Gut Feelings:
How the microbiome influences behavior

Jane A. Foster, PhD

St. Joseph's Healthcare Hamilton

McMaster University HEALTH SCIENCES

THE BRAIN-BODY INSTITUTE

The Speaker

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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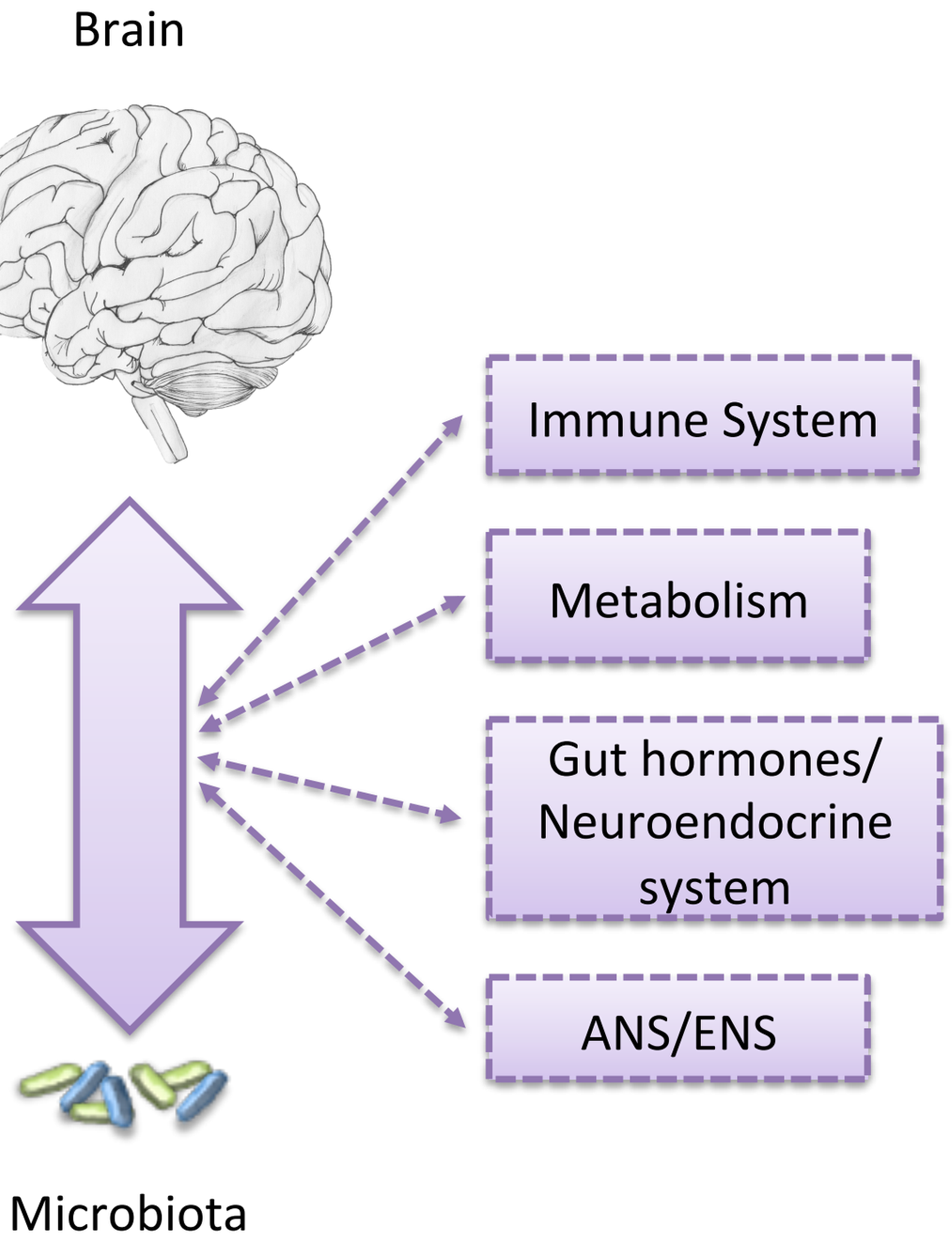
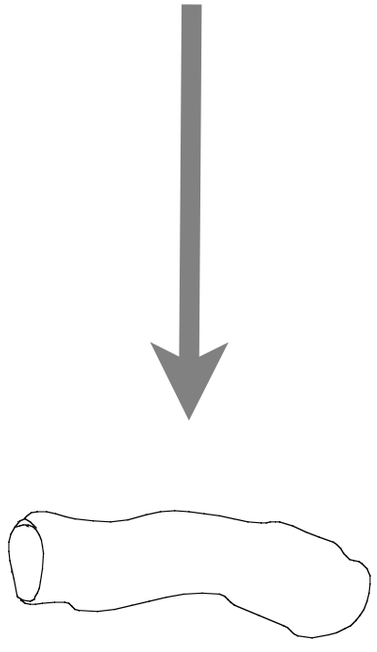
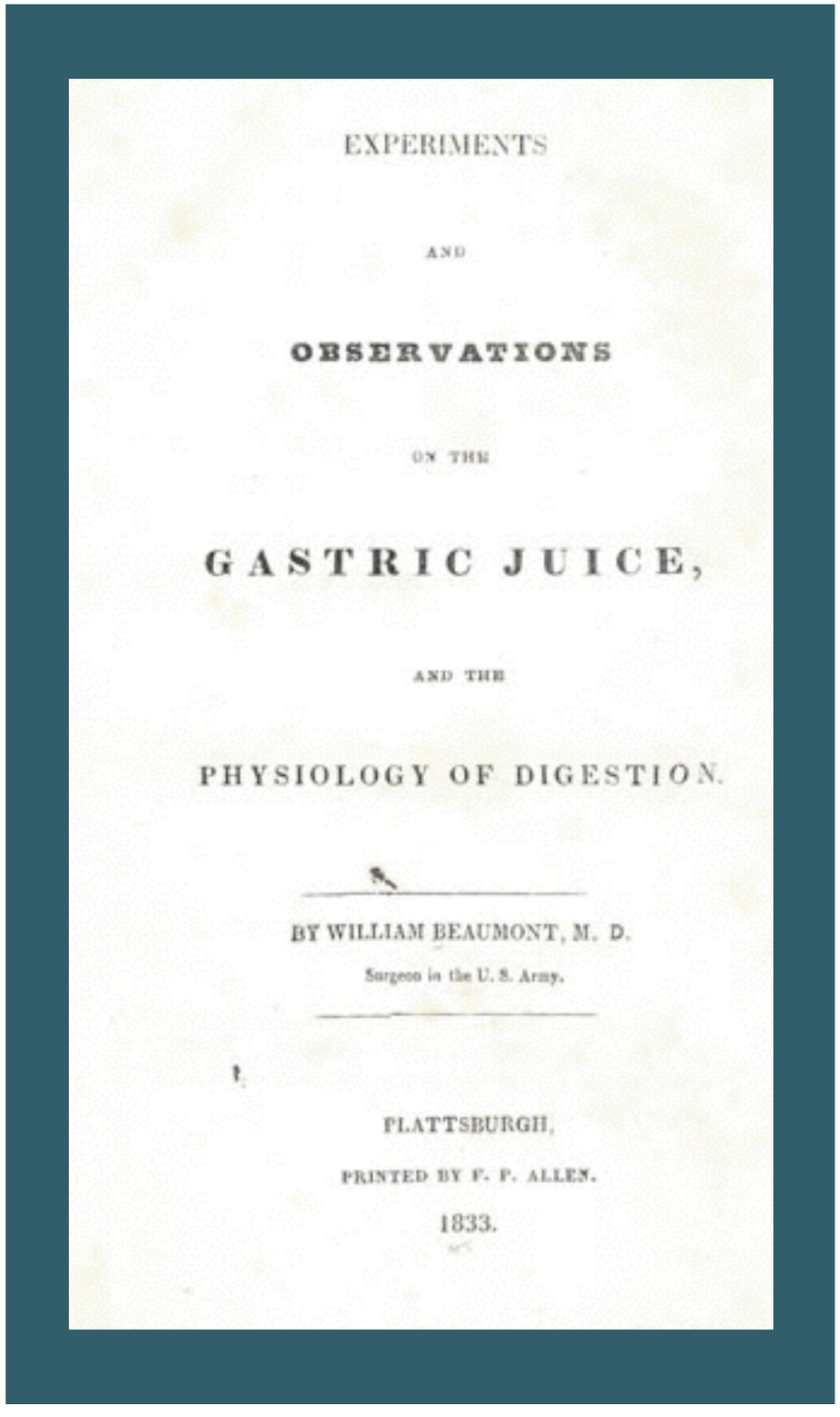
Gut-Brain Axis



THE BRAIN MODULATES GUT FUNCTION

1833 - Beaumont





EXPERIMENTS

AND

OBSERVATIONS

ON THE

GASTRIC JUICE,

AND THE

PHYSIOLOGY OF DIGESTION.

BY WILLIAM BEAUMONT, M. D.

Surgeon in the U. S. Army.

PLATTSBURGH,

PRINTED BY F. P. ALLEN.

1833.

THE BRAIN MODULATES GUT FUNCTION

- Association of emotional state and GI function in patients with functional bowel disorders

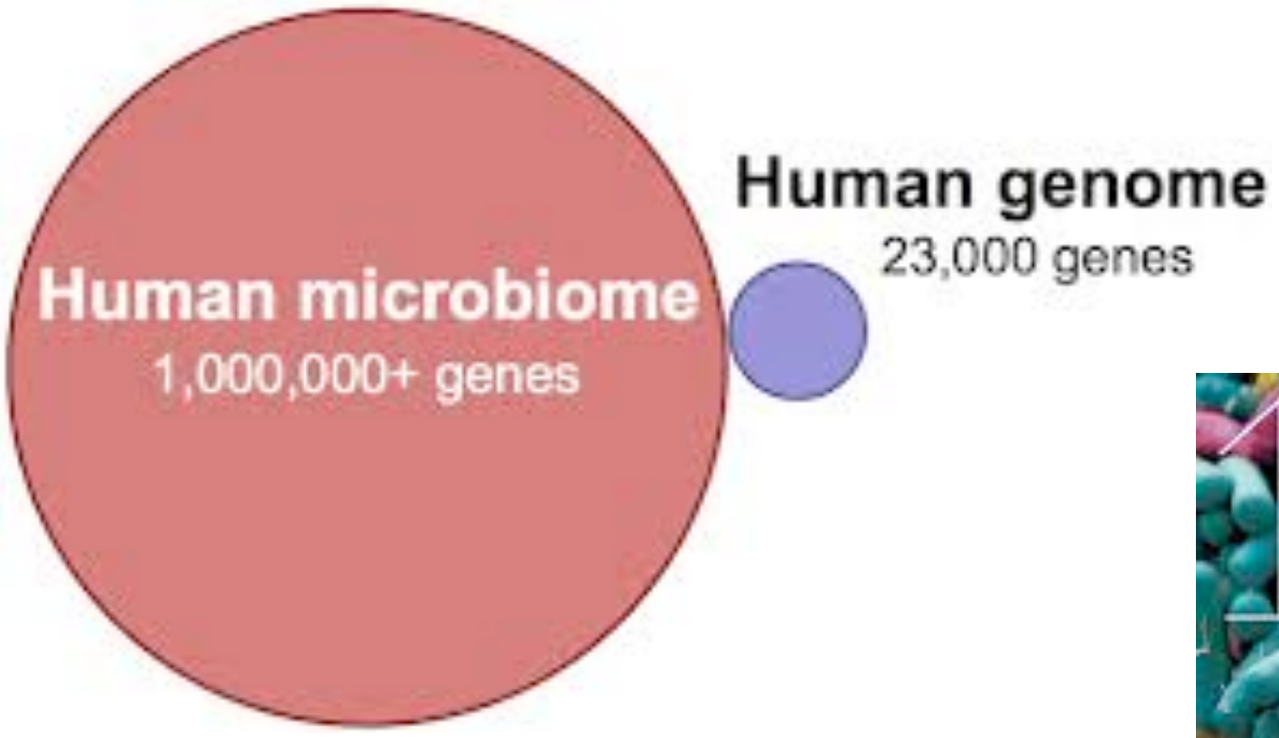
- In healthy volunteers, alterations in gut function are associated with experimental stressors

