


**Wellness from Within:**  
Novel Insights into the Microbiota-Gut-Brain axis  
for Metabolic and Mental Health

**Dr. Harriët Schellekens**  
Lecturer in Anatomy & Neuroscience

[HSchellekens - Google Scholar](#)

 [@harschellekens](#)



The gut-brain axis: A gut feeling.....



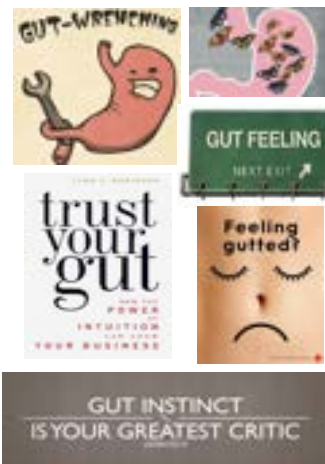
*"All diseases begin in the gut"*  
Hippocrates (c. 460 – c. 370 BC)

*"Let food be thy medicine and  
medicine be thy food"*

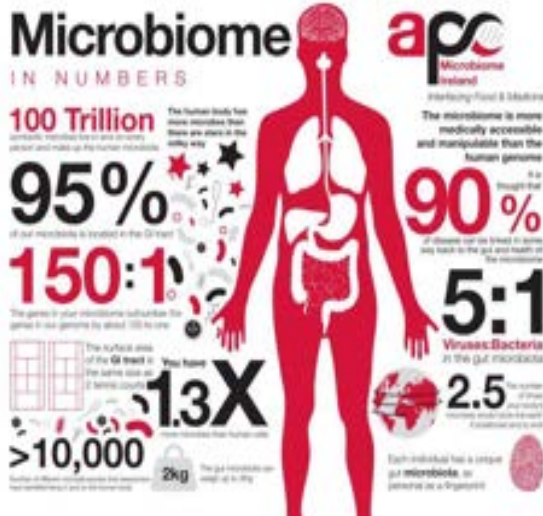
*"A healthy diet is essential  
for a healthy gut and a  
healthy mind"*



**...language of gut-brain**



# The gut-brain axis: Living in a Microbial world...



The last decade has seen an enormous expansion on our knowledge of the microbiome.

Humans and other animals share a mutualistic relationship with resident microorganisms



mind your microbiome

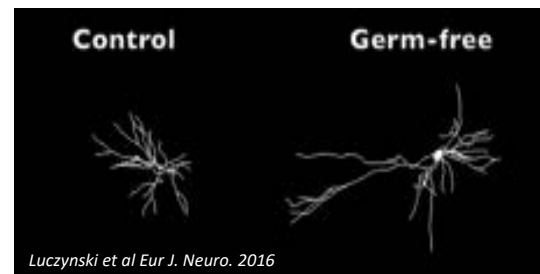
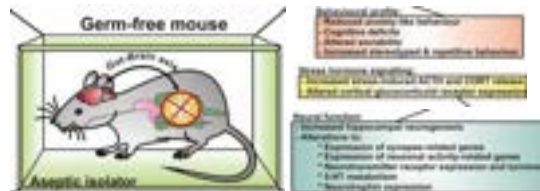
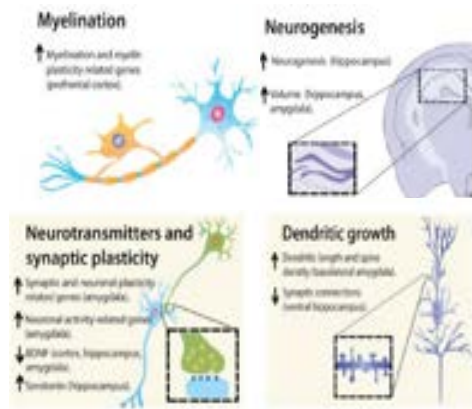
The microbiota contributes to host energy metabolism and alter the way we store fat, how we balance levels of glucose in the blood, and how we respond to hormones that make us feel hungry or full.

Gut microbiota can shape brain and behaviour.

# The Evidence: The gut microbiota is critical for brain and behavior



Without microbes, brains do NOT develop normally



Clarke et al., Mol Psychiatr 2013; Hoban et al. Trans Psychiatr 2016; Hoban et al., Mol Psychiatr 2017

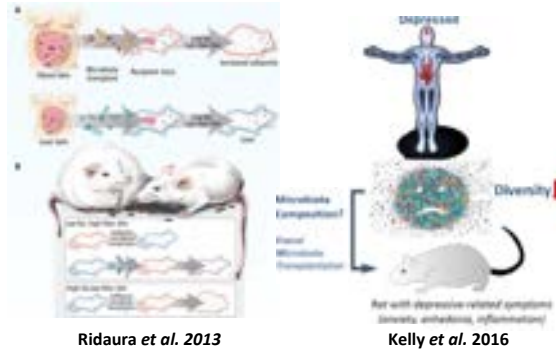
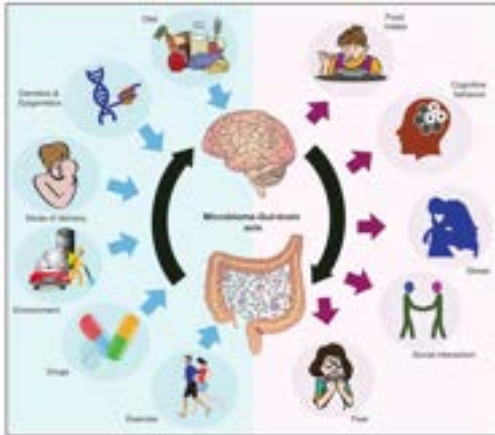
# PLEASE PASS THE MICROBIOTA!!



