





The microbiome and stress-related psychiatric disorders: A prescription for therapeutic targeting of the gut-brain axis

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2nd COLOTAN Symposium Thursday 20th January 2022





Living in a Microbial World....







Gut Feelings

Microbiome Ireland

- Brain-Gut-Microbiome Axis
- Health and Disease
- Psychiatry and Disorders of gut-brain axis
- Preclinical Research/Signalling Pathways
- Translation, causality and moving towards mechanisms?
 - Psychotropic drugs and the gut microbiome





Grenham, Clarke et al., Frontiers in Physiology 2011





The brain-gut –(microbiota) axis





Clarke et al., Pharmacological Reviews 2019



Brain-Gut-Microbiota Axis



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Microbiota, Brain and Behaviour





Clarke et al., Encyclopedia Metagenomics 2013





Microbiota Regulates Anxiety





Clarke et al., Mol Psychiatry 2013

Germ-free animals have lower anxiety-like behaviours

Probiotic reduces anxiety-like behaviours





b













Microbiota Controls Stress Response









Bravo et al., PNAS Sept 2011





The Germ-free Phenotype







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Spichak et al., Drug Dis Today 2019



Tryptophan – A (microbial) Building Block







Clarke et al., Pharmacological Reviews 2019





Microbiota Regulates Tryptophan Metabolism



Behavioural Brain Research 277 (2015) 32–48



Serotonin, tryptophan metabolism and the brain-gut-microbiome axis S.M. O'Mahony^{a,b,1}, G. Clarke^{a,C,+,1}, Y.E. Borre^a, T.G. Dinan^{a,C}, J.F. Cryan^{a,b}



Molecular Psychiatry (2013) 18, 666 – 673 © 2013 Macmillan Publishers Limited All rights reserved 1359-4184/13 www.nature.com/mp

ORIGINAL ARTICLE

npg

The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner G Clarke^{1,2}, S Grenham¹, P Scully¹, P Fitzgerald¹, RD Moloney¹, F Shanahan^{1,3}, TG Dinan^{1,2} and JF Cryan^{1,4}



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Acute Stress alters Host Tryptophan Metabolism



Received: 24 January 2020	Revised: 6 April 2020	Accepted: 17 Apri	2020			
DOI: 10.1111/nmo.13881						Check for updates
ORIGINAL ARTIC	CLE			Neurogastreentendog	Annaly NGM WILE	Ŷ
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Joshua M. Lyte ¹ Nancy Kelley-Lou	Cassandra E Ighnane ² Tii	. Gheorghe ¹ mothy G. Din	Michael S. Go an ^{1,3} John F.	oodson ² Cryan ^{1,4}	Gerard Clarke ^{1,3} 💿	
Experime	ental groups			RE	ACUTE STRAINT STRESS	
Conventional	Germ-free	Tryptophan	5-HTP	5-HT	Microbiota influence	25
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Colonise Germ-fre	d		Sie Sie Sie Sie			





Ireland

Interfacing Food & Medicine





Microbiota influences acute stress response of the gut-brain axis serotonergic system in a region and sex-dependent manner.

Tryptamine

Cell Host & Microbe
Previews

A Microbial Drugstore for Motility

John F. Cryan,^{1,2,*} Gerard Clarke,^{2,3} Timothy G. Dinan,^{2,3} and Harriet Schellekens^{1,2}



Gheorghe et al., Curr Opin Pharm 2019

















Translational Research



fi r what's next



How to recognize the moods of an Irish setter





Physiol Rev 99: 1877–2013, 2019 Published August 28, 2019; doi:10.1152/physrev.00018.2018

THE MICROBIOTA-GUT-BRAIN AXIS

John F. Cryan, Kenneth J. O'Riordan, Caitlin S. M. Cowan, Kiran V. Sandhu, Thomaz F. S. Bastiaanssen, Marcus Boehme, Martin G. Codagnone, Sofia Cussotto, Christine Fulling, Anna V. Golubeva, Katherine E. Guzzetta, Minal Jaggar, Caitriona M. Long-Smith, Joshua M. Lyte, Jason A. Martin, Alicia Molinero-Perez, Gerard Moloney, Emanuela Morelli, Enrique Morillas, Rory O'Connor, Joana S. Cruz-Pereira, Veronica L. Peterson, Kieran Rea, Nathaniel L. Ritz, Eoin Sherwin, Simon Spichak, Emily M. Teichman, Marcel van de Wouw, Ana Paula Ventura-Silva, Shauna E. Wallace-Fitzsimons, Niell, Hyland, Gerard Clarke, and Timothy G. Dinan



RESEARCH PAPER



OPEN ACCESS Check for updates

Guidelines for reporting on animal fecal transplantation (GRAFT) studies: recommendations from a systematic review of murine transplantation protocols

Kate R. Secombe[®], Ghanyah H. Al-Qadami^a, Courtney B. Subramaniam^a, Joanne M. Bowen^a, Jacqui Scott^{a,b}, Ysabella Z.A. Van Sebille^c, Matthew Snelson^d, Caitlin Cowan^e, Gerard Clarke^f, Cassandra E. Gheorghe^g, John F. Cryan[®], and Hannah R. Wardill^{a,b}





Transfer of Depressive Phenotype











Sucrose preference (1% sucrose)

Elevated Plus Maze





Kelly et al., J Psych Res 2016



Anhedonia-like behaviours transferred via gut microbiota

Decreased Tryptophan Serotenegic Deficiency Anxiety-like behaviours transferred via gut microbiota

Tryptophan metabolism Profile transferred via gut microbiota





Irritable Bowel Syndrome



Disorder of gut-brain axis interactions



Insula cortex (IC)

Thalamus (THAL)

Mertz et al., Gastroenterology 2000





 Received: 2 April 2020
 Revised: 12 August 2020
 Accepted: 17 August 2020

 DOI: 10.1111/nmo.13985
 Comparison
 Comparison

ORIGINAL ARTICLE





Saccharomyces boulardii CNCM I-745 modulates the microbiotagut-brain axis in a humanized mouse model of Irritable Bowel Syndrome

Marco Constante | Giada De Palma | Jun Lu | Jennifer Jury | Liam Rondeau Alberto Caminero | Stephen M. Collins | Elena F. Verdu () | Premysl Bercik ()



Only the microbiota from IBS subjects with comorbid anxiety induced both GI dysfunction and anxiety-like behaviours in the recipient animals





Psychiatric Comorbidity in IBS





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Are Gut Feelings the Real Deal?









Perspectives

Microbiome Ireland Interfacing Food & Medicine

The gut microbiota plays a role in determining mental health we can mine for, and target with, psychobiotics

Probiotics

- Prebiotics
- Diet
 - Faecal transplants
- Microbial consortia
- Metabolites



Erzh







B. longum reduces stress response in healthy human volunteers





Psychobiolic

Placebo

Visit



Placebo

VISIT^





Full-length Article

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

John R. Kelly ^{a,b}, Andrew P. Allen ^{a,b}, Andriy Temko ^c, William Hutch ^d, Paul J. Kennedy ^a, Niloufar Farid ^b, Eileen Murphy ^e, Geraldine Boylan ^d, John Bienenstock ^f, John F. Cryan ^{a,g}, Gerard Clarke ^{a,b}, Timothy G. Dinan ^{a,b,*}





Interfacing Food & Medicine

CrossMark



Towards Psychobiotics: Focus on Mechanisms









Long-Smith et al 2019, Annual Review Pharmacology and Toxicology







Promising preclinical and clinical research

- Regulates behaviours and physiology relevant to psychiatry and neurogastroenterology
- > Microbiome as a driver of psychiatric comorbidity?
- Mechanistic insights and focus on causation
- Signalling pathways common neurobiological ground?
- Microbial-based strategies for the treatment of stress-related gut-brain axis disorders?







Drug-Microbiome Interactions



Hefner et al., Int Rev Psych 2013

Clarke et al., 2019, Pharmacological Reviews

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Factors Defining the Gut Microbiome



Characteristics of gut microbiome

Stable and chaotic periods

> Diversity narrows in disease states

What about xenobiotics?





Drug-Microbiome Interactions





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Clarke et al., Pharmacological Reviews 2019





OPEN

Citation: Transl Psychiatry (2013) **3**, e309; doi:10.1038/tp.2013.83 © 2013 Macmillan Publishers Limited All rights reserved 1365-7852/13

www.nature.com/tp

ORIGINAL ARTICLE

Antipsychotics and the gut microbiome: olanzapine-induced metabolic dysfunction is attenuated by antibiotic administration in the rat

KJ Davey^{1,2}, PD Cotter^{1,3}, O O'Sullivan^{1,3}, F Crispie³, TG Dinan^{1,4}, JF Cryan^{1,5} and SM O'Mahony^{1,5}

Psychopharmacology (2012) 221:155-169 DOI 10.1007/s00213-011-2555-2

ORIGINAL INVESTIGATION

Gender-dependent consequences of chronic olanzapine in the rat: effects on body weight, inflammatory, metabolic and microbiota parameters

Kieran J. Davey • Siobhain M. O'Mahony • Harriet Schellekens • Orla O'Sullivan • John Bienenstock • Paul D. Cotter • Timothy G. Dinan • John F. Cryan



ARTICLE





Open Access

Prebiotic attenuation of olanzapineinduced weight gain in rats: analysis of central and peripheral biomarkers and gut microbiota

Amy Chia-Ching Kao¹, Sonia Spitzer¹, Daniel C. Anthony², Belinda Lennox¹ and Philip W. J. Burnet¹











Contents lists available at ScienceDirect

The gut microbiome influences the bioavailability of olanzapine in rats

Conall R. Strain^{a,e}, Fiona Fouhy^{a,e}, Catherine Stanton^{a,e,f}, Timothy G. Dinan^{a,f}, Niall P. Hyland^{a,g}, Gerard Clarke^{a,f}, John F. Cryan^{a,b,*}, Brendan T. Griffin^{a,c,*}

Sofia Cussotto^{a,b,1}, Jacinta Walsh^{a,c,1}, Anna V. Golubeva^{a,b}, Alexander V. Zhdanov^d,

EBioMedicine

EBioMedicine 66 (2021) 103307

journal homepage: www.elsevier.com/locate/ebiom





Experimental timeline a)



SEVIER

Olanzapine - Pharmacokinetics a)







RESEARCH



RESEARCH ARTICLE SUMMARY

MICROBIOTA

Discovery and inhibition of an interspecies gut bacterial pathway for Levodopa metabolism

Vayu Maini Rekdal, Elizabeth N. Bess, Jordan E. Bisanz, Peter J. Turnbaugh*, Emily P. Balskus*







Dose Dependent Effects - psychotropics

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Psychopharmacology (2019) 236:1671-1685 https://doi.org/10.1007/s00213-018-5006-5

ORIGINAL INVESTIGATION

Differential effects of psychotropic drugs on microbiome composition and gastrointestinal function

Sofia Cussotto^{1,2} • Conall R. Strain^{1,3} • Fiona Fouhy^{1,3} • Ronan G. Strain^{1,3} • Veronica L. Peterson^{1,2} • Gerard Clarke^{1,4} • Catherine Stanton^{1,3,4} • Timothy G. Dinan^{1,4} • John F. Cryan^{1,2}



> Dose dependent effects in vitro

Lower microbial exposure escitalopram, fluoxetine better?

Compositional alterations in vivo after 28 days



Genue L



Dose Dependent Effects - psychotropics

500 1.000



Article

Nature | Vol 597 | 23 September 2021 |

Bioaccumulation of therapeutic drugs by human gut bacteria

https://doi.org/10.1038/s41586-021-03891-8				
Received: 25 February 2019				
Accepted: 10 August 2021				
Published online: 8 September 2021				
Check for updates				

Martina Klünemann^{19,21}, Sergej Andrejev^{130,21}, Sonja Blasche^{1,2,21}, Andre Mateus^{1,21}, Prasad Phapale¹, Saravanan Devendran¹, Johanna Vappiani³, Bernd Simon¹, Timothy A. Scott⁴, Eleni Kafkia², Dimitrios Konstantinidis¹, Katharina Zirngibl^{1,2}, Eleonora Mastrorilli¹, Manuel Banzhaf^{1,11}, Marie-Therese Mackmull^{1,12}, Felix Hövelmann¹, Leo Nesme¹¹³, Ana Rita Brochado^{1,14}, Lisa Maier^{1,15}, Thomas Bock^{1,16}, Vinita Periwal^{1,2}, Manjeet Kumar¹, Yongkyu Kim¹, Melanie Tramontano¹¹⁰, Carsten Schultz^{1,17}, Martin Beck^{1,18}, Janosch Hennig¹¹⁹, Michael Zimmermann¹, Daniel C. Sévin², Filipe Cabreiro^{4,5,20}, Mikhail M. Savitski¹, Peer Bork^{1,67,8}, Athanasios Typas¹⁵² & Kiran R. Patil^{1,2}



- Stable communities of five gut bacterial species (Bacteroides thetaiotaomicron, Eubacterium rectale, Lactobacillus gasseri, Ruminococcus torques and Streptococcus salivarius) in the presence and in the absence of duloxetine.
- E. rectale is the most sensitive to duloxetine among the five species in vitro
- In vivo, presence of duloxetine markedly shifted the community composition, allowing E. rectale to increase its abundance by over 100-fold

Metabolite secretion by duloxetine bioaccumulator, S. salivarius, in response to duloxetine could boost E. rectale





Dose Dependent Effects





- > Each dot represents a patient taking a specific drug dose, and is classified into one of the four enterotypes
- Change in the prevalence of the Bacteroides 1 and Bacteroides 2 enterotypes in patients with increasing metformin dosage (Bacteroides 2 enterotype is also associated with disease)
- For statins, dosage analysis strengthens the reported observation of microbiome shifts towards a heathier state away from the Bacteroides 2 enterotype





Stick or Twist?



Brain, Behavior, and Immunity 95 (2021) 25-26



Brief Commentary

Metformin, the gut microbiome and neurogenesis: Lessons learned in rebirth of an old drug

Gerard Clarke^{a, b, c, *}





Review Article

Gut Microbiota-Immune-Brain Interactions in Chemotherapy-Associated Behavioral Comorbidities

Kelley R. Jordan, BS ^[]²; Brett R. Loman, PhD³; Michael T. Bailey, PhD^{1,3,4}; and Leah M. Pyter, PhD^{1,2,5}





Brain, Behavior, and Immunity 95 (2021) 401-412

Manipulations of the gut microbiome alter chemotherapy-induced inflammation and behavioral side effects in female mice

C.V. Grant^a, B.R. Loman^b, M.T. Bailey^{a,b,c}, L.M. Pyter^{a,d,e,*}



OPEN Chemotherapy-induced neuroinflammation is associated with disrupted colonic and bacterial homeostasis in female mice

B. R. Loman (), K. R. Jordan², B. Haynes², M. T. Bailey^{1,2,4} & L. M. Pyter^{2,3,5*}









- > Many psychotropic drugs have antimicrobial effects *in vitro*, dose-dependent effects assessed for some
- > Evidence *in vivo* from animal studies of compositional alterations
- > Associations reported in human studies that are likely dose dependent
- > Unclear in many cases if these compositional alterations in vivo are 'good' or 'bad'
- > Antipsychotic-induced remodelling of the gut microbiome associated with weight gain
- > For statins and metformin, remodelling might change to healthier state
- Possibility of bioaccumulation and the impact on host gastrointestinal physiology and immune system complicates predictions
- > Future of drug discovery will have to take account of the gut microbiome



Leprun and Clarke, Current Opinion Pharmacology 2019





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Laboratory of NeuroGastroenterology











Thank you

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