

# Microbes Messing with your Mind: Implications for Physiology, Brain and Behaviour

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and Faculty Investigator, APC**

**Alimentary Pharmabiotic Centre Public Forum,  
World Digestive Health Day, May 27<sup>th</sup> 2014**

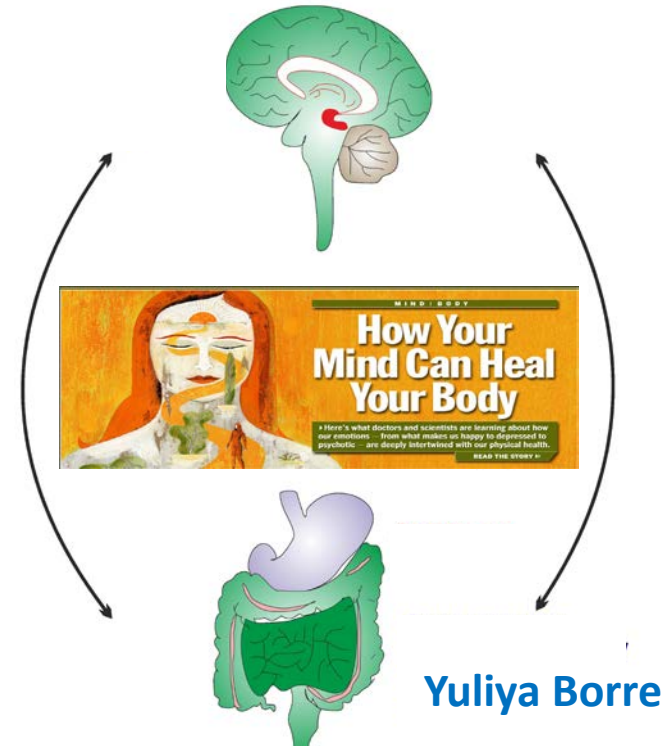
GENIEUR.EU  
Genes in irritable bowel  
syndrome

- Brain-Gut-Microbiota Axis
- Health and Disease
- Irritable Bowel Syndrome (IBS)
- Anxiety, Depression, Stress and Cognition
- ‘Mind altering microbes’
- Therapeutic opportunities?

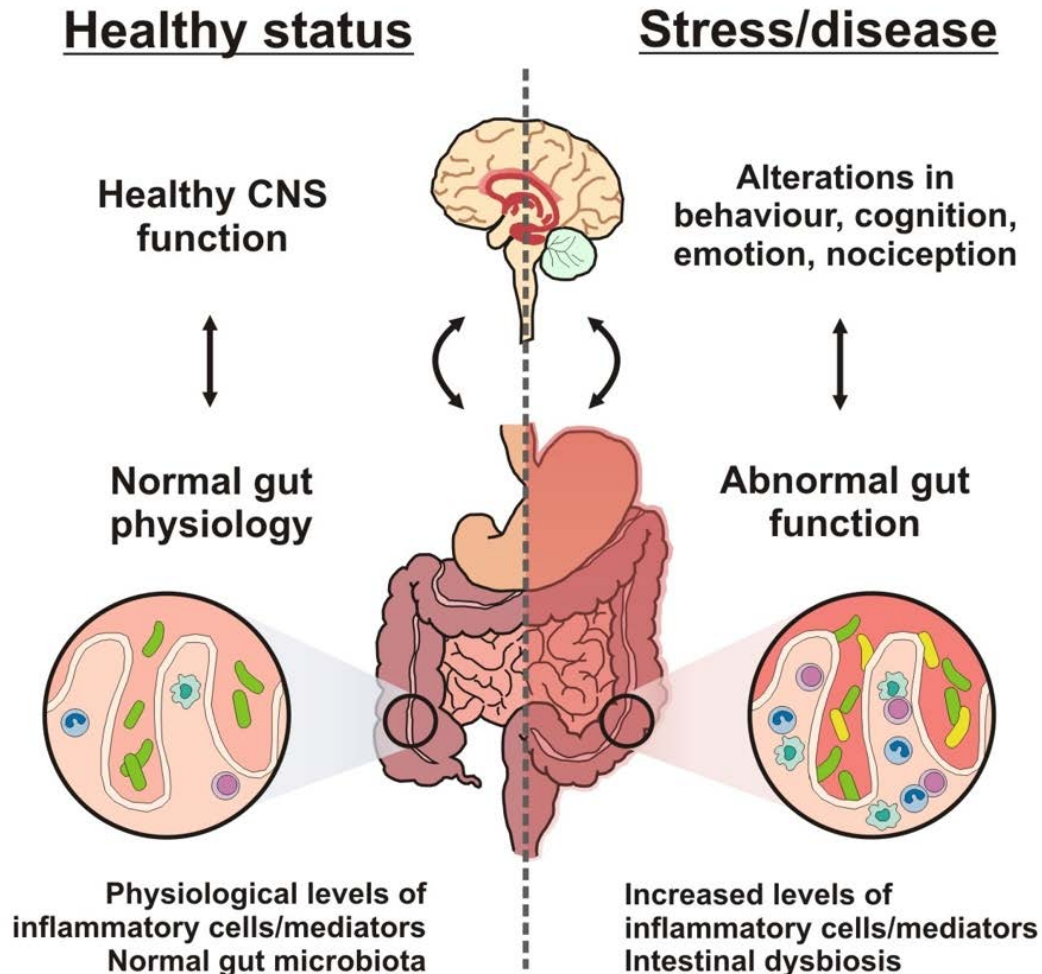


# Brain-Gut Axis

- Bidirectional communication system between the brain and the gut
- Brain can influence gastrointestinal function
- Gut can influence brain
- Neural, hormonal and immunological routes
- Dysregulation important in disorders like IBS



# Brain-Gut-Microbiota Axis





## The microbiota link to irritable bowel syndrome

### An emerging story

Ian B. Jeffery,<sup>1</sup> Eamonn M.M. Quigley,<sup>2</sup> Lena Öhman,<sup>3</sup> Magnus Simrén<sup>3</sup> and Paul W. O'Toole<sup>1,2,\*</sup>

## REVIEWS

te

## A role for the gut microbiota in IBS

*Stephen M. Collins*



### Key points

- Animal studies have demonstrated that changes in the gut microbiota result in altered host function, in domains relevant to IBS (gut motility, visceral pain responses, intestinal permeability, and brain function and behaviour)
- Gut microbiota composition is altered in at least a subset of patients with IBS (most commonly diarrhoea-predominant IBS), but no microbial 'signature' that could act as an IBS biomarker has been identified
- Considerable interest exists in the ability of bacteria to produce substances that interact with the host to influence gut and brain function, which include fatty acids, tryptophan and neurotransmitters
- Dysbiosis in IBS is characterized by a loss of microbial diversity and temporal instability; contributing factors include diet, stress, infection, antibiotic usage, immune activation and low-grade inflammation
- The gut microbiota from patients with IBS, but not healthy individuals, can induce gut dysfunction in mice reminiscent of that seen in IBS, strongly suggesting that the microbiota contributes to the expression of IBS
- Emerging evidence supports the efficacy of select and limited microbiota-directed therapies in treating IBS, and to date these include prebiotics, probiotics and selected antibiotics

