Can the Gut Microbiome Control the Brain?

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Ostrava January 31st 2018
Ah, on what little things does happiness depend.

Oscar Wilde

OSCAR WILDE
THE NIGHTINGALE AND THE ROSE
Illustrated by Freire Wright and Michael Foreman
Gut Feelings

- Brain-Gut-Microbiome Axis
- Health and Disease
- ‘Mind altering microbes’
- Anxiety, Depression, Stress and Cognition
- Tryptophan availability and metabolism
- Translational implications and opportunities for intervention?

The Human Microbiome Project Says the Human Body Has 100 Trillion Microscopic Life Forms Living In It.
Brain-Gut-Microbiome Axis

Grenham, Clarke et al., Frontiers in Physiology 2011
Signalling Along the Brain-Gut-Microbiota axis

Cryan and Dinan, Nat Rev Neurosci Oct 2012
Where do we get our microbiota from?

Prenatal (sterile)  Birth  Postnatal (colonized)

Grenham et al., 2011
What Shapes our Gut Microbiota?

Human Genetics Shape the Gut Microbiome

Julia K. Goodrich,1,2 Jillian L. Waters,1,2 Angela C. Poole,1,2 Jessica L. Sutter,1,2 Omry Koren,1,2,7 Ran Blekhman,1,8 Michelle Beaumont,9 William Van Treuren,4 Rob Knight,4,5,8 Jordana T. Bell,3 Timothy D. Spector,3 Andrew G. Clark,1 and Ruth E. Ley1,2,*

Figure 1 | Factors that can influence the composition and function of the human gut microbiota.
It's a gut feeling: How the gut microbiota affects the state of mind

Adam D. Farmer, Holly A. Randall and Qasim Aziz
Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour

John F. Cryan¹,² and Timothy G. Dinan¹,³

Abstract | Recent years have witnessed the rise of the gut microbiota as a major topic of research interest in biology. Studies are revealing how variations and changes in the

Microbiota–gut–brain axis

Germ-free studies
Infection studies
Probiotic studies
Antibiotic studies
Faecal transplantation studies
Germ-Free Living?

Figure 2. Reyniers’s isolator; (1) technician, (2) electrical outlet, (3) air outlet, (4) mobile truck, (5) entrance/exit autoclave, (6) viewing port.


Kirk, R, Bulletin of the History of Medicine, 2012
Microbiota, Brain and Behaviour

Clarke et al., Encyclopedia Metagenomics 2013
Stressors

“It’s not stress that kills us, it is our reaction to it.”

Hans Selye
Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice

Nobuyuki Sudo¹,², Yoichi Chida¹, Yuji Aiba³,⁴, Junko Sonoda¹, Naomi Oyama¹, Xiao-Nian Yu¹, Chiharu Kubo¹ and Yasuhiro Koga³

¹Department of Psychosomatic Medicine and ²Department of Health Care Administration & Management, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, ³Department of Infectious Diseases, Tokai University School of Medicine, Isehara, Kanagawa, Japan and ⁴Wakamoto Pharmaceutical Co., Ltd, Chiba, Japan.

A

ACTH

Corticosterone

(pg/ml)

(ng/ml)

Time (min)

Time (min)

Basal

1 h restraint

Basal

1 h restraint

SPF

GF

Restraint

SPF

GF

Bifidobacterium

EPEC

ΔTir

http://apc.ucc.ie
Microbiota Determines Amygdala Volume & Dendritic Morphology

Adult microbiota-deficient mice have distinct dendritic morphological changes: differential effects in the amygdala and hippocampus

Paulina Luczynski¹, Swain O. Whelan², Colm O’Sullivan², Gerard Clarke¹,², Fergus and Jol

DOI: 10.

