Gut Microbiome and (Ageing) Brain Function

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Brain & Body Closely Interact

The Brain-Gut Axis

How Your Mind Can Heal Your Body

Naliboff et al. 2006
The Language of Gut-Brain Axis

- "It takes GUTS! to teach Anatomy"
- "Gut Feelings"
- "Gut Instinct is Your Greatest Critic"
- "Trust Your Gut"
- "Butterflies in My Stomach and Other School Hazards"
- "Go with your gut"
- "Between gut instincts, gut feelings and gut reactions my abs get a great workout."

[Images of various books and illustrations related to gut health and the gut-brain axis]
Stressors

- Traffic congestion
- Economic recession
- Brexit uncertainty
- Child care challenges
- High mortgage rates
- Low returns on investments
- No tenants problem
- Complex decision-making
- Political instability
Neuroscience, Molecular Biology, and the Childhood Roots of Health Disparities
Building a New Framework for Health Promotion and Disease Prevention

Jack P. Shonkoff, MD
W. Thomas Boyce, MD
Bruce S. McEwen, PhD

A scientific consensus is emerging that the origins of adult disease are often found among developmental and biological disruptions occurring during the early years of life. These early experiences can affect adult health in 2 ways—either by cumulative damage over time or by the biological embedding of adversities during sensitive developmental periods. In both cases, there can be a lag of many years, even decades, before early adverse experiences are expressed in the form of disease. From both basic research and policy perspectives, confronting the origins of disparities in physical and mental health early in life may produce greater effects than attempting to modify health-related behaviors or improve access to health care in adulthood.

Lupien et al., Nat Rev Neuroscience, 2009

<table>
<thead>
<tr>
<th>Effect on HPA axis</th>
<th>Outcome</th>
<th>Programming effects</th>
<th>Differentiation effects</th>
<th>Potentiation/incubation effects</th>
<th>Maintenance/manifestation effects</th>
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<td>Lupien et al., Nat Rev Neuroscience, 2009</td>
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<td>(maternal separation)</td>
<td>(severe trauma)</td>
<td>(PTSD)</td>
<td>(PTSD)</td>
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“It’s not stress that kills us, it is our reaction to it”
Hans Selye
Stress Alters Brain-Gut Axis

Dinan & Cryan, Neurogastro & Motil. 2013
Living in a Microbial World...
Where do we get our microbiota from?

Grenham et al., 2011
Programming infant gut microbiota: influence of dietary and environmental factors

Gut microbiota composition correlates with diet and health in the elderly

Marcus J. Claesson1,2*, Ian B. Jeffery1,2*, Susana Conde3, Susan E. Power1, Eibhlin M. O’Connor1,2, Siobhán Cusack1, Hugh M. B. Harris1, Mairead Coakley4, Bhuvaneswari Lakshminarayanan4, Orla O’Sullivan4, Gerald F. Fitzgerald1,2, Jennifer Deane1, Michael O’Connor5,6, Norma Harnedy5,6, Kieran O’Connor6,7,8, Denis O’ Mahony5,6,8, Douwe van Sinderen1,2, Martina Wallace9, Lorraine Brennan9, Catherine Stanton2,4, Julian R. Marchesi10, Anthony P. Fitzgerald3,11, Fergus Shanahan2,12, Colin Hill1,2, R. Paul Ross2,4 & Paul W. O’Toole1,2

Alterations in intestinal microbiota composition are associated with several chronic conditions, including obesity and inflammatory diseases. The microbiota of older people displays greater inter-individual variation than that of younger adults. Here we show that the faecal microbiota composition from 178 elderly subjects formed groups, correlating with residence location in the community, day-hospital, rehabilitation or in long-term residential care. However, clustering of subjects by diet separated them by the same residence location and microbiota groupings. The separation of microbiota composition significantly correlated with measures of frailty, co-morbidity, nutritional status, markers of inflammation and with metabolites in faecal water. The individual microbiota of people in long-stay care was significantly less diverse than that of community dwellers. Loss of community-associated microbiota correlated with increased frailty. Collectively, the data support a relationship between diet, microbiota and health status, and indicate a role for diet-driven microbiota alterations in varying rates of health decline upon ageing.
Adding fuel to the fire: the impact of stress on the ageing brain

Jack A. Prenderville, Paul J. Kennedy, Timothy G. Dinan, and John F. Cryan

Alimentary Pharmabiotic Centre, University College Cork, Cork, Ireland

Gut microbiota and Extreme Longevity

Elena Bari, Claudio Franceschi, Simone Rampelli, Marco Severgnini, Rita Orsini, Silvia Turolla, Clarisa Consolandi, Sara Grinia, Maria Scordi, Daniela Menz, Miriam Capir, and Marco Candela

SPECIAL SECTION AGING

Perspective

Gut microbiota and aging

Paul W. O'Toole and Ian B. Jeffery

A

RDA1

PC1

64-69
70-79
80-89
90-94

Increasing age (years)
Microbiome & Metabolome Play key role in Longevity Projects

Elie Metchnikoff (1845-1916) Nobel Prize 1908

HUMAN LONGEVITY, INC.