# Irritable Bowel Syndrome

## Alimentary Pharmacology & Therapeutics

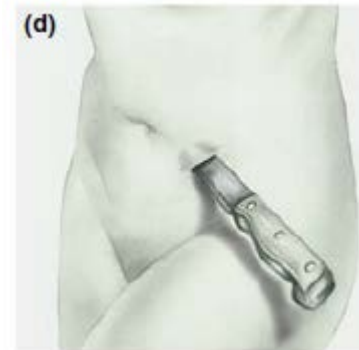
### Reactivity to images in health and irritable bowel syndrome

H. R. CARRUTHERS\*, J. MORRIS†, N. TARRIER‡ & P. J. WHORWELL\*

#### Altered Bowel Habit

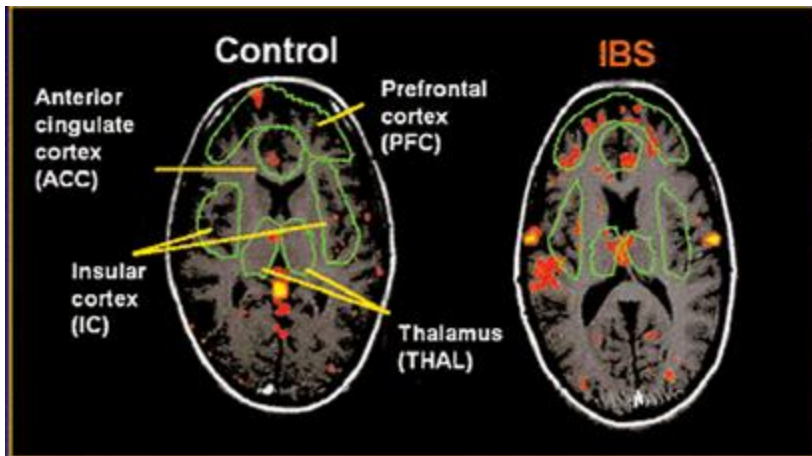


#### Abdominal Pain

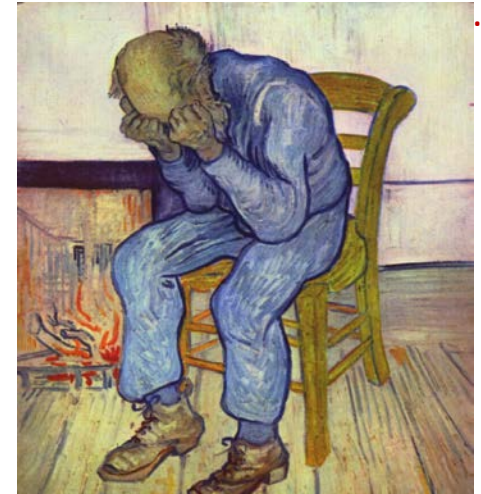


# CNS Dysfunction in IBS

- **Psychiatric comorbidity**
  - Depression
  - Anxiety
- **Visceral Hypersensitivity**



Mertz et al., Gastroenterology 2000



Vincent van Gogh's "At Eternity's Gate"



The Scream (Edvard Munch)

# Cognition

Learning

Planning

Memory

Problem  
Solving

Attention

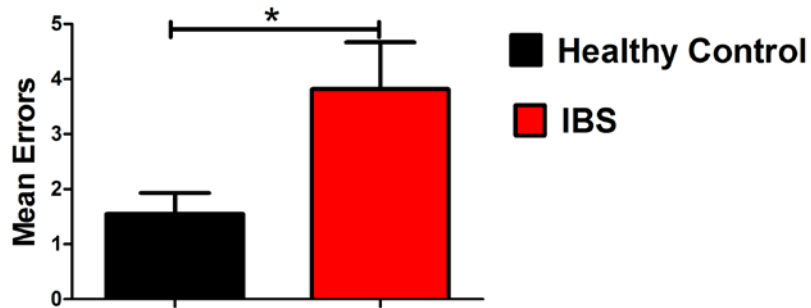
Decision  
Making





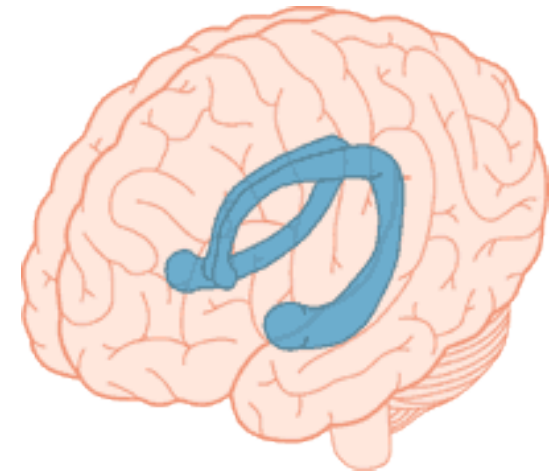
# Altered Cognition in IBS

## Baseline: Visuospatial memory deficit

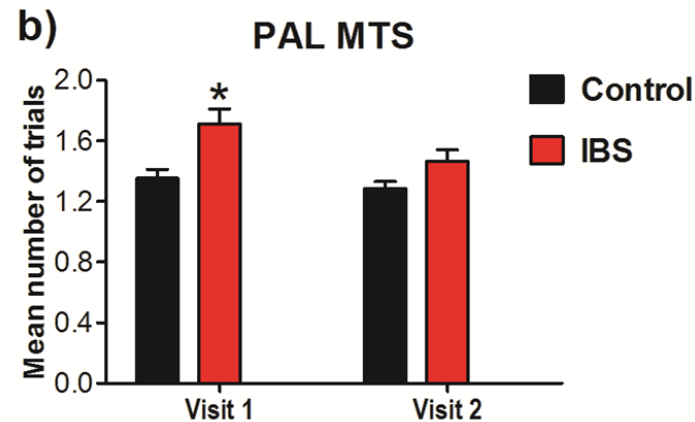
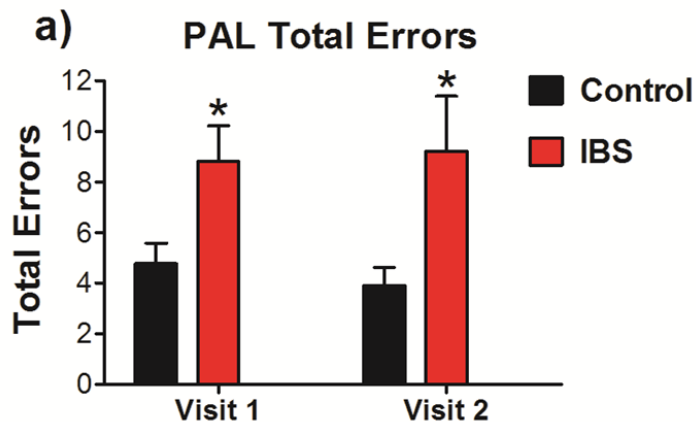