- Affective state alters pain perception in IBS patients

- Strong association of generalized anxiety disorder and IBS

- CNS acting drugs often prescribed and evidence of effective for treatment of GI patients

Aziz and Thompson, 1998



SCIENTIFIC AMERICAN™

Mental Health May Depend on Creatures in the Gut

The microbiome may yield a new class of psychobiotics for the treatment of anxiety, depression and other mood disorders

By Charles Schmidt | Feb 17, 2015

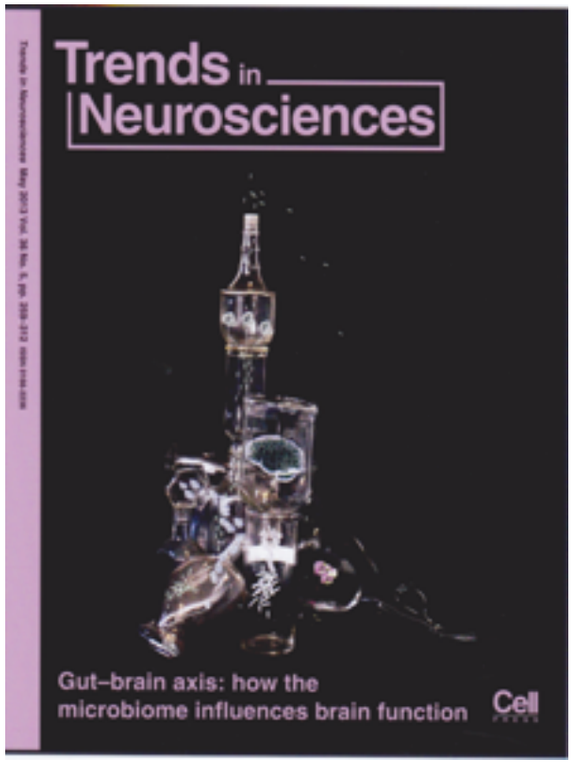

The Economist
The Catholic church's unholy mess
Paul Ryan: the man with the plan
Generation Xhausted
China, victim of the Olympics?
On the origin of specie
Microbes maketh man
AUGUST 18TH - 24TH 2012
Worldwide cover

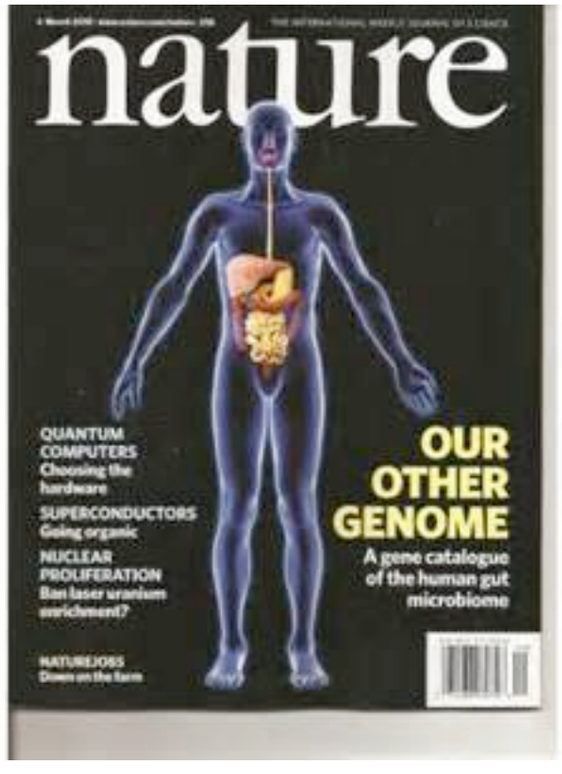

Science
The Gut Microbiota
AAAS


nature
FELLOW TRAVELLERS


The New York Times Magazine
THE SECRET LIVES OF
Germs


SCIENTIFIC AMERICAN
Your Inner Ecosystem
In your body, bacteria outnumber your own cells 10 to 1. Who's in control?


Trends in Neurosciences
Gut–brain axis: how the microbiome influences brain function
Cell

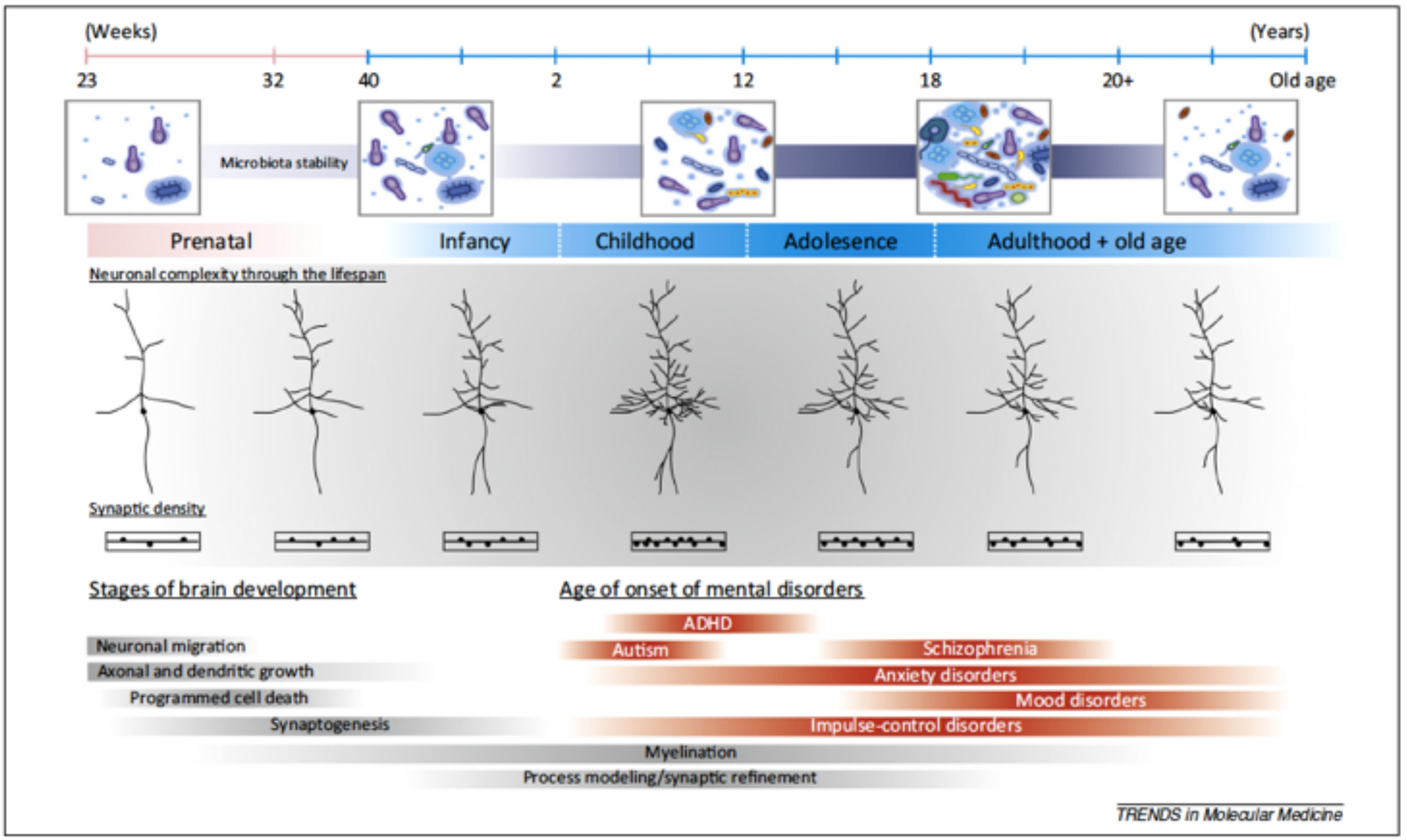

nature
QUANTUM COMPUTERS
Choosing the hardware
SUPERCONDUCTORS
Going organic
NUCLEAR PROLIFERATION
Ban laser uranium enrichment?
OUR OTHER GENOME
A gene catalogue of the human gut microbiome


Trends in Microbiology
Microbiomas e Inclusión Social
Studying human microbiomes without forgetting the human
Cell

What do we know about microbiota?

- The GI tract of an adult human contains 100 trillion viable bacteria
- More than 1000 species represented in healthy individuals:
  - high interpersonal variability in bacterial composition
  - gut microbiota profile show minimal intrapersonal variability over time
- Host and microbiota have a symbiotic relationship
- Microbiota are essential to host pathogen defense, nutrient uptake and metabolism, and **are central to brain development**
- An individual's profile of microbiota is influenced by genetics, age, sex, and diet

- Exposure to microbes and colonization occurs starting at birth and continues through development
- In healthy infants, dynamic changes in microbiota composition and diversity over the first year of life - influenced by diet (breast vs bottle-fed) and mode of delivery (vaginal vs c-section)