Bacteria, fungi, and viruses outnumber human cells 10:1

The human microbiome:
- Consists of 100 trillion cells
- Can be considered an organ
- Has a weight of ~ 3 pounds
- Contributes to metabolism
- Impacts health and disease
- Was discovered in mid 20th century
- Is still poorly understood

Brad Perkins, Human Longevity Wired Health Talk April 2015
(A) Bacterial-derived signals NO and ncRNAs regulate C. elegans longevity.

(B) Metformin increases C. elegans lifespan via effects on bacterial folate metabolism.

(C) L. plantarum drive Drosophila growth under low-nutrient conditions via the longevity modulator TOR.

(D) Different bacterial species elicit specific transcriptional responses in C. elegans.

Heintz & Mair, Cell 2014, 156; Pages 408–411
Reduction of Alzheimer's disease beta-amyloid pathology in the absence of gut microbiota


(Submitted on 8 Sep 2015 (v1), last revised 16 Sep 2015 (this version, v2))

Alzheimer's disease is the most common form of dementia in the western world, however there is no cure available for this devastating neurodegenerative disorder. Despite clinical and experimental evidence implicating the intestinal microbiota in a number of brain disorders, its impact on Alzheimer's disease is not known. We generated a germ-free mouse model of Alzheimer's disease and discovered a drastic reduction of cerebral Ab amyloid pathology when compared to control Alzheimer's disease animals with intestinal microbiota. Sequencing bacterial 16S rRNA from fecal samples revealed a remarkable shift in the gut microbiota of conventionally-raised Alzheimer's disease mice as compared to healthy, wild-type mice. Colonization of germ-free Alzheimer mice with harvested microbiota from conventionally-raised Alzheimer mice dramatically increased cerebral Ab pathology. In contrast, colonization with microbiota from control wild-type mice was ineffective in increasing cerebral Ab levels. Our results indicate a microbial involvement in the development of Alzheimer's disease pathology, and suggest that microbiota may contribute to the development of neurodegenerative diseases.

Neutrophil ageing is regulated by the microbiome

Dachuan Zhang¹,², Grace Chen¹,², Deepa Manwani³, Arthur Mortha⁴,⁵, Chunliang Xu¹,², Jeremiah J. Faith⁵,⁶, Robert D. Burk³, Yuya Kunisaki¹,²†, Jung-Eun Jang¹,², Christoph Scheiermann¹,²†, Miriam Merad⁴,⁵ & Paul S. Frenette¹,²,⁷
**Microbiota-Brain-Gut Axis**

**BIOACTIVES**

**STRESS**

**DIET/NUTRITION**

**PROBIOTICS**

**METABOLISM**

**APPETITE**

**DIGESTIVE HEALTH**

**FOOD REWARD**

**COGNITION**

**MENTAL HEALTH**

**AGEING**

Functional Foods & Ingredients
Live Biotherapeutics

Schellekens et al
Strategies used to investigate the role of the microbiota–gut–brain axis in health and disease

Cryan and Dinan, Nat Rev Neurosci Oct 2012
Luczynski et al

REVIEW

Growing up in a Bubble: Using Germ-Free Animals to Assess the Influence of the Gut Microbiota on Brain and Behavior
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, Ohi-machi, Kanagawa, Japan
Germ Free Mice: Understanding the impact of microbiota on brain function

Normal gut microbiota modulates brain development and behavior

Rochellys Diaz Heijtz a,b,1, Shugui Wang c, Farhana Anuar d, Yu Qian a,b, Britta Björkholm d, Annika Samuelsson d, Martin L. Hibberd c, Hans Forssberg b,e, and Sven Pettersson c,d,1

Departments of aNeuroscience, and bMicrobiology, Cell and Tumor Biology, Karolinska Institutet, 171 77 Stockholm, Sweden; bStockholm Brain Institute, 171 77 Stockholm, Sweden; Genome Institute of Singapore, 02-01 Genome Institute 138672, Singapore; and dDepartment of Women’s and Children’s Health, Karolinska Institutet, 171 76 Stockholm, Sweden

Edited by Arturo Zychlinsky, Max Planck Institute for Infection Biology, Berlin, Germany, and accepted by the Editorial Board January 4, 2011 (received for review October 26, 2010)