Kennedy et al., Psychological Medicine 2013

## Hippocampus



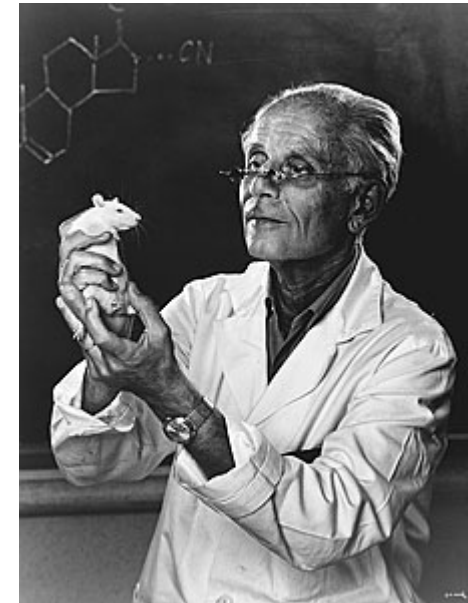
## 6 & 12 months: Consistent memory deficit



# Stressors

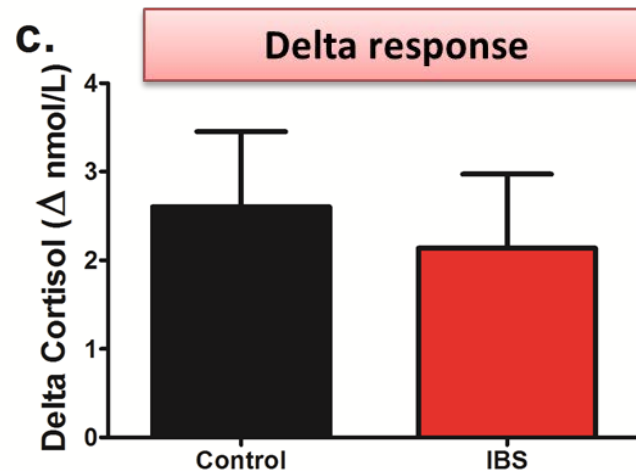
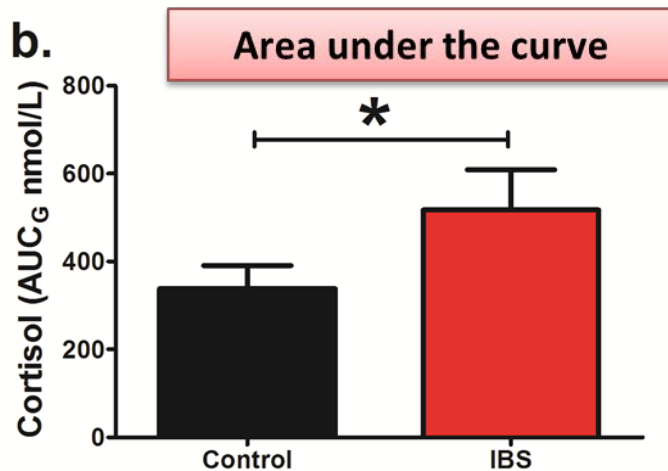
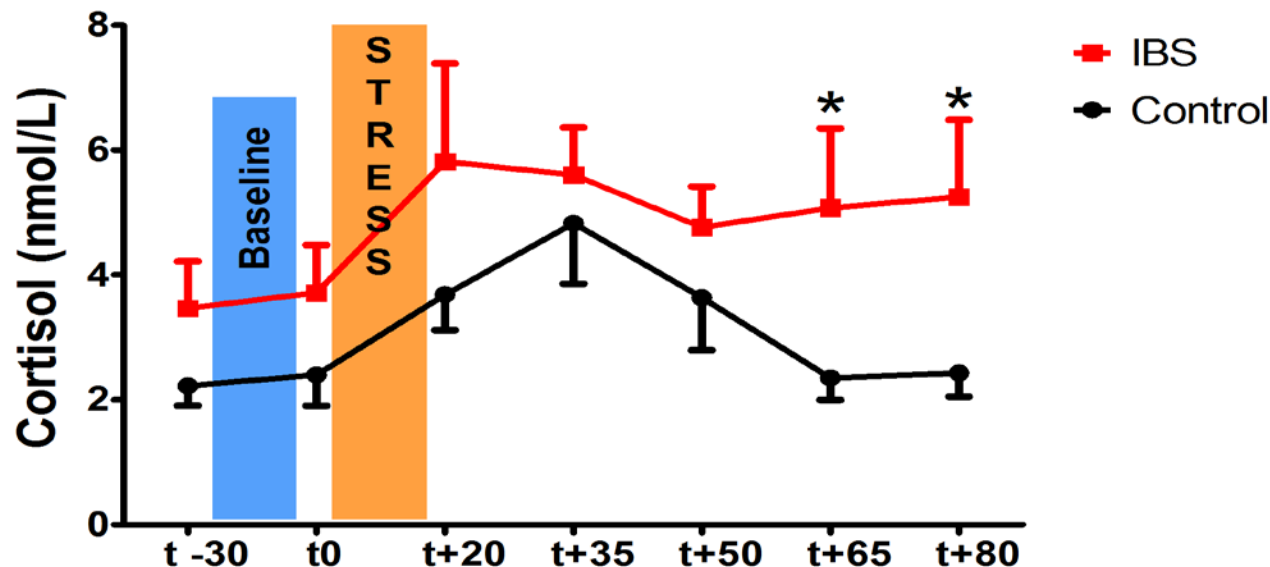