MICROBIOTA MEDIATOR OF GUT-BRAIN FUNCTION

TRANSFORMING FAT TO THIN

TRANSFERRING THE BLUES



Ridaura et al. 2013

Kelly et al. 2016

✓ FMT has illustrated the *influence of microbiota on our METABOLIC AND MENTAL HEALTH*

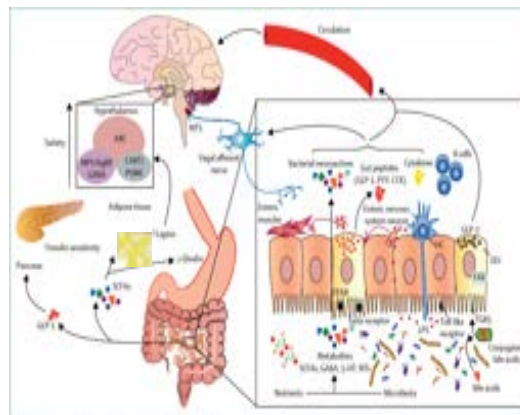
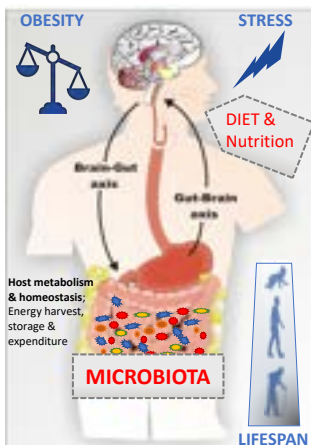
# Microbiome-Gut-Brain Axis in Obesity & Stress



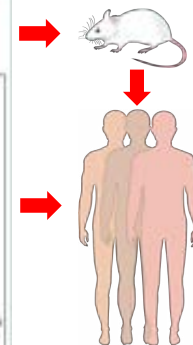
GUT-BRAIN AXIS

MOLECULAR MECHANISM

TRANSLATION

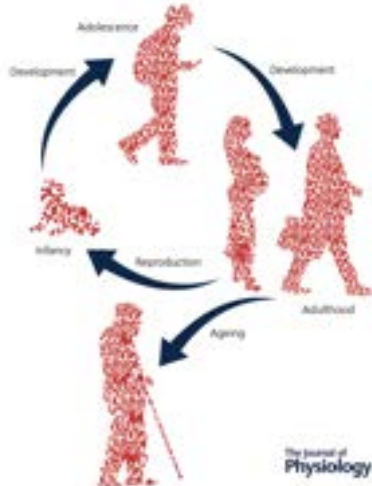


Torres-Fuentes, Schellekens, et al, Lancet Gastro & Hepat 2017



METABOLIC & MENTAL HEALTH

# Across the Lifespan



Dinan and Cryan, *J. Physiol*, 2017

Morris et al., 2020, *Current Biology* 30, 1-14  
October 5, 2020 © 2020 The Authors. Published by Elsevier Inc.  
<https://doi.org/10.1016/j.cub.2020.07.046>

## Current Biology

### Enduring Behavioral Effects Induced by Birth by Caesarean Section in the Mouse

Graphical Abstract

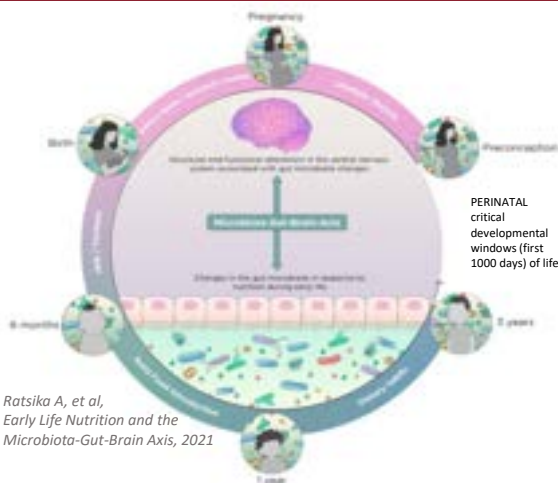
Authors  
Livia M. Morris, Anne V. Galbano, Gerard M. Whithney, Catherine Stanton, Timothy G. Dinan, John F. Cryan

Correspondence  
jcryan@but.ie

In Brief  
Recent evidence points to an important role for the microbiome in regulating brain function and behavior. Here, Morris et al. show that birth by C-section results in a different pattern of microbial colonization with long term behavioral consequences in the mouse. Targeting the gut microbiota reverses several behavioral effects of C-section.

...unique needs across the lifespan

# Priming for Life: (Early-life) Stress



Ratsika A, et al, *Early Life Nutrition and the Microbiota-Gut-Brain Axis*, 2021

JCI INSIGHT

### Identifying a biological signature of prenatal maternal stress

James M. Rivera, Ali S. Shalika, Fergus R. McCarthy, Louise C. Boney, James M. Collins, Sarah P. Brennan, Gillian Brown, John F. Cryan, Florentin G. Blaud, Gerard Clarke, and Subhrajit M. Bhattacharya

- MILK FAT GLOBULE, POLYPHENOLS, FISH OIL, OMEGAs, FATTY ACIDS, PREBIOTICS, PROBIOTICS

[O'Mahony et al., *Eur J Neurosci*. 2020; Neufeld et al., *Neuronal Signal*. 2020; Donoso et al., *Neurobiol Stress*. 2020; Schverer et al., *Neurosci Biobehav Rev*. 2020; Egerton et al., *Nutr Neurosci*. 2020; Provensi, et al., *PNAS*, 2019; Donoso et al., *Int J Neuropsychopharmacol*, 2019; Donoso et al., *Psychoneuroendocrinology*. 2020; Butler et al., *Nutrients*, 2020]

# Microbiota and ageing: FOREVER YOUNG?



Brain, Behavior, and Immunity

Special Issue: 8th Gut-to-Brain Axis

Spotlight Microbiota: Age-related alterations in microbial gut-brain axis in the mouse

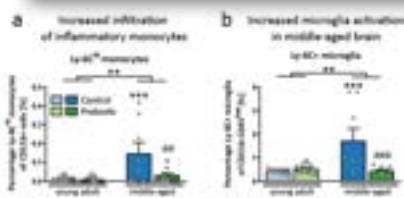
Marie Perle<sup>1</sup>, Elizabeth A. Whittam<sup>1</sup>, Jennifer J. Pender<sup>1</sup>, Jack A. Brinkley<sup>1</sup>, Laurel M. Matney<sup>1</sup>, T. Scott<sup>1</sup>, Sara Wash<sup>1</sup>, Jay Wargo<sup>1</sup>, & Paul Hain<sup>1</sup>, Catherine Stanton<sup>1</sup>, Timothy G. Dinan<sup>1</sup>, John F. Cryan<sup>1</sup>

