

Trends in Neurosciences May 2013 Vol. 36 No. 5, pp. 259–312 ISSN 0166-2236

Trends in **Neurosciences**



**Gut–brain axis: how the
microbiome influences brain function**

Cell
PRESS

Gut Feelings- How our gut regulates our brain & behavior

Jane A. Foster, PhD



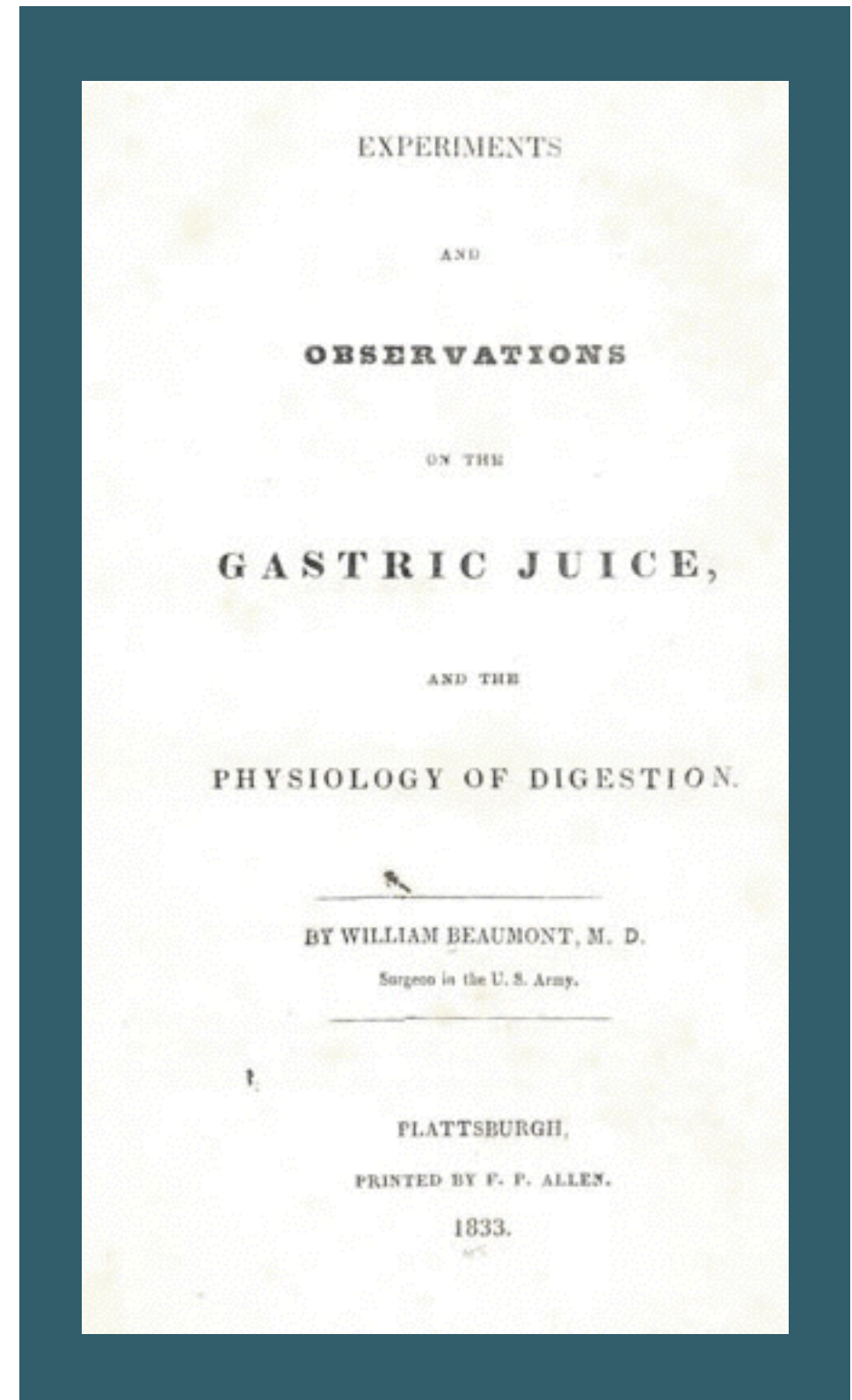
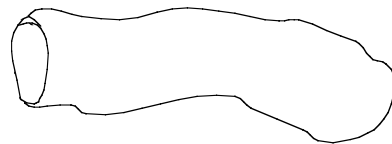
Trudeau trumps Trump on list of World's Most Powerful