*"It's not stress that kills us, it is our reaction to it".*  
Hans Selye



child  
care  
THE  
**50** year  
mortgage



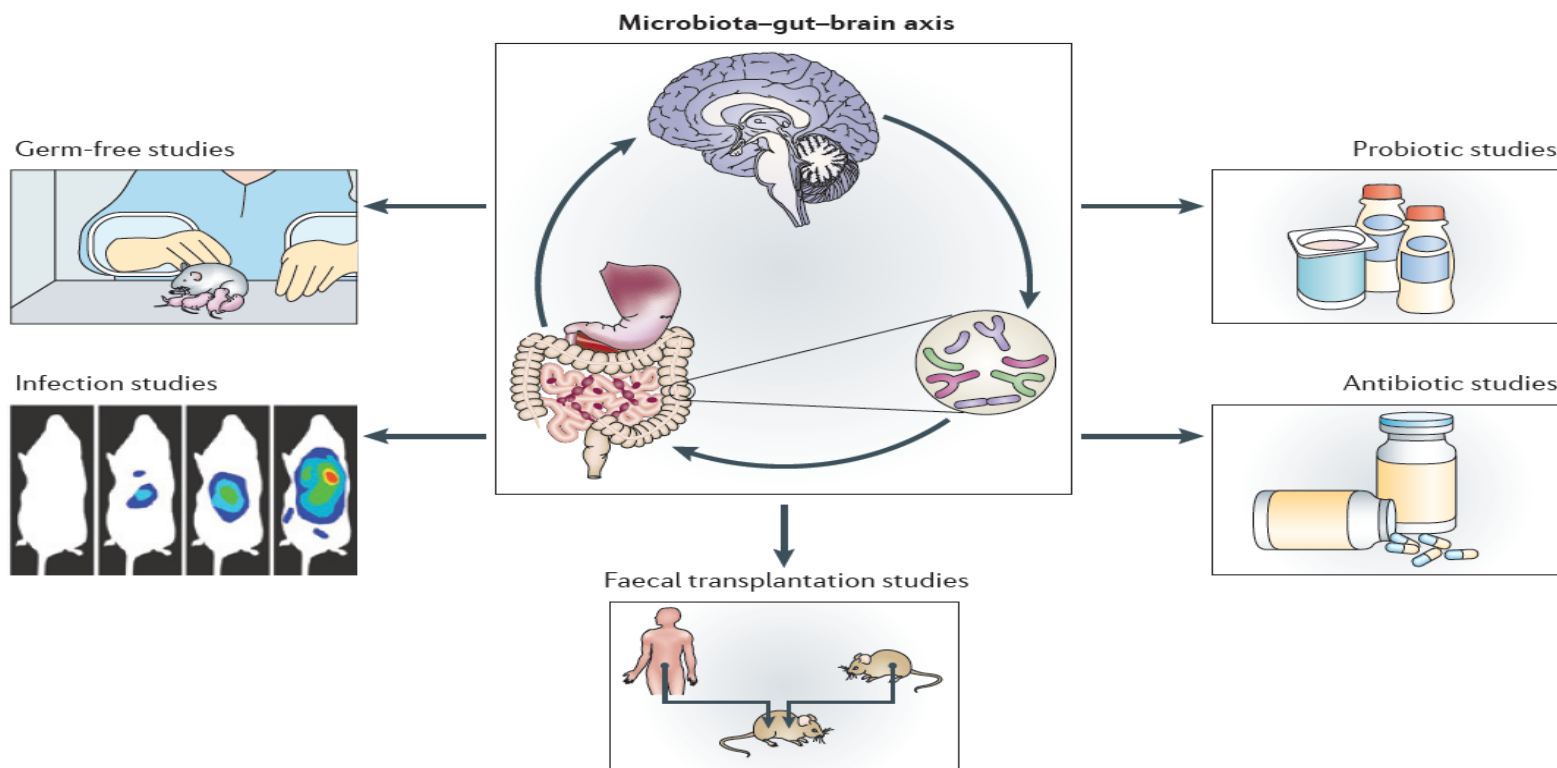


Kennedy et al., Psychological Medicine 2014

# Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour

John F. Cryan<sup>1,2</sup> and Timothy G. Dinan<sup>1,3</sup>

**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





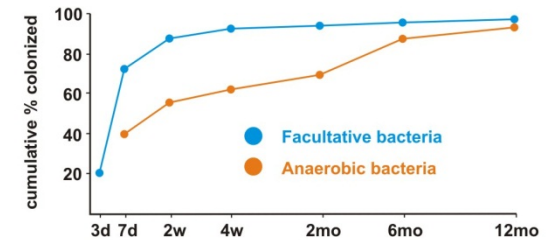
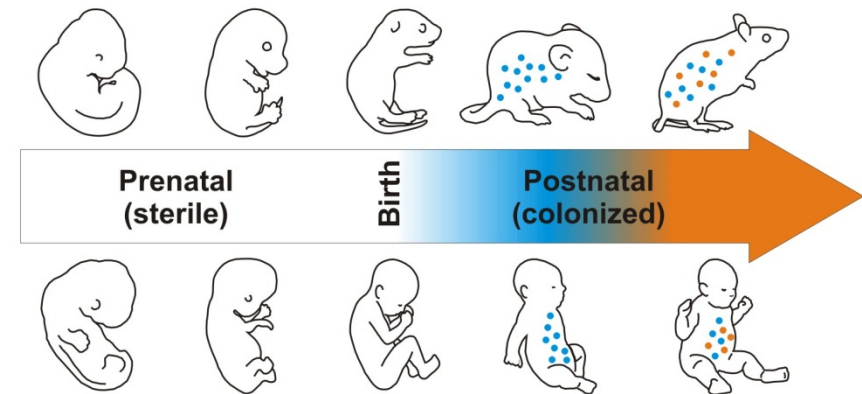
➤ Sterile uterus

➤ First exposure to bacteria during birth

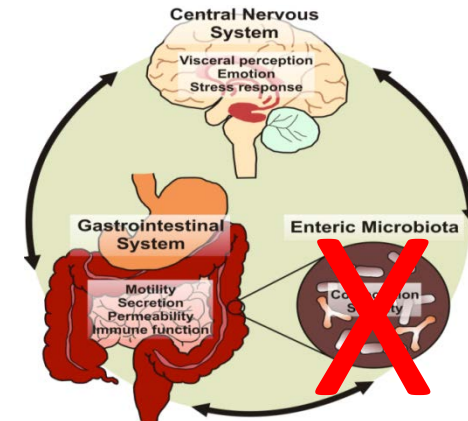
➤ Postnatal colonisation of the gut

➤ Germ free animals-from their 'mother's womb untimely ripped'