**PREBIOTIC (OligofructoseE-Inulin)**

*Fibre-not-fast cars as answer to mid-life (microbiome) crisis!*

Mid-life microbiota crisis: middle age is associated with pervasive immunometabolic alterations that are reversed by targeting the gut microbiome

Marie Perle<sup>1</sup>, Elizabeth A. Whittam<sup>1</sup>, Jennifer J. Pender<sup>1</sup>, Jack A. Brinkley<sup>1</sup>, Laurel M. Matney<sup>1</sup>, T. Scott<sup>1</sup>, Sara Wash<sup>1</sup>, Jay Wargo<sup>1</sup>, & Paul Hain<sup>1</sup>, Catherine Stanton<sup>1</sup>, Timothy G. Dinan<sup>1</sup>, John F. Cryan<sup>1</sup>



nature aging LETTERS

Letter | Published 09 August 2021

**Microbiota from young mice counteracts selective age-associated behavioral deficits**

Marcus Bechtel<sup>1,2</sup>, Katherine E. Guzzetta<sup>1,2</sup>, Thomas F. S. Bastiaansen<sup>1,2</sup>, Marcel van de Woude<sup>1,2</sup>, Gerard M. Moloney<sup>1,2</sup>, Andreu Cusi-Grau<sup>1,2</sup>, Simon Spichak<sup>1,2</sup>, Loreta Ciavarella-Randini<sup>1,2</sup>, Patrick Fitzgerald<sup>1,2</sup>, Enrique Merino<sup>1,2</sup>, Nathaniel L. Bitt<sup>1,2</sup>, Miral Jagger<sup>1,2</sup>, Caitlin S. M. Owens<sup>1,2</sup>, Fiona Crispie<sup>1,2</sup>, Francesco Donoso<sup>1,2</sup>, Evelyn Hallgren<sup>1,2</sup>, Marta C. Neto<sup>1,2</sup>, Maria Schett<sup>1,2</sup>, Anna W. Golubeva<sup>1,2</sup>, Rachel S. Fitzgerald<sup>1,2</sup>, Marcus J. Claesson<sup>1,2</sup>, Paul D. Cocher<sup>1,2</sup>, Olivia K. O'Leary<sup>1,2</sup>, Timothy G. Dinan<sup>1,2</sup> and John F. Cryan<sup>1,2,3</sup>

**Extended Data Fig. 1 | Brained Animals** (Continued from using the experimental design of age-related alterations in the gut microbiome, prebiotic and brain monocytes, and microglia activation and behavior)

# Develop Microbiota-targeted approaches



**DIET**

**ANNUAL REVIEWS**

*Annual Review of Pharmacology and Toxicology*

**Microbiota-Gut-Brain Axis: New Therapeutic Opportunities**

Catherine Long-Smith,<sup>1</sup> Kenneth J. O'Riordan,<sup>2</sup> Gerard Clarke,<sup>1</sup> Catherine Stanton,<sup>1</sup> Timothy G. Dinan,<sup>1</sup> and John F. Cryan<sup>1,2</sup>



**Review**

**Psychobiotics: A Novel Class of Psychotropic**

Timothy G. Dinan, Catherine Stanton, and John F. Cryan

...a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illnesses

**METABOLIC & MENTAL HEALTH**

# Clinical studies supporting probiotics with anti-obesity effects



**Effect of probiotic (VSL#3) and omega-3 on lipid profile, insulin sensitivity, inflammatory markers, and gut colonization in overweight adults: a randomized, controlled trial**

*Journal of Clinical Endocrinology and Metabolism*, 2019

**Lactobacillus gasseri ESX11 Supplementation Reduces the Visceral Fat Accumulation and Waist Circumference in Obese Adults: A Randomized, Double-Blind, Placebo-Controlled Trial**

*Journal of Clinical Endocrinology and Metabolism*, 2019

**The Probiotic Strain *H. aliciae* HA4597<sup>®</sup> Improves Weight Loss in Overweight Subjects under Moderate Hypocaloric Diet: A Proof-of-Concept, Multicenter Randomized, Double-Blind Placebo-Controlled Study**

*Nutrients*, 1 June 2021

**Effects of a multi-strain probiotic supplement for 12 weeks in circulating endotoxin levels and cardiometabolic profiles of medication-naïve T2DM patients randomized clinical trial**

*Journal of Clinical Endocrinology and Metabolism*, 2020

**Effect of multi-strain probiotics (VSL#3) in weight management in overweight/obese adults: a 12-week double-blind, randomized, placebo-controlled study**

*Journal of Clinical Endocrinology and Metabolism*, 2020

**Intervention with *Akkermansia muciniphila* in obese human volunteers: a proof-of-concept exploratory study**

*Journal of Clinical Endocrinology and Metabolism*, 2020

**Probiotics With or Without Fiber Controls Body Fat Mass, Associated With Serum Zonulin, in Overweight and Obese Adults—Randomized Controlled Trial**

*Journal of Clinical Endocrinology and Metabolism*, 2020

**Targeting the Intestinal Microbiota to Prevent Type 2 Diabetes and Enhance the Effect of Metformin on Glycaemia: A Randomized Controlled Pilot Study**

*Diabetes Care*, 2020

**Improvements to postprandial glucose control in subjects with type 2 diabetes: a multicenter, double-blind, randomized placebo-controlled trial of a novel probiotic formulation**

*Journal of Clinical Endocrinology and Metabolism*, 2020

MECHANISM?

# Towards Psychobiotics: Clinical evidence



**Assessment of psychotropic-like properties of a probiotic formulation (*Lactobacillus helveticus* R01) in rats and hu**

*Journal of Clinical Endocrinology and Metabolism*, 2019

**Lost in translation? The potential psychobiotic *Lactobacillus rhamnosus* (JB-1) fails to modulate stress or cognitive performance in healthy male subjects**

*Journal of Clinical Endocrinology and Metabolism*, 2020

***Bifidobacterium longum* 1714 as a translational psychobiotic: modulation in health**

*Journal of Clinical Endocrinology and Metabolism*, 2020

***Bifidobacterium longum* 1714<sup>®</sup> Strain Modulates Brain Activity of Healthy Volunteers During Social Stress**

*Journal of Clinical Endocrinology and Metabolism*, 2020

TRANSLATION?