By Jackson Proskow Global News



THE BRAIN MODULATES GUT FUNCTION

1833 - Beaumont



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

Gut-brain Axis

Bidirectional and continual communication

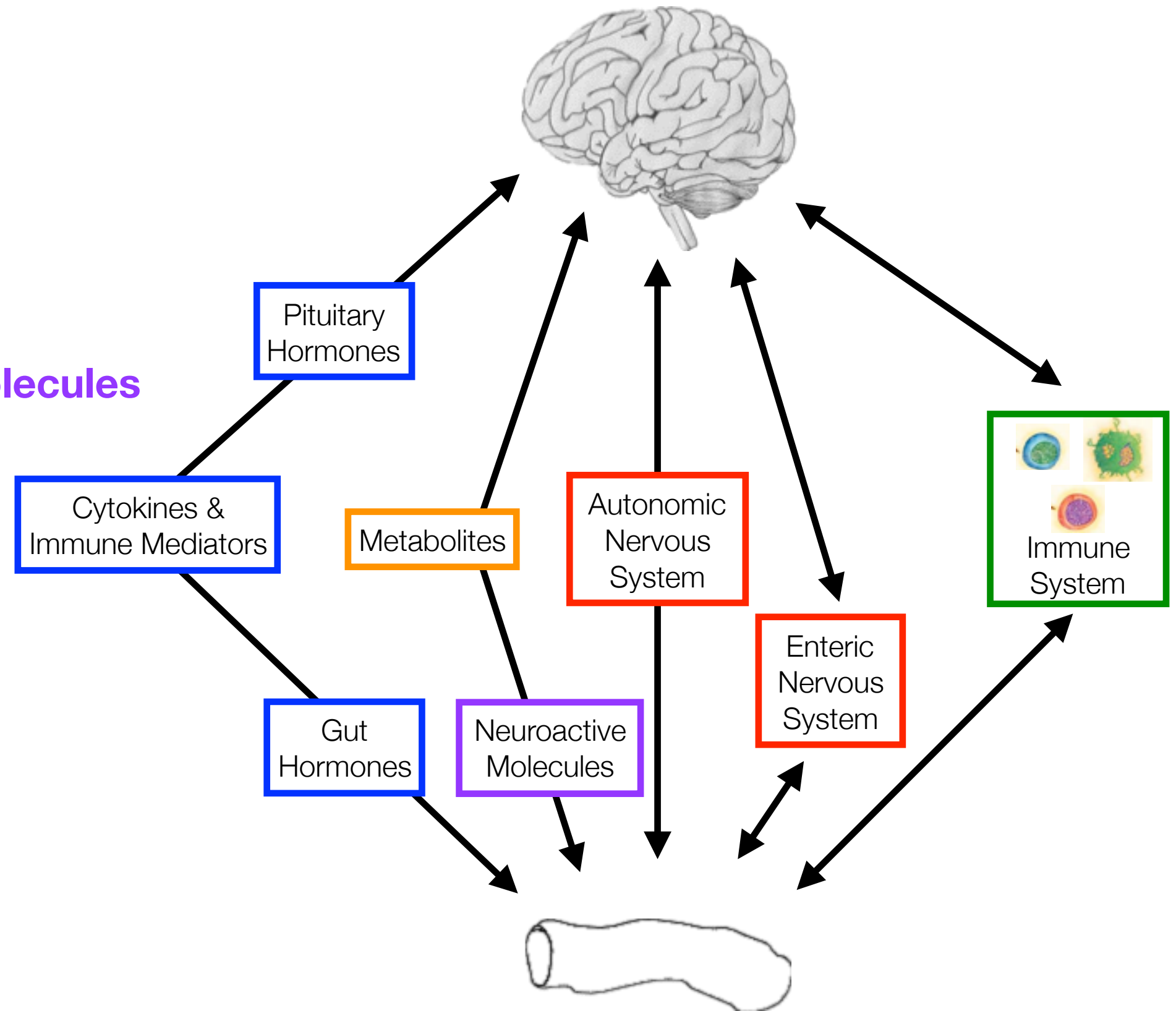
1. Neural

2. Humoral

3. Cellular

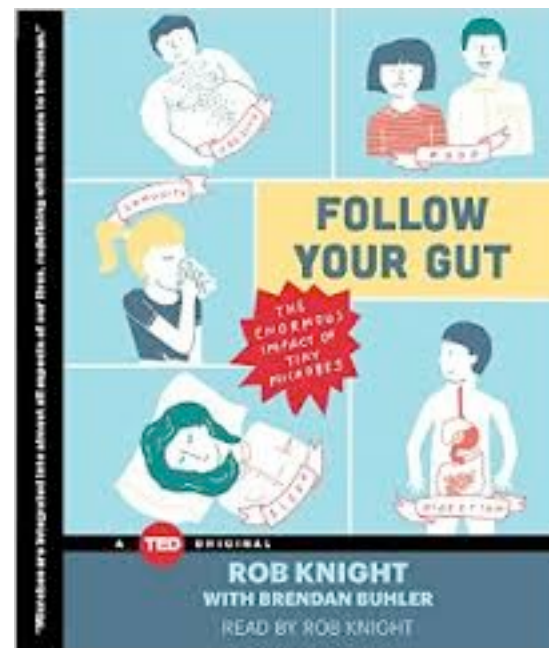
4. Metabolites

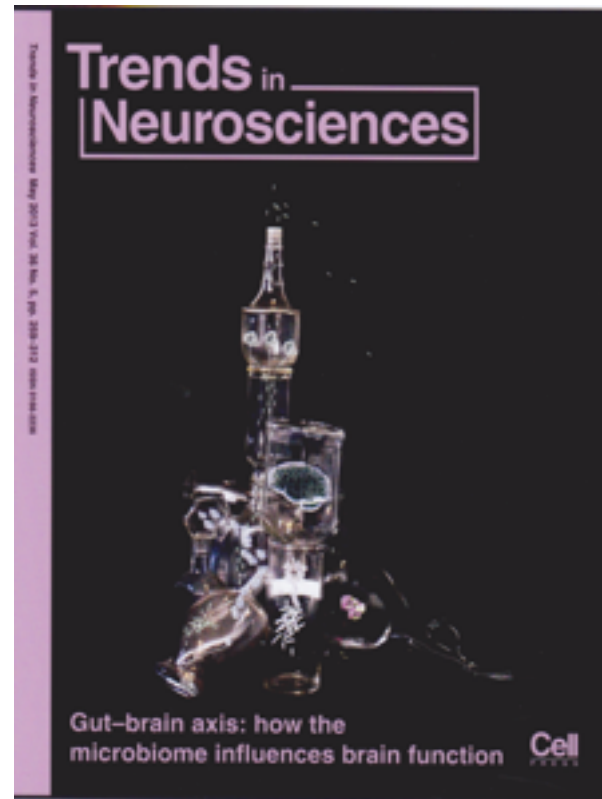
5. Neuroactive molecules



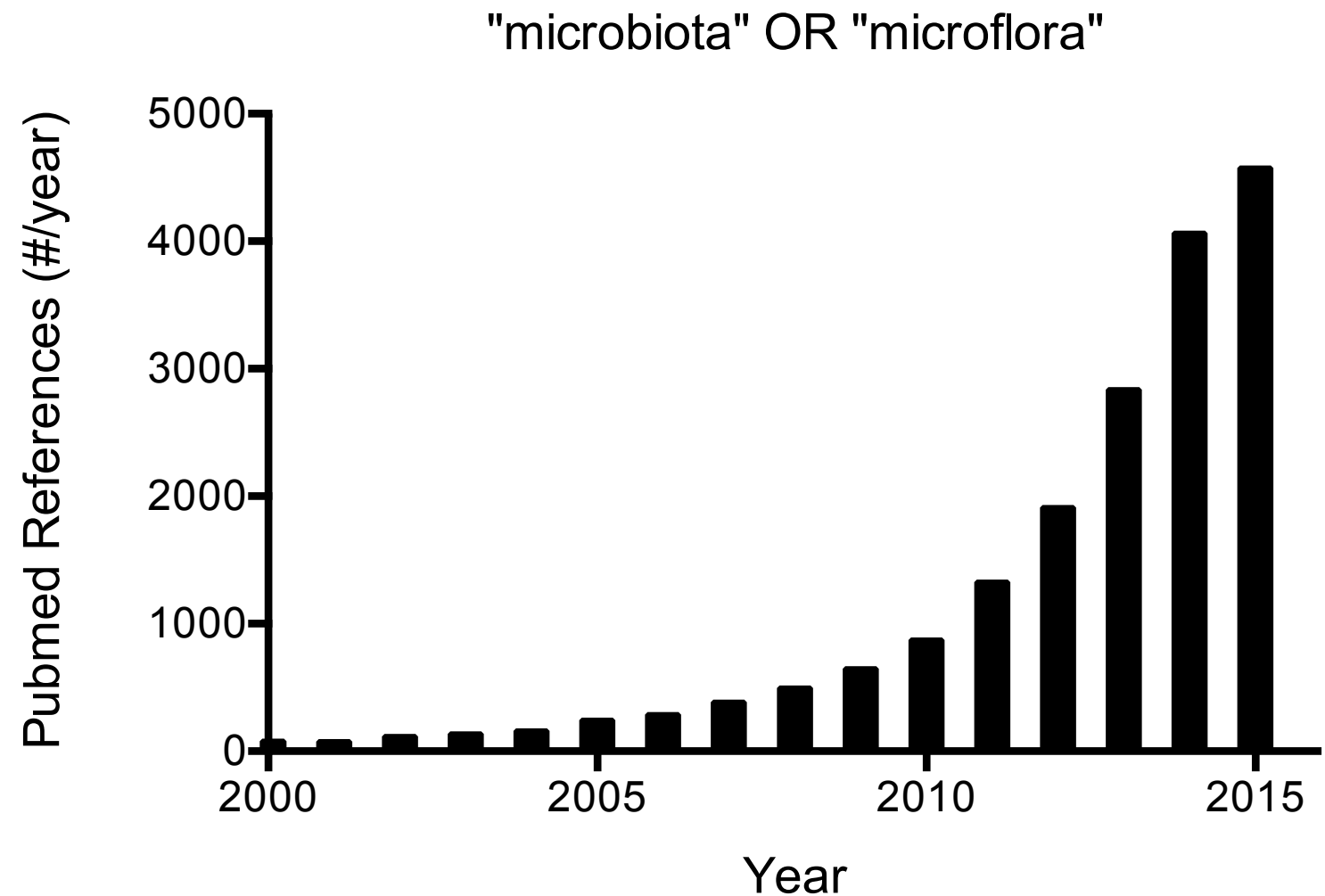
Everyday language of the Gut-Brain Axis

It's Good To Be **Gutsy**



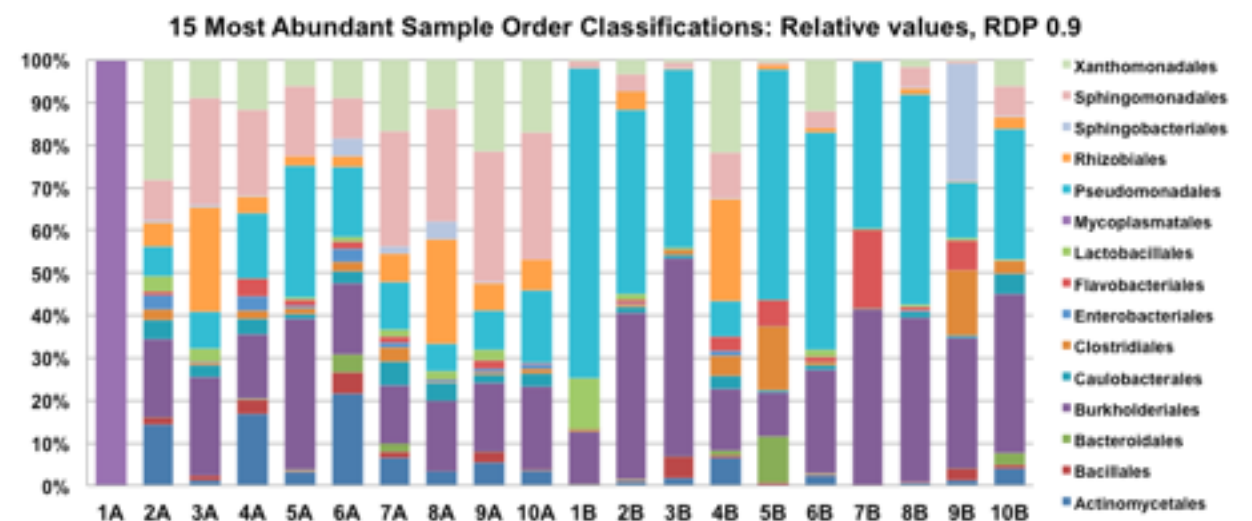
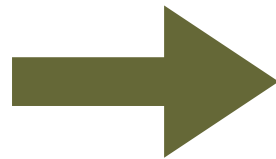


PubMed - timeline of publications “microbiota”



Why the emergence?

- Due to technology
 - Prior work used culture methods - we could only see what we could culture; most microbiota can not be cultured
 - Much of the focus previously was on pathogens - not commensals
- Metagenomics provides diversity and abundance of microbiota populations through isolation and sequencing of bacterial 16S ribosomal RNA from fecal or cecal samples (or other body regions)



Scientific American. May 2012

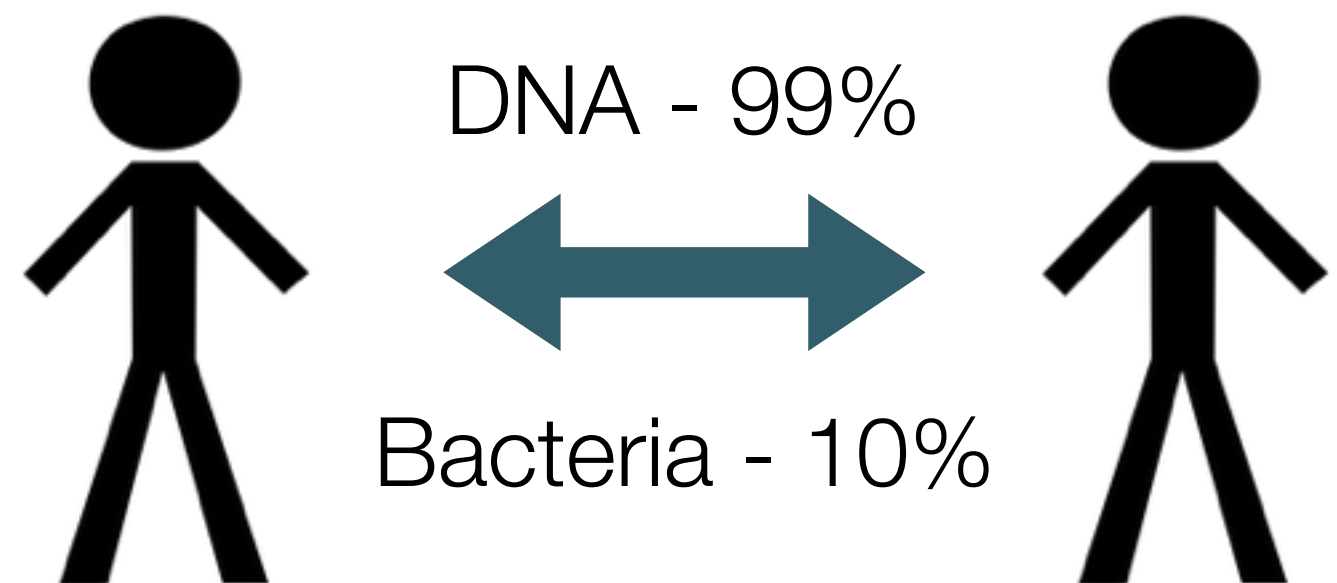
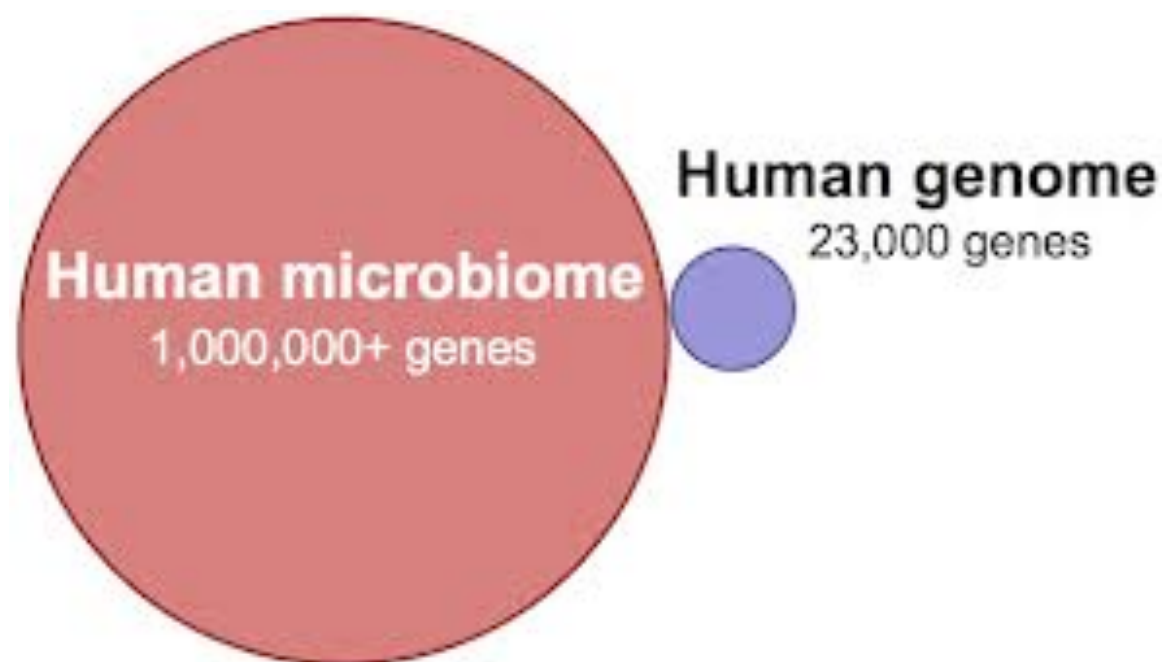
Leading Edge

Commentary

Cell 164, January 28, 2016 ©2016 Elsevier Inc.

Are We Really Vastly Outnumbered? Revisiting the Ratio of Bacterial to Host Cells in Humans

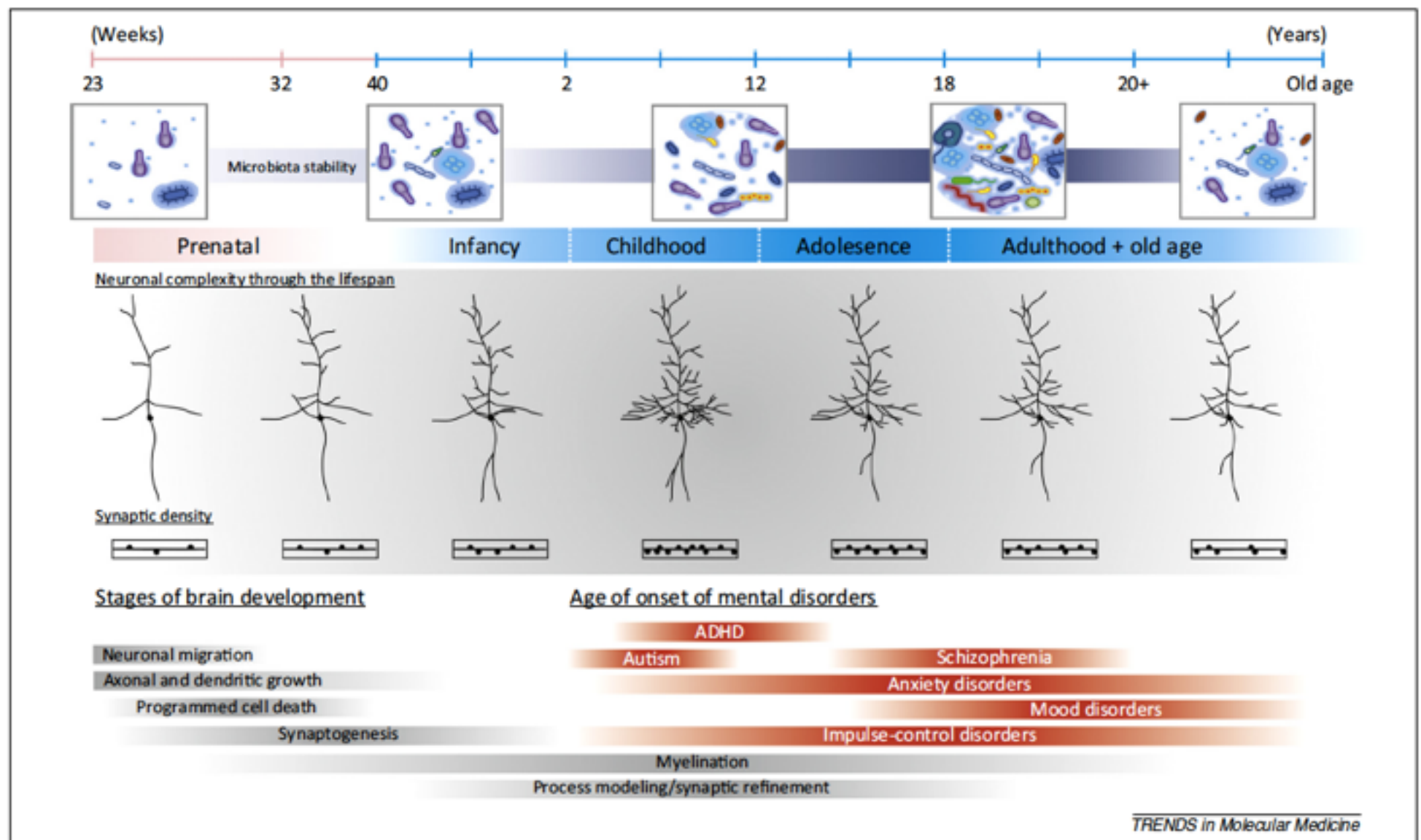
Ron Sender,¹ Shai Fuchs,^{2,3,*} and Ron Milo^{1,*}



What do we know about microbiota?

- The GI tract of an adult human contains 100 trillion viable bacteria
- 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)



More recently ...