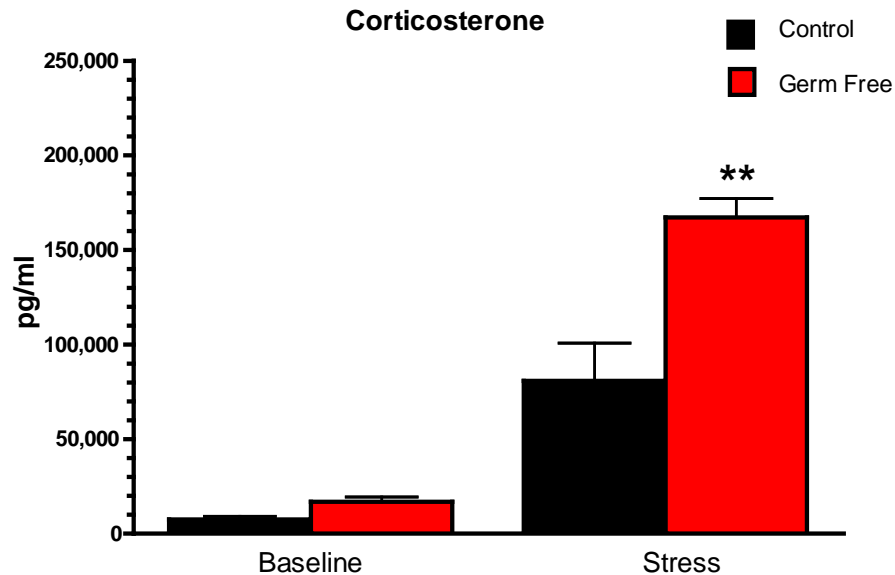
Macbeth, William Shakespeare



Grenham, Clarke et al., Frontiers in Physiology 2011

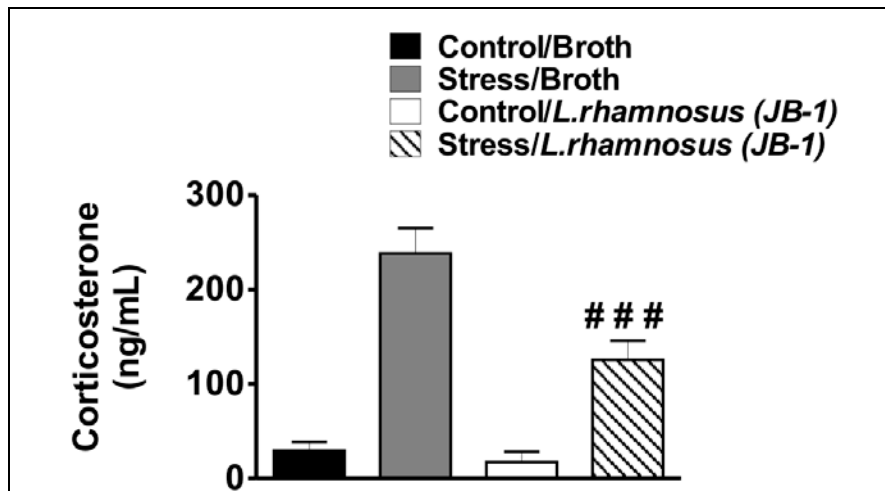


# Microbiota Controls Stress Response



**Germ-free animals  
have an exaggerated  
stress response**

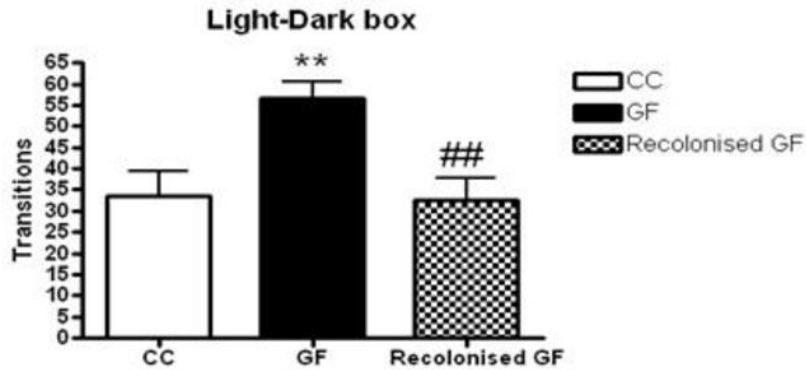
*Clarke et al., Mol Psychiat 2013*



**Probiotic Reduces  
Stress-induced  
Corticosterone Levels**

*Bravo et al., PNAS Sept 2011*

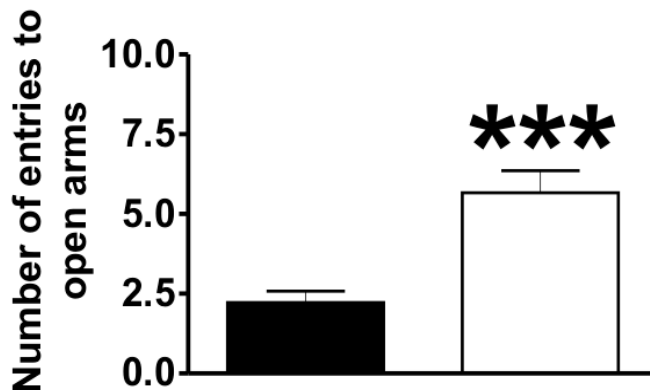
# Microbiota Regulates Anxiety



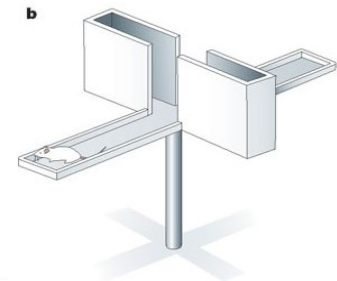
**Germ-free animals  
have lower anxiety-like  
behaviours**

*Clarke et al., Mol Psychiat 2013*

**Probiotic Reduces  
Anxiety-like behaviours**



*Bravo et al., PNAS Sept 2011*



# Microbiota Regulates Anxiety

Scream adapted, New Scientist, March 12 2013

<http://www.footballoffthepitch.com/2014/03/award-winning-david-moyes-artwork.html>