Reduced anxiety-like behavior and central neurochemical change in germ-free mice

K. M. Neufeld, *,† N. Kang, *,‡ J. Bienenstock, *,§ & J. A. Foster, *

*Brain-Body Institute, St. Joseph’s Healthcare, Hamilton, ON, Canada

ORIGINAL ARTICLE

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

G Clarke 1,2, S Grenham 1, P Scully 1, P Fitzgerald 1, RD Moloney 1, F Shanahan 1,3, TG Dinan 1,2 and JF Cryan 1,4
Abnormal Brain Development in Male Mice Lacking Microbiota

BDNF expression in the Hippocampus

- **Control**
- **Germ free**

Fold Change ($2^{ΔΔCT}$)

5-HT

- **Control**
- **Germ free**

ng/g tissue

Clarke et al., Mol Psychiact 2013
Adult Hippocampal Neurogenesis is Regulated by the Microbiome

O’Leary & Cryan, TiPS Dec 2014

Ogbonnaya et al., Biol Psychiat 2015
Microbiota Determines Amygdala Volume & Dendritic Morphology

Increased Volume

Increased spine density

GF BLA pyramidal neurons had more thin, stubby, and mushroom spines.

CC = Conventionally Colonised
GF = Germ Free

Dendritic Hypertrophy of Basolateral Amygdala Neurons

Control

Germ-free

Regulation of prefrontal cortex myelination by the microbiota

AE Hoban\textsuperscript{1,2}, RM Stilling\textsuperscript{1,2}, FJ Ryan\textsuperscript{1,3}, F Shanahan\textsuperscript{1}, TG Dinan\textsuperscript{1,4}, MJ Claesson\textsuperscript{1,3}, G Clarke\textsuperscript{1,4,5,6} and JF Cryan\textsuperscript{1,2,5,6}

**Upregulated in GF**
- Myelin-related genes (14.9%)
- Activity-induced genes (27.7%)
- Other genes

**Effects More Pronounced in Males than Females**

Electron Microscopy
Lacking a strong blood-brain barrier, germ-free mice (left) can't prevent a radioactive tracer (yellow) from entering the brain the way that mice with microbes (middle) can. But adding microbes to germ-free mice (right) restores the blood-brain barrier.
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 Schwierzke⁷, Olaf Utermöhlen⁵, Eunyoung Chun⁸, Wendy S Garrett⁸, Kathy D McCoy⁹, Andreas Diefenbach⁷, Peter Staeheli⁴, Bärbel Stecher¹⁰, Ido Amit² & Marco Prinz¹,¹¹
GUT MICROBIOTA

Microbiota and neuroimmune signalling—Metchnikoff to microglia

John F. Cryan and Timothy G. Dinan

[Diagram showing interactions between microglia, synaptic pruning, development and plasticity, infection, ageing and NDD, immune response, neuroinflammation, innate immune system, blood factors, and microglia abundance and activity.]
Autism spectrum disorders

- Neurodevelopmental disorder with high heritability
- 1.1% general population
- 4:1 male/female ratio
- 3 symptom domains (DSM-IV)
  - Abnormal social interaction
  - Impaired communication
  - Repetitive behaviours

Other associated symptoms:
- Cognitive impairment
- Seizures
- Anxiety
- Hyperactivity
- Sensory deficits
- GI distress (<90% of patients)
Social Deficits in Mice lacking Microbes

Sociability

Mouse

Empty

Conventional

Germ free

Social Cognition

Novel

Familiar

Conventional

Germ free

Desbonnet et al. Mol Psychiatry 2014
Friends with Social Benefits: Microbes as drivers of brain evolution and development?

“NOTHING IN BIOLOGY MAKES SENSE EXCEPT IN THE LIGHT OF EVOLUTION”
(Theodosius Dobzhansky)

Microbiota, Neurodevelopment & Mental Illness

Borre et al. Trends Mol 2014
Feeding the brain and nurturing the mind: Linking nutrition and the gut microbiota to brain development

Manu S. Goyal\textsuperscript{a,1}, Siddarth Venkatesh\textsuperscript{b,c,1}, Jeffrey Milbrandt\textsuperscript{d,e}, Jeffrey I. Gordon\textsuperscript{b,c,2}, and Marcus E. Raichle\textsuperscript{a,2}

\textsuperscript{a}Neuroimaging Laboratory, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO 63110; \textsuperscript{b}Center for Genome Sciences and Systems Biology, Washington University School of Medicine, St. Louis, MO 63110; \textsuperscript{c}Center for Gut Microbiome and Nutrition Research, Washington University School of Medicine, St. Louis, MO 63110; \textsuperscript{d}Department of Genetics, Washington University School of Medicine, St. Louis, MO 63110; and \textsuperscript{e}Hope Center for Neurological Disorders, Washington University School of Medicine, St. Louis, MO 63110

