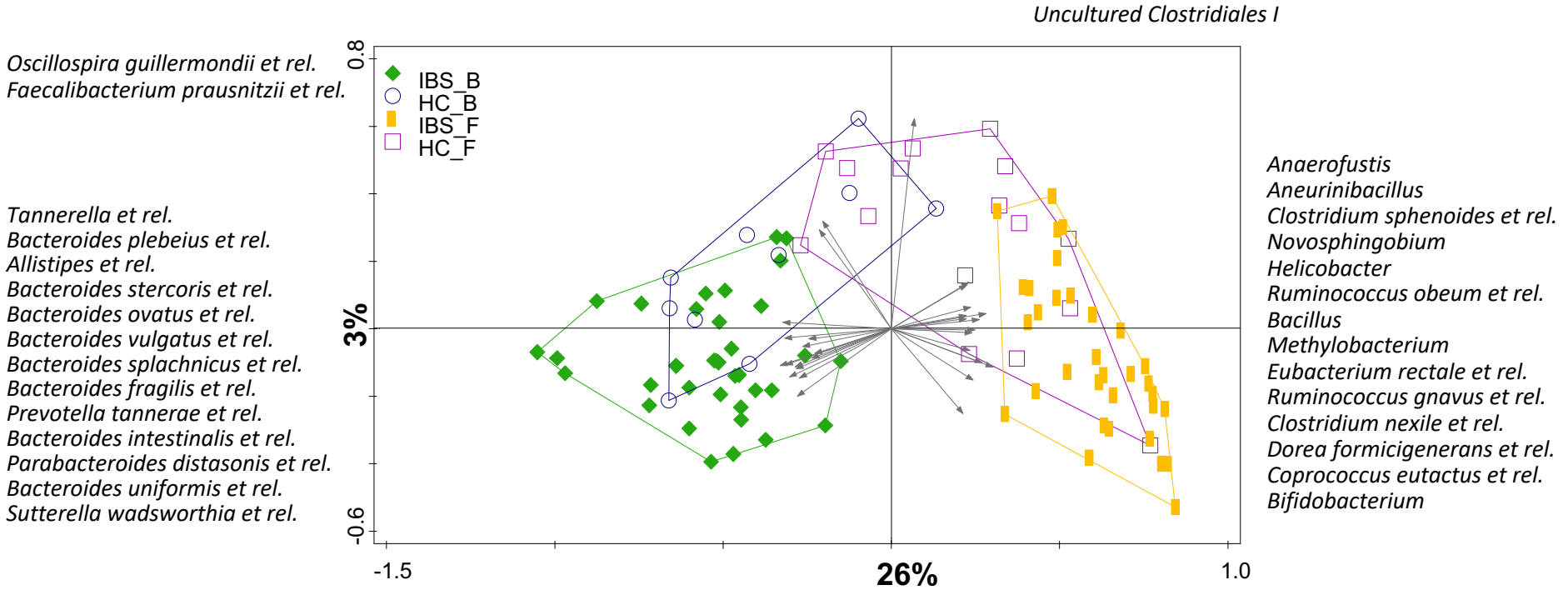
METHODS: The databases PubMed, Cochrane Library, Web of Science, and Embase were searched for studies published until February 28, 2018, for case–control studies detecting gut microbiota in patients with IBS. Methodological quality was assessed using the Newcastle–Ottawa Scale. The α-diversity and alterations of gut microbiota in patients with IBS compared with HCs were analyzed.

RESULTS: Sixteen articles involving 777 patients with IBS and 461 HCs were included. Quality assessment scores of the studies ranged from 5 to 7. For most studies, patients with IBS had a lower α-diversity than HCs in both fecal and mucosal samples. Relatively consistent changes in fecal microbiota for patients with IBS included increased Firmicutes, decreased Bacteroidetes, and increased Firmicutes:Bacteroidetes ratio at the phylum level, as well as increased Clostridia and Clostridiales, decreased Bacteroidia and Bacteroidales at lower taxonomic levels. Results for mucosal microbiota were inconsistent.

CONCLUSIONS: Alterations of gut microbiota exist in patients with IBS and have significant association with the development of IBS. Further studies are needed to draw conclusions about gut microbiota changes in patients with IBS.

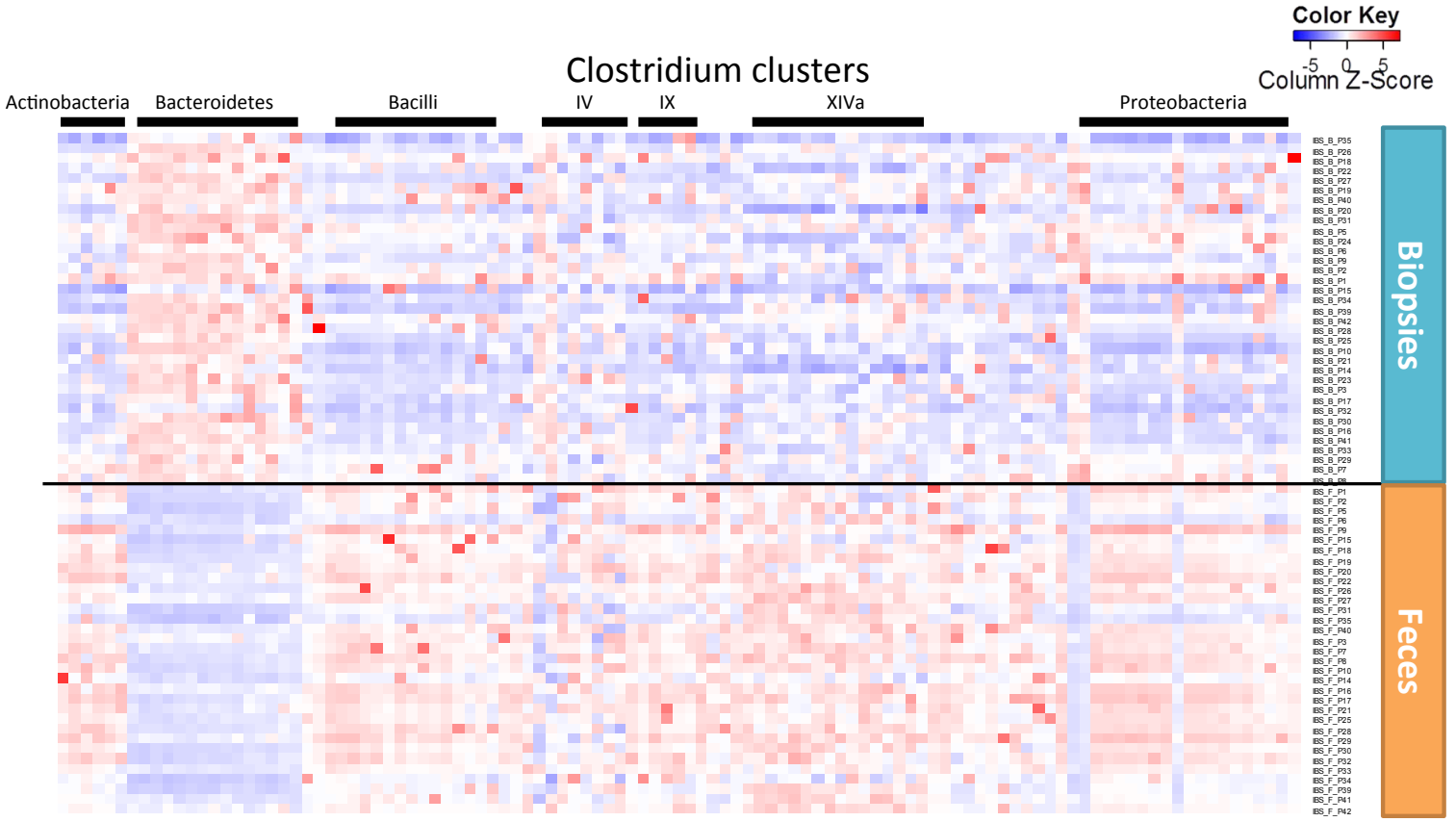
TRANSLATIONAL IMPACT: This knowledge might improve the understanding of microbial signatures in patients with IBS and would guide future therapeutic strategies.