## Microbiota and body weight control: Weight watchers within?

MOLECULAR METABOLISM

Serena Bescaini<sup>1,2</sup>, Sarah-Jane Leigh<sup>1,2</sup>, Aoibhne Laville<sup>1,2</sup>, Rubén García-Gerard Clarke<sup>1,2</sup>, Harriet Schellekens<sup>1,2</sup>, John F. Cryan<sup>1,2,3</sup>

**ABSTRACT**

**Background:** Despite several decades of research, managing body weight remains an unmet clinical need. Individuals with dysregulated body weight, such as obesity and cachexia, exhibit several gut microbiota signatures. The gut microbiota for body weight control, as it responds to intervention and plays an important role in the biotransformation of nutrients.

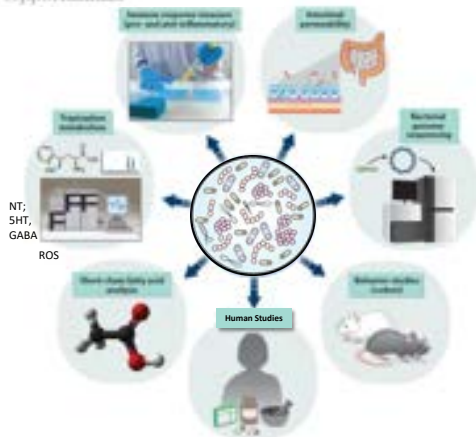
**Scope of the review:** This review provides an overview of the role of the gut microbiota in two body weight dysregulation-related disorders, namely obesity and cachexia. Second, we discuss interventions for body weight control, including caloric restriction, intermittent fasting, ketogenic diet, bariatric surgery, probiotic foods – effects on body weight and gut microbiota composition. This approach was used to identify potential targets for weight control and gut microbiota configuration.

**Major conclusions:** Despite extensive associations between body weight and gut microbiota, the translation of microbiota-related interventions for body weight control in humans. More research is needed with a combination of strategies to manage body weight and future research is needed with a combination of strategies to manage body weight and future research is needed with a combination of strategies to manage body weight.



## BUGS TO DRUGS: Pharmaceutical approach to mine microbes & metabolites

Annual Review of Pharmacology and Toxicology  
Microbiota-Gut-Brain Axis: New Therapeutic Opportunities



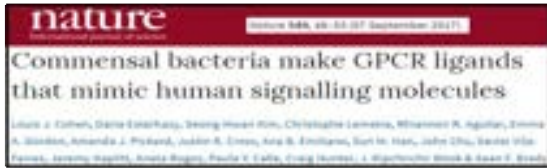
[Long-Smith, et al., 2020]

Targeted approach for the **IDENTIFICATION** of functional bacterial strains and their metabolites and to gain **MECHANISTIC** insight into gut bacteria-derived metabolites as modulators gut-brain axis function



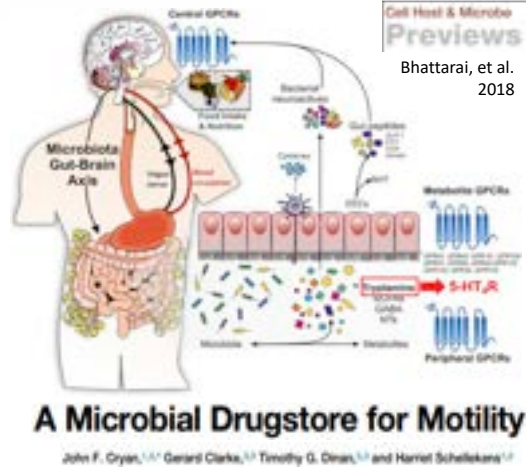
Human GPCRs cell lines currently available: GHS-R1a, OXTR, VP, 5-HT2A, 5-HT2B, 5-HT2C, GLP-1R, MCR3, D1, D2, CB1

# The Gut Feeling: GPCRs Enlighten the Way for Gut Microbiota-Metabolite Bioactivity



Microbiota-derived GPCR ligands impact local and systemic host physiology

MINE MICROBES FOR GPCR MODULATION



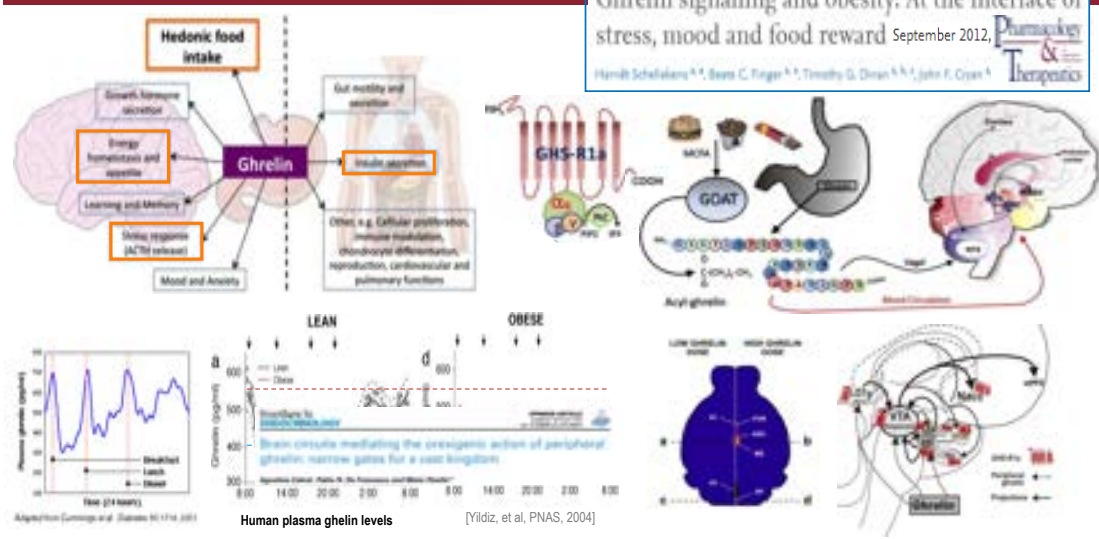
# Ghrelin and the GHSR-1a receptor



Ghrelin signalling and obesity: At the interface of stress, mood and food reward

September 2012, *Pharmacology & Therapeutics*

Harriet Schellekens<sup>1,2</sup>, Beate C. Finger<sup>1,2</sup>, Timothy G. Dinan<sup>1,2</sup>, John F. Cryan<sup>1,2</sup>