**Probiotics  
Microbiota  
Transplanation**

**Antibiotics  
Infection  
Microbiota  
Transplanation**

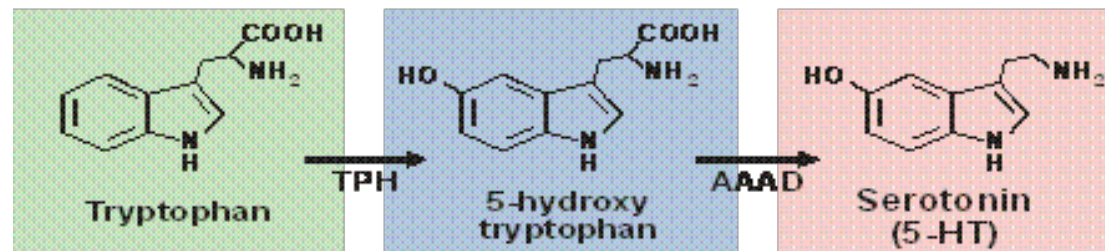
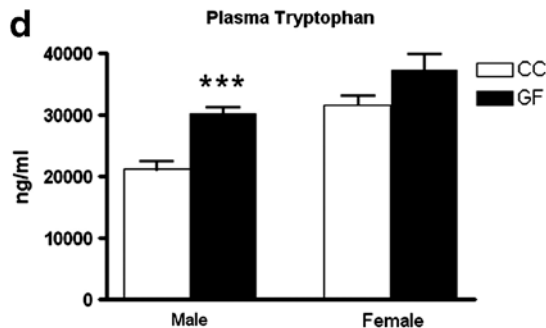
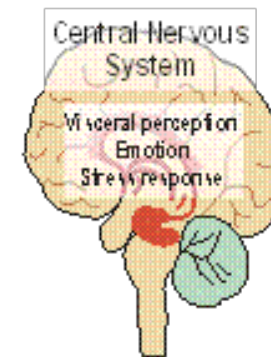
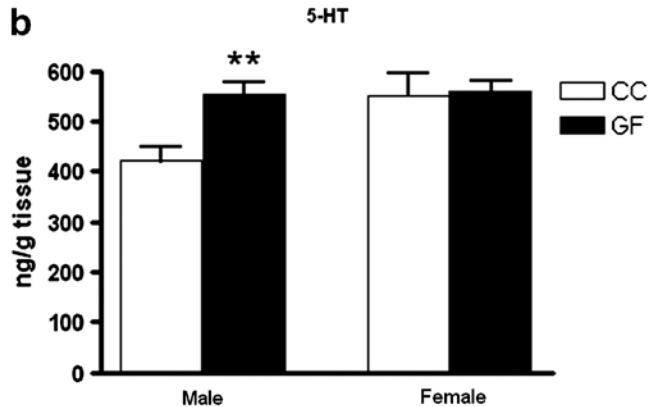


# Microbiota and Depression

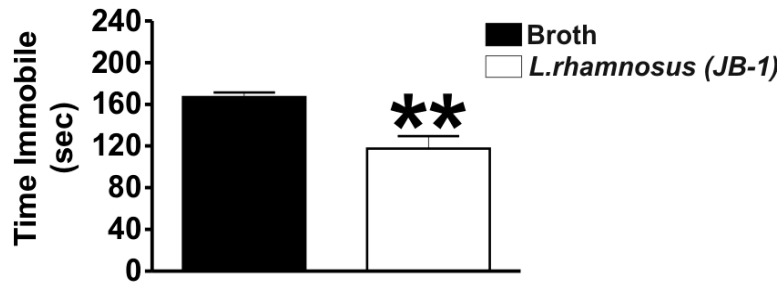
## ORIGINAL ARTICLE

### The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner

G Clarke<sup>1,2</sup>, S Grenham<sup>1</sup>, P Scully<sup>1</sup>, P Fitzgerald<sup>1</sup>, RD Moloney<sup>1</sup>, F Shanahan<sup>1,3</sup>, TG Dinan<sup>1,2</sup> and JF Cryan<sup>1,4</sup>