Redundancy analysis (RDA) of faecal and mucosal microbiota in IBS and healthy subjects

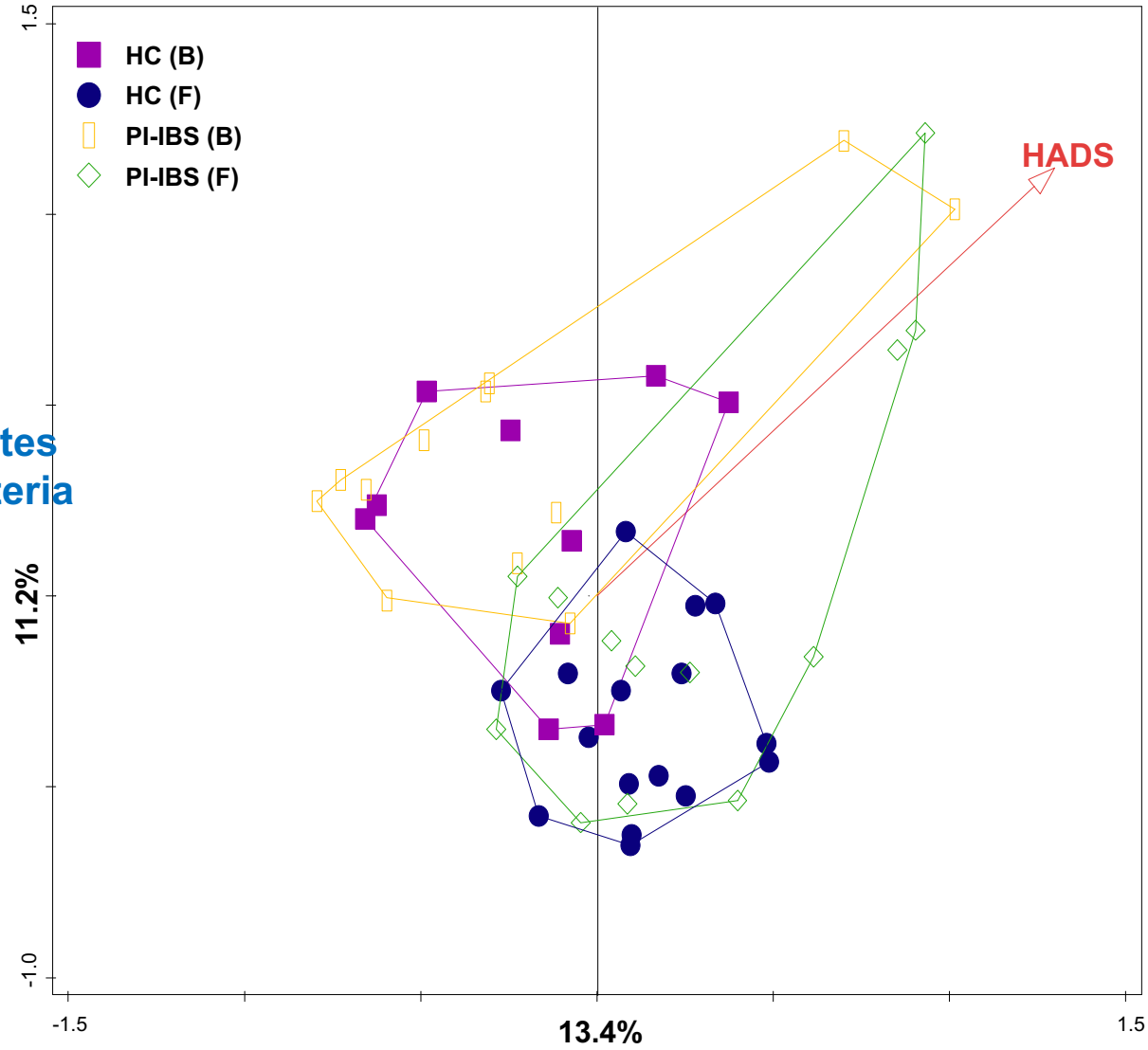


Sundin J et al, Aliment Pharmacol Ther 2015;41:342-51

Faecal and mucosal microbiota in IBS



RDA plot of faecal and mucosal microbiota in PI-IBS and HC



Bacteroidetes
(*Prevotella*)

Bacteroidetes
Proteobacteria

C. clusters IV & XIVa

Sundin J et al, Aliment Pharmacol Ther 2015;41:342-51

Microbial composition in IBS

What is the reason for these inconsistent results?

Microbial metabolites in IBS

Systematic Review and Meta-Analysis

Medicine

OPEN

Alterations in fecal short-chain fatty acids in patients with irritable bowel syndrome

A systematic review and meta-analysis

Qinghua Sun, MD, Qiong Jia, PhD, Lijin Song, MD, Liping Duan, MD*

Summary of meta-analytical results.

IBS Patients vs HC

Measurement	Number of studies	Model	Overall SMD (IBS – HC)	95% CI	SMD Significance (*P* value)	I^2 (%)	Heterogeneity Significance (*P* value)
Amount of acetate	8	Fixed effect	0.05	[−0.16, 0.27]	.62	44	.09
Proportion of acetate	4	Fixed effect	−0.27	[−0.59, 0.05]	.09	57	.07
Amount of propionate	8	Random effects	−0.04	[−0.52, 0.44]	.86	76	<.01
Proportion of propionate	**4**	**Fixed effect**	**0.44**	**[0.12, 0.76]**	**< .01**	**0**	**.58**
Amount of butyrate	7	Fixed effect	0.12	[−0.11, 0.35]	.31	50	.06
Proportion of butyrate	4	Random effects	0.05	[−0.68, 0.78]	.89	80	<.01
Amount of isobutyrate	4	Random effects	−0.15	[−0.91, 0.60]	.69	81	<.01
Proportion of isobutyrate	4	Fixed effect	0.25	[−0.07, 0.56]	.13	0	.47
Amount of valerate	4	Fixed effect	−0.03	[−0.35, 0.28]	.84	51	.11
Proportion of valerate	4	Random effects	−0.19	[−1.07, 0.69]	.67	86	<.01
Amount of isovalerate	4	Random effects	−0.38	[−1.18, 0.42]	.35	83	<.01
Proportion of isovalerate	4	Random effects	−0.43	[−1.54, 0.69]	.45	91	<.01