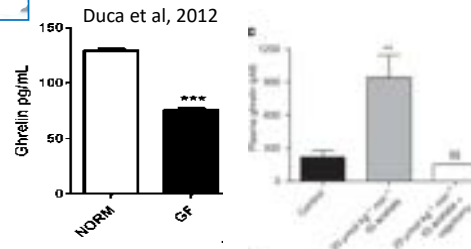
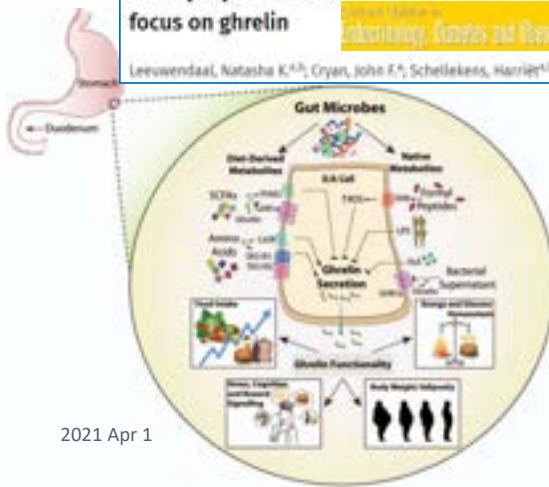




## Gut peptides and the microbiome

focus on ghrelin

Leeuwendaal, Natasha K<sup>1,2</sup>; Ryan, John F<sup>1</sup>; Schellekens, Harrijet<sup>1,2</sup>



Changes in microbial composition and diversity have been correlated with changes in gut peptide secretion, and specific gut bacteria have been shown to be capable of modulating EECs

## Mining the GUT Microbiota for Ghrelin Receptor modulation



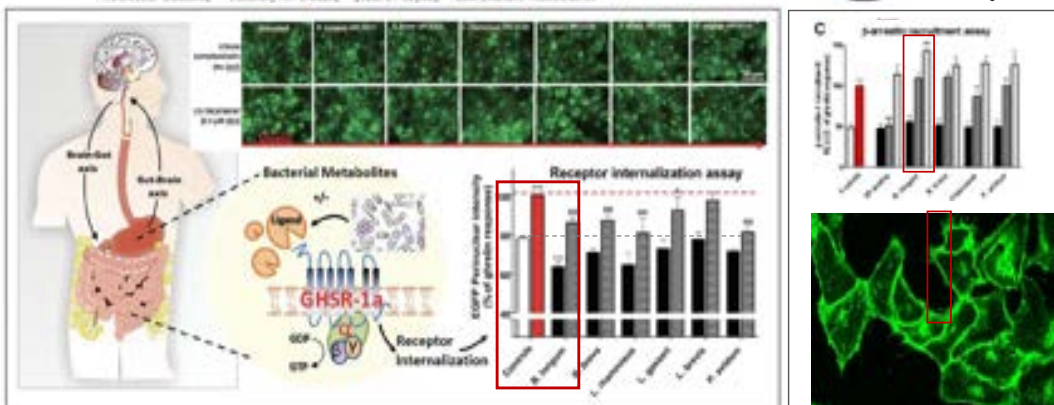
# APC1472 has inverse agonist activity & bias towards $\beta$ -arrestin-mediated ghrelin signaling



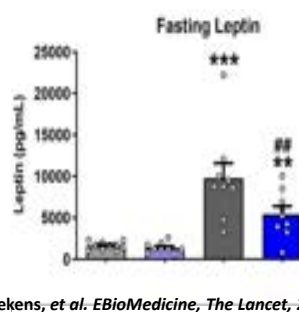
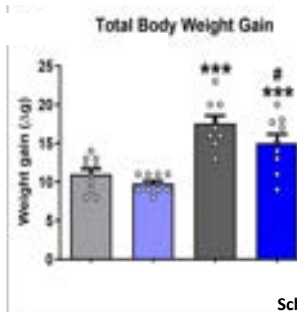
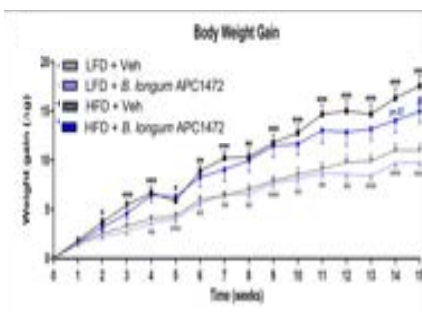
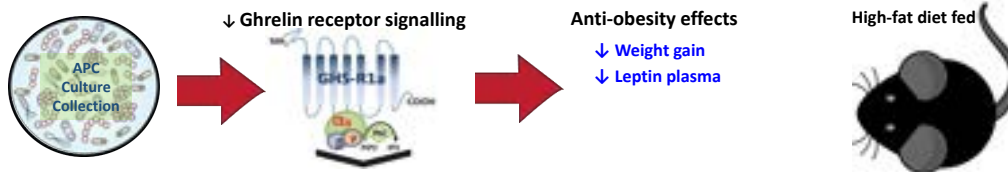
## FASEB Short-chain fatty acids and microbiota metabolites attenuate ghrelin receptor signaling

09 October 2018 | Cristina Torres-Farres,<sup>1,2</sup> Anna V. Golubeva,<sup>1,2</sup> Alexander V. Zhilov,<sup>3</sup> Shanna Wallace,<sup>1,2</sup> Silvia Arboleya,<sup>1,2</sup> Dmitri B. Popyrevsky,<sup>4</sup> Sahar El Aidi,<sup>1,2</sup> Paul Ross,<sup>5</sup> Bernard L. Ruy,<sup>6</sup> Catherine Stanton,<sup>1,2</sup> Timothy G. Dinan,<sup>1,2</sup> John F. Cryan,<sup>1,2</sup> and Harriet Schellekens<sup>1,2</sup>