- Several studies have shown that the gut-brain axis may play an important role in brain development, behaviour, and mood
- In particular, studies have examined the impact of probiotics on stress systems in healthy individuals
- Several studies have show benefit of probiotic consumption in healthy individuals
 - improved mood (Benton et al 2007)
 - influenced brain activity in emotional centers in healthy individuals (Tillisch et al 2013)
 - showed a beneficial effect on anxiety and depressive measures and reduced stress hormone levels (Messaoudi et al 2011)

Changing Gut Bacteria Through Diet Affects Brain Function

Consumption of Fermented Milk Product With Probiotic Modulates Brain Activity

KIRSTEN TILLISCH,¹ JENNIFER LABUS,¹ LISA KILPATRICK,¹ ZHIGUO JIANG,¹ JEAN STAINS,¹ BAHAR EBRAT,¹ DENIS GUYONNET,² SOPHIE LEGRAIN-RASPAUD,² BEATRICE TROTIN,² BRUCE NALIBOFF,¹ and EMERAN A. MAYER¹

¹Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California; and ²Danone Research, Palaiseau, France

GASTROENTEROLOGY 2013;144:1394-1401

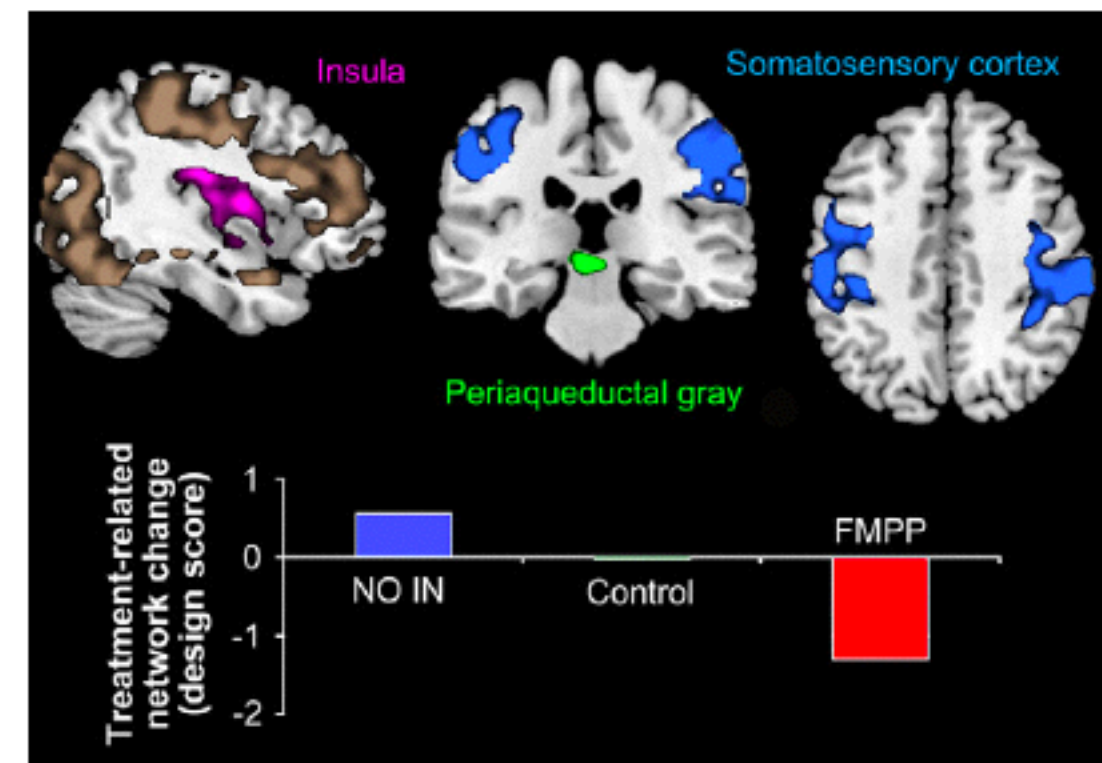
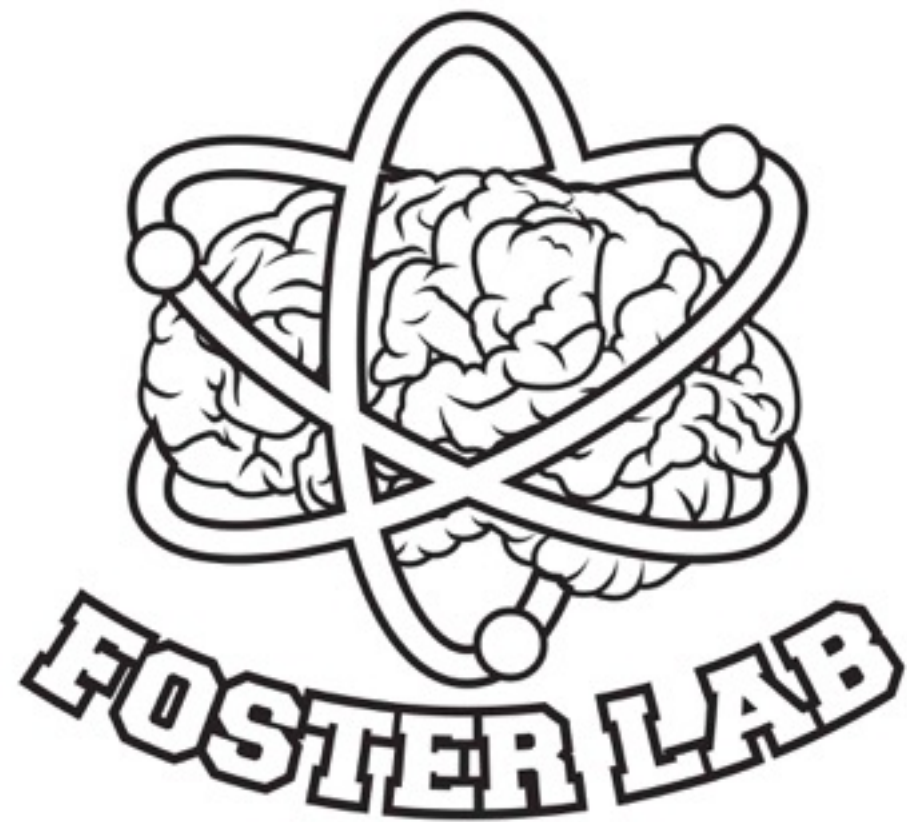


Figure 1. A distributed network of brain regions showing decreases in the FMPP group during the emotional faces attention task is shown in the shaded regions. Three regions of interest selected from the network for study in the resting state are highlighted in *pink* (insula), *green* (periaqueductal gray), and *blue* (somatosensory regions). The change in network strength with intervention is depicted graphically.



BEHAVIOUR

BRAIN

MICROBIOTA

DIET

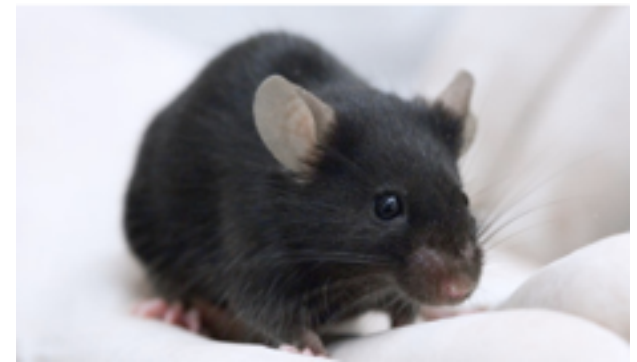
GENETICS

STRESS

HOUSING

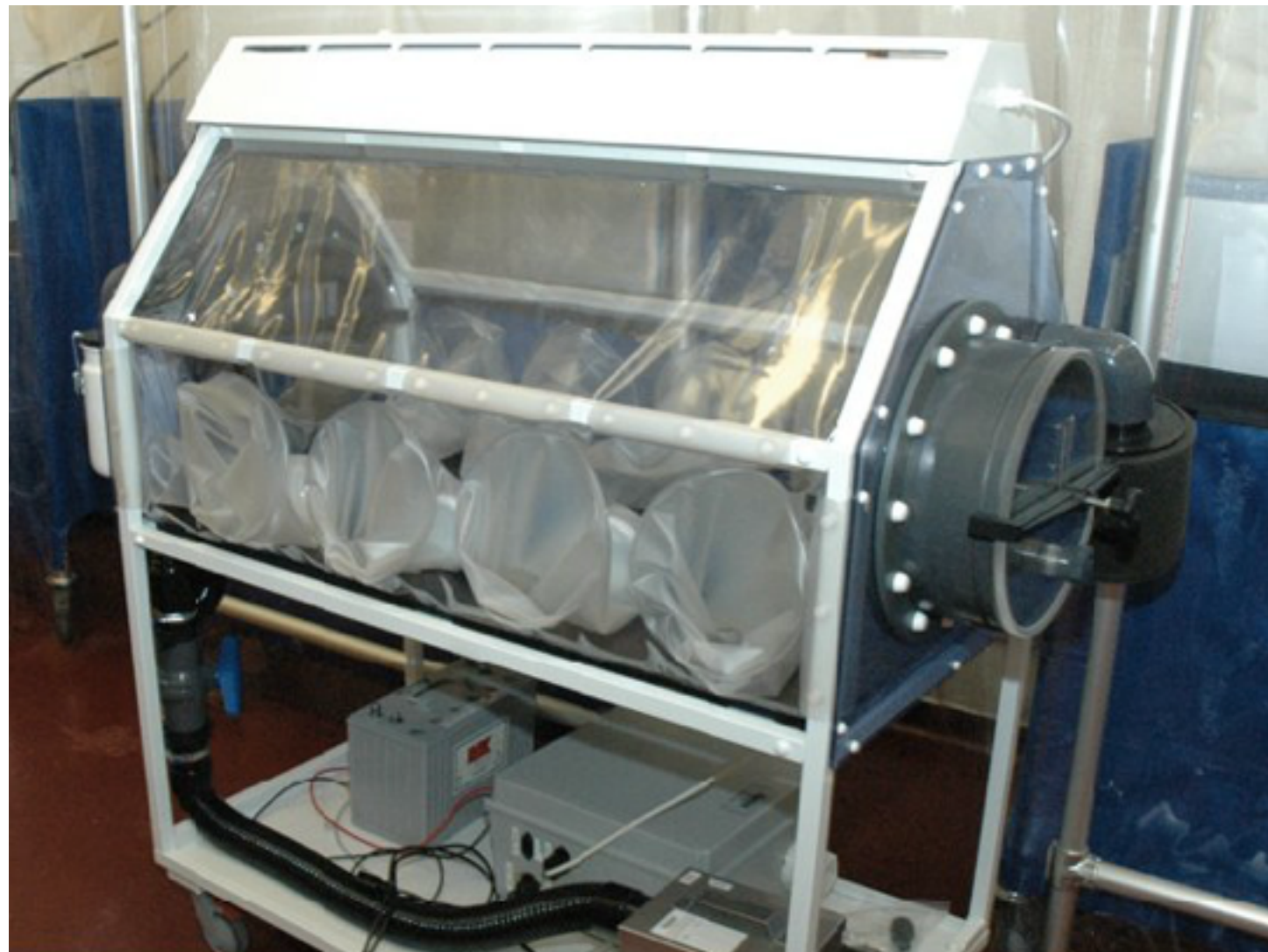
PROBIOTICS

ANTIBIOTICS



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

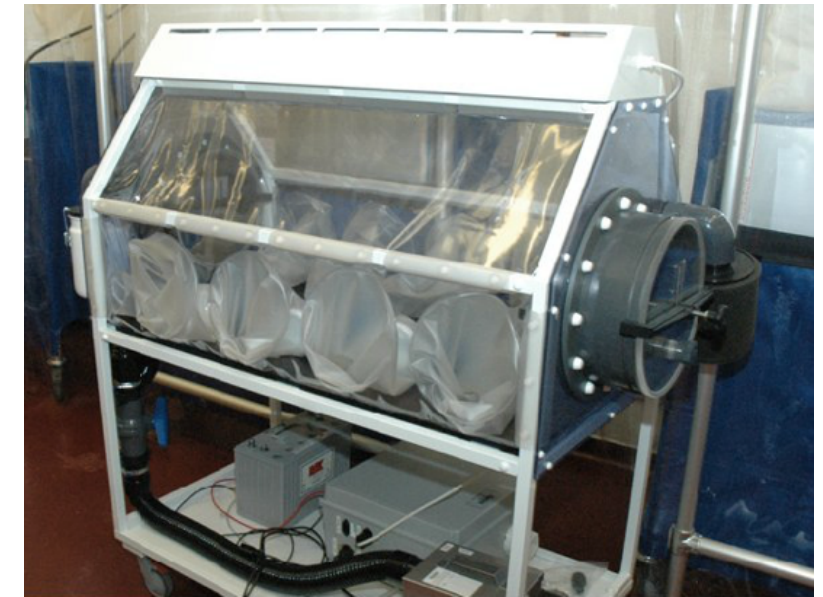


The starting point...

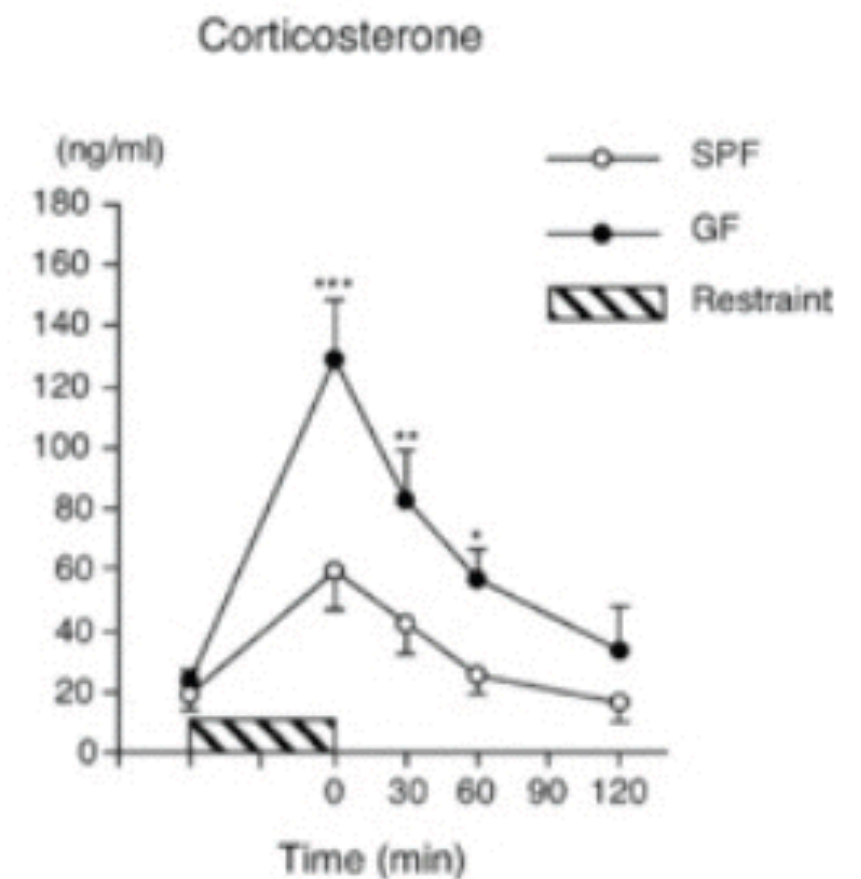
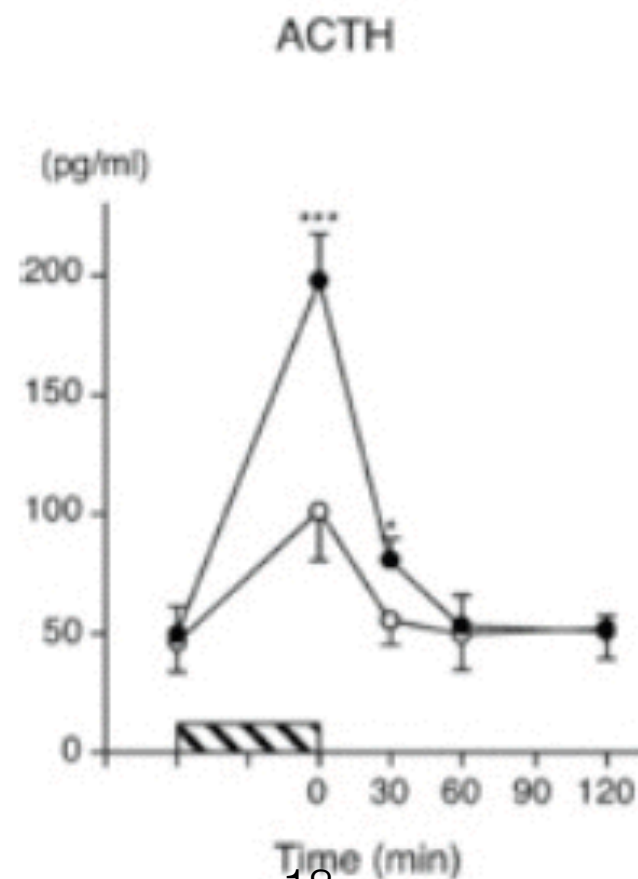
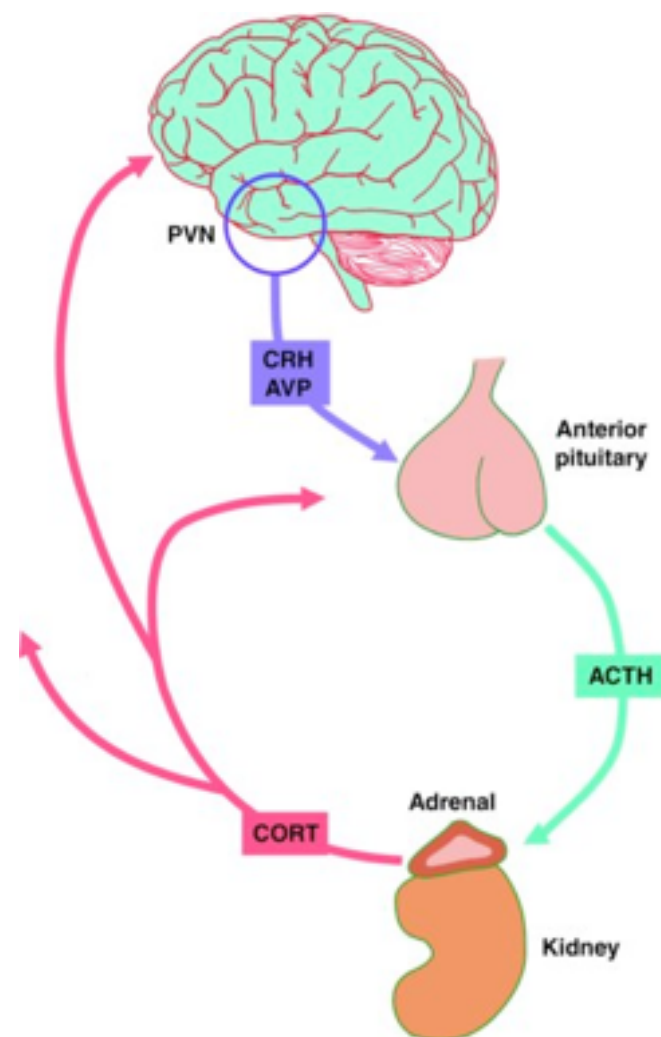
Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice

Nobuyuki Sudo^{1,2}, Yoichi Chida¹, Yuji Aiba^{3,4}, 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 ⁴Wakamatsu Pharmaceutical Co. Ltd, Ohi-machi, Kanagawa, Japan



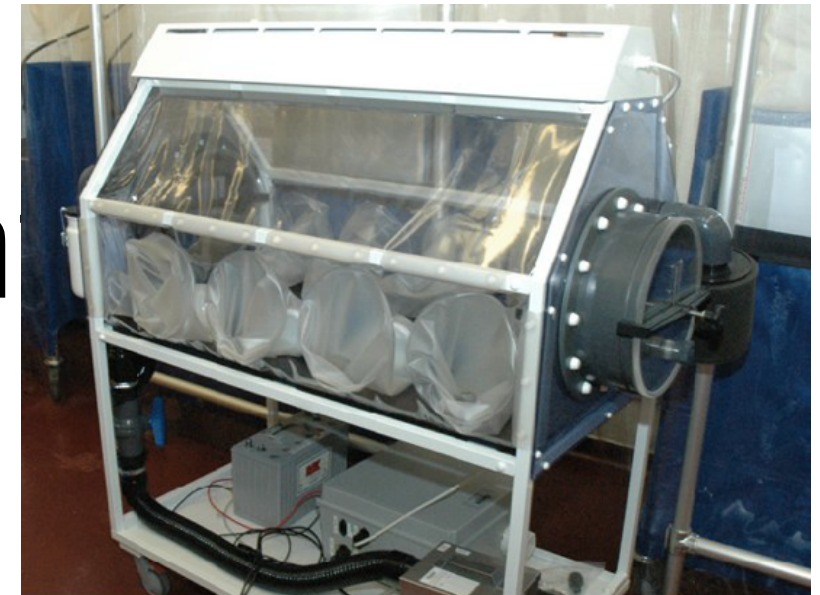
Germ-free mice showed exaggerated stress response



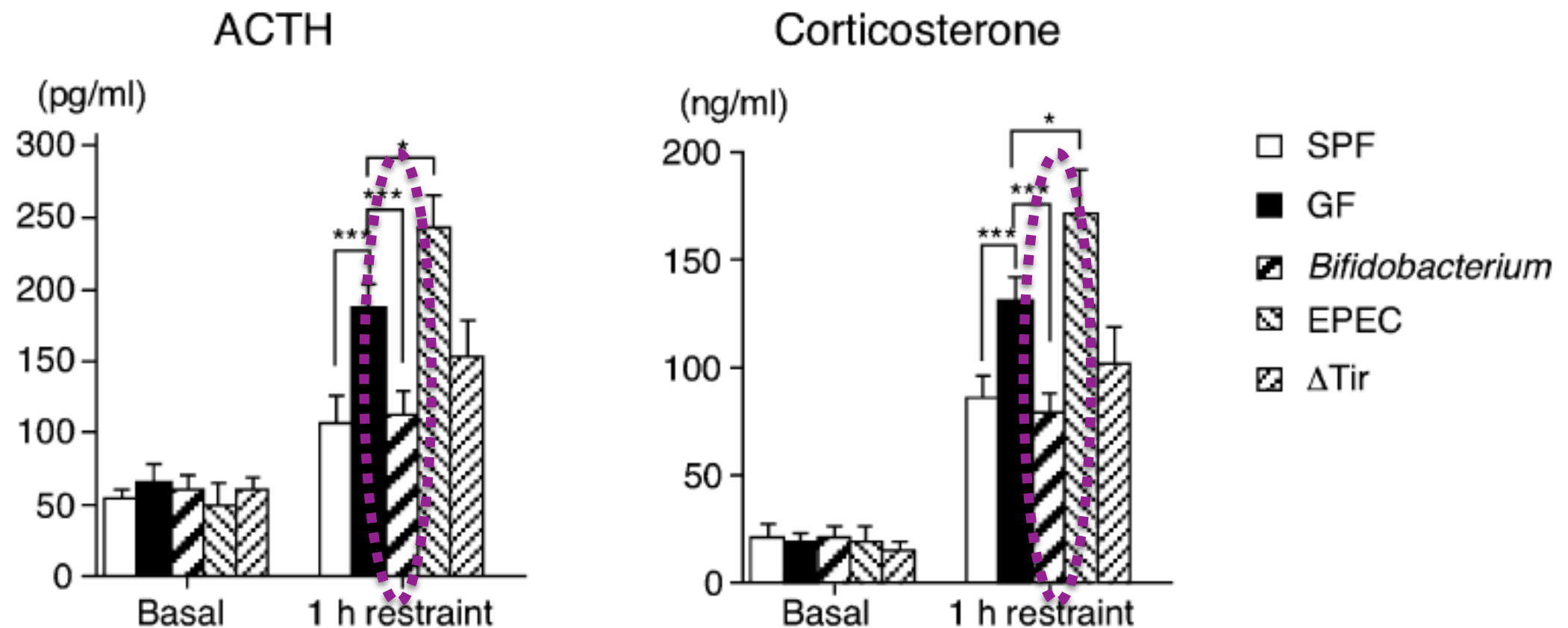
Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice

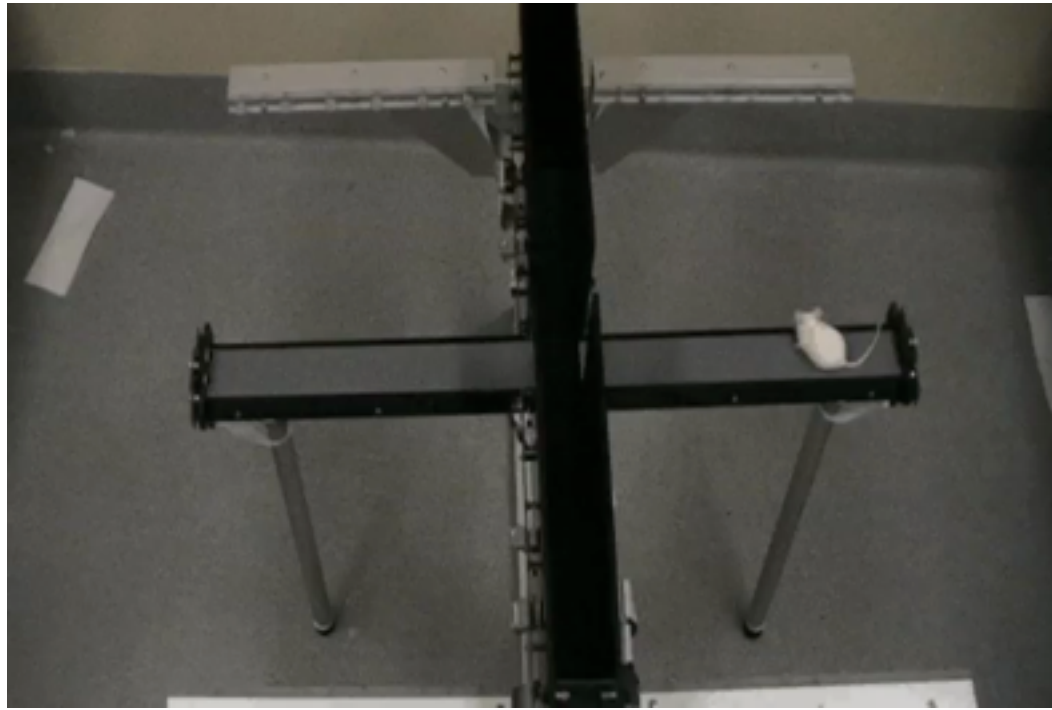
Nobuyuki Sudo^{1,2}, Yoichi Chida¹, Yuji Aiba^{3,4}, Junko Sonoda¹, Naomi Oyama¹, Xiao-Nian Yu¹, Chiharu Kubo¹ and Yasuhiro Koga³

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



Colonization with *Bifidobacterium* normalized stress response





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

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



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 Forsberg^{b,e}, and Sven Pettersson^{c,d,1}

Molecular Psychiatry (2012), 1–8

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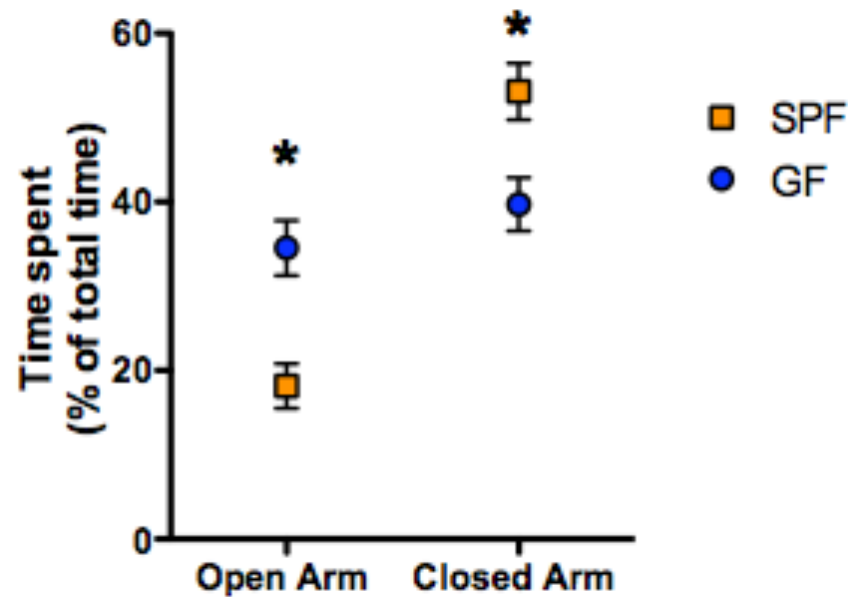
www.nature.com/mp



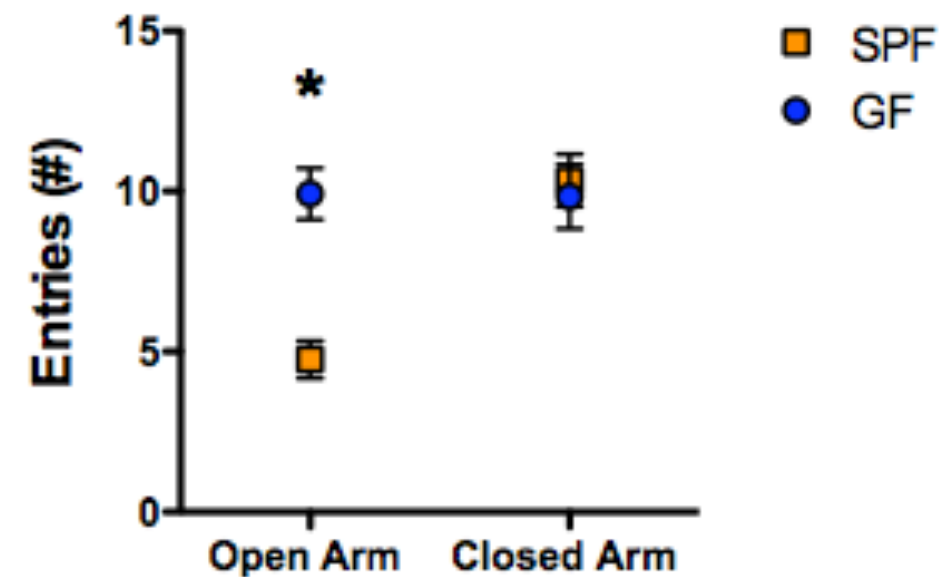
ORIGINAL ARTICLE

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

G Clarke^{1,2}, S Grenham¹, P Scully¹, P Fitzgerald¹, RD Moloney¹, F Shanahan^{1,3}, TG Dinan^{1,2} and JF Cryan^{1,4}

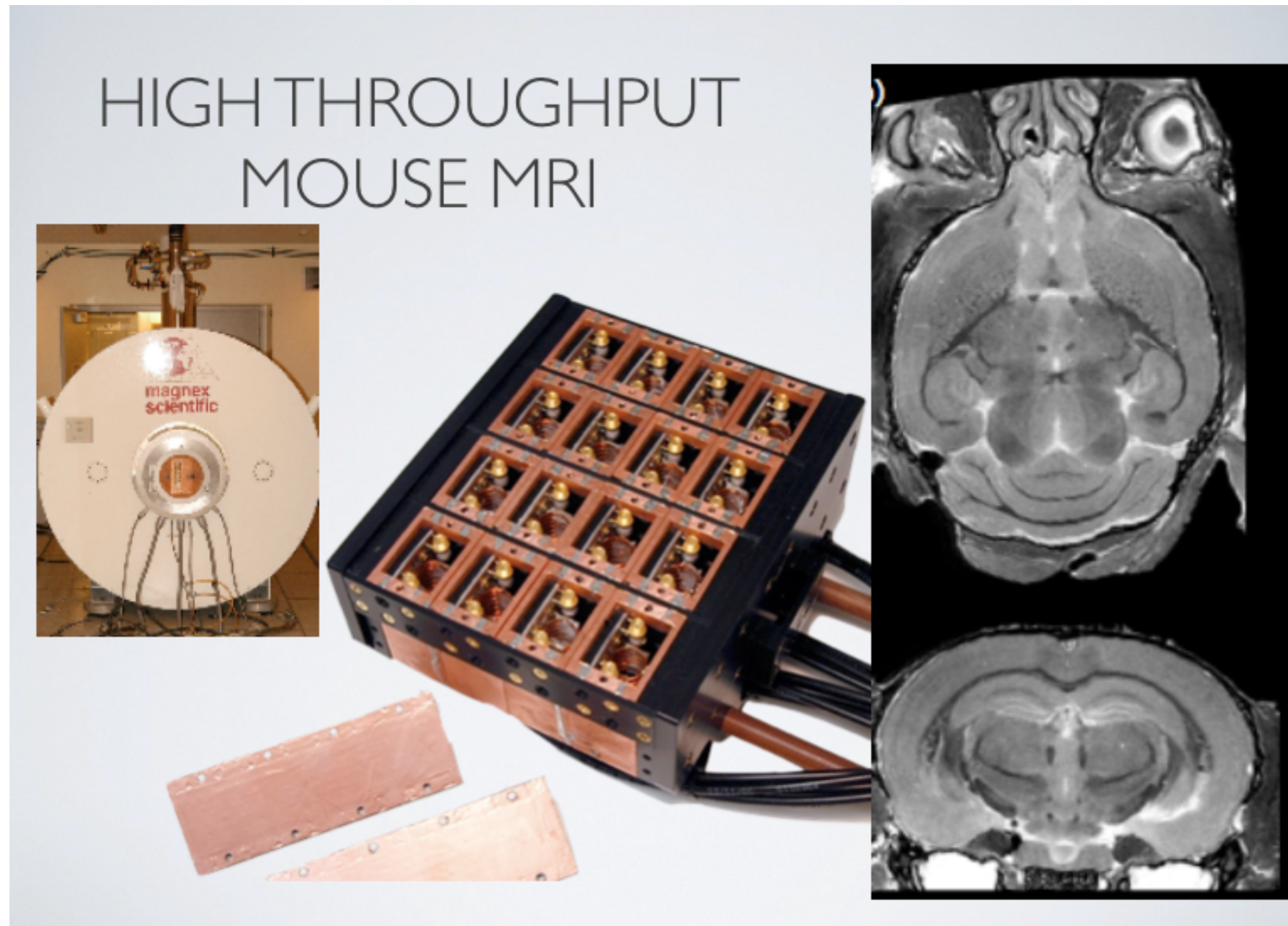


GF mice spent more time in the open arms of the EPM



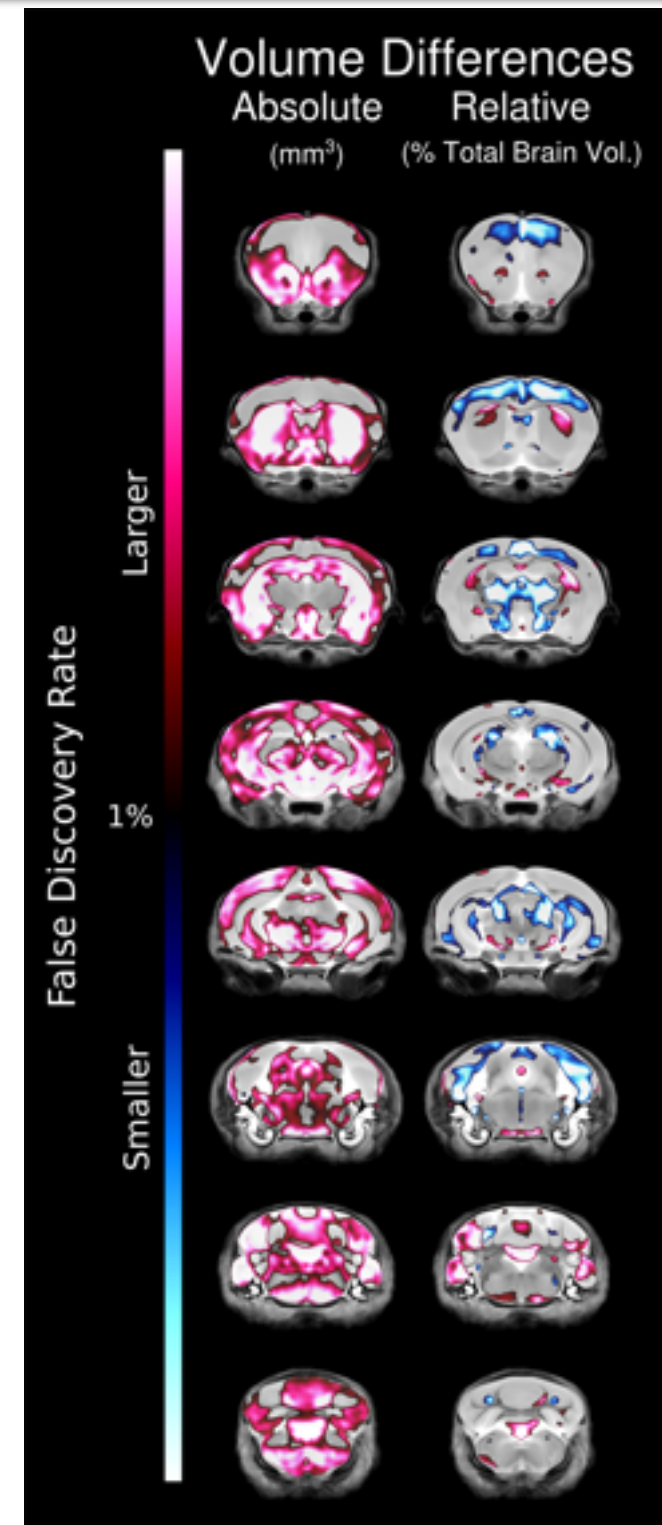
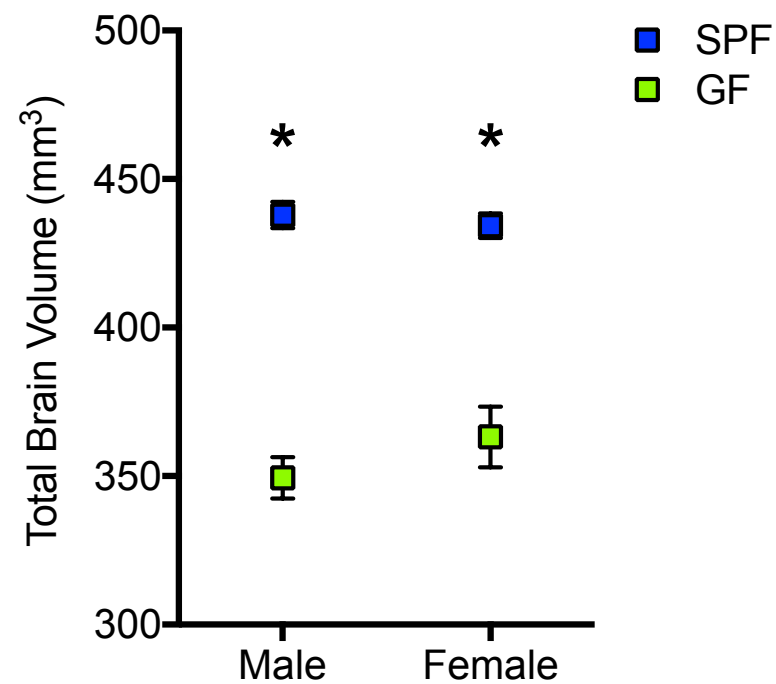
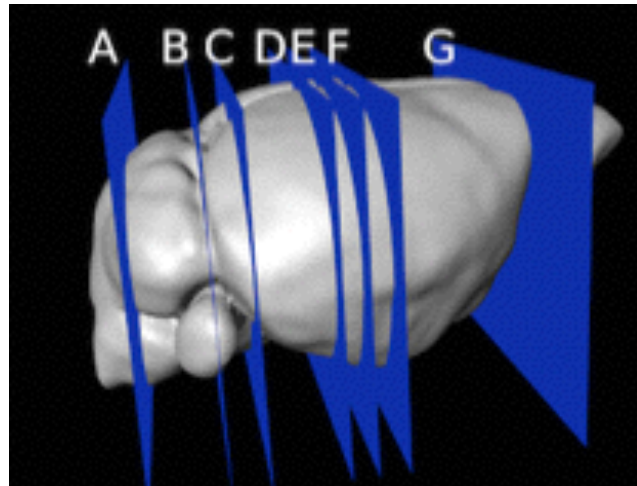
GF mice showed increased open arm entries

Do GF mice have differences in brain structure?



In collaboration with Jacob Ellegood and Jason Lerch at Sick Kids

Do GF mice have differences in brain structure?



In collaboration with Jacob Ellegood and Jason Lerch at Sick Kids

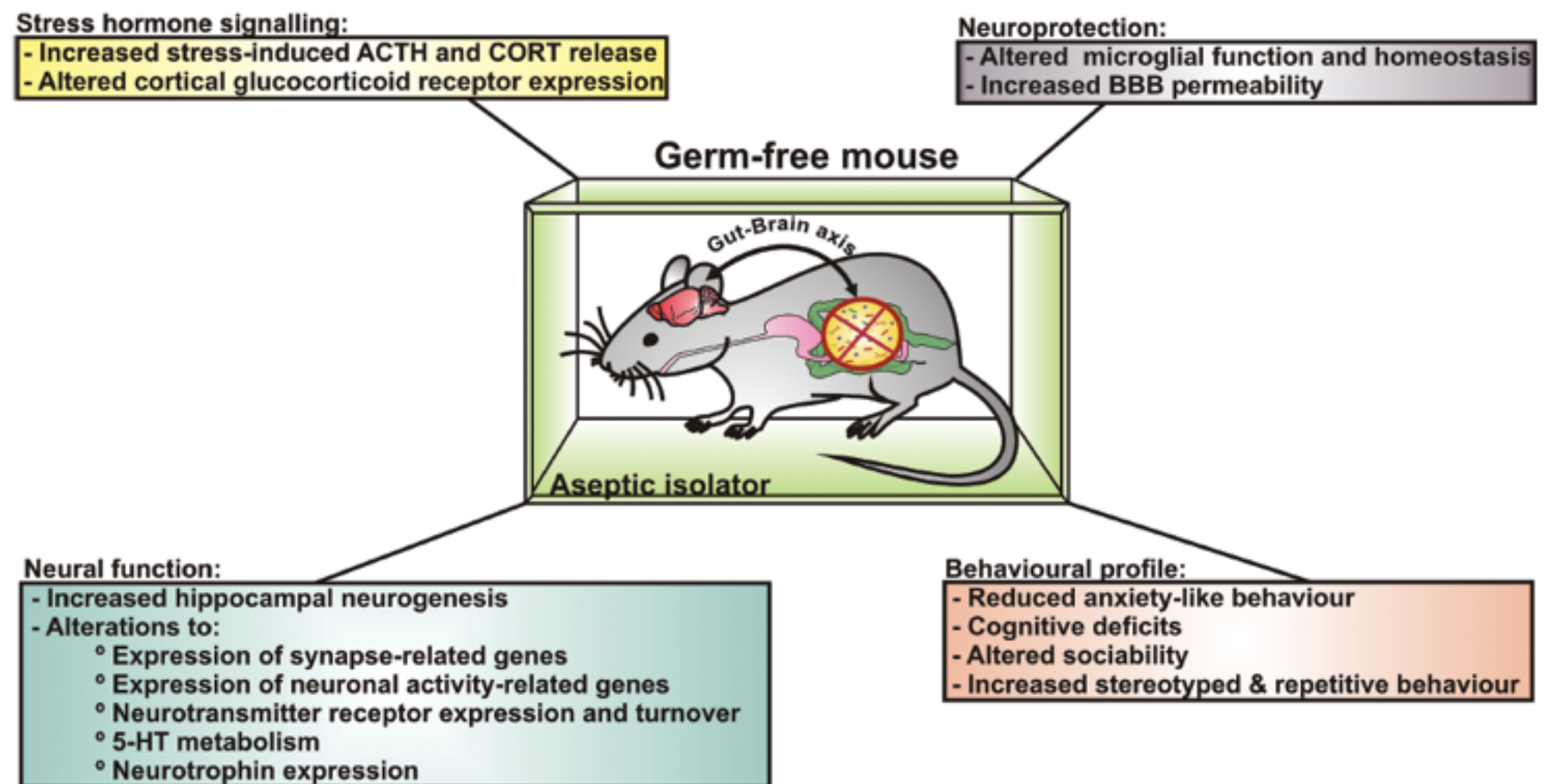
Several CNS genes altered in GF mice are known to influence anxiety-like behaviour

- Brain derived neurotrophic factor
- Serotonin receptors
- Serotonin transporter
- NMDA receptors
- Glucocorticoid receptors
- GABA receptors
- and more

Sudo et al, 2004; Neufeld et al, 2011a, b; Heijtz et al, 2011; Gareau et al, 2011; Clarke et al, 2012; Braniste et al, 2014; Erne et al, 2015; Stilling et al 2015; Yano et al, 2015; Arentsen et al, 2015

Summary of Findings in GF mice

- microbiota influence behaviour, stress circuitry, stress responsively, and brain structure



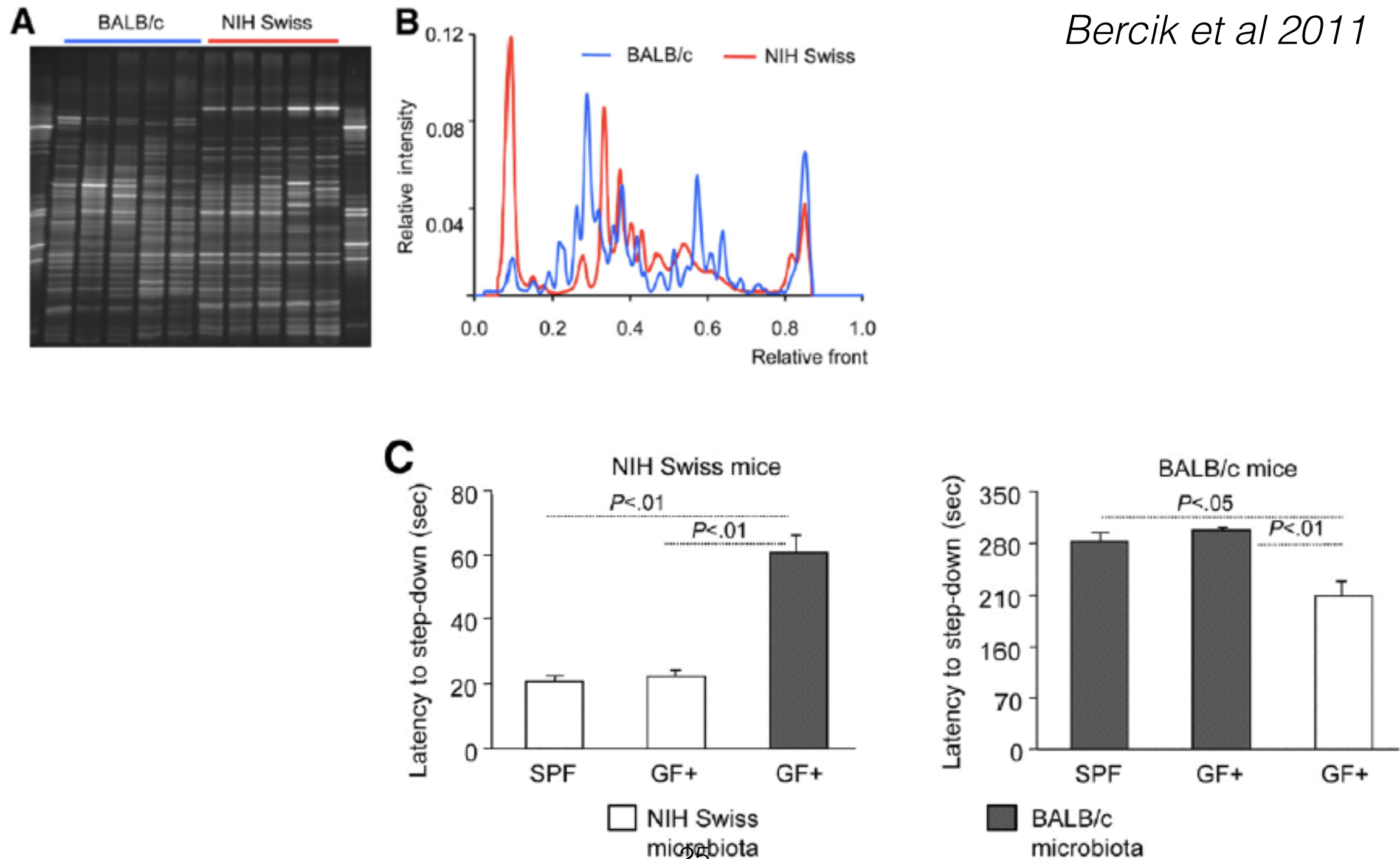
IMPORTANCE OF ENTERIC NERVOUS SYSTEM

West et al, 2016; McVey Neufeld et al, 2013

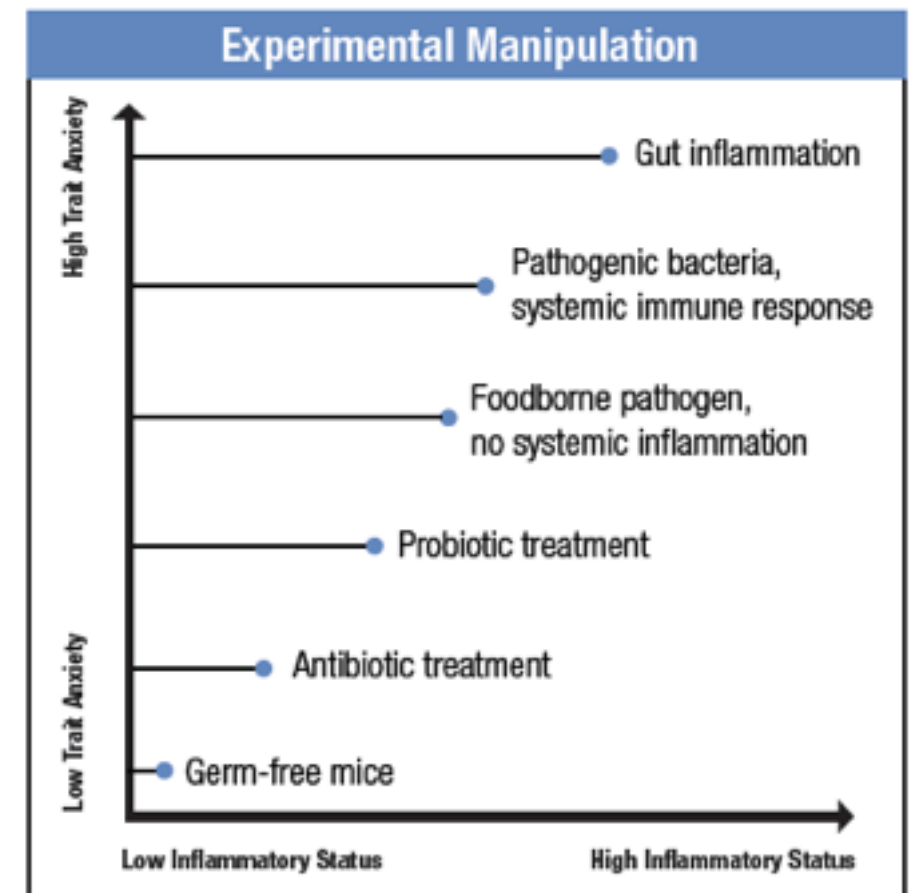
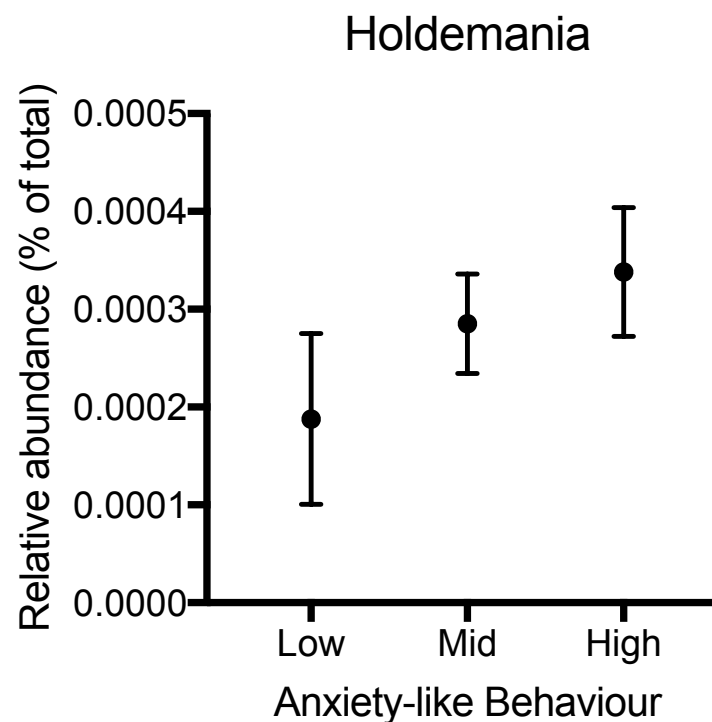
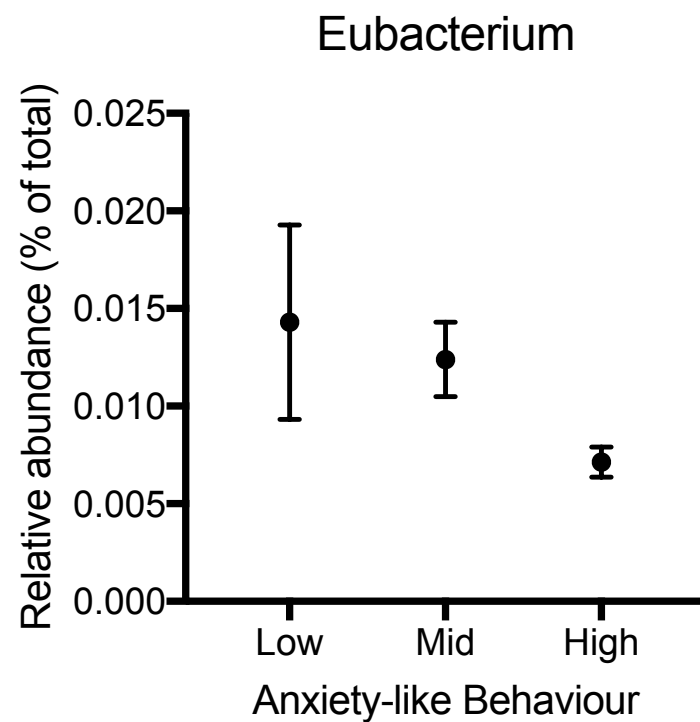
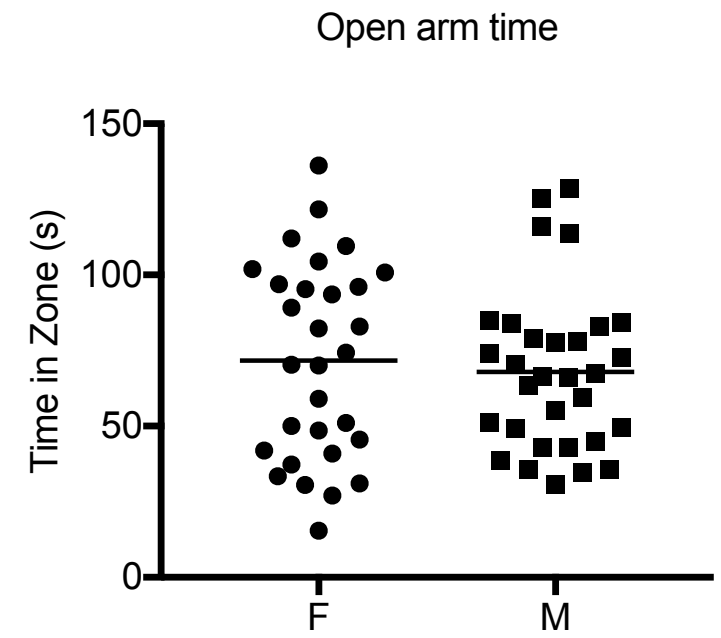
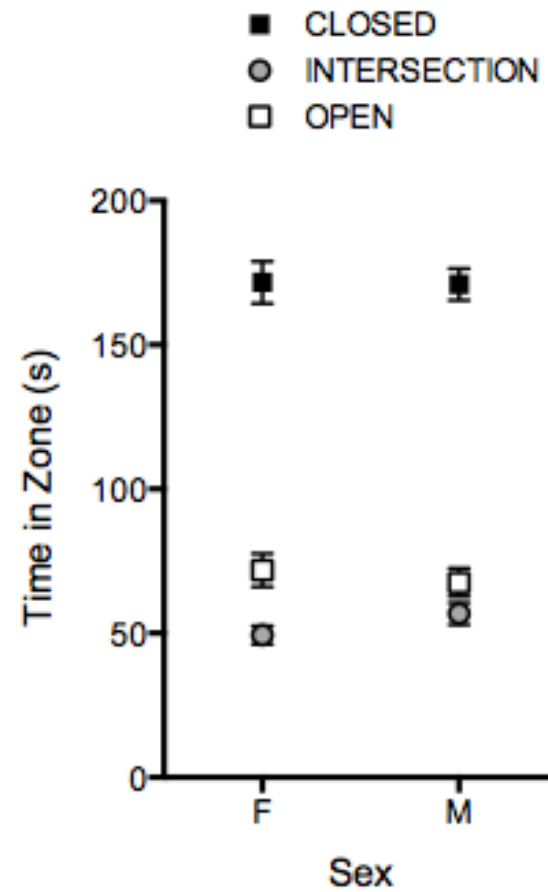
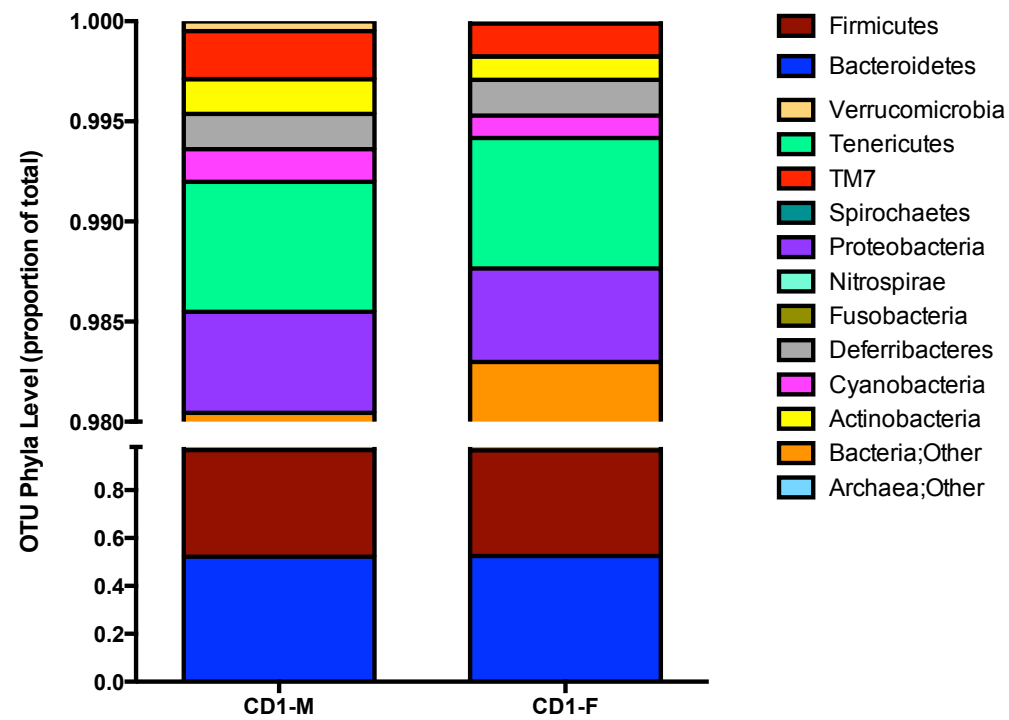
Luczynski et al 2016; Int J Neuropsychopharm

The host microbiota contributes to anxiety-like phenotype

Bercik et al 2011



16s rRNA analysis of bacterial composition

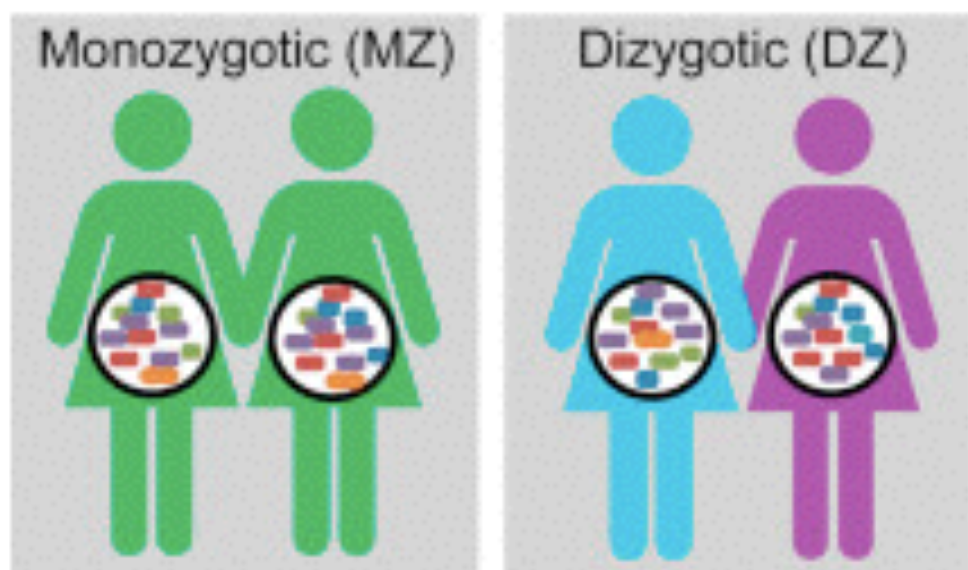


Significant contribution of host genetics to composition of the microbiome

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,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,*}

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

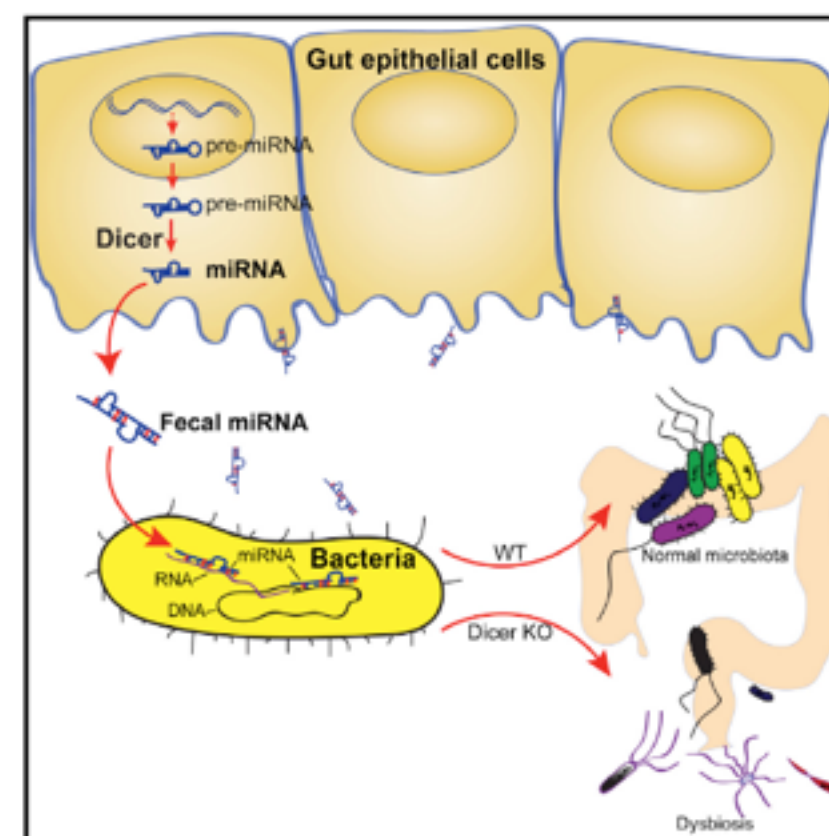


MZ twins have a more similar microbiota than DZ twins

Cell Host & Microbe

The Host Shapes the Gut Microbiota via Fecal MicroRNA

Graphical Abstract

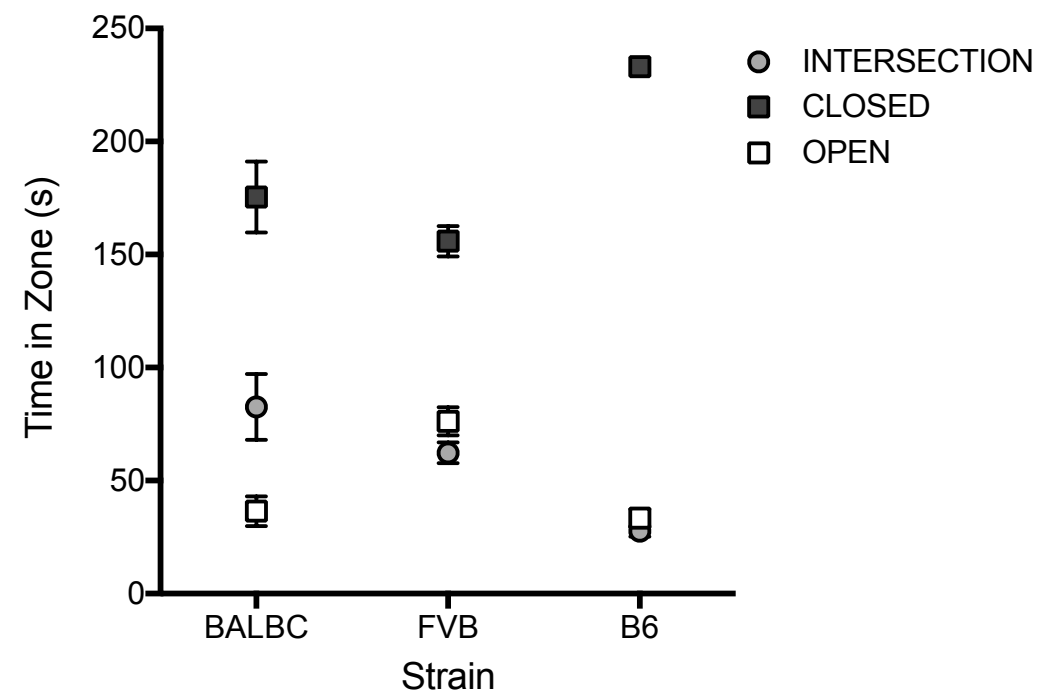


Authors

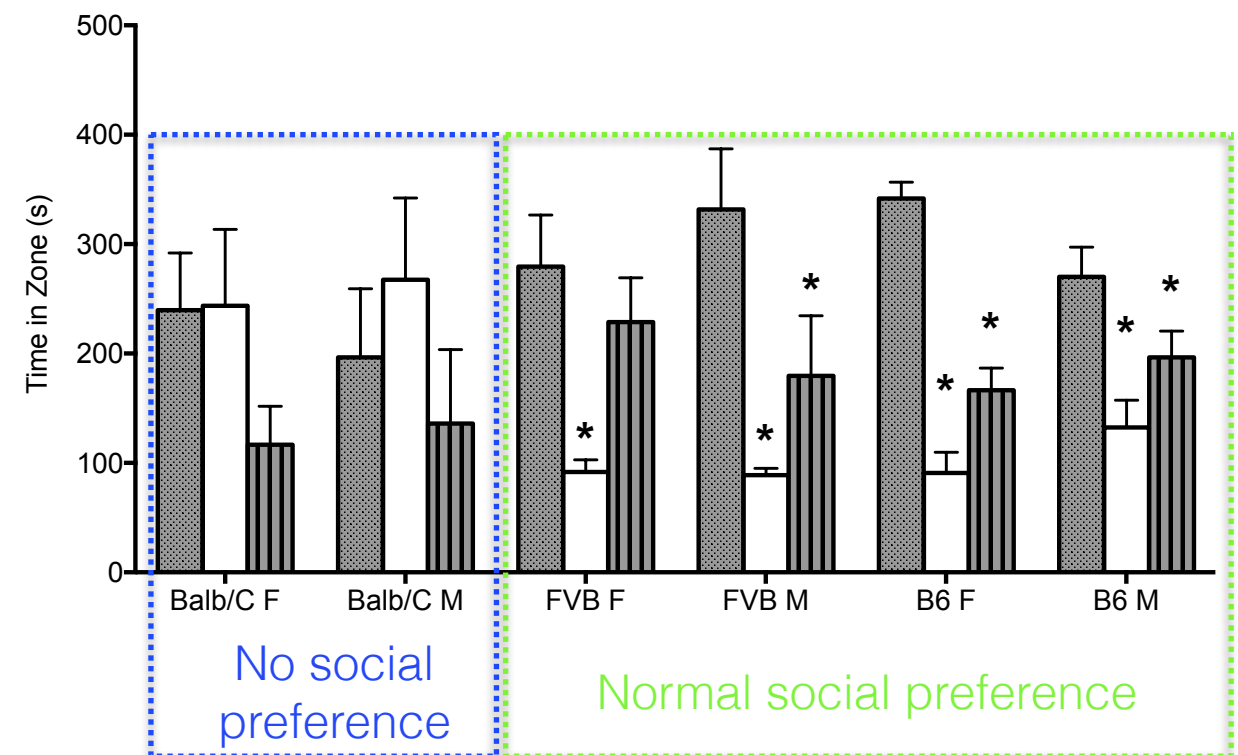
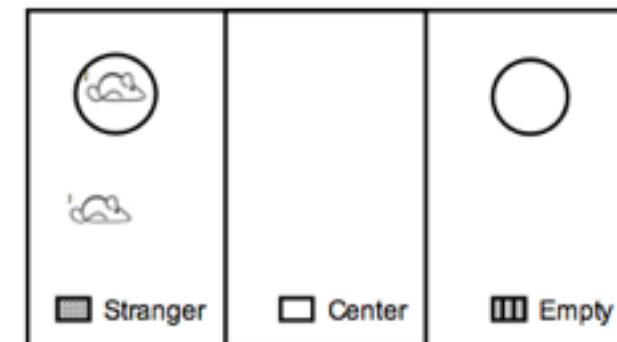
Shirong Liu, Andre Pires da Cunha,
Rafael M. Rezende, ...,
Laurie E. Comstock, Roopali Gandhi,
Howard L. Weiner

Host Genetics influences Behaviour

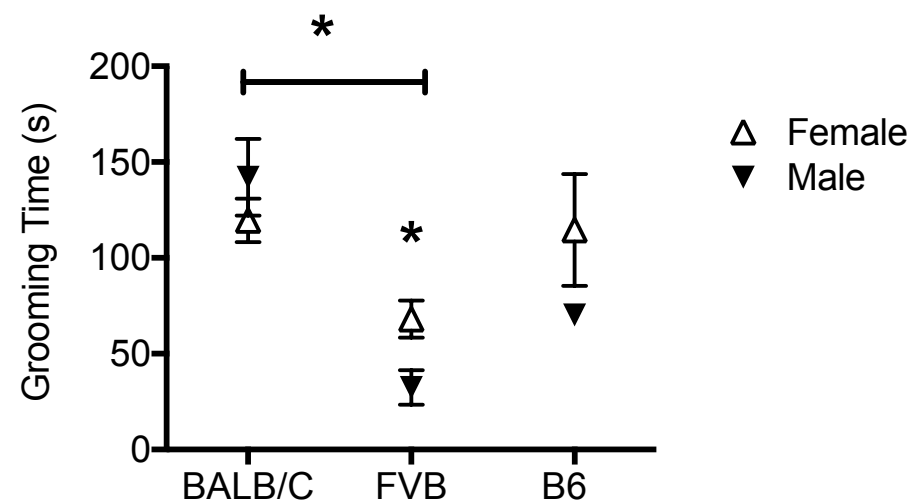
Anxiety-like behaviour



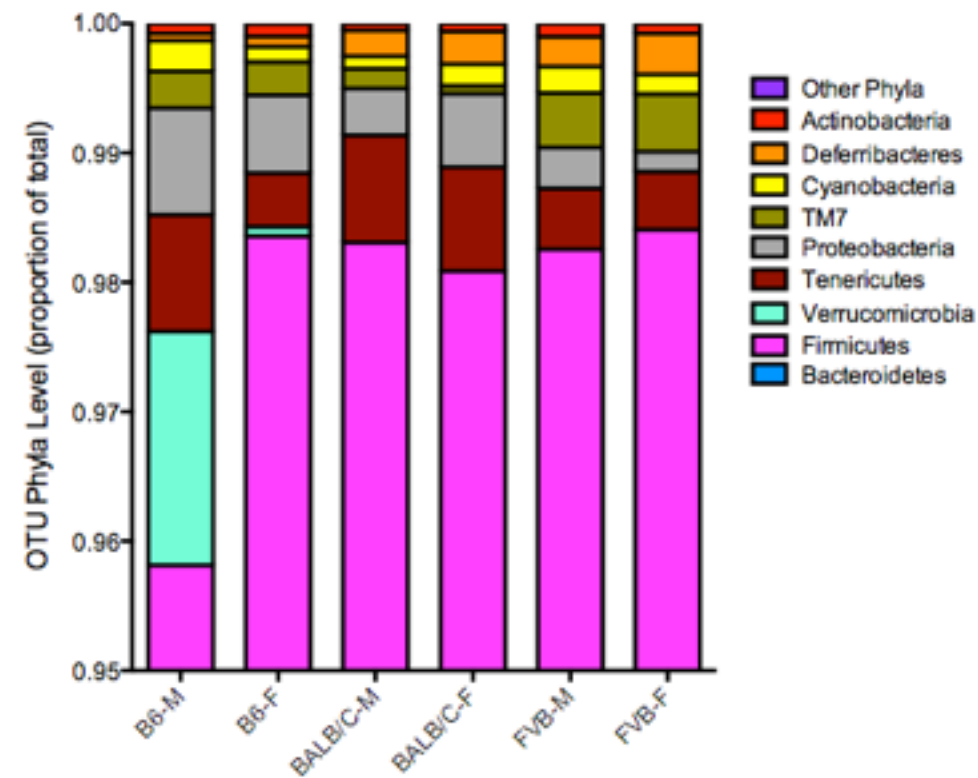
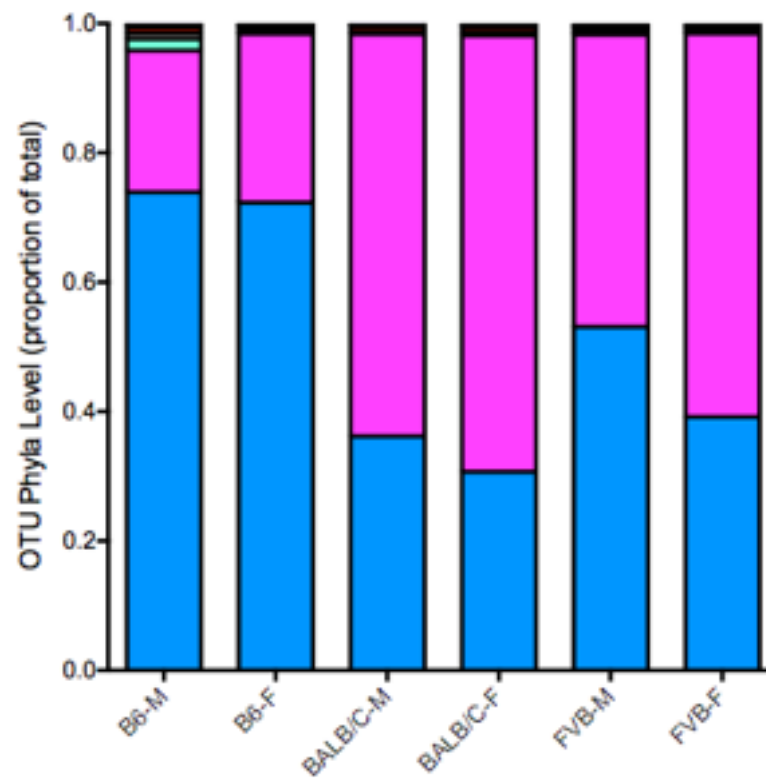
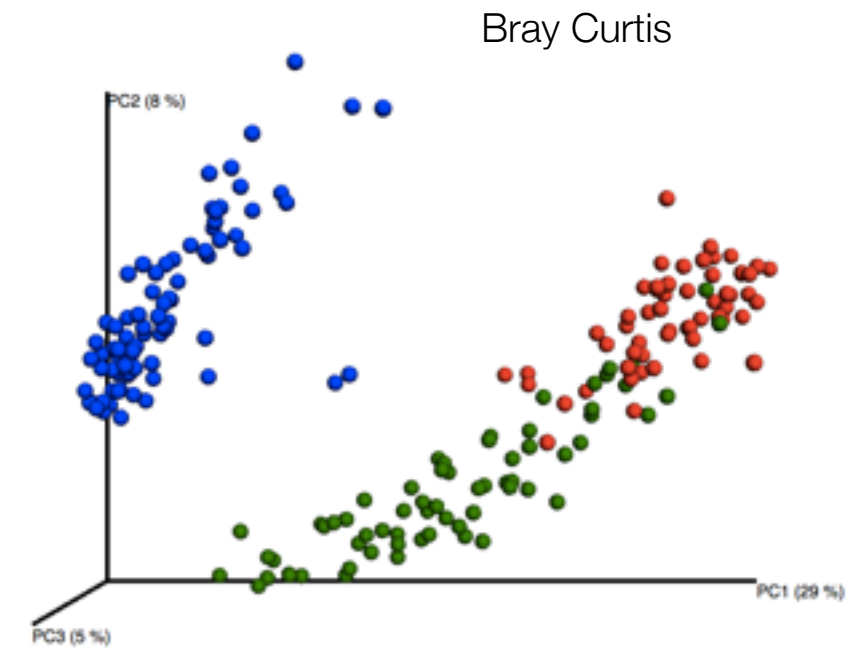
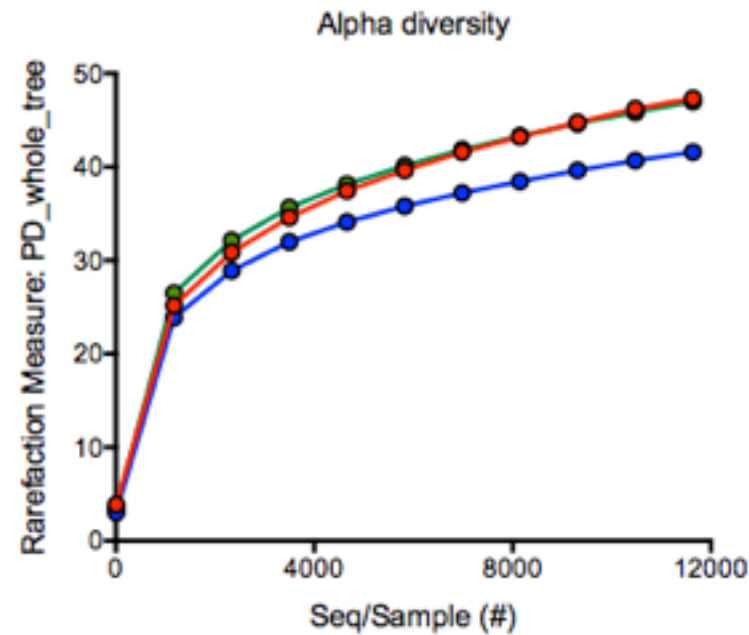
Social behaviour



Self-grooming behaviour

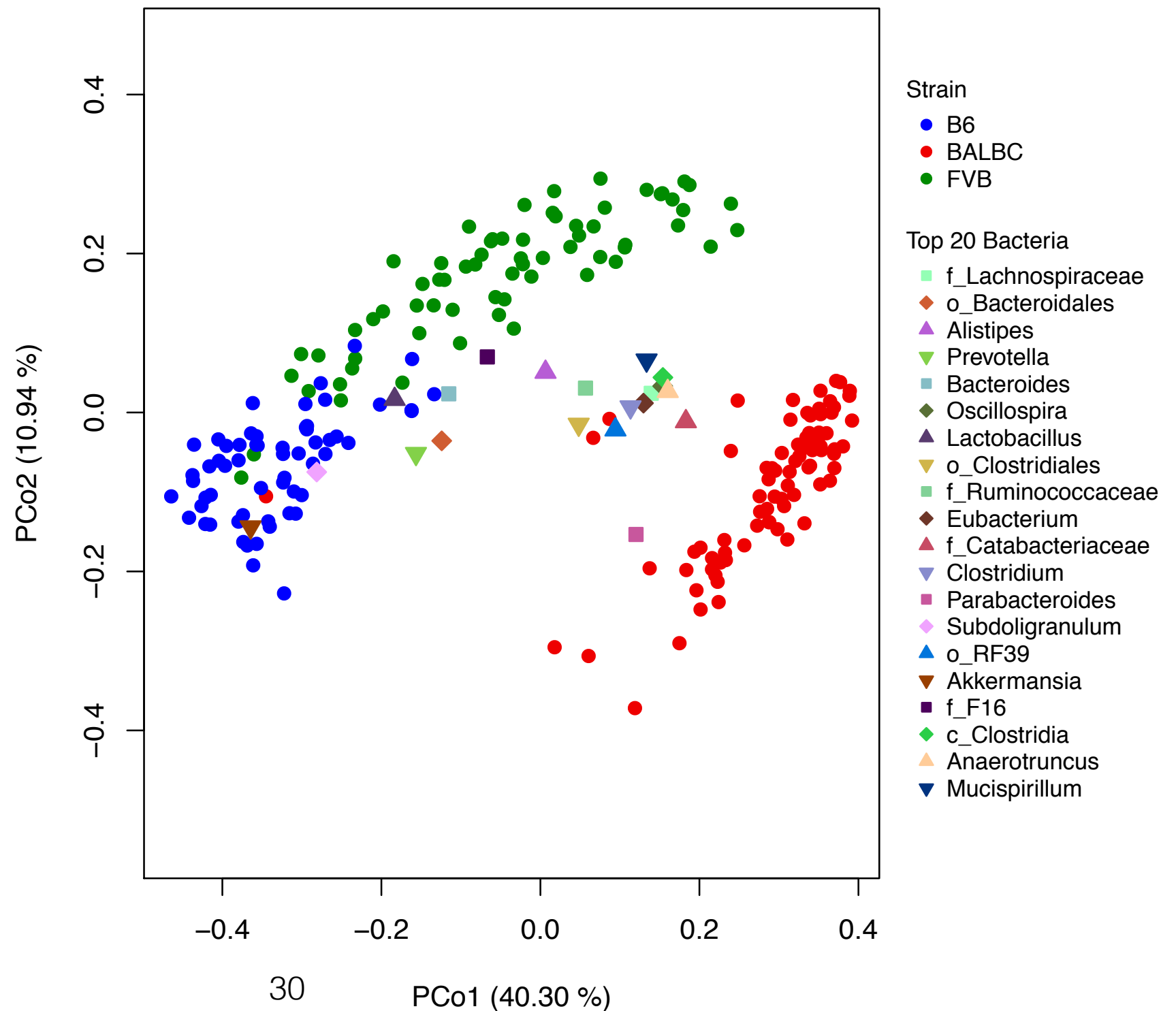


Host Genetics influences bacteria composition