Subgroup analysis: IBS-C vs HC

Measurement	Number of studies	Model	Overall SMD (IBS-C – HC)	95% CI	SMD Significance (*P* value)	I^2 (%)	Heterogeneity Significance (*P* value)
Amount of acetate	2	Fixed effect	−0.43	[−0.91, 0.05]	.08	0	.92
Amount of propionate	**2**	**Fixed effect**	**−0.91**	**[−1.41, −0.41]**	**< .01**	**0**	**.82**
Amount of butyrate	**2**	**Fixed effect**	**−0.53**	**[−1.01, −0.04]**	**.03**	**37**	**.21**

Subgroup analysis: IBS-D vs HC

Measurement	Number of studies	Model	Overall SMD (IBS-D – HC)	95%-CI	SMD Significance (*P* value)	I^2 (%)	Heterogeneity Significance (*P* value)
Amount of acetate	3	Random effects	−0.08	[−0.75, 0.58]	.80	70	.04
Amount of propionate	3	Random effects	−0.38	[−1.53, 0.78]	.52	89	<.01
Amount of butyrate	**3**	**Fixed effect**	**0.34**	**[0.00, 0.67]**	**.05**	**26**	**.26**

Knowledge Gaps in Gut-Brain Interaction

- The specificity of alterations in gut microbiota (disorders)
- Why probiotics do(n't) work?

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.

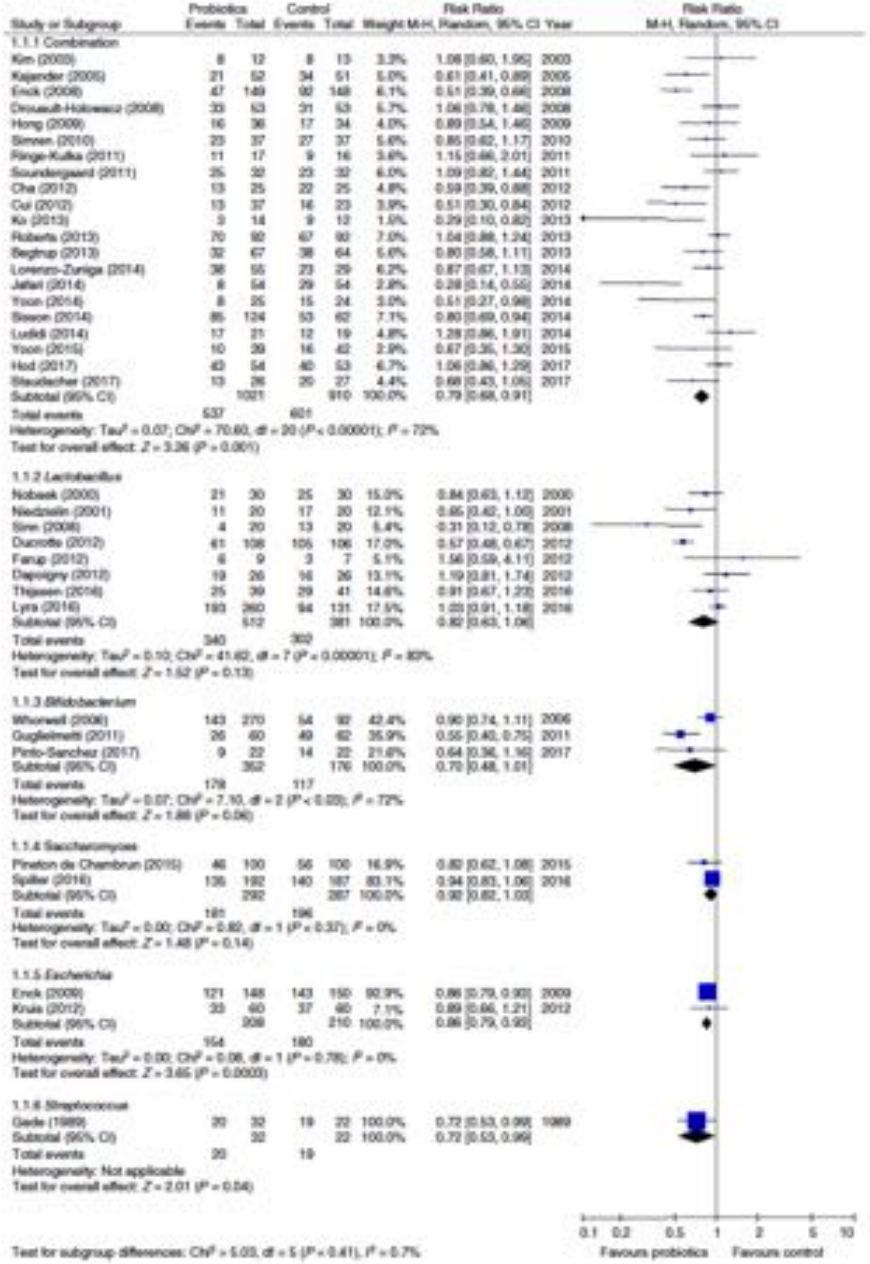


FIGURE 2 Forest plot of randomised controlled trials of probiotics vs placebo in irritable bowel syndrome: effect on persistence of symptoms

Knowledge Gaps in Gut-Brain Interaction

- The specificity of alterations in gut microbiota (disorders)
- Why probiotics do(n't) work?
- FMT!?

FMT – Consensus report

AP&T Alimentary Pharmacology and Therapeutics

Consensus report: faecal microbiota transfer – clinical applications and procedures

J. König*, A. Siebenhaar†, C. Högenauer‡, P. Arkkila§, M. Nieuwdorp¶,**, T. Norén*, C. Y. Ponsioen¶, U. Rosien†, N. G. Rossen¶, R. Satokari§, A. Stallmach††, W. de Vos§,‡‡, J. Keller†,a & R. J. Brummer*,a

*Örebro, Sweden.
†Hamburg, Germany.
‡Graz, Austria.
§Helsinki, Finland.
¶Amsterdam, The Netherlands.
**Gothenburg, Sweden.
††Jena, Germany.
‡‡Wageningen, The Netherlands.