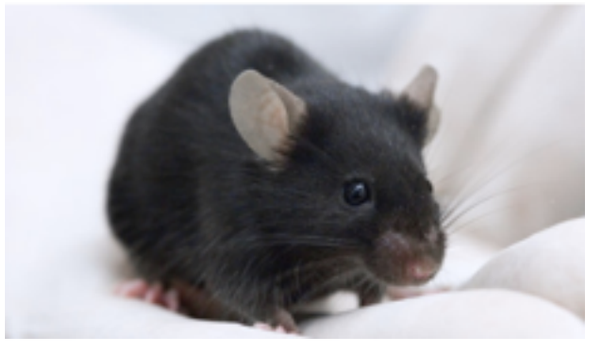


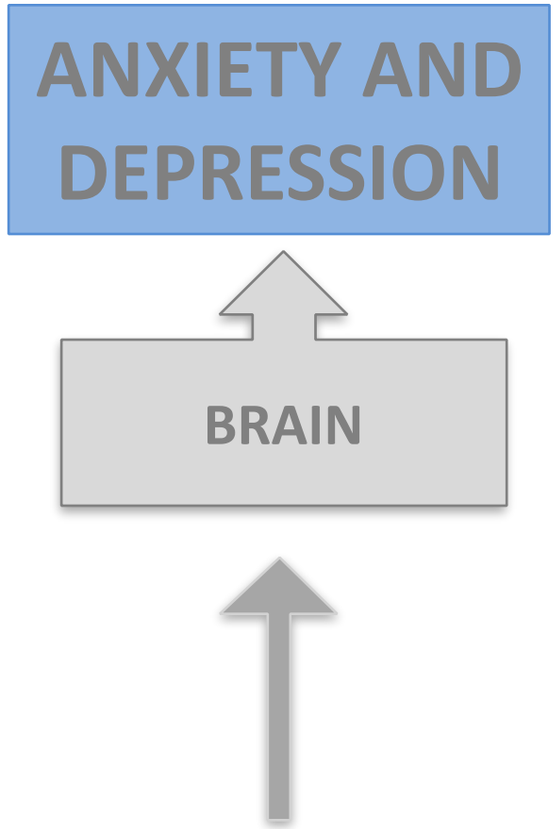
Borre et al 2014

Foster Lab Research

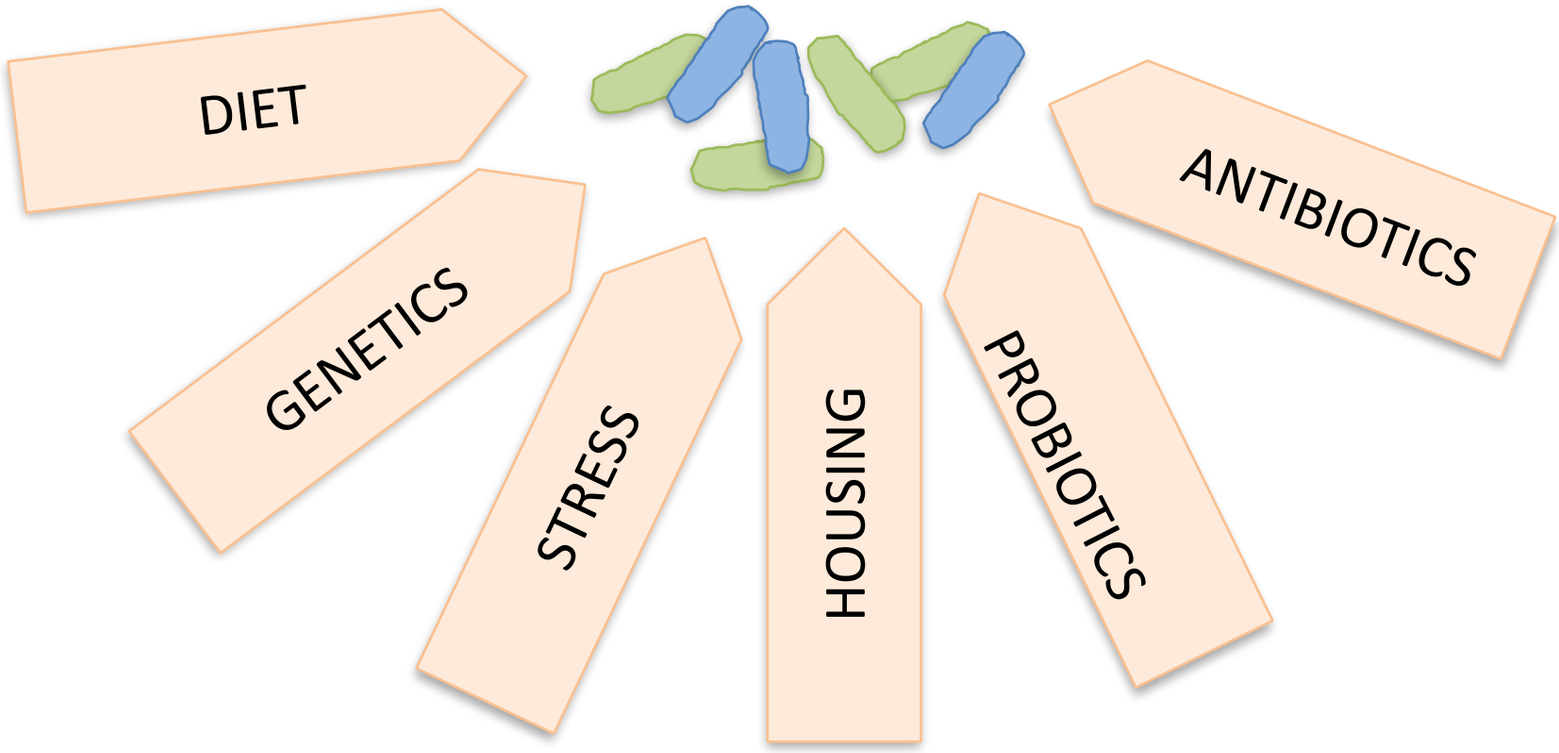
- We use animal models to understand how brain-body communication influences brain development and behaviour

- We are interested in understanding how changes in brain-body communication contribute to mental illness



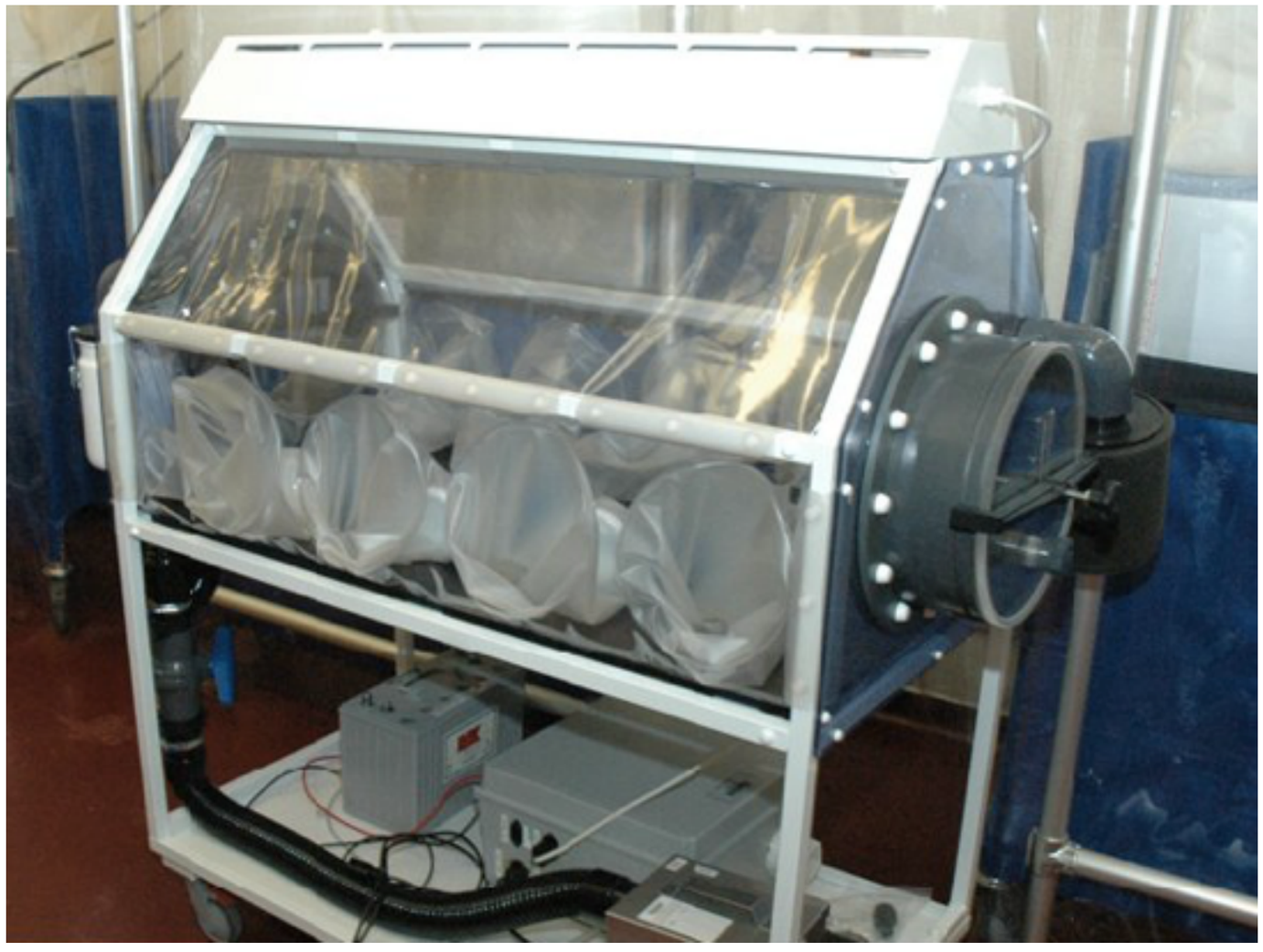


Do microbiota influence brain function and behaviour?



The germ-free (GF) mouse

- model was established in 1957
- GF mice are raised in a sterile/gnotobiotic environment and therefore have no commensal bacteria



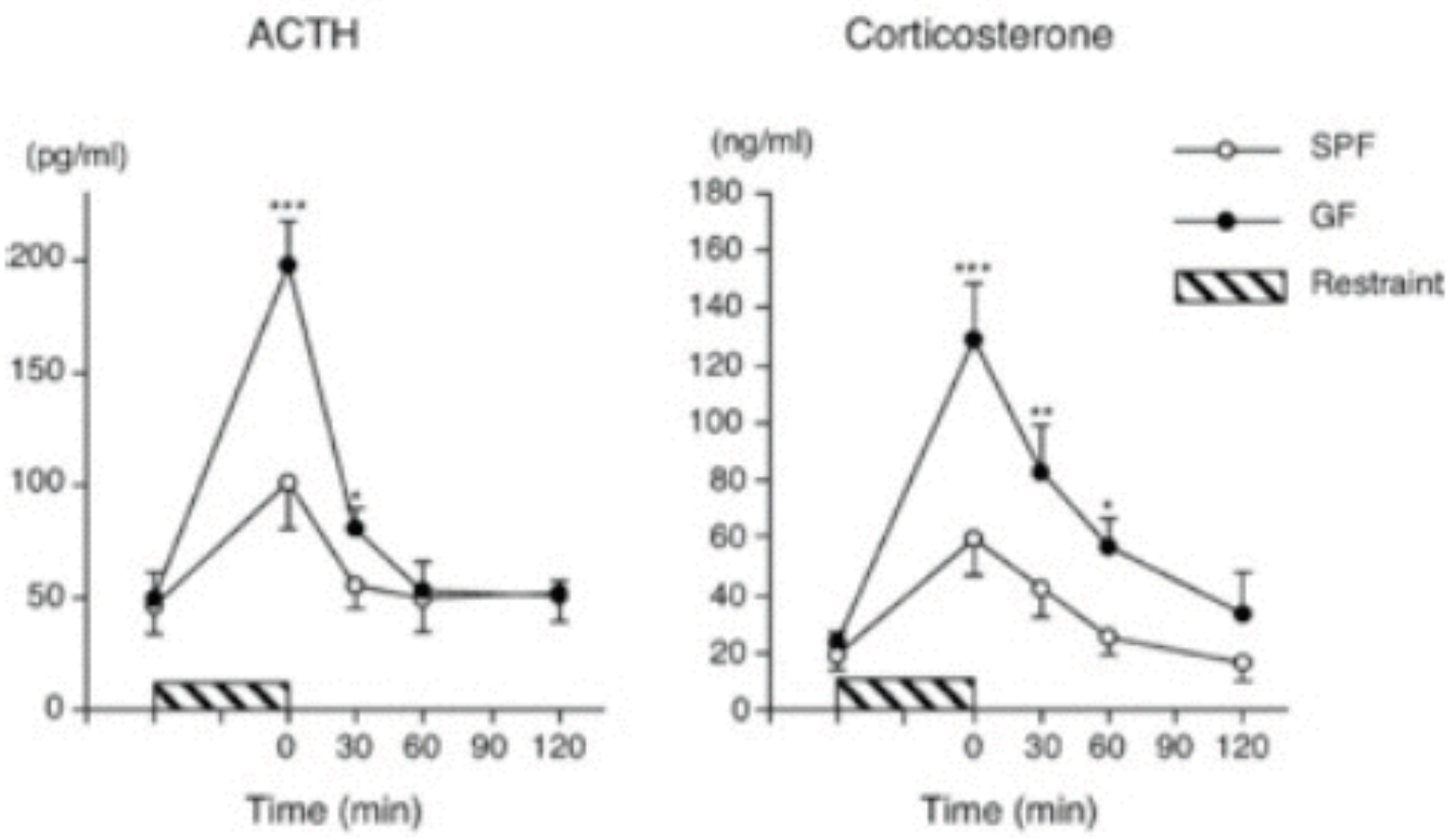
The starting point…

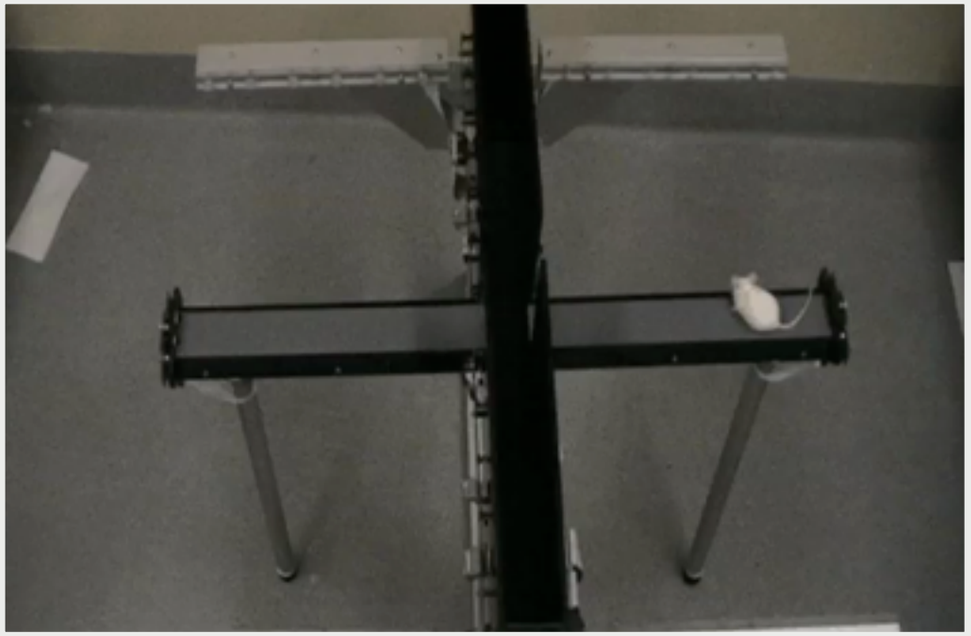
J Physiol 558.1 (2004) pp 263–275

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

Nobuyuki Sudo[1,2], Yoichi Chida[1], Yuji Aiba[3,4], Junko Sonoda[1], Naomi Oyama[1], Xiao-Nian Yu[1], Chiharu Kubo[1] and Yasuhiro Koga[3]