HIGH THROUGHPUT CELLULAR ASSAYS

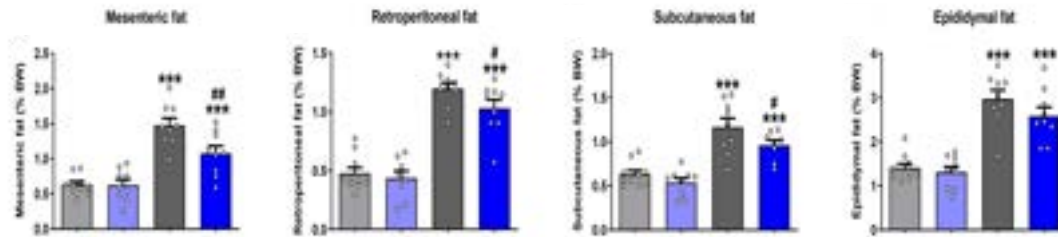
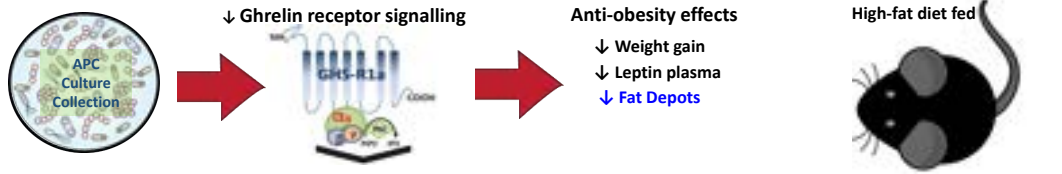


# Bifidobacteria Longum APC1472 attenuates weight gain



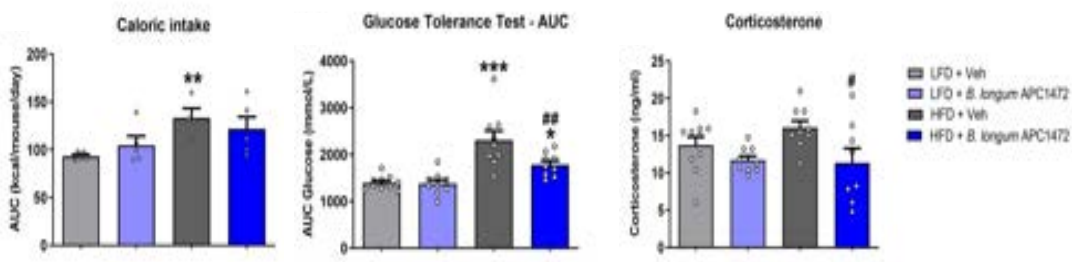
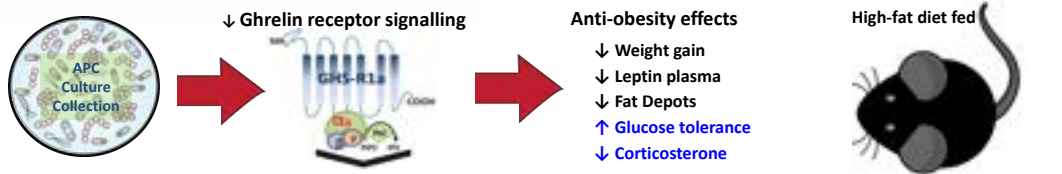
Schellekens, et al. *EBioMedicine, The Lancet*, 2021

## Bifidobacteria Longum APC1472 attenuates weight gain



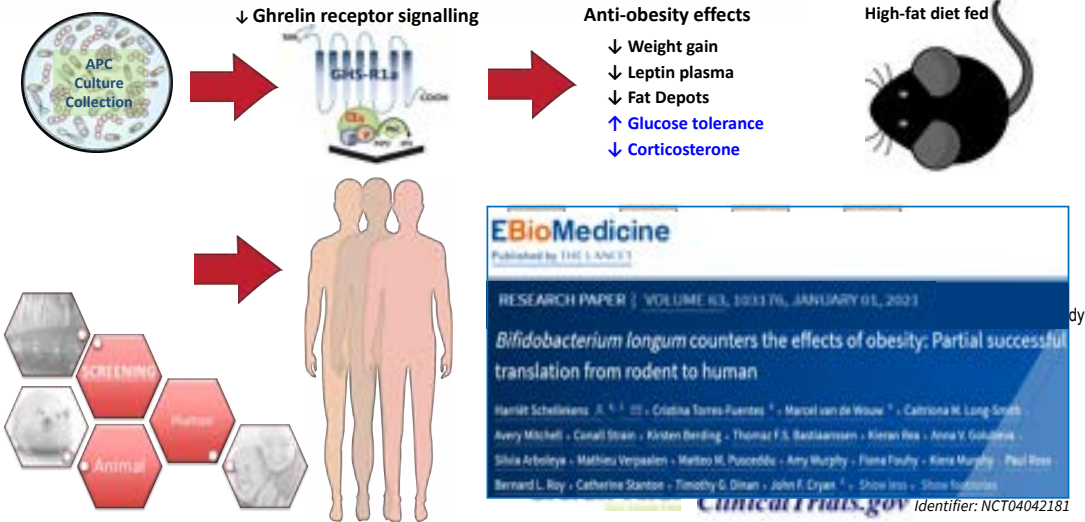
Schellekens, et al. *EBioMedicine, The Lancet*, 2021

## Bifidobacteria Longum APC1472 improves glucose tolerance AND reduces stress hormone



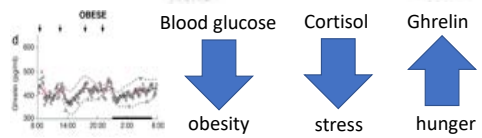
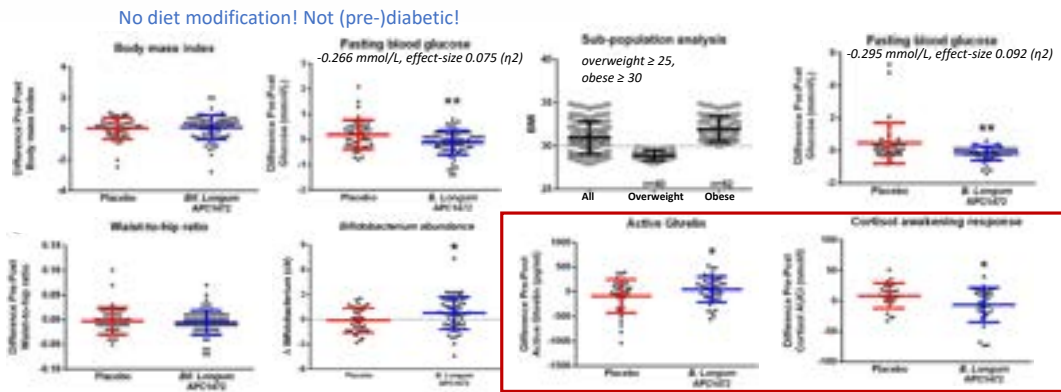
Schellekens et al. *EBioMedicine The Lancet* 2021