Aliment Pharmacol Ther 2017; **45**: 222–239

FMT - IBS

FMT in irritable bowel syndrome (IBS)

Key recommendations on FMT in IBS

	Level of evidence	Level of agreement
FMT in IBS should only be performed in a research setting	N/A	100%
Primarily IBS patients in whom a disturbed microbiota seems to be present should be included in studies, i.e. patients who: (i) developed IBS or experienced deteriorated IBS symptoms after a gastrointestinal infection (post-infectious IBS) (ii) developed IBS or experienced deteriorated IBS symptoms after antibiotic treatment	LOW	90%
Preferably IBS patients in whom standard treatments (such as dietary changes, smooth muscle relaxants and reassurance therapy) have failed should be selected for studies	LOW	90%
No evidence for a specific route is available so far, but administration of the transplant in the proximal, right colon, by colonoscopic procedure, seems preferable	LOW	80%
Placebo-controlled study design is important as placebo response in IBS is known to be high (40%)	HIGH	100%

Aliment Pharmacol Ther 2017; 45: 222–239

FMT - IBS

The Effect of Allogenic Versus Autologous Fecal Microbiota Transfer on Symptoms, Visceral Perception and Fecal and Mucosal Microbiota in Irritable Bowel Syndrome: A Randomized Controlled Study

Savanne Holster, MSc[1], Carl Mårten Lindqvist, PhD[1], Dirk Repsilber, PhD[1], Anne Salonen, PhD[2], Willem M. de Vos, PhD[2,3], Julia König, PhD[1] and Robert J. Brummer, MD, PhD[1]

Study Highlights

WHAT IS KNOWN

- ✓ Gut microbiota might play a role in the pathophysiology of IBS.
- ✓ FMT has been suggested as a potential treatment to improve symptoms in IBS.

WHAT IS NEW HERE

- ✓ A single FMT by colonoscopy may have beneficial effects in IBS.
- ✓ Allogenic FMT (stool from healthy donors) does not seem to be significantly superior to autologous FMT (own stool).
- ✓ FMT has an effect on both fecal as well as mucosal microbiota.
- ✓ Already bowel cleansing and processing of the fecal material (autologous FMT) have an effect on symptoms and fecal as well as mucosal microbial composition.

TRANSLATIONAL IMPACT

- ✓ Results of this study may give an insight in the physiological changes induced by FMT in IBS patients.

Clinical and Translational Gastroenterology 2019;10:e-00034. https://doi.org/10.14309/ctg.0000000000000034

FMT-IBS - Study outline

S_x - Symptoms (GSRS-IBS, IBS-SSS)

Qs - Questionnaires (IBS-QOL, HADS, SF-36, 5Q-5D-5L)

FFQ - Food frequency

FS - Fecal sample

B_x - Biopsies

FMT - IBS

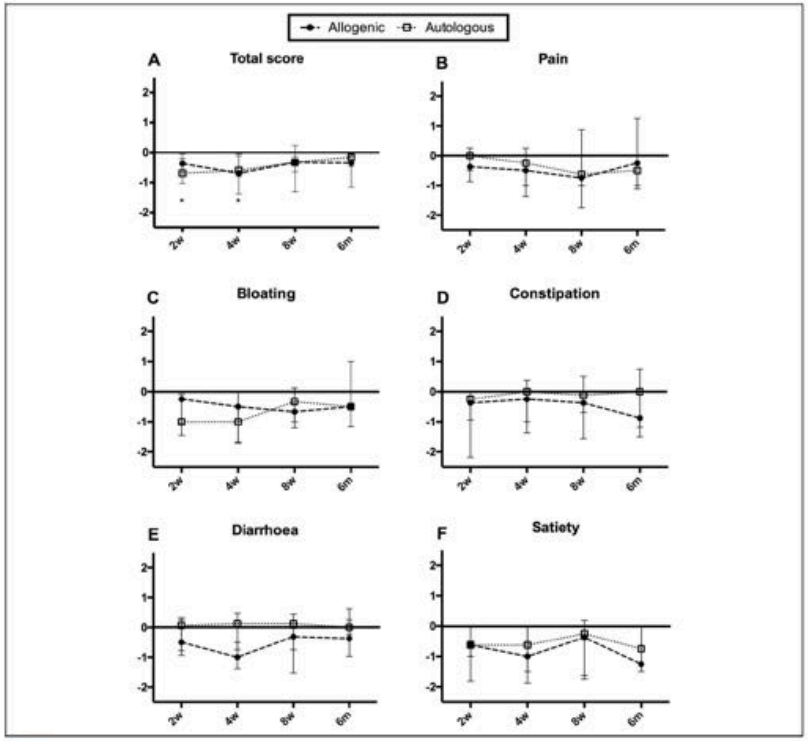


Figure 1. Baseline-corrected GSRS-IBS scores at different time points after FMT. Median and interquartile ranges (IQRs) are shown. (**a**) Total scores. (**b**–**f**) Respective subscores. No statistical significance was found between the allogenic and the autologous groups. In the allogenic group, total scores were significantly reduced 2 weeks and 4 weeks after FMT compared with baseline. * $P < 0.05$. GSRS-IBS, gastrointestinal symptom rating scale, IBS version.

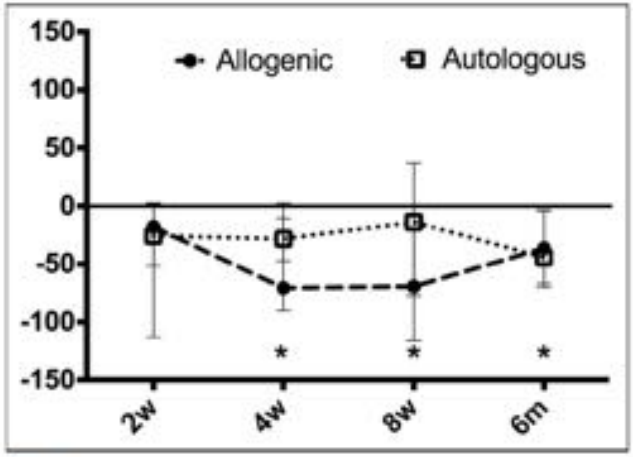


Figure 2. Baseline-corrected IBS-SSS scores at different time points after fecal microbiota transfer (FMT). Median and interquartile ranges (IQRs) are shown. No statistical significant differences were found between the allogenic and the autologous groups. In the allogenic group, total scores were significantly reduced 4 weeks, 8 weeks, and 6 months after FMT compared to baseline. * $P < 0.05$. IBS-SSS, IBS-severity scoring system.