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





Neurogastroenterology & Motility

Neurogastroenterol Motil (2011) 23, 255–e119 doi: 10.1111/j.1365-2982.2010.01620.x

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

K. M. NEUFELD,*,† N. KANG,*,‡ J. BIENENSTOCK*,§ & J. A. FOSTER*,‡

PNAS

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]

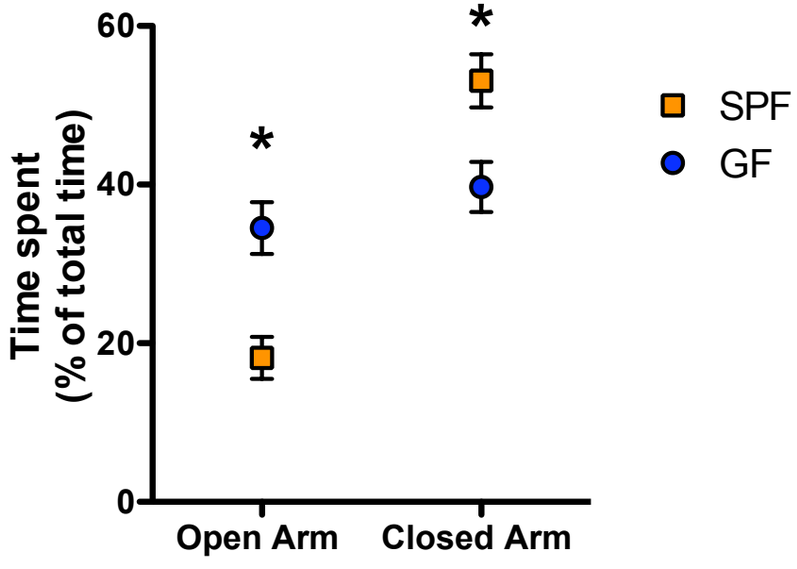
Molecular Psychiatry (2012), 1 – 8

www.nature.com/mp

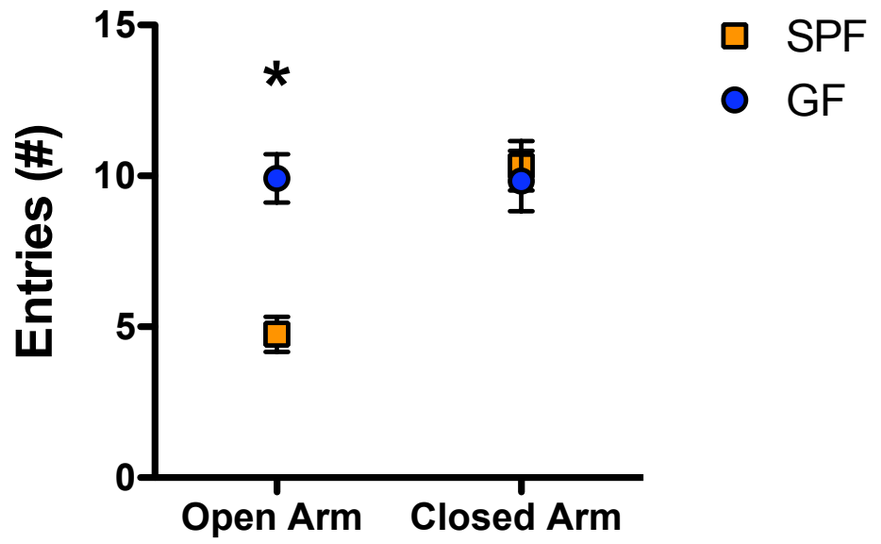
ORIGINAL ARTICLE

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]



GF mice spent more time in the open arms of the EPM



GF mice showed increased open arm entries

Several CNS genes altered in GF mice are known to influence anxiety-like behaviour

- Brain derived neurotrophic factor
- Serotonin receptors
- Serotonin transporter
- NMDA receptors
- Glucocorticoid receptors

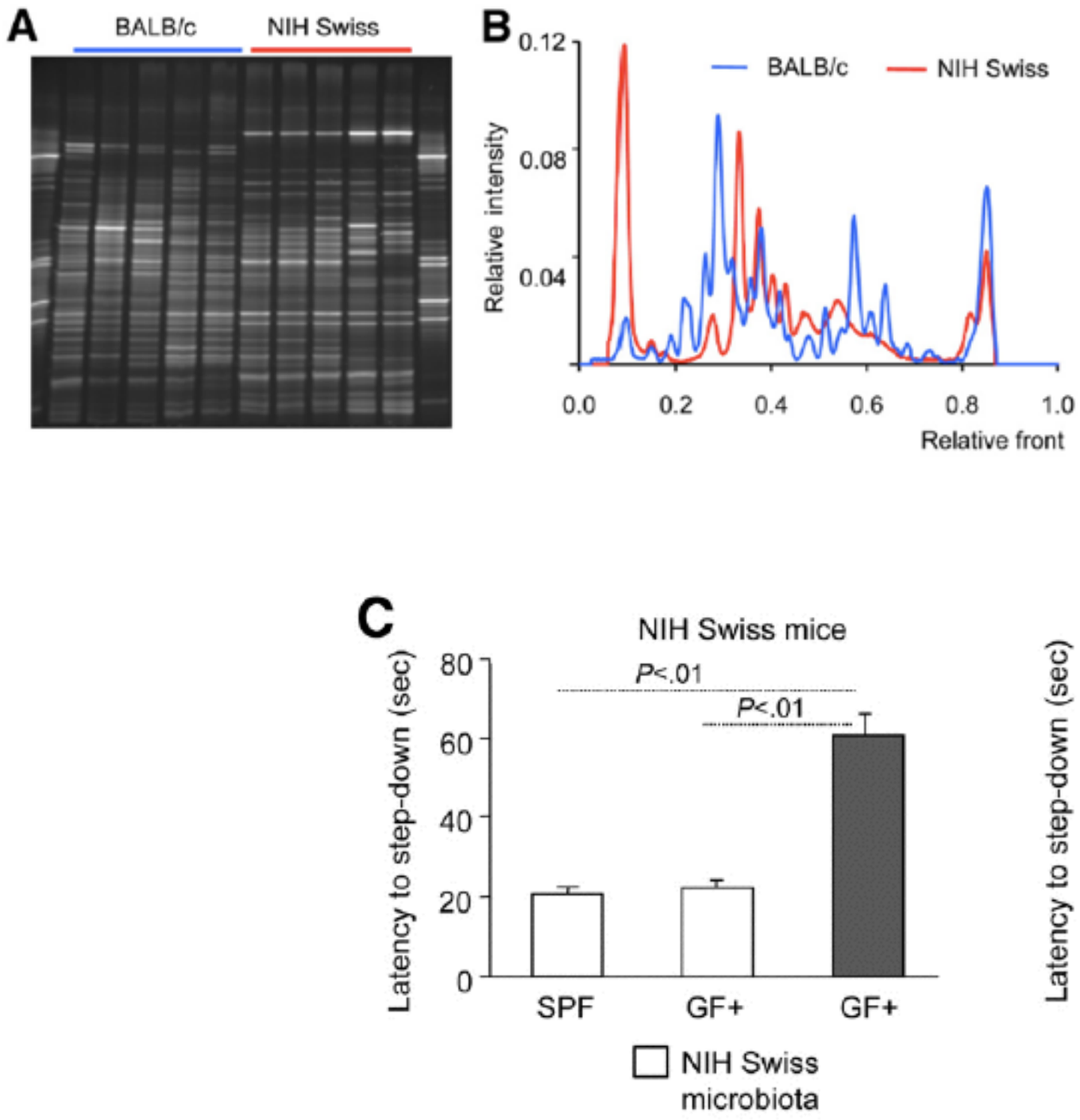
DIFFERENCES INFLUENCED BY STRAIN AND SEX

Lessons from germ-free mice

- microbiota influence anxiety-like behaviour
- microbiota influence the development of stress circuits and stress-reactivity
- Question is:

Whether or not the microbiota itself are mediating the effects observed in GF mice?

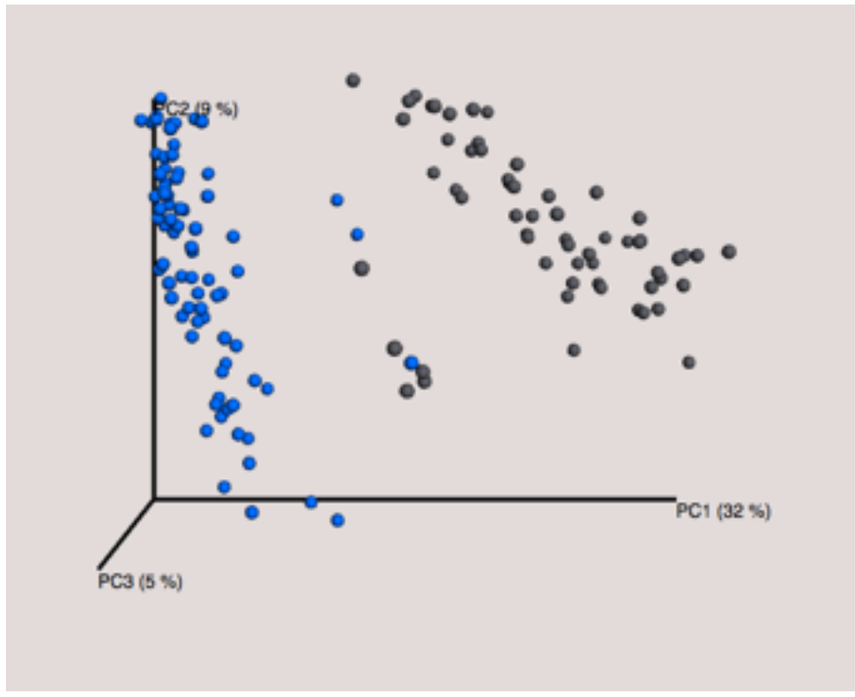
The host microbiota contributes to anxiety-like phenotype