# Translational validation of Bifidobacteria Longum APC1472 anti-obesity effects in overweight/obese humans



# Bifidobacteria Longum APC1472 effects in overweight/obese humans

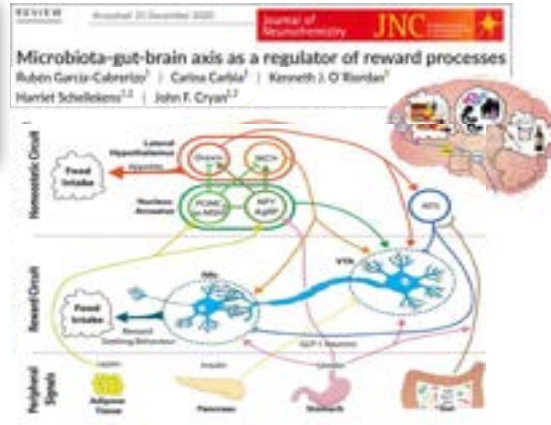
Normal fasting blood sugar <5.6mmol/L  
Prediabetic 5.6 to 7.0 mmol/L



.....findings reinforce the concept of the link between metabolic disease, mental health, and the potential amelioration of both via microbiome targeted approaches

Schellekens, et al. EBioMedicine, The Lancet, 2021

# Psychiatric disorders, Mood and Reward



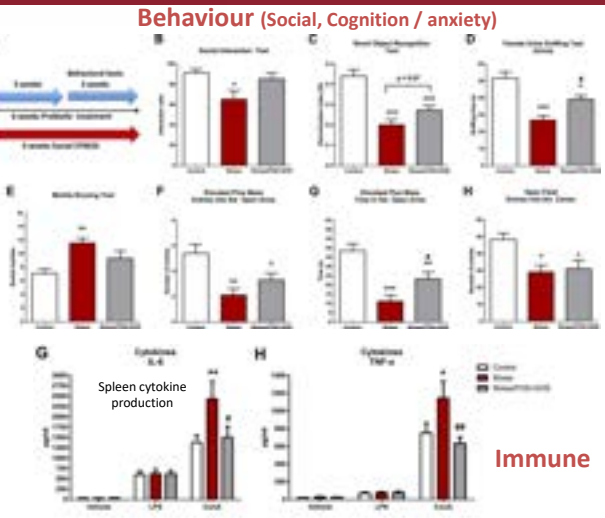
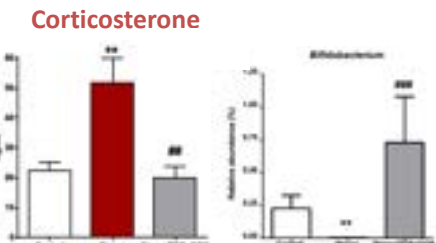
- Kelly, et al., The role of the gut microbiome in the development of **schizophrenia**. Schizophrenia Research, 2021.
- O'Connor, et al., Strain differences in behaviour and immunity in aged mice: Relevance to **Autism**. Behavioural Brain Research, 2021.

# PREBIOTICS fructo- and galacto- oligosaccharides (FOS/GOS) have anxiolytic and antidepressant like effects



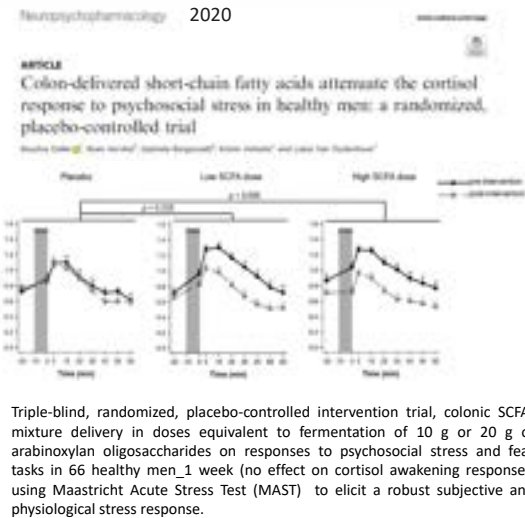
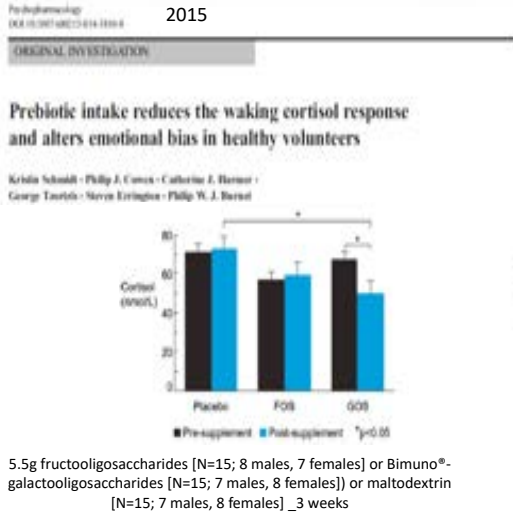
**Archival Report**  
 479 | © 2017 Society of Biological Psychiatry  
 Biological Psychiatry October 1, 2017; 62(4):472-481 www.sciencedirect.com  
**Targeting the Microbiota-Gut-Brain Axis: Prebiotics Have Anxiolytic and Antidepressant-like Effects and Reverse the Impact of Chronic Stress in Mice**  
 Aislinn Bannock, Shira Antelman, Rachel D. Moloney, Shannon S. Peterson, Kiera Murphy, Gerard Clarke, Catherine Stanton, Timothy S. Dinan, and John F. Cryan

Chronic social unpredictable stress (6 week social defeat/overcrowding)



Exaggerated interleukin 6 response to concanavalin A (jack bean legume lectin)

# Towards Psychobiotic diet: Clinical evidence



# Towards a Psychobiotic Diet

**Nutritional psychiatry: Towards improving mental health by what you eat**  
European Neuropsychopharmacology (2019)  
Roger A.H. Adan<sup>1,2,3,4</sup>, Eline M. van der Beek<sup>1,2,3</sup>, Jan K. Buitelaar<sup>1,2,3</sup>, John F. Cryan<sup>1,2,3,4</sup>, Johannes Hebebrand<sup>2</sup>, Suzanne Higgs<sup>1</sup>, Harriet Schellekens<sup>1</sup>, Suzanne L. Dickson<sup>2,3,4</sup>

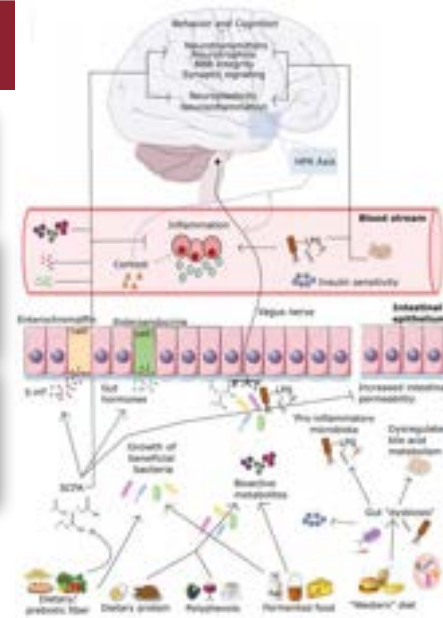
**Feeding the microbiota-gut-brain axis: diet, microbiome, and neuropsychiatry**  
Kirstin V. Sandhu<sup>1</sup>, Eoin Sheehan<sup>1</sup>, Harriet Schellekens<sup>1</sup>, Catherine Stanton<sup>1</sup>, Timothy G Dinan<sup>1</sup>, John F Cryan<sup>1</sup>

**Diet and the Microbiota-Gut-Brain Axis: Sowing the Seeds of Good Mental Health**  
09 March 2021  
Kirstin Berding,<sup>1</sup> Klara Vckova,<sup>1</sup> Wolfgang Marx,<sup>1</sup> Harriet Schellekens,<sup>1,2</sup> Catherine Stanton,<sup>1,2</sup> Gerard Clarke,<sup>1,2</sup> Felice Jacka,<sup>1,2,3</sup> Timothy G Dinan,<sup>1,2</sup> and John F Cryan<sup>1,2</sup>

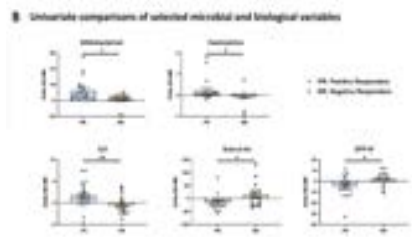
FIBRE



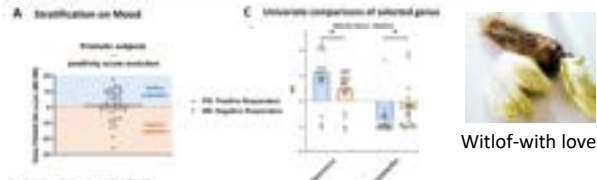
KEFIR



# Towards PERSONALISED Psychobiotic diet



Food4gut, clinicaltrials.gov: NCT03852069, <https://clinicaltrials.gov/ct2/show/NCT03852069>



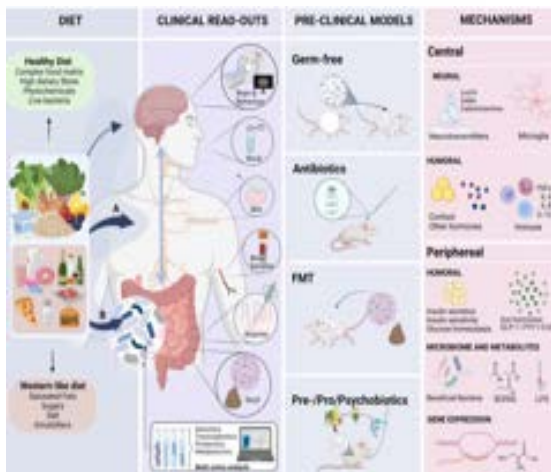
Witlof-with love?

- A randomized, single-blinded, multicentric, placebo-controlled trial (n=106 obese patients), receiving 16 g/d of native inulin or maltodextrin combined with dietary advice to consume inulin-rich or -poor vegetables for 3 months & CR.
- **Inulin supplementation in obese subjects had moderate beneficial effect on emotional competence and cognitive flexibility.**
- **Positive responders** exhibiting **specific microbial signature** -elevated Coprococcus levels at baseline- were more prone to benefit from prebiotic supplementation in terms of mood.
- Positive correlation of positivity score with Bifidobacterium, Haemophilus, IL-8, Dipeptidylpeptidase-4 (degrades incretins like GLP1) and subcutaneous fat mass, which can **predict or mediate the beneficial effects of inulin on behaviour in obesity.**

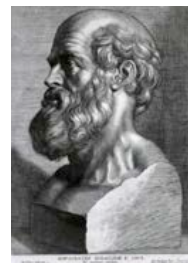
➤ **Inulin intake may improve mood in obese subjects exhibiting a specific microbial profile.**



## The Microbiome-Gut-Brain Axis & Nutritional Neuroscience



- Overall relatively little data as yet
- Small studies, Observational, no dose
- No consistent readouts, Behavior versus Biomarker
- Mechanisms (in)completely understood
- Microbiome & Metabolites rarely measured
- Integrated nutritional intervention
- **Mechanistic studies and Human interventions**



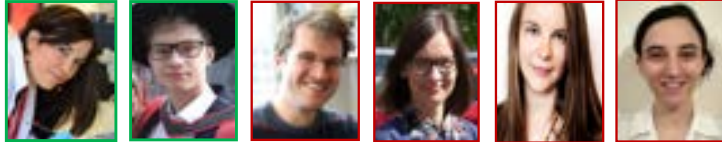
**“Let Food  
\_for your microbes\_  
be thy medicine!  
“For Mind \_Body\_Soul”**

Harriët Schellekens, et al., Nutritional Neuroscience, 2022

# Alumni & Current Lab members

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## Collaborators & acknowledgements

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LATE MLYLE



Dairy for life