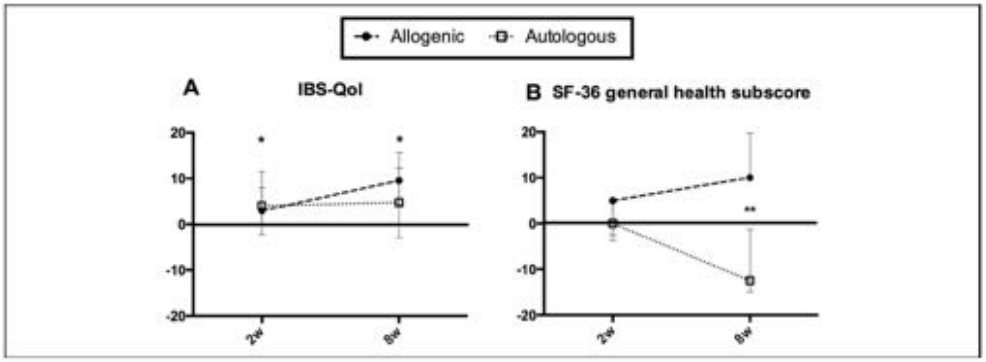
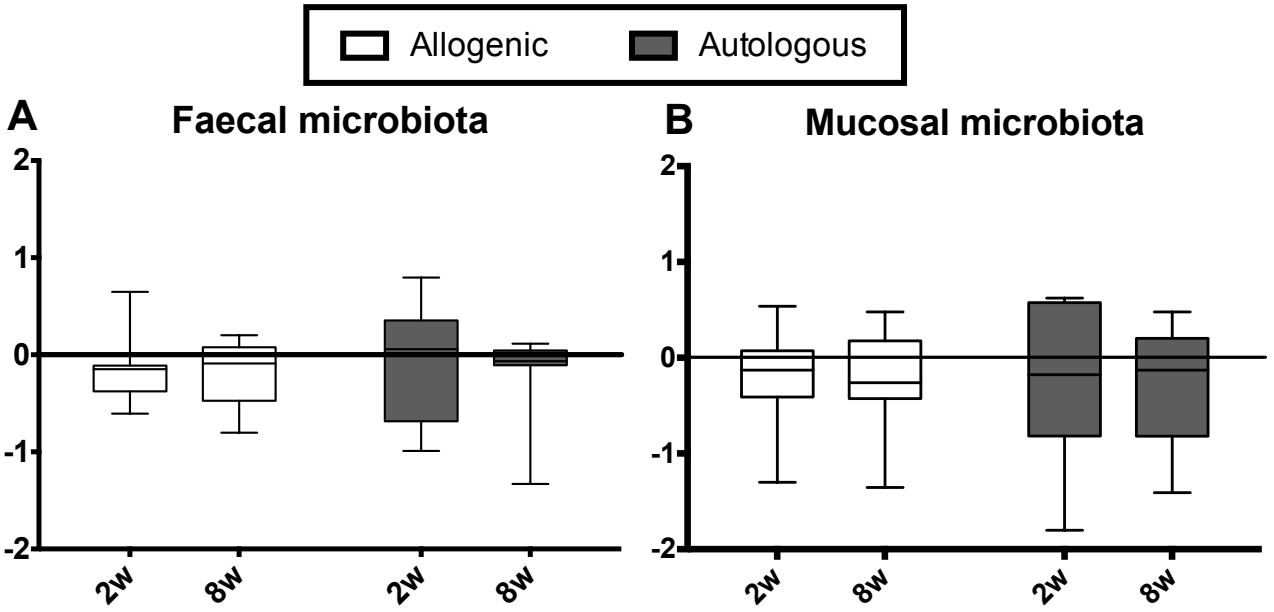


Figure 3. Baseline-corrected quality of life (IBS-QoL) and health status (SF-36) scores at different time points after fecal microbiota transfer (FMT). Median and interquartile ranges (IQRs) are shown. (**a**) IBS-QoL scores. No statistical significant differences were found between the allogenic and the autologous groups. In the allogenic group, total scores were significantly increased 2 weeks and 8 weeks after FMT compared with baseline. * $P < 0.05$. (**b**) Short form 36 (SF-36) subscore general health. Scores differed significantly between the allogenic and the autologous groups 8 weeks after FMT. ** $P < 0.01$.

Clinical and Translational Gastroenterology 2019;10:e-00034. https://doi.org/10.14309/ctg.0000000000000034

FMT - IBS



Baseline-corrected **Shannon diversity index** in faecal (A) and mucosal (B) samples two and eight weeks after FMT. No significant differences were found.

Clinical and Translational Gastroenterology 2019;10:e-00034. https://doi.org/10.14309/ctg.0000000000000034

IBS – FMT gene expression

Table 1: Number of significantly up-and downregulated Gene Set Enrichment Analysis pathways.

Comparisons	Allogenic FMT		Autologous FMT	
	Upregulated pathways	Downregulated pathways	Upregulated pathways	Downregulated pathways
2 weeks after FMT versus baseline	161	0	3	37
8 weeks after FMT versus baseline	24	38	26	80
8 weeks versus 2 weeks after FMT	0	128	0	16

Pathways with a false discovery rate <0.05 were considered to be statistically significantly differentially expressed. GSEA – Gene Set Enrichment Analysis. FMT – faecal microbiota transfer.

Clinical and Translational Gastroenterology 2019;10:e-00034. https://doi.org/10.14309/ctg.0000000000000034

FMT – reflections

Adverse events

RCT – what control condition?

Immune *vs*. metabolic effects

Exclusion criteria donor

Etc….

FMT – Future Directions

Identify successful donor-responder match

Identify proper FMT design (route/repetitions/ etc.)

Donor preparation (anaerobe)

Synthetic stool

New indications

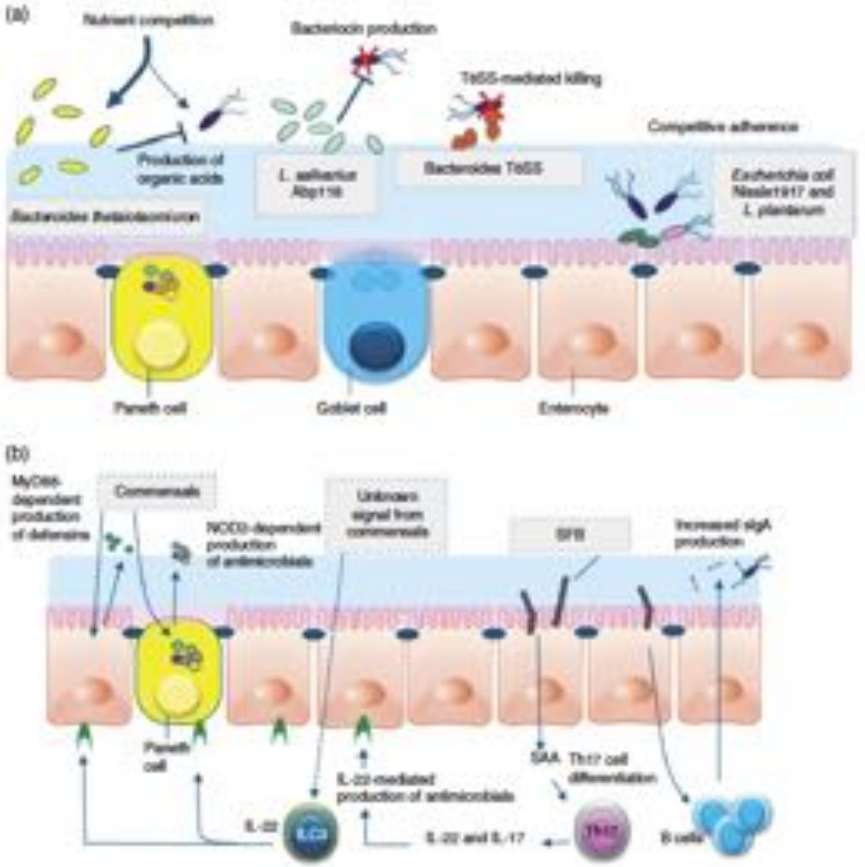
Knowledge Gaps in Gut-Brain Interaction

- The specificity of alterations in gut microbiota (disorders)
- Why probiotics do(n't) work?
- FMT!?
- Intestinal barrier function and blood brain barrier

Can probiotics modulate human disease by impacting intestinal barrier function?