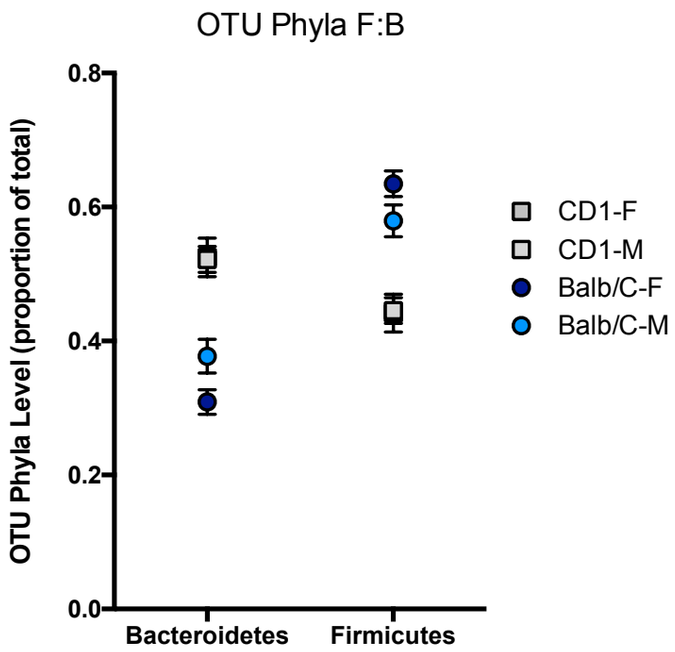
Bercik et al 2011

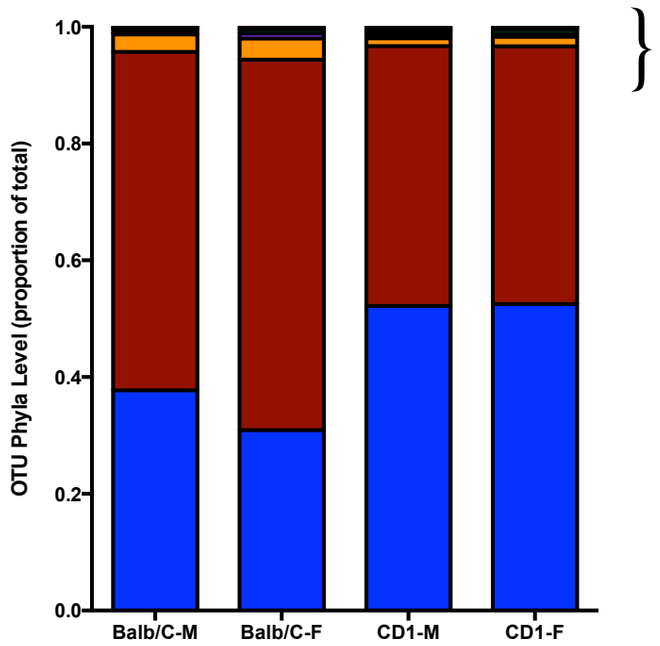
Balb/C vs. CD1

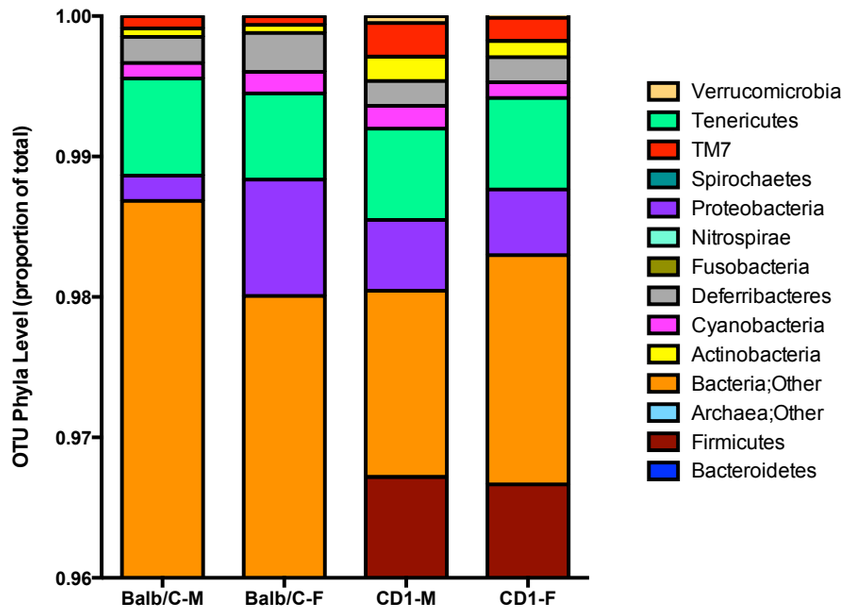
- CD1
- Balb/C



Two clusters using Bray-Curtis Distance







16s rRNA analysis of bacterial composition

Lessons from host genetics

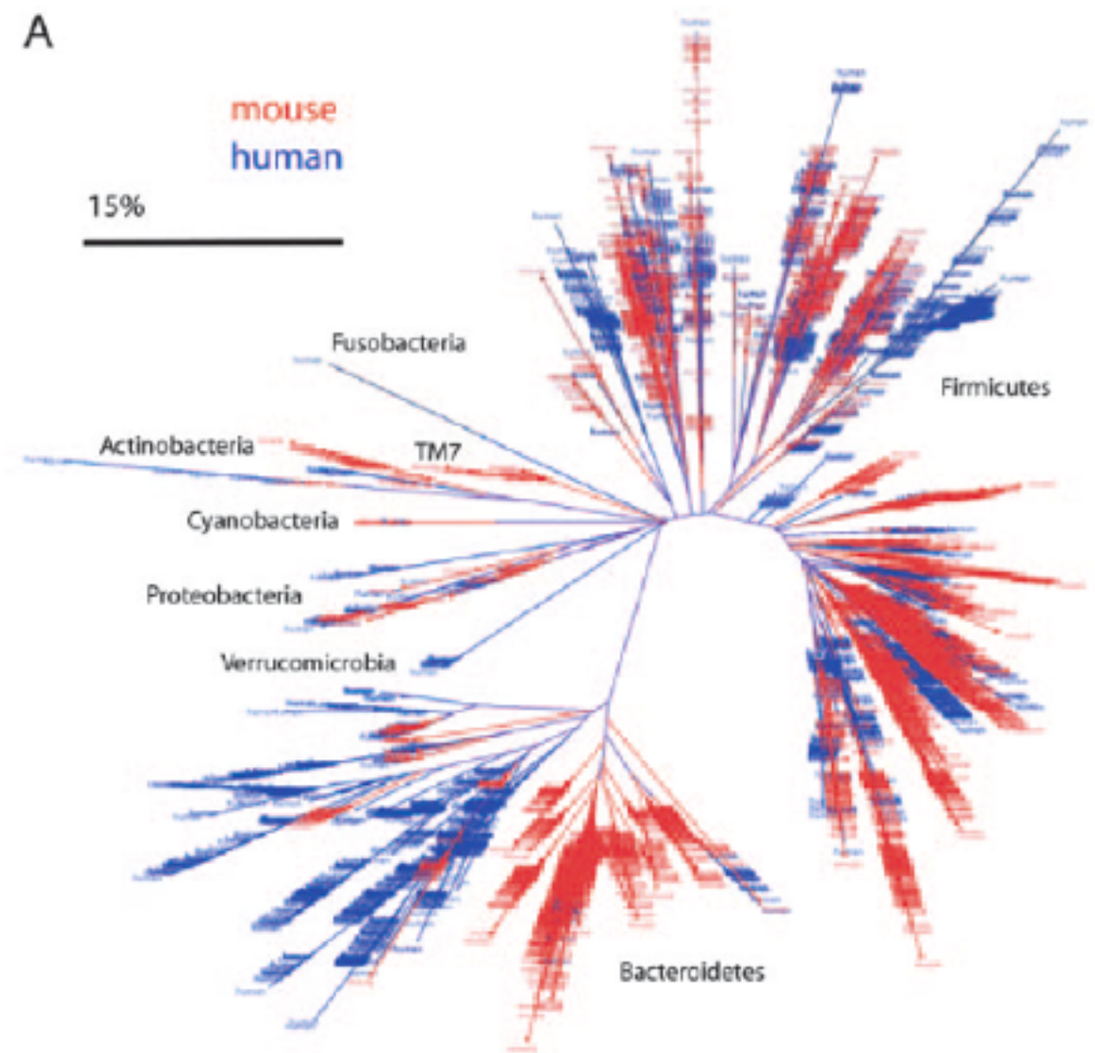
- Using different strains of mice we show that:
  - ★ Balb/C and CD1 mice show differences in microbiota composition and diversity
  - ★ Differences in anxiety-like behaviour and activity can be linked to microbiota composition at the phyla level
  - ★ HPA axis activation to immune challenge is associated with microbiota composition at the phyla level
- Additional ongoing analysis will determine whether species differences in microbiota can be linked with behaviour, stress reactivity, and brain structure

Microbiota in humans and mice

- At the species level, microbiota in mice are unique when compared to human microbiota

- At the division level, there is considerable similarity between mice and human microbiota

- Two bacterial division, the Bacteriodetes and the Firmicutes dominate in both mice and human microbiota

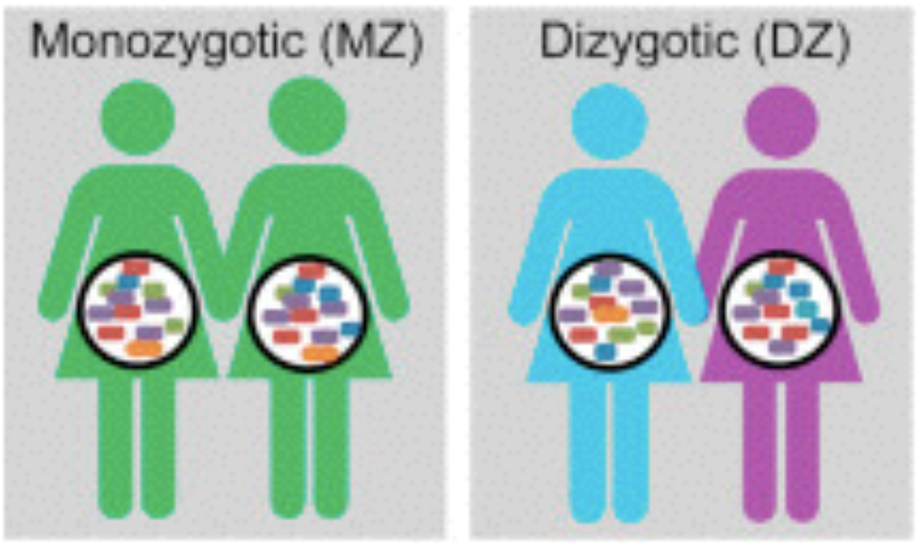


Ley et al 2005, PNAS, 102:11070-75

Human Genetics Shape the Gut Microbiome

Cell *159*, 789–799, November 6, 2014 ©2014 Elsevier Inc.