Edited by Ruslan Medzhitov, Yale University School of Medicine, New Haven, CT, and approved October 6, 2015 (received for review June 12, 2015)

The human gut contains a microbial community composed of tens of trillions of organisms that normally assemble during the first 2–3 y of postnatal life. We propose that brain development needs to be viewed in the context of the developmental biology of this “microbial organ” and its capacity to metabolize the various diets we consume. We hypothesize that the persistent cognitive abnormalities seen in children with undernutrition are related in part to their persistent gut microbiota immaturity and that specific regions of the brain that normally exhibit persistent juvenile (neotenous) patterns of gene expression, including those critically involved in various higher cognitive functions such as the brain’s default mode network, may be particularly vulnerable to the effects of microbiota immaturity in undemourished children. Furthermore, we postulate that understanding the interrelationships between microbiota and brain metabolism in childhood undernutrition could provide insights about responses to injury seen in adults. We discuss approaches that can be used to test these hypotheses, their ramifications for optimizing nutritional recommendations that promote healthy brain development and function, and the potential societal implications of this area of investigation.
Could potential probiotic administration in adulthood affect stress-related anxiety and depression?

The word ‘probiotic’ is derived from the Greek meaning ‘for life’ and refers to live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.

Elie Metchnikoff (1845-1916)
Nobel Prize 1908
Probiotic Reduces Anxiety and Behavioural Despair

Probiotic Alters GABA Receptors in various Brain areas

Bravo et al., PNAS Sept 2011
How do Bacteria Signal to the Brain?- Role of Vagus Nerve

Bravo et al.,
PNAS Sept 2011

Bravo et al. PNAS 2011;108:15661-15662
Fecal Microbiota Transplantation — An Old Therapy Comes of Age

The New York Times

Ciarán P. Kelly, M.D.

A Promising Pill, Not So Hard to Swallow

By PAM BELUCK

Thursday, October 25, 2012

Have you the guts for faecal transplants?
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.
Stress and the Microbiota-Gut–Brain Axis in Health and Disease

“A state of gut” will markedly affect your “state of mind”.

Cryan and Dinan, Nat Rev Neurosci Oct 2012

Thanks to PENICILLIN...He Will Come Home!

Healthy status
- Normal behaviour, cognition, emotion, nociception
- Healthy levels of inflammatory cells and/or mediators
- Normal gut microbiota

Stress/disease
- Alterations in behaviour, cognition, emotion, nociception
- Altered levels of inflammatory cells and/or mediators
- Intestinal dysbiosis

Healthy CNS function

Abnormal CNS function

Healthy gut function

Abnormal gut function

- 20th century- kill microbes via antibiotics
- 21st century- bacteria have beneficial effects on health
Dr. Kieran Rea
Dr. Cristina Torres
Dr. Anna Golubeva
Dr. Karen Scott
Dr. Cara Heuston
Dr. Roman Stilling
Dr. John Kelly
Dr. Jahangir Sajjad
Dr. Gerry Moloney
Dr. Andrew Allen
Dr. Paul Kennedy
Dr. Anand Gururajan
Dr. Eoin Sherwin
Dr. Kiran Sandu
Dr. Marcus Boehme
Dr. Gilliard Lach
Dr. Daniela Felice
Dr. Thorsten Becker
Dr. Barbara Chruscicka
Dr. Matteo Pusceddo
Dr. Susan Kleiman
Dr. Emanuela Morelli
James O’Leary
Ciaran O’Leime
Livia Morais
Alan Hoban
Clara Seira Oriach
Brunno Rocha
Levone
Veronica Peterson
Rory O’Connor
Dalia Kandil
Eileen Curran
Pauline Luczynski,
Ruairi Robertson
Chiara Minuto
Clementine Druelle
Anne-Marie Cusack
Shauna Wallace-Fitzsimmons
Marcel van der Wouw
Karen O’Connor

Prof. Ted Dinan
Prof. Caitriona O’Driscoll
Prof. Fergus Shanahan
Dr. Yvonne Nolan
Prof. Ken O’Halloran
Dr. Ken Nally
Dr. Silvia Melgar,
Dr. Niall P. Hyland
Dr. Siobhain O’Mahony
Dr. Brendan Griffin
Dr. Gerard McGlackan
Dr. Olivia O’Leary
Prof Louise Kenny

Prof. Geraldine Boylan
Dr. Gerard O’Keeffe
Dr. Ger Clarke
Dr. Harriet Schellekens
Prof Catherine Stanton
Prof Paul Ross
Dr. Paul Cotter
Prof Paul O’Toole
Prof Colin Hillr
John Bienenstock/Paul Forsythe, McMaster University
Dr. Andrew Holmes, NIH, USA
'The depression started when I realised how much I was spending on yoghurts'