Peter A. Bron[1]*†, Michiel Kleerebezem[2]†, Robert-Jan Brummer[3], Patrice D. Cani[4], Annick Mercenier[5], Thomas T. MacDonald[6], Clara L. Garcia-Ródenas[5] and Jerry M. Wells[2]

British Journal of Nutrition (2017), **117**, 93–107



Knowledge Gaps in Gut-Brain Interaction

- The specificity of alterations in gut microbiota (disorders)
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- Generally: MoA of Gut-Brain interactions in humans

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- Mental health and Gut-Brain Axis

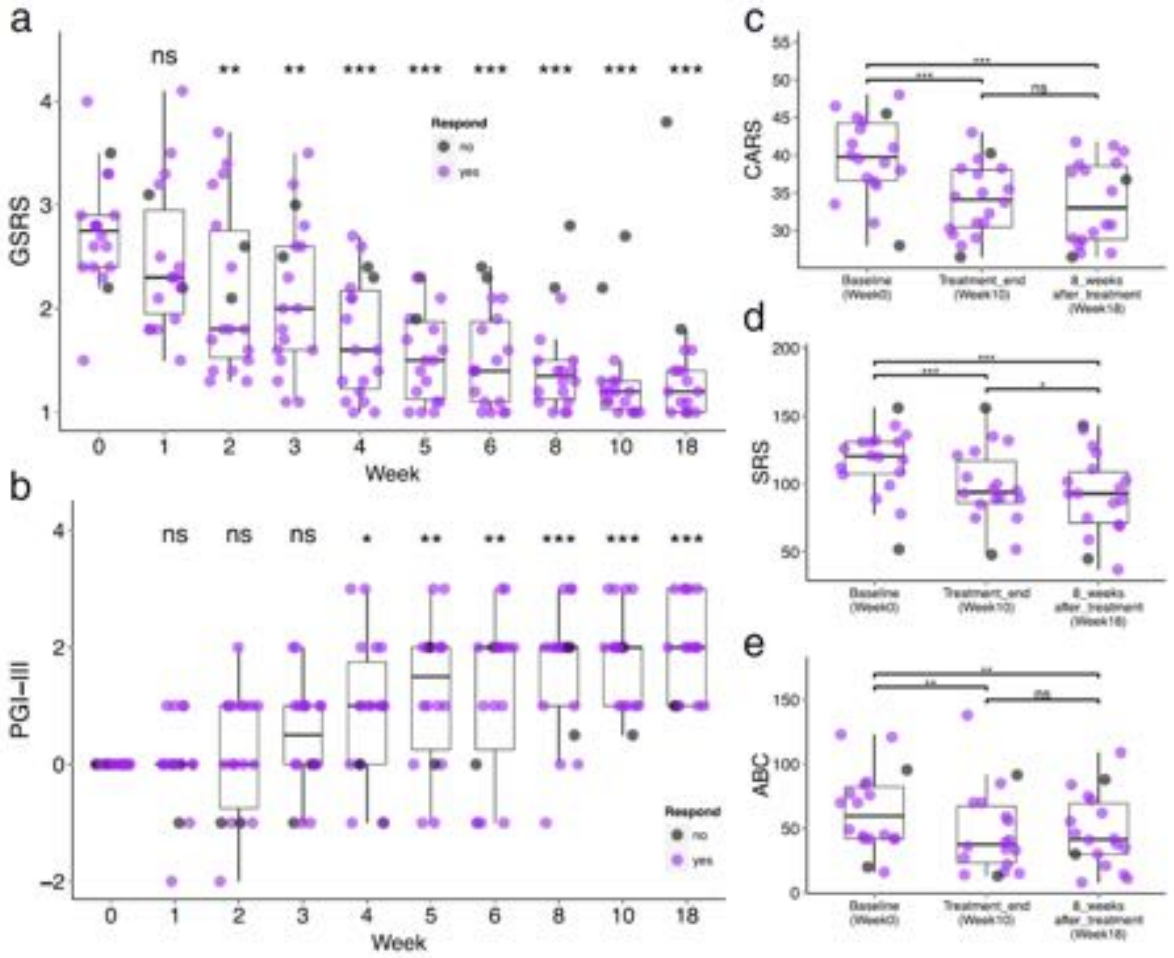
Kang et al. Microbiome (2017) 5:10
DOI 10.1186/s40168-016-0225-7

Microbiome

RESEARCH Open Access

Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study

Dae-Wook Kang[1†], James B. Adams[2†], Ann C. Gregory[3,15†], Thomas Borody[4], Lauren Chittick[5,15], Alessio Fasano[6], Alexander Khoruts[7,8,9], Elizabeth Geis[2], Juan Maldonado[1], Sharon McDonough-Means[10], Elena L. Pollard[2], Simon Roux[5,15], Michael J. Sadowsky[8,11], Karen Schwarzberg Lipson[12], Matthew B. Sullivan[3,5,15,16*], J. Gregory Caporaso[12,13*] and Rosa Krajmalnik-Brown[1,14*]



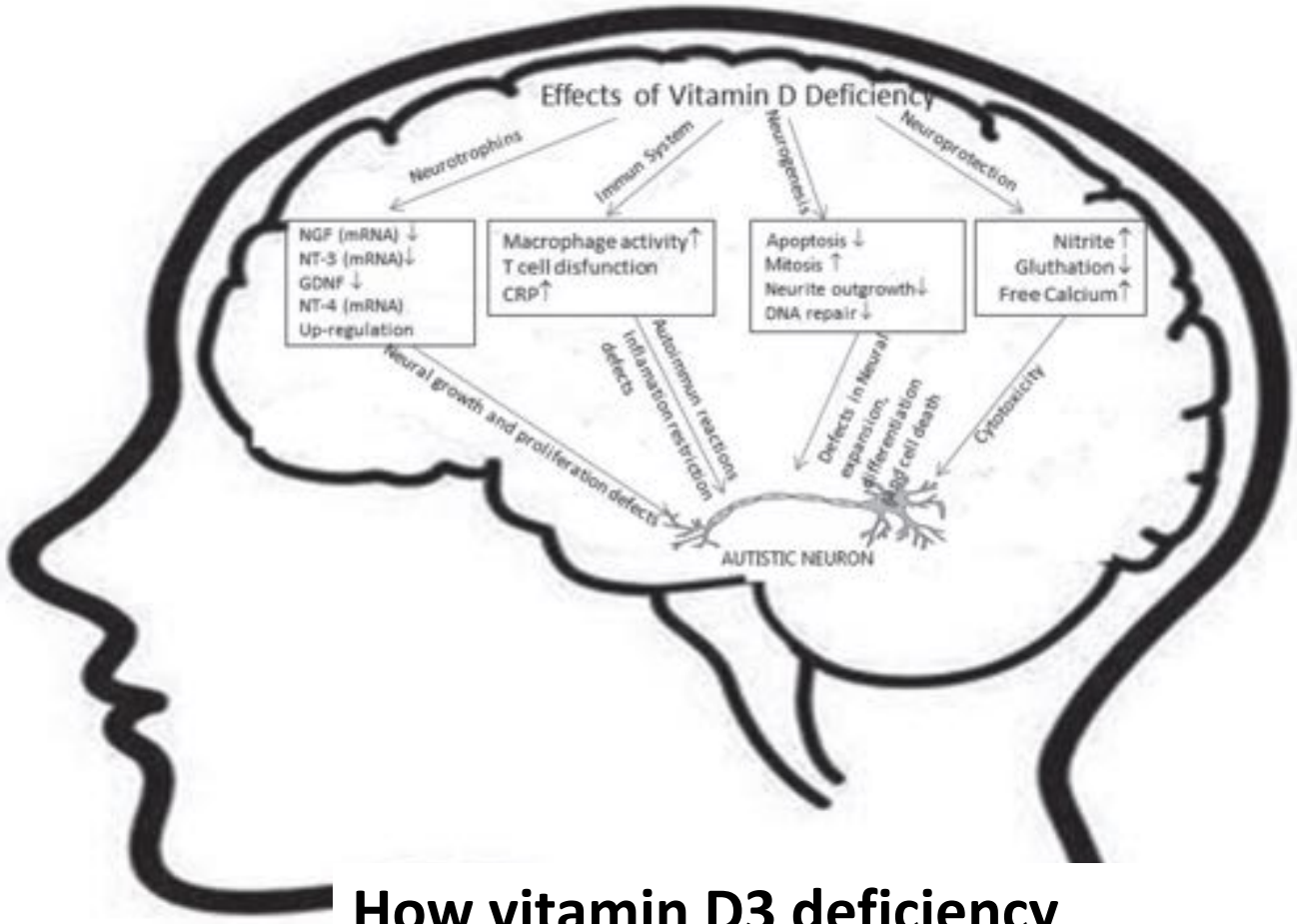
a) Gastrointestinal symptom rating scale