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,[3] William Van Treuren,[4] Rob Knight,[4,5,6] Jordana T. Bell,[3] Timothy D. Spector,[3] Andrew G. Clark,[1] and Ruth E. Ley[1,2,*]

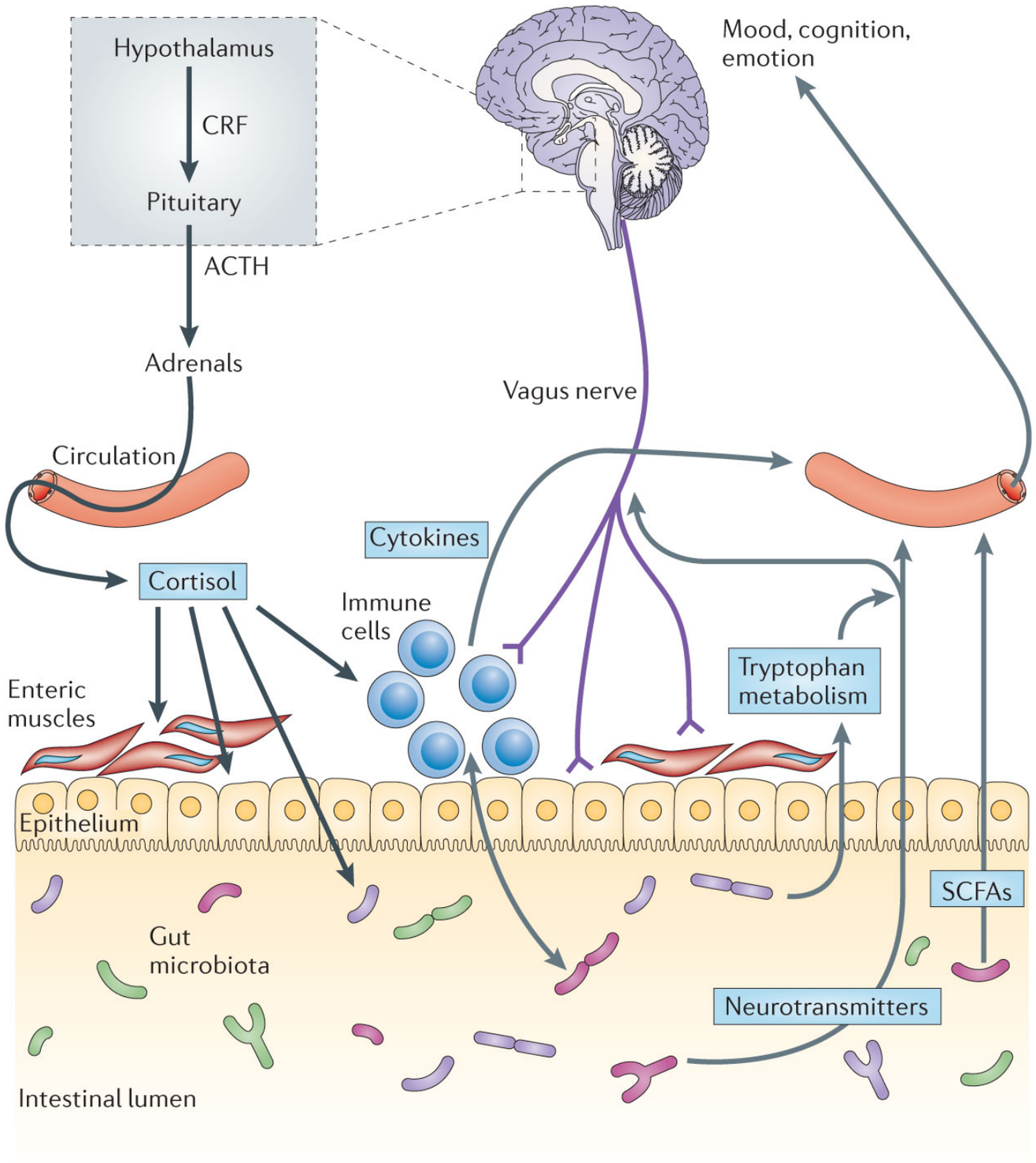


MZ twins have a more similar microbiota than DZ twins

45% contribution of host genetics to composition of the microbiome

How do microbiota communicate with the brain?

1. **Neural**
2. **Humoral**
3. **Cellular**
4. **Metabolites**
5. **Neuroactive molecules**



Nature Reviews | Neuroscience

Neurochemicals are present in bacteria

- Has been known for decades - what's new is the consideration of there role outside the gut interior milieu
- Partial list of neurochemicals
  - GABA – Bacillus, Lactobacillus, Clinical bacterial pathogens
  - Somatostatin - Bacillus subtilis
  - Dopamine – Escherichia, Bacillus, Lactococcus, Lactobacillus, Strep.
  - Serotonin – Streptococcus, Enterococcus, Escherichia, Lactobacillus
  - Acetylcholine – Lactobacillus, Bacillus
  - Short chain fatty acids – fermentation, numerous strains
- Specific receptors have been demonstrated - 100% homology of E. coli EnvY gene for high affinity opioid binding site

New Scientist

OPINION 22 January 2014

Psychobiotics: How gut bacteria mess with your mind

Gut bugs can change the way our brains work, offering new ways to relieve problems like stress, anxiety and depression, say two leading professors

PNAS

News Feature: Microbes on the mind

Could the gut microbiome have a critical role in brain and behavior? The notion is starting to gain acceptance amongst both researchers and funders.

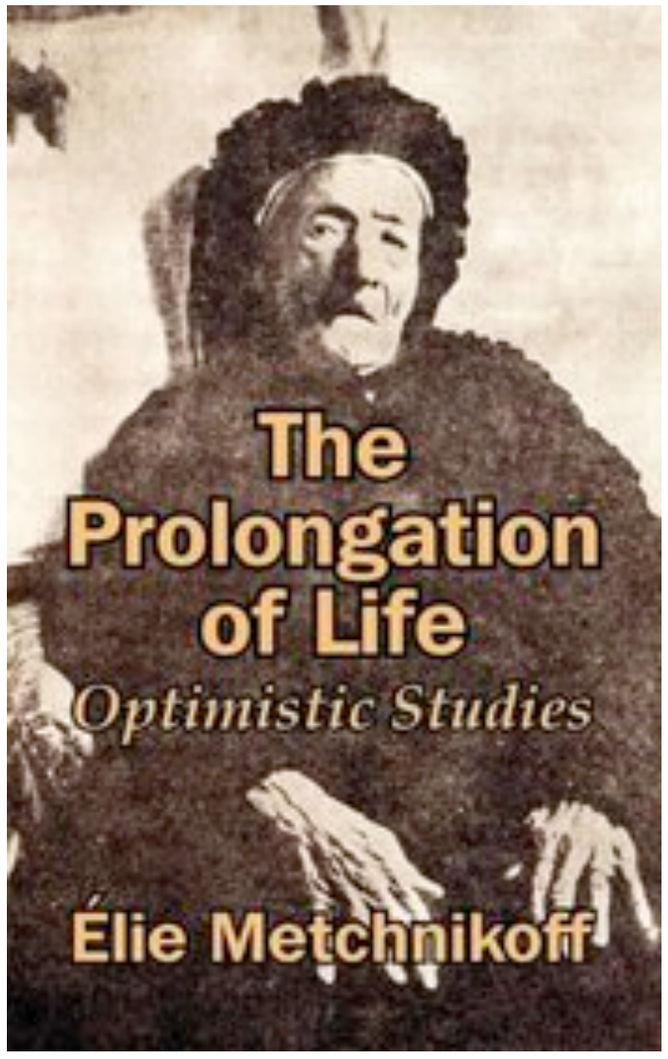
Helen H. Shen
Science Writer

PNAS | July 28, 2015 | vol. 112 | no. 30 | 9143–9145

Newsmax health

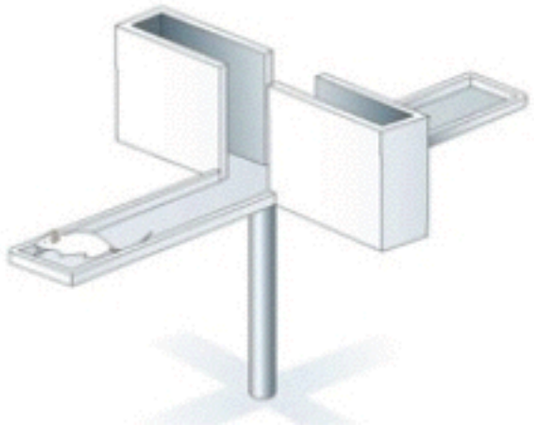
Wednesday October 14, 2015

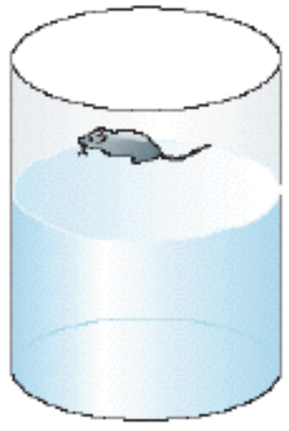
5 Vital Probiotics That Boost Your Brainpower

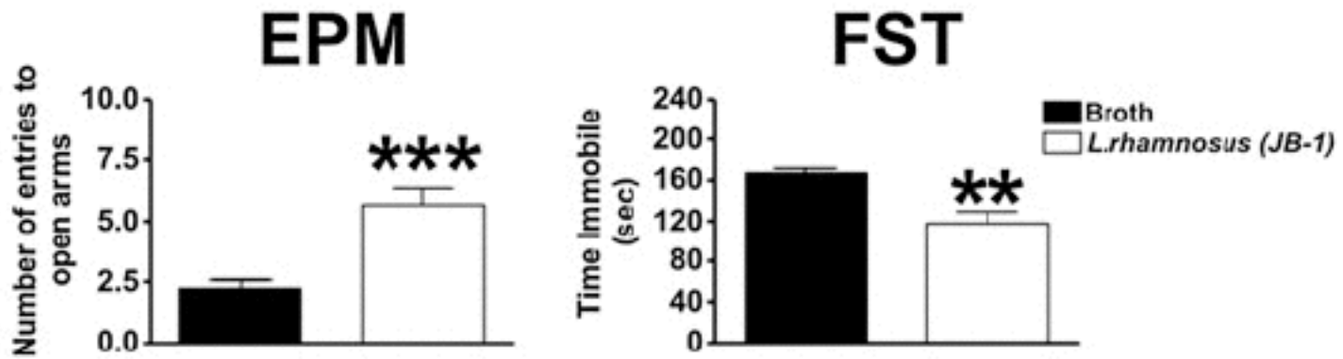


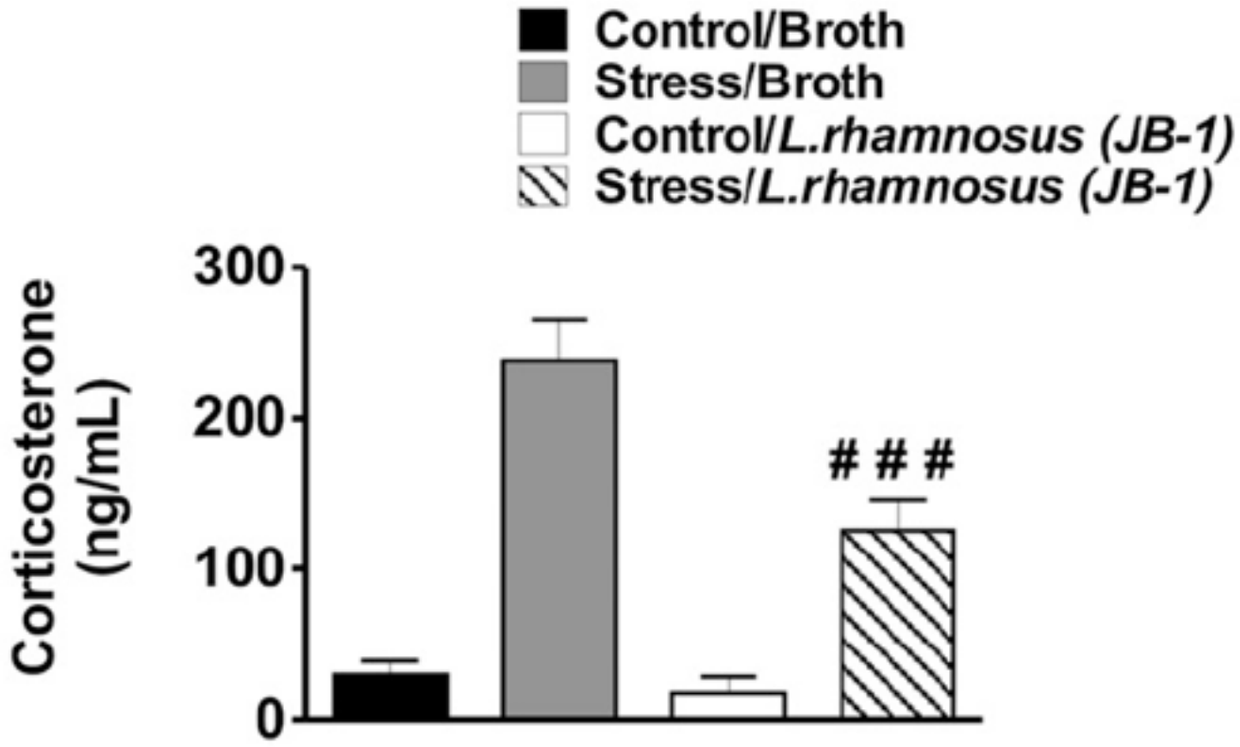
- Elie Metchnikoff, Russian scientist, Nobel Prize in 1908
- Inspired Minoru Shirota to investigate the connection between bacteria and good GI health
- Shirota is the inventor of Yakult - the yogurt-like probiotic drink containing Lactobacillus casei strain Shirota - 1930

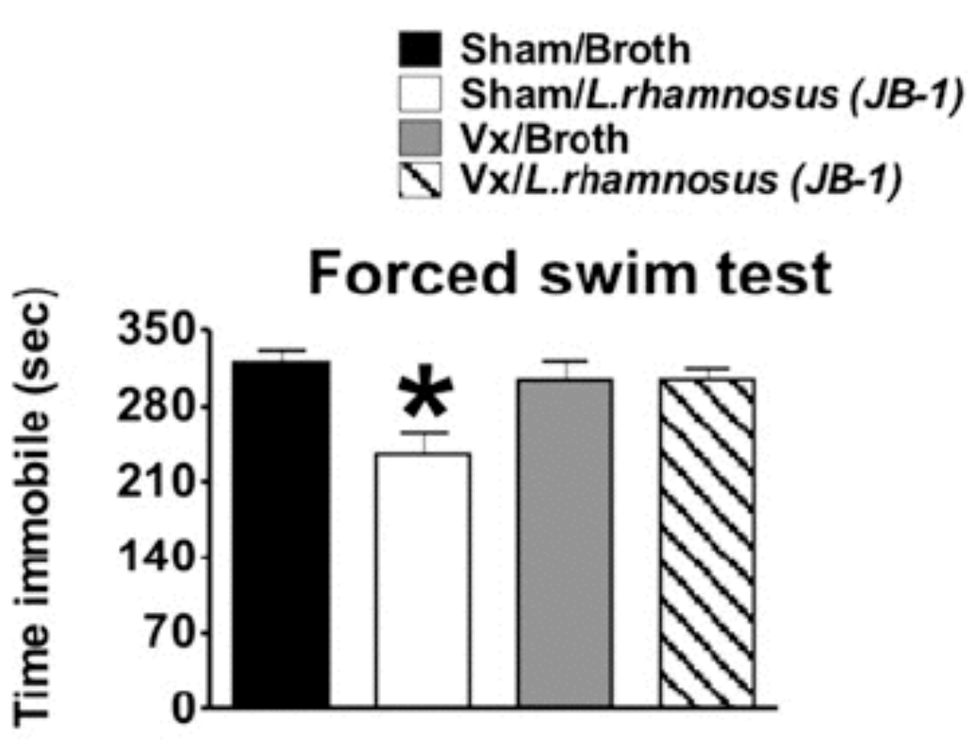
Probiotics influence anxiety-like and depressive-like behaviour in mice











Bravo et al 2011

Evidence of a link between microbiota and anxiety and depression is slowly emerging

British Journal of Nutrition

Assessment of psychotropic-like properties of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in rats and human subjects

- *Lactobacillus helveticus* (R0052) and *Bifidobacterium longum* (R0175) or placebo administered to healthy volunteers for 30 days

- Reduced self-report psychological stress levels

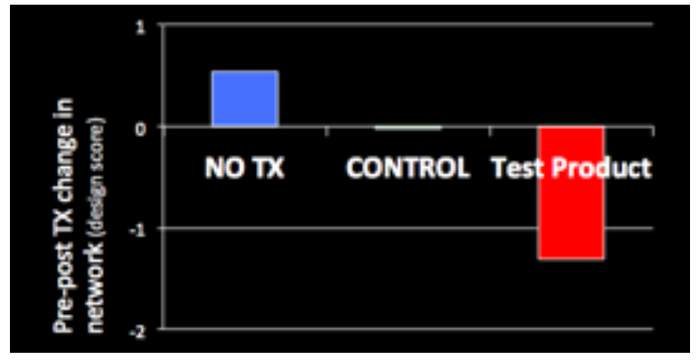
Messoudi et al 2011

Evidence of a link between microbiota and anxiety and depression is slowly emerging

ScienceDaily
Your source for the latest research news

Web address:
http://www.sciencedaily.com/releases/2013/05/130528180900.htm

Changing Gut Bacteria Through Diet Affects Brain Function



- Commercially available Fermented Milk Product with Probiotics (*Bifidobacterium anaimalis, Lactococcus lactis, L. delbrueckii, Streptococcus thermophilus)*

- 28 days administration to healthy women

- reduced activity in widely distributed brain network 4 week post treatment to negative emotion recognition task

Tillisch et al 2013

Evidence of a link between microbiota and anxiety and depression is slowly emerging

A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood ☆

Laura Steenbergen [a,b,*], Roberta Sellaro [a,b], Saskia van Hemert [c], Jos A. Bosch [d], Lorenza S. Colzato [a,b]

Brain, Behavior, and Immunity

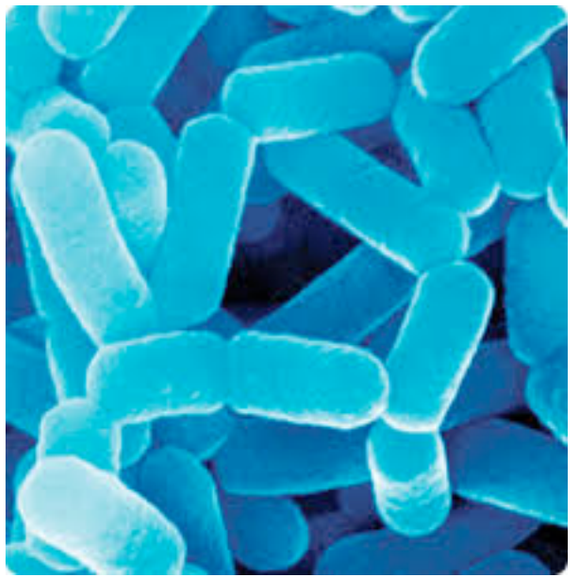
- 28 days administration of "Ecologic Barrier" containing *B. bifidum* W23, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, and *L. lactis* (W19&W58) compared to placebo to healthy individuals

- Probiotic groups showed reduction in cognitive reactivity to sad mood, specifically aggressive and ruminative thoughts

Steenbergen et al in press

What are the good bacteria?

Bifidobacteria (Actinobacteria)



Lactobacillus (Firmicutes)

Microbiota and Major Depression

Neurogastroenterology & Motility

Neurogastroenterol Motil (2014) **26**, 1155–1162 doi: 10.1111/nmo.12378

Correlation between the human fecal microbiota and depression

A. NASERIBAFROUEI,* K. HESTAD,†,‡ E. AVERSHINA,§ M. SEKELJA,§ A. LINLØKKEN,* R. WILSON* & K. RUDI*,§

Brain, Behavior, and Immunity

Altered fecal microbiota composition in patients with major depressive disorder

Haiyin Jiang[a,1], Zongxin Ling[a,1], Yonghua Zhang[b,1], Hongjin Mao[c], Zhanping Ma[d], Yan Yin[c], Weihong Wang[e], Wenxin Tang[c], Zhonglin Tan[c], Jianfei Shi[c], Lanjuan Li[a,2], Bing Ruan[a,*]

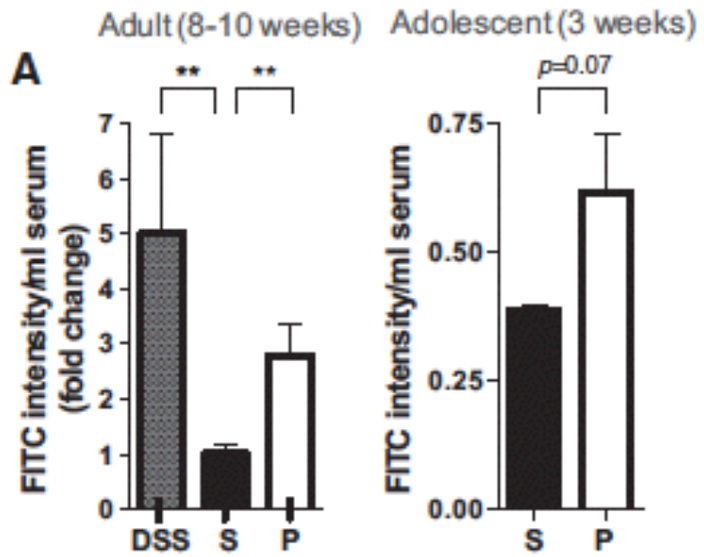
in press

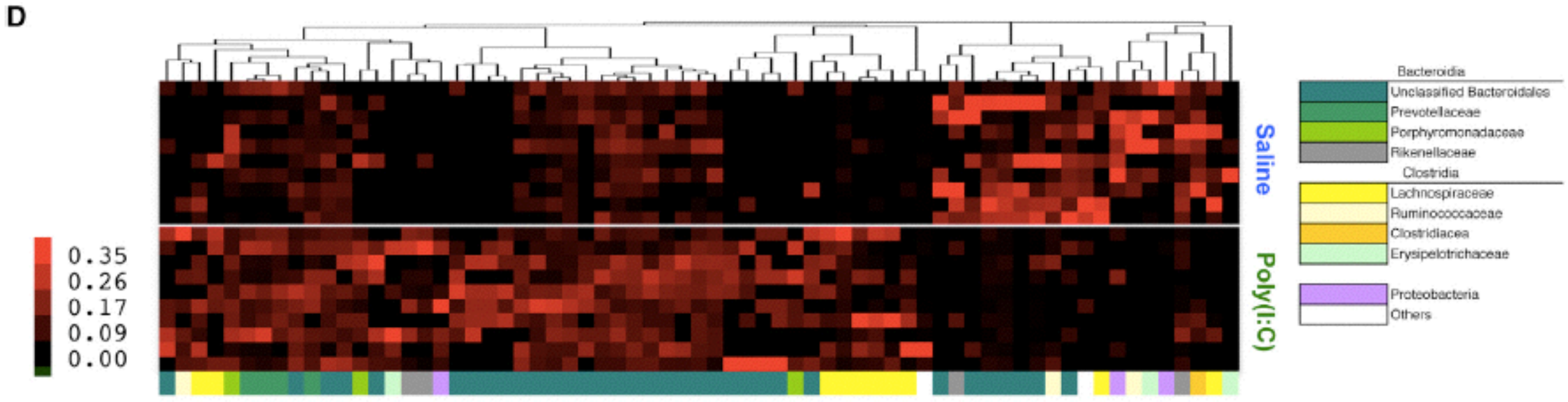
Does the gut–brain axis play a role in childhood neurodevelopmental disorders, such as autism?

- GI disturbances are prevalent is children with autism (Buie et al., 2010)
- The number of GI symptoms is shown to be associated with the severity of autism (Adams et al., 2011)
- Several studies have now reported changes in microbiota profile in patients with autism (Finegold et al., 2002, Song et al., 2004, Parracho et al., 2005, Finegold et al., 2010, Adams et al., 2011, Williams et al., 2011, Williams et al., 2012)
- Studies considering possible mechanisms for gut-brain communication in autism suggest that an altered metabolic phenotype in association with microbiota dysbiosis may contribute to ASD (MacFabe et al., 2007, Williams et al., 2011).
- Short term treatment with antibiotics has been reported to improve in behavioural symptoms is some patients with autism (Sandler et al., 2000)

Probiotics and Autism

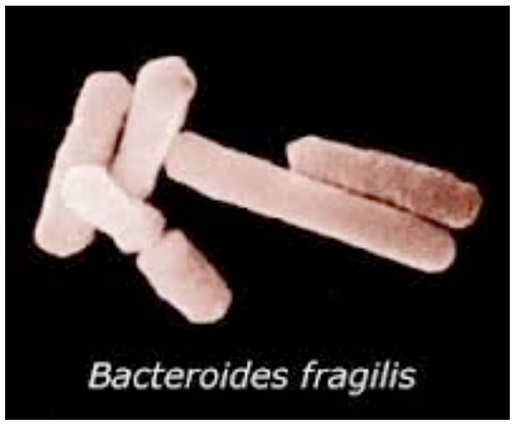
Exposure to viral or bacterial infection *in utero* leads to autistic-like behaviour in offspring



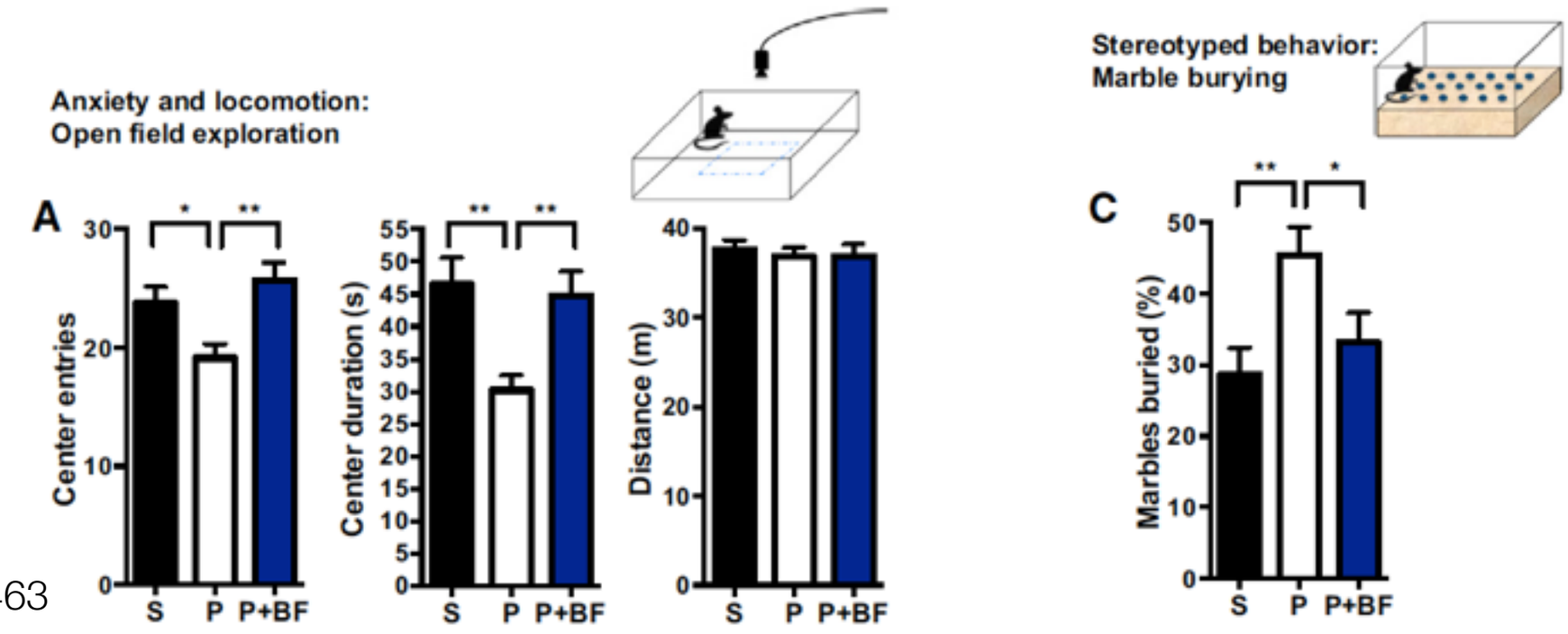


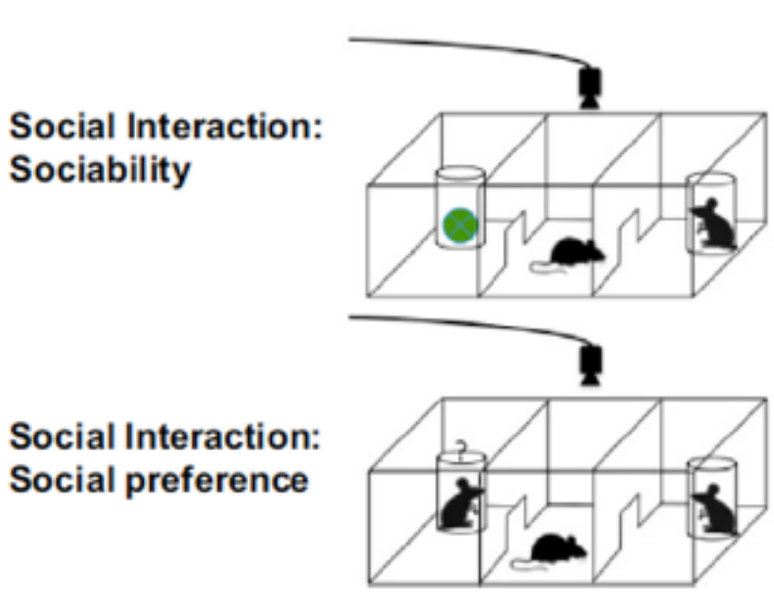
Hsiao et al 2013 - Cell 155:1451-1463

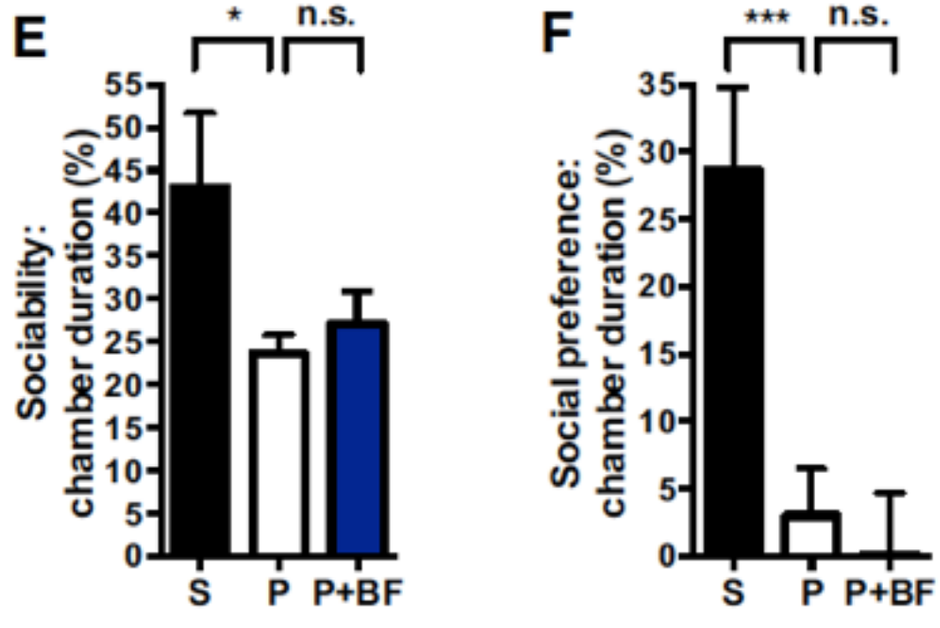
Probiotics and Autism



Hsiao et al 2013 - Cell 155:1451-1463







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Amy R. Romijn and Julia J. Rucklidge

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Ciarán P. Kelly, M.D.

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A Systematic Review

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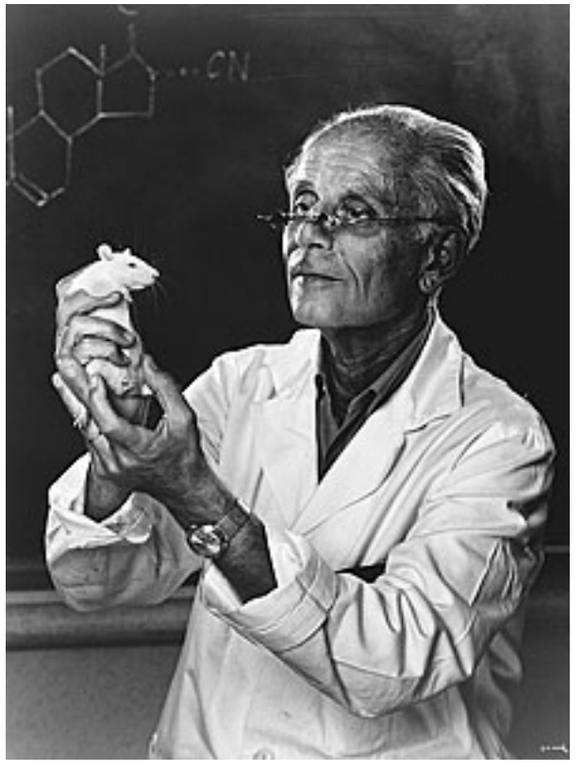
n, M.D., Ph.D.,
ı.D.

Giovanni Cammarota, MD, Gianluca Ianiro, MD, and Antonio Gasbarrini, MD

J Clin Gastroenterol • Volume 48, Number 8, September 2014

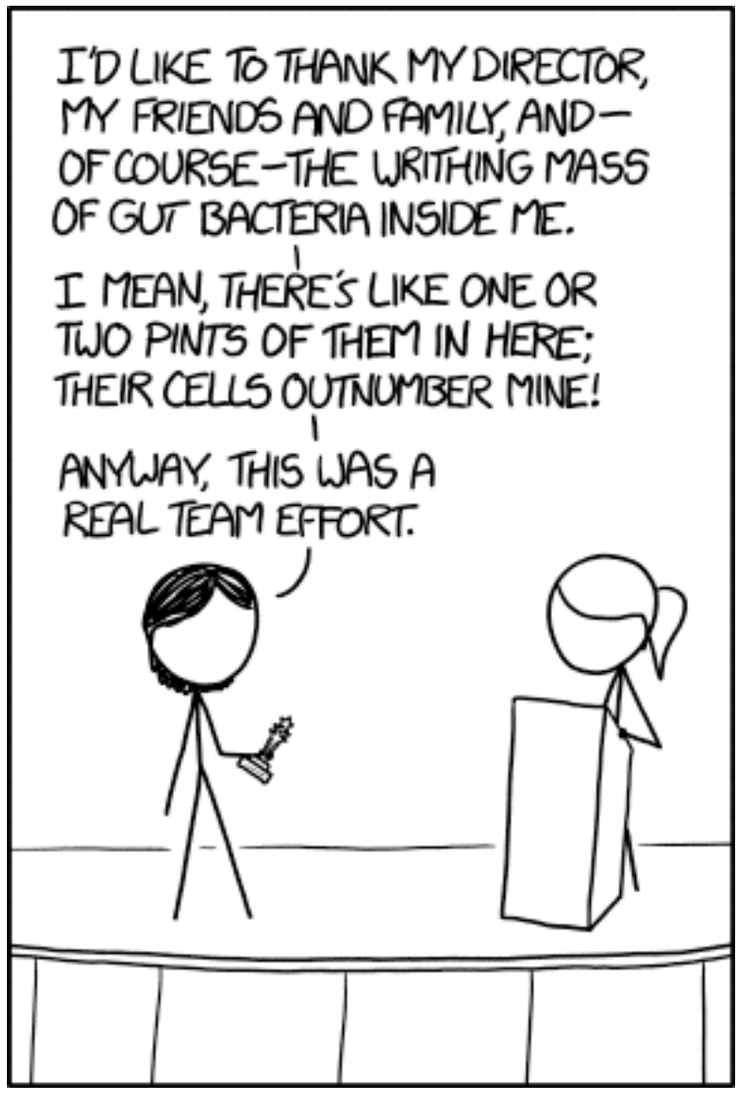
“It’s not stress that kills us, its our reaction to it”

–Hans Seyle



“Your state of mind is dependent on your state of gut”

–John Cryan



Former Lab Members

Jonathon Lai
Kelly Rilett
Karen-Anne McVey-Neufeld
Cammy Halgren
Linda Zhou
Robyn MacKenzie

Current Lab Members

Shawna Thompson
Roksana Khalid
Douglas Chung
Sureka Pavalantharajah
Daiana Pogacean
Katerina Liaconis

Collaborators

Aadil Bharwani
Wolfgang Kunze
John Bienenstock
Kathy McCoy
Andrew MacPherson
Jason Lerch
Jacob Ellegood
Miriam Friedel
OBI POND research group

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