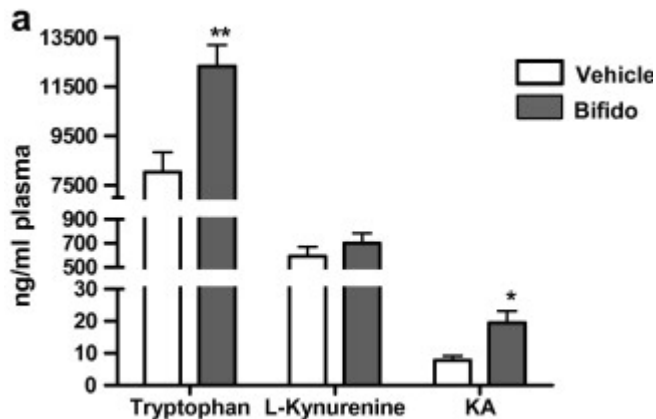


# Microbiota and Depression



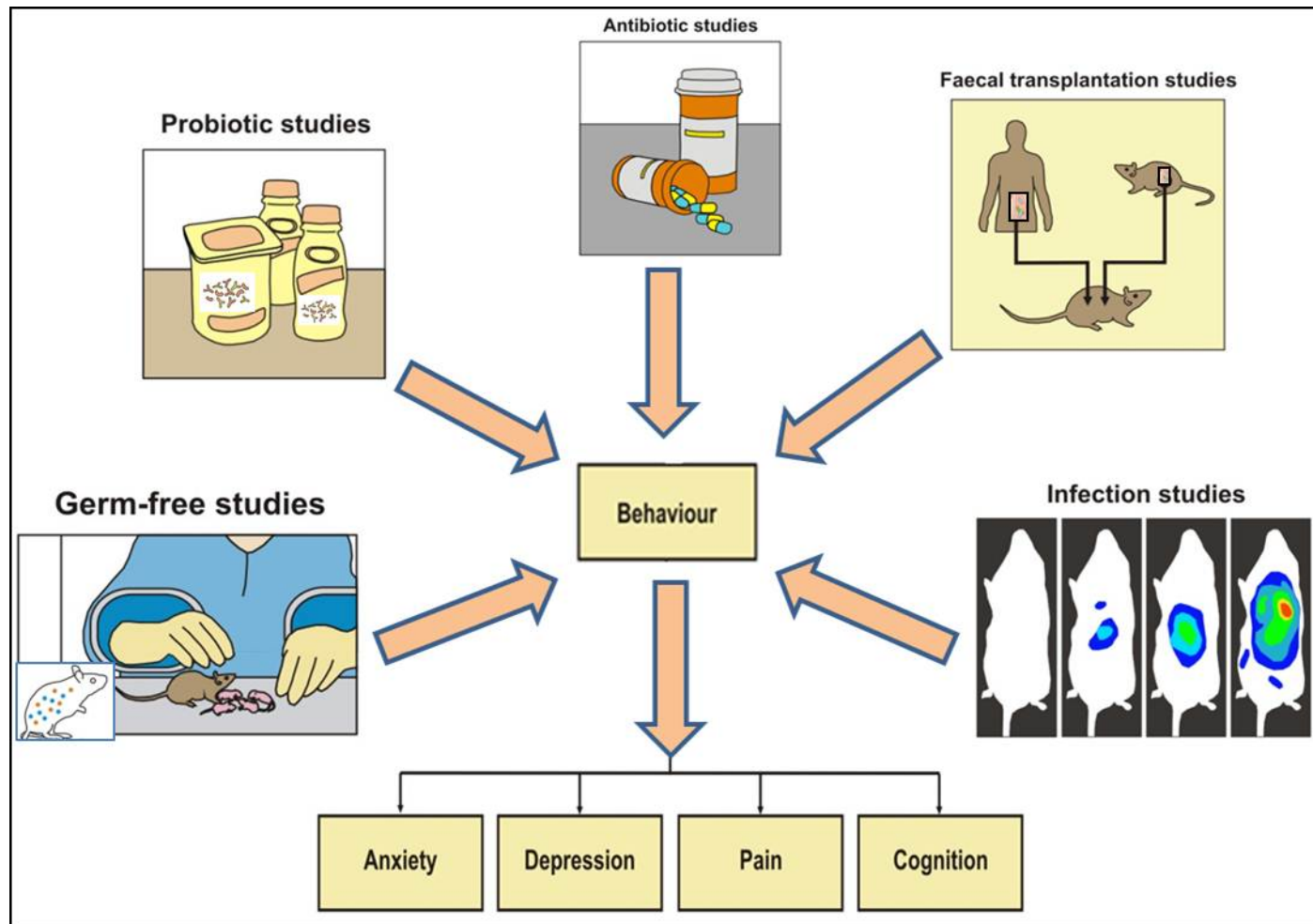
*Bravo et al., PNAS Sept 2011*

**Probiotic Reduces  
Depressive-like  
Behaviours**



*Desbonnet et al., J Psych Res 2008*

**Probiotic Increases  
Circulating  
Tryptophan**



## Review article: probiotics for the treatment of irritable bowel syndrome – focus on lactic acid bacteria

G. Clarke<sup>\*,†</sup>, J. F. Cryan<sup>\*,‡</sup>, T. G. Dinan<sup>\*,†</sup> & E. M. Quigley<sup>\*,§</sup>

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<sup>‡</sup>Department of Anatomy &  
Neuroscience, University College  
Cork, Cork, Ireland.

<sup>§</sup>Department of Medicine, University  
College Cork, Cork, Ireland.

### SUMMARY

#### Background

Irritable bowel syndrome (IBS) is a poorly understood, yet highly prevalent functional gastrointestinal disorder (FGID). The withdrawal, due to adverse events, of a number of pharmacological agents that were approved for the treatment of IBS has left a therapeutic vacuum for patients suffering from the disorder.



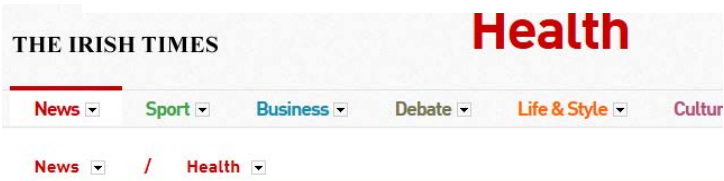


## REVIEW

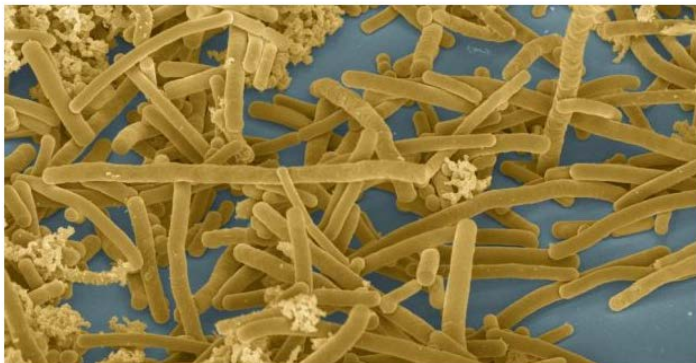
# Psychobiotics: A Novel Class of Psychotropic

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

Here, we define a psychobiotic as a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness. As a class of probiotic, these bacteria are capable of producing and delivering neuroactive substances such as gamma-aminobutyric acid and serotonin, which act on the brain-gut axis. Preclinical evaluation in rodents suggests that certain psychobiotics possess antidepressant or anxiolytic activity. Effects may be mediated via the vagus nerve, spinal cord, or neuroendocrine systems. So far, psychobiotics have been most extensively studied in a liaison psychiatric setting in patients with irritable bowel syndrome, where positive benefits have been reported for a number of organisms including *Bifidobacterium infantis*. Evidence is emerging of benefits in alleviating symptoms of depression and in chronic fatigue syndrome. Such benefits may be related to the anti-inflammatory actions of certain psychobiotics and a capacity to reduce hypothalamic-pituitary-adrenal axis activity. Results from large scale placebo-controlled studies are awaited.



‘Psychobiotics’ offer potential in improving mental health, researchers find



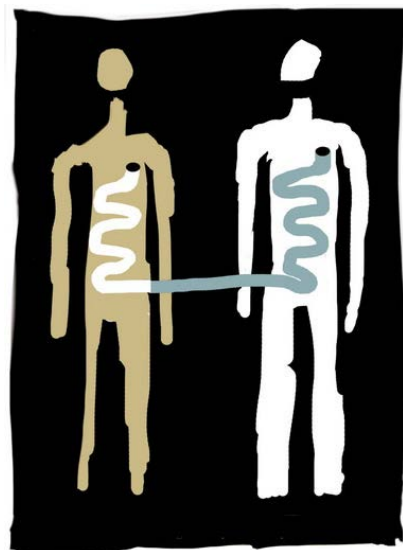
The NEW ENGLAND JOURNAL of MEDICINE

## EDITORIAL



### Fecal Microbiota Transplantation — An Old Therapy Comes of Age

Ciarán P. Kelly, M.D.



IRISHTIMES.com

Thursday, October 25, 2012

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The Irish Times - Tuesday, July 24, 2012

### Have you the guts for faecal transplants?

#### Neurogastroenterology & Motility

*Neurogastroenterol Motil* (2013) **25**, 713–719

doi: 10.1111/nmo.12198

#### VIEWPOINT

### Melancholic microbes: a link between gut microbiota and depression?

T. G. DINAN & J. F. CRYAN

Alimentary Pharmabiotic Centre, University College Cork, Cork, Ireland

DRUG DEVELOPMENT

# Microbiome therapy gains market traction

*Wave of investment suggests drugs from body-dwelling bacteria are heading for the clinic.*



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## *Second Genome Enters Into Agreement with Pfizer Inc. on Microbiome Research Initiative in Obesity*

Posted by [Todd](#) on Thursday, May 1, 2014 · [Leave a Comment](#)

### *The Latest*

Second Genome Enters Into Agreement with Pfizer Inc. on Microbiome Research Initiative in Obesity

## LETTER

doi:10.1038/nature12820

### Diet rapidly and reproducibly alters the human gut microbiome

Lawrence A. David<sup>1,2†</sup>, Corinne F. Mat  
Alisha V. Ling<sup>3</sup>, A. Sloan Devlin<sup>4</sup>, Yug V