b) Parent global impressions-III

c) Childhood autism rating scale

d) Social responsiveness scale

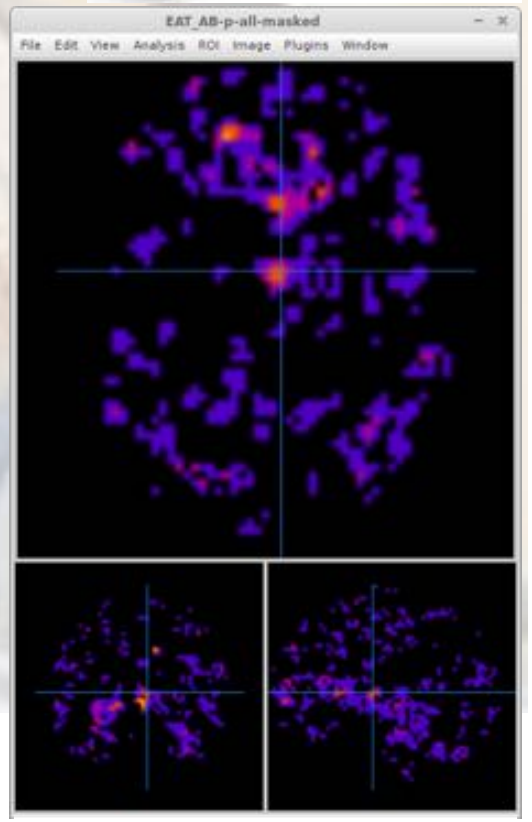
e) Aberrant behavior checklist



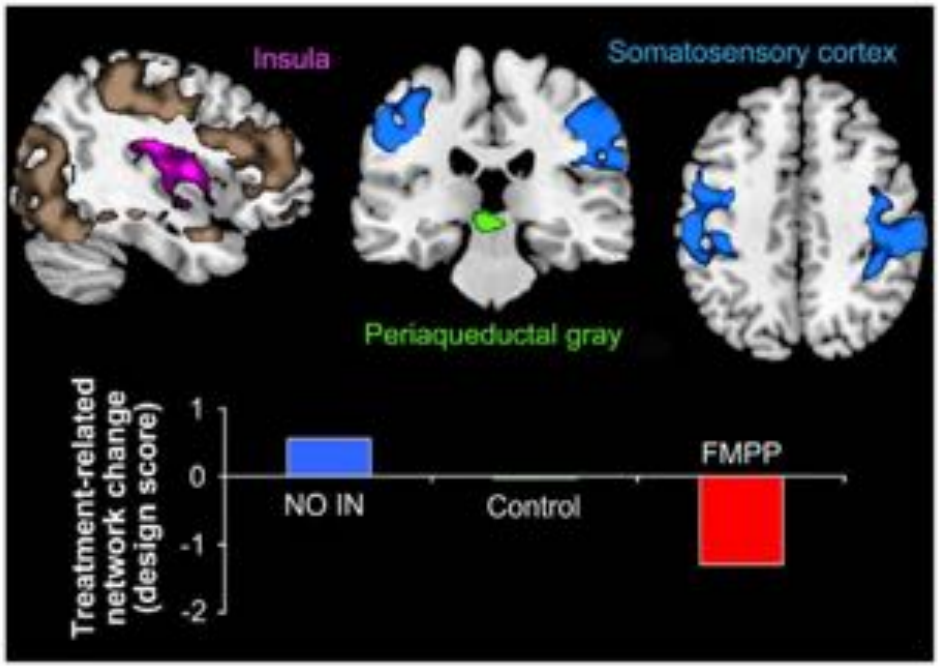
How vitamin D3 deficiency might form an ‘autistic’ neuron

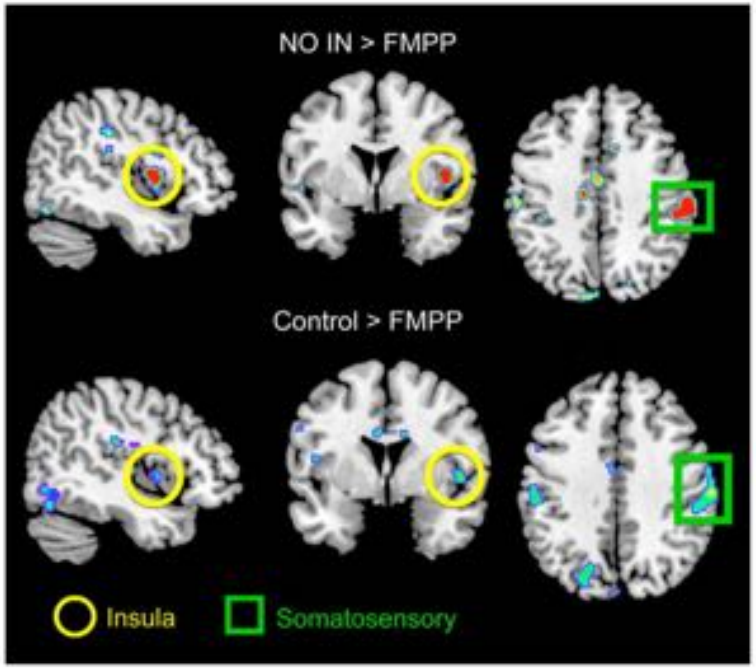
Functional brain imaging (fMRI) can be used to study …

- How/where the brain perceives signals from elsewhere in the body
- How these signals are processed and which brain centers are involved
- How the brain interacts with in/external signals, such as food intake, gut microbiome
- How e.g. mood or stress affects these processes