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Microbes & neurodevelopment – Absence of microbiota during early life increases activity-related transcriptional pathways in the amygdala

Roman M. Stilling¹,²,*, Feargal J. Ryan¹,²,¹, Alan E. Hoban¹,²,¹, Fergus Shanahan¹, Gerard Clarke¹,²,³, Marcus J. Claesson¹,², Timothy G. Dinan¹,²,³, John F. Cryan¹,²,*

CC = Conventionally Colonised
GF = Germ Free
Anatomical correlates of abnormal fear and anxiety can be localised to the amygdala in germ-free animals using cued fear conditioning.
The gut microbiota influences blood-brain barrier permeability in mice

Viorica Braniste,1,4 Maha Al-Asmakh,1* Czeslawa Kowal,2* Farhana Anuar,1 Afrouz Abbaspour,1 Miklós Tóth,3 Agata Korecka,1 Nadja Bakocevic,4 Ng Lai Guan,4 Parag Kundu,5 Balázs Gulyás,3,5 Christer Halldin,3,5 Kjell Hultenby,6 Harriet Nilsson,7 Hans Hebert,7 Bruce T. Volpe,8

Host microbiota constantly control maturation and function of microglia in the CNS

Daniel Erny1,12, Anna Lena Hrabě de Angelis1,12, Diego Jaitin2, Peter Wieghofer1,3, Ori Staszewski1, Eyal David2, Hadas Keren-Shaul2, Tanel Mahlakoiv4, Kristin Jakobshagen5, Thorsten Buch6, Vera Schwierzeck7, Olaf Utermöhlen5, Eunyoung Chun8, Wendy S Garrett8, Kathy D McCoy9, Andreas Diefenbach7, Peter Staeheli4, Bärbel Stecher10, Ido Amit2 & Marco Prinz1,11
Neuroanatomy and Physiology of Brain Dysfunction in Sepsis

Aurelien Mazeraud\textsuperscript{a,b,c}, Quentin Pascal, DVM\textsuperscript{a}, Franck Verdonk\textsuperscript{a,b}, Nicholas Heming, MD, PhD\textsuperscript{c}, Fabrice Chrétien, MD, PhD\textsuperscript{a,b,d}, Tarek Sharshar, MD, PhD\textsuperscript{a,c,e,*}

![Diagram showing the pathophysiological processes during sepsis-associated encephalopathy (SAE).](image)

**Fig. 1.** Schematic representation of pathophysiologic processes during sepsis-associated encephalopathy (SAE). PTSD, posttraumatic stress disorder.
Review

Serotonin, tryptophan metabolism and the brain-gut-microbiome axis

S.M. O’Mahony\textsuperscript{a,b,1}, G. Clarke\textsuperscript{a,c,*,1}, Y.E. Borre\textsuperscript{a}, T.G. Dinan\textsuperscript{a,c}, J.F. Cryan\textsuperscript{a,b}

**Behavioural Effects**
- Visceral pain
- Emotion
- Stress response
- Appetite
- Addiction
- Sexuality

**CNS Effects**
- Motor control
- Circadian rhythm
- Cerebellar regulation
- Body temperature
- CNS vascular tone

**GI Effects**
- Gastric secretion
- Gastrointestinal motility
- Intestinal secretions
- Colonic tone
- Pancreatic secretion

“Of course you feel great. These things are loaded with antidepressants.”
The Kynurenine Pathway

O’Mahony et al, Behavioural Brain Research 2015
Kynurenines: Tryptophan’s metabolites in exercise, inflammation, and Alzheimer’s

An Observational Cohort Study of the Kynurenine to Tryptophan Ratio in Sepsis: Association with Impaired Immune and Microvascular Function

Christabelle J. Darcy¹, Joshua S. Davis¹,²,⁹, Tonia Woodberry¹, Yvette R. McNeil¹, Dianne P. Stephens³, Tsin W. Yeo¹,², Nicholas M. Anstey¹,²*

1 Global Health Division, Menzies School of Health Research and Charles Darwin University, Darwin, Northern Territory, Australia, 2 Division of Medicine, Royal Darwin Hospital, Darwin, Northern Territory, Australia, 3 Intensive Care Unit, Royal Darwin Hospital, Darwin, Northern Territory, Australia

Fig. 3. Activity, uptake, and conversion of tryptophan and its metabolites in peripheral tissues during unchallenged conditions. 5-HT, 5-hydroxytryptamine; Trp, tryptophan; NAD⁺, nicotinamide adenine dinucleotide; Kyn, kynurenine; 5-HTT, 5-HT transporter; GPR35, G protein-coupled receptor 35; AhR, aryl hydrocarbon receptor; 5-HIAA, 5-hydroxyindoleacetic acid.
The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner.

G Clarke, S Grenham, P Scully, P Fitzgerald, RD Moloney, F Shanahan, TG Dinan, and JF Cryan.
Transcriptional Regulation of Kynurenine Pathway Metabolism in Hippocampus

CON GF exGF

Hippocampus Dissection → Total RNA Extraction → miRCURY LNA™ microRNA Array → miRNA qPCR Validation → Target Validation

Male

Female

Moloney et al., Behavioural Brain Research 2017
Microbiota alteration is associated with the development of stress-induced despair behavior

Ioana A. Marin\textsuperscript{1,2,3}, Jennifer E. Goertz\textsuperscript{1,2}, Tiantian Ren\textsuperscript{4}, Stephen S. Rich\textsuperscript{5}, Suna Onengut-Gumuscu\textsuperscript{5}, Emily Farber\textsuperscript{5}, Martin Wu\textsuperscript{4}, Christopher C. Overall\textsuperscript{1,2}, Jonathan Kipnis\textsuperscript{1,2,3,4} & Alban Gaultier\textsuperscript{1,2,3,4}

Restoring intestinal \textit{Lactobacillus} levels normalized stress-induced behavior and suppressed kynurenine production

Figure 3. Treatment with probiotic \textit{L. reuteri} ameliorates the escape behavior induced by chronic stress.
Research Paper

Microbiota-related Changes in Bile Acid & Tryptophan Metabolism are Associated with Gastrointestinal Dysfunction in a Mouse Model of Autism

Anna V. Golubeva, Susan A. Joyce, Gerard Moloney, Aurelijus Burokas, Eoin Sherwin, Silvia Arboleya, Ian Flynn, Dmitri Khochanskiy, Angela Moya-Pérez, Veronica Peterson, Kieran Rea, Kiera Murphy, Olga Makarova, Sergey Burakov, Niall P. Hyland, Catherine Stanton, Gerard Clarke, Cormac G.M. Gahan, Timothy G. Dinan, John F. Cryan.
“For example, if they detected high levels of amino acid Tryptophan," he explained, "they concluded that person was calm and approachable."
Review article

Brain-gut-microbiota axis: challenges for translation in psychiatry

John R. Kelly MD, Gerard Clarke PhD, John F. Cryan PhD, Timothy G. Dinan MD, PhD

Alimentary Pharmabiotic Centre, APC Microbiome Institute, University College Cork, Cork, Ireland
Department of Psychiatry and Neurobehavioural Science, University College Cork, Cork, Ireland
Department of Anatomy and Neuroscience, University College Cork, Cork, Ireland

Cryan et al., Trends in Pharmacol. Sci. 2002

Gary Larson
Altered Microbiota in Depression

Kelly et al., J Psych Res 2016

Reduced microbial diversity in depression

Prevotella, a genus of Gram-negative bacteria, is reduced in depression

Eggerthella
Holdemania
Paraprevotella
Prevotella
Dialister
Mogibacterium
Gelria
Turicibacter
Transfer of Depressive Phenotype

Anhedonia-like behaviours transferred via gut microbiota

Anxiety-like behaviours transferred via gut microbiota

Tryptophan metabolism Profile transferred via gut microbiota

Kelly et al., J Psych Res 2016
Drugging the gut microbiome

Why is my hangover so bad?

It’s not just the booze giving you a hangover – it’s the microbes in your stomach
Psychobiotics:
Timothy G. Dinan, Catherina Penders

Here, we define a psychobiotic as a microorganism that, when taken in adequate amounts, confers a health benefit on the host. Psychobiotics, such as gamma-aminobutyric acid and probiotics, have shown promise in improving brain health and behavior. So far, psychobiotics have been used in diseases such as Crohn's disease, where positive effects on mood and inflammatory actions of certain psychobiotics have been observed. Large-scale placebo-controlled studies are needed to further investigate these effects.
Effect of *Lactobacillus rhamnosus* HN001 in Pregnancy on Postpartum Symptoms of Depression and Anxiety: A Randomised Double-blind Placebo-controlled Trial


Allen et al., 2016, Trans Psych
Targeting the Microbiota-Gut-Brain Axis: Prebiotics Have Anxiolytic and Antidepressant-like Effects and Reverse the Impact of Chronic Stress in Mice

Aurelijus Burokas, Silvia Arboleya, Rachel D. Moloney, Veronica L. Peterson, Kiera Murphy, Gerard Clarke, Catherine Stanton, Timothy G. Dinan, and John F. Cryan

Prebiotic reverses consequences of chronic stress

Social behaviour and cognition

Anxiety
Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers

Kristin Schmidt • Philip J. Cowen • Catherine J. Harmer • George Tzortzis • Steven Errington • Philip W. J. Burnet

![Cortisol level graph](image-url)
Feedina the microbiota-gut-brain axis:

A randomised trial of the effect of omega-3 polyunsaturated fatty acid supplements on the human intestinal microbiota

Henry Watson, ¹ Suparna Mitra, ² Fiona C Croden, ³ Morag Taylor, ⁴ Henry M Wood, ⁴ Sarah L Perry, ¹ Jade A Spencer, ⁵ Phil Quirke, ⁴ Giles J Toogood, ⁶ Clare L Lawton, ³ Louise Dye, ³ Paul M Loadman, ⁵ Mark A Hull ¹

SCFAs
↑ Butyrate
↑ Acetate
↑ Propionate

SCFAs
↓ Butyrate
↓ Acetate
↓ Propionate

Gut Microbiota

Regulates satiety hormones
PYY, CCK, GLP-1

Improve mood disorders

Increase in anxiety
Induce depression
A randomised controlled trial of dietary improvement for adults with major depression (the ‘SMILES’ trial)

Felice N. Jacka¹,⁴,⁹,¹⁰,¹³*, Adrienne O’Neil¹,²,¹³, Rachelle Opie⁵,¹³, Catherine Itsiopoulos⁵, Sue Cotton³, Mohammedreza Mohebbi¹, David Castle⁴,¹¹, Sarah Dash¹,¹³, Cathrine Mihalopoulos⁷, Mary Lou Chatterton⁷, Laima Brazionis⁵,⁶, Olivia M. Dean¹,⁴,¹²,¹³, Allison M. Hodge⁸ and Michael Berk¹,¹³,¹²,¹³

Fig. 2 MADRS scores for dietary support and social support control groups at baseline and endpoint. Effect size: Cohen’s $d = -1.16$ (95% CI = -1.73, -0.59). Baseline data $n = 67$; 12 week data $n = 56$
Fecal microbiota transplantation in metabolic syndrome: History, present and future

P. F. de Groot, M. N. Frissen, N. C. de Clercq, and M. Nieuwdorp

1928
By Alexander Fleming discovers penicillin

1917
Isolation of E. coli strain E. coli by Pasteur (1874-1905)

1910
Boycott is handled by human health with gut immune suppression by Helicobacter (1845-1910)

1697
Book on ancient power of stool by Hahnemann (1440-1792)

1681
John Linnecor describes presence of microbes in stool

17th century
First local transplantation in animals by Genskowp (1773-1849)

16th century
Infections of the microbial flora in systemic complaints by H. Wace (1388-1933)

4th century
The secrets of PMS use in Traditional Chinese Medicine by De Zhang (283–343)

Future Prospects
- Fecal microbiota transplant (FMT) as functional medicine
- Advances in culturing possibilities
- Effective disease treatment
- Personalized medicine

1905
First description of gut microbial composition with weight status in mice

1906
Turnough process identify it to be a transmissible trait through PMS in mice

2005
Kim describes differences in gut microbiome composition with weight status in mice

2011
Arahaneg draws the enterotypes of the human gut microbiome

2012
Kashin shows estimate of disease control can be predicted by microbiome analysis

2016
Li shows differential microbiome transplant is dependent on donor and recipient microbial transcriptomes
The role of the gut microbiota in sepsis

Bastiaan W Haak, W Joost Wiersinga

Endogenous modulators of the gut microbiota during sepsis
- Increased production of opioids
- Decreased bile-salt concentration
- Gastrointestinal dysmotility
- Increased production of catecholamines
- Loss of epithelial integrity in the intestine

External modulators of the gut microbiota during clinical sepsis care
- Antibiotics
- SOD/SSD
- Gastric-acid inhibition
- Enteral/parenteral feeding
- Sedatives
- Opioids
- Catecholamines

Potential consequences of dysbiosis during sepsis
- Decreased systemic SCFA levels
- Potentially increased risk of acute kidney injury
- Increased microbial virulence
- Bacterial translocation in systemic and lymphatic circulation
- Reduced modulation of systemic immune responses
- Potentially increased risk of sepsis-induced muscle wasting
Enhancing Recovery From Sepsis
A Review

Figure 2. A Conceptual Model of the Potential Network of Factors and Interactions Important to Determining a Patient's Clinical Course and Long-term Outcome After Sepsis
Summary & Conclusions

- Gut microbiota is both stress-susceptible and can regulate stress response
- Regulates behaviours and physiology relevant to neuropsychiatric disorders
- Tryptophan availability/Kynurenine metabolism
- Translation to clinic?
- Microbial-based strategies for the treatment of stress-related disorders?

Kelly et al., Frontiers Neuroscience 2017
Vatican City - Pope Francis announced today that he was going to award automatic sainthood to all microbiome researchers worldwide for "Doing God's Work".
Acknowledgements

Laboratory of NeuroGastroenterology
International Society for Serotonin Research

Formerly Serotonin Club

The 19th Meeting of the International Society for Serotonin Research

Serotonin on the ‘WILD ATLANTIC WAY’
University College Cork
Ireland
15th-19th July 2018

List of Symposia

- Delineating the Neural Circuits Underlying Serotonin Modulation of Fear and Anxiety.
- 5-HT1F Receptor Agonists, The New Kids On The Block for Antimigraine Treatment.
- Serotonin Transport Proteins in Ecstasy: SEERTS and OCTS in a Frenzy.
- Lucky 7 (5-HT7 Receptors): New Functions for a (relatively) New Colleague.
- Delving Deep into 5-HT Neurons: Probing Patterns and Regulation of 5-HT Transcriptomes and Translatomes.
- Improving our Understanding of Serotonin in the Neurobiology of Psychosis.
- Towards a Multiscale, Multispecies Perspective of Serotonergic Function.
- Serotonin, Inflammation and Behaviour.
- The Role of Serotonin in Synaptic Structure and Plasticity.
- Multilevel Assembly of Serotonin Circuits and Its Impact on Emotional and Motivated Behaviors.
- Serotonin Regulation of Dendritic Spines.
- Serotonin and Mental Illness: From Its Development to Adult Dysfunction.
- Feedback Control of Serotonin in Behavior and Antidepressant Response.
- Serotonin and Autism Spectrum Disorder Hyperserotonemia and Beyond.

Special Session 1
Gut-Brain-Microbiome Axis

- Impact of Serotonin at the Microbial & Immune Interface on Gut-Brain Signaling.
- Serotonin as a Modulator of the Gut-Brain-Microbiome Axis in Depression and other Mental Health Disorders.
- Serotonin Revisited – New Insights in Disturbed Functions in the Gastrointestinal Tract.

Special Session 2
5-HT Receptor Signaling and Heteromerization

- Novel Functional Crosstalk and Heteromerization of Serotonin Receptors in Mood and Social Behaviour.
- Serotonin Receptor Complexes as Key Players in CNS Function.
- Three Crucial Factors that Underpin 5-HT2CR Function: Location, Location, Location.

Young Investigator Travel Award applications submission deadline is Friday December 15th 2017.
For application details contact Dr. Kelly Berg (berg@uhscsu.edu)
General registration and abstract submission open early 2018

Further details: http://www.serotonincork.org/
7th International Human Microbiome Consortium (IHMC) meeting
26th-28th June, Killarney, Ireland

For registration & further details go to:  http://apc.ucc.ie/ihmc-2018/
APEX Postdoctoral Programme
hosted by APC Microbiome Ireland

Co-funded by EU H2020
20 Postdoctoral Fellows
Microbiome Research
2 Calls: closing 9th April 2018 & 2019
EU Mobility rules apply
3-6 month secondment to industry
http://apc.ucc.ie/apex/
Thank you

g.clarke@ucc.ie

The Daily Mail, London Sept 2011