**Chris Kresser**

HEALTH for the 21ST CENTURY

ARTICLES

EBOOKS

PRO<sup>h1</sup>

### RHR: You Are What Your Bacteria Eat: The Importance of Feeding Your Microbiome – With Jeff Leach

## ARTICLE

by CHRIS KRESSER

111 comments

doi:10.1038/nature11319

### Gut microbiota composition correlates with diet and health in the elderly

Marcus J. Claesson<sup>1,2\*</sup>, Ian B. Jeffery<sup>1,2\*</sup>, Susana Conde<sup>3</sup>, Susan E. Power<sup>1</sup>, Eibhlís M. O'Connor<sup>1,2</sup>, Siobhán Cusack<sup>1</sup>, Hugh M. B. Harris<sup>1</sup>, Mairead Coakley<sup>4</sup>, Bhuvaneswari Lakshminarayanan<sup>4</sup>, Orla O'Sullivan<sup>4</sup>, Gerald F. Fitzgerald<sup>1,2</sup>, Jennifer Deane<sup>1</sup>, Michael O'Connor<sup>5,6</sup>, Norma Harnedy<sup>5,6</sup>, Kieran O'Connor<sup>6,7,8</sup>, Denis O'Mahony<sup>5,6,8</sup>, Douwe van Sinderen<sup>1,2</sup>, Martina Wallace<sup>9</sup>, Lorraine Brennan<sup>9</sup>, Catherine Stanton<sup>2,4</sup>, Julian R. Marchesi<sup>10</sup>, Anthony P. Fitzgerald<sup>3,11</sup>, Fergus Shanahan<sup>2,12</sup>, Colin Hill<sup>1,2</sup>, R. Paul Ross<sup>2,4</sup> & Paul W. O'Toole<sup>1,2</sup>



## REVIEW ARTICLE

### Priming for health: gut microbiota acquired in early life regulates physiology, brain and behaviour

G Clarke (g.clarke@ucc.ie)<sup>1,2\*</sup>, SM O'Mahony<sup>1,3\*</sup>, TG Dinan<sup>1,2</sup>, JF Cryan<sup>1,3</sup>

1.Alimentary Pharmabiotic Centre, University College Cork, Cork, Ireland

2.Department of Psychiatry, University College Cork, Cork, Ireland

3.Department of Anatomy and Neuroscience, University College Cork, Cork, Ireland

#### Keywords

Behaviour, Brain Development, Breastfeeding, Early Life, Microbiota

#### Correspondence

G Clarke, Department of Psychiatry/Alimentary Pharmabiotic Centre, 1.15 Biosciences Institute, University College Cork, Cork, Ireland.

Tel: +353 214 901 408 |

#### ABSTRACT

The infant gut microbiome is dynamic, and radical shifts in composition occur during the first 3 years of life. Disruption of these developmental patterns, and the impact of the microbial composition of our gut on brain and behaviour, has attracted much recent attention. Integrating these observations is an important new research frontier.

**Conclusion:** Early-life perturbations of the developing gut microbiota can impact on the central nervous system and potentially lead to adverse mental health outcomes.

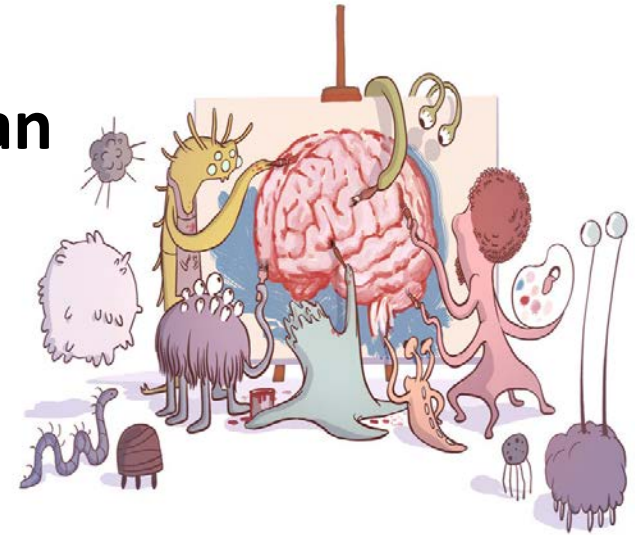


#### Key notes

- Preclinical studies have shown that gut microbiota development in the gastrointestinal tract can alter brain function and regulate complex behaviours.
- Clinical studies indicate that disruptions to normal early-life gastrointestinal colonisation might be linked to central nervous system dysfunction and that microbial colonisation of the gastrointestinal tract in infants coincides with critical periods of central nervous system and gut-brain axis development.
- Increased knowledge about adverse and beneficial colonisation events is urgently required.

# Summary & Conclusions

- Gut microbiota can control stress response
- Implicated in Anxiety, Depression, Cognition and Pain
- Can regulate the supply of tryptophan
- Implications for IBS and beyond
- Translation to clinic?
- Microbial-based strategies for the treatment of brain disorders? All probiotics not created equal!
- Treat your gut microbes well!



[www.npr.org](http://www.npr.org)



## Looking for Healthy Volunteers

Are you a healthy male aged between 18 and 40 years?

Are you interested in participating in a study investigating the role of **probiotics** in cognitive function and mood?

**All participants will receive €125 in vouchers upon completion of the study, to cover costs and expenses.**

For further details, please contact:

Andrew Allen at [probiotic2014@gmail.com](mailto:probiotic2014@gmail.com)

This study is being conducted by the Alimentary Pharmabiotic Centre (APC). The APC is a UCC/Teagasc Research Centre funded by Science Foundation Ireland and industry, focusing on gastrointestinal health and development of therapies for debilitating disorders such as Crohn's disease, colitis, irritable bowel syndrome (IBS) and food poisoning (<http://apc.ucc.ie>).



# Acknowledgements



## Spoke 3: Brain-Gut-Microbiota Axis

NEUROSCIENCE anxiety  
PUBLIC HEALTH  
stress  
Microbiota  
COGNITION  
VISCERAL PAIN metabolic disease  
depression AUTISM



**BRAIN & BEHAVIOR**  
RESEARCH FOUNDATION  
Awarding **NARSAD** Grants



University College Cork  
School of Medicine

GENIEUR.EU  
Genes in irritable bowel  
syndrome



AMERICAN NEUROGASTROENTEROLOGY AND MOTILITY SOCIETY

**cost**  
EUROPEAN COOPERATION  
IN SCIENCE AND TECHNOLOGY

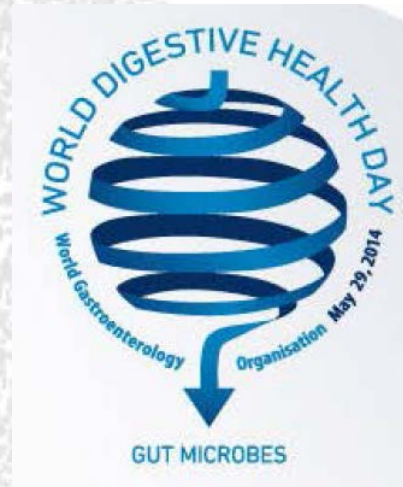


Fondúireacht Eolaíochta Éireann  
Science Foundation Ireland



**Thank you**

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Science Foundation Ireland

The Daily Mail, London Sept 2011