Dietary intervention affects brain responses



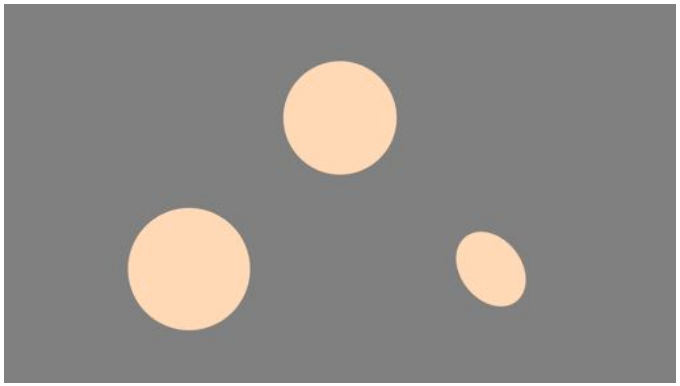


Tillisch et al., 2013

fMRI paradigm

"EAT" paradigm = Emotional Attention Task

Liebermann et al., 2007



Match shapes (MS)

Match emotions (ME)

Analysis model: ME - MS

Knowledge Gaps in Gut-Brain Interaction

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- Why probiotics do(n't) work?
- FMT!?
- Intestinal barrier function and blood brain barrier
- Generally: MoA of Gut-Brain interactions in humans
- Mental health and Gut-Brain Axis
- Personalised strategy

Knowledge Gaps in Gut-Brain Interaction

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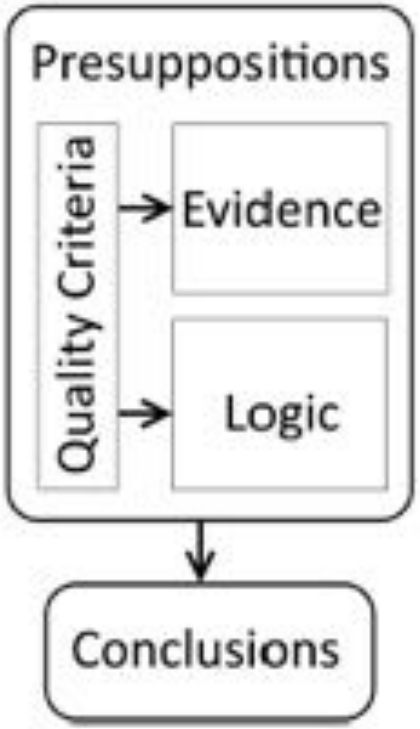
- Mental health and Gut-Brain Axis
- Personalised strategy
- The RCT issue

Perspective: Fundamental Limitations of the Randomized Controlled Trial Method in Nutritional Research: The Example of Probiotics

Dennis Zeilstra,[1] Jessica A Younes,[2] Robert J Brummer,[3] and Michiel Kleerebezem[4]

[1]Independent researcher, Nutriz, Enschede, The Netherlands; [2]Winclove Probiotics, Amsterdam, The Netherlands; [3]Nutrition-Gut-Brain Interactions Research Centre, Faculty of Health and Medicine, School of Medical Sciences, Örebro University, Örebro, Sweden; and [4]Host Microbe Interactomics Group, Wageningen University, Wageningen, The Netherlands

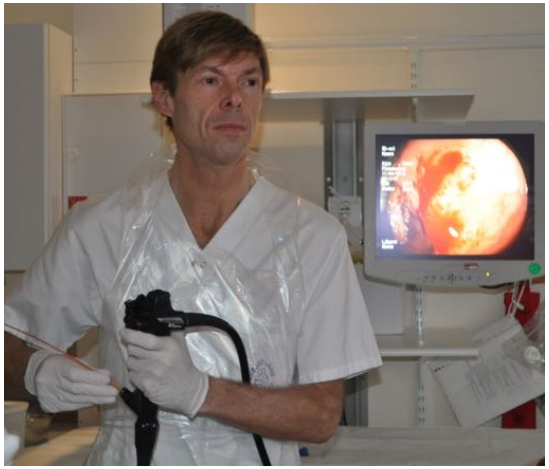
Adv Nutr 2018;9:1–11

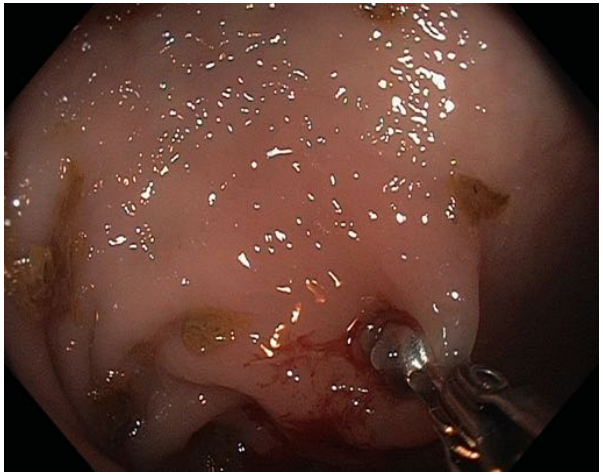


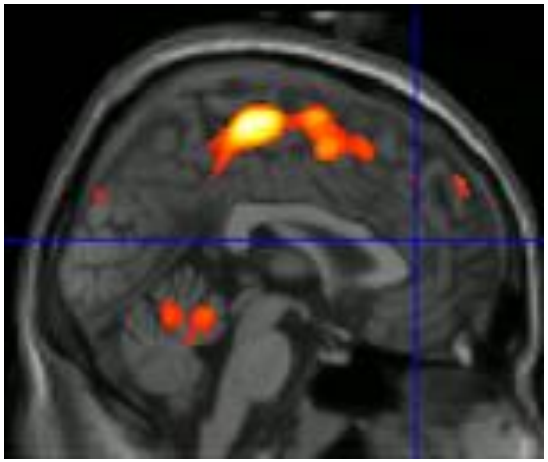
Presuppositions:

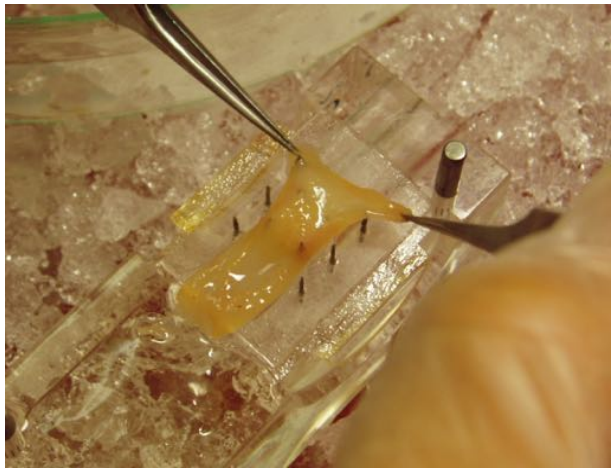
- Uniformity/ effect modifying factors
- Independence of effects/ interactions
- Intervention/placebo well defined

Bridging science and practice….









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- providing new innovations for improving gut health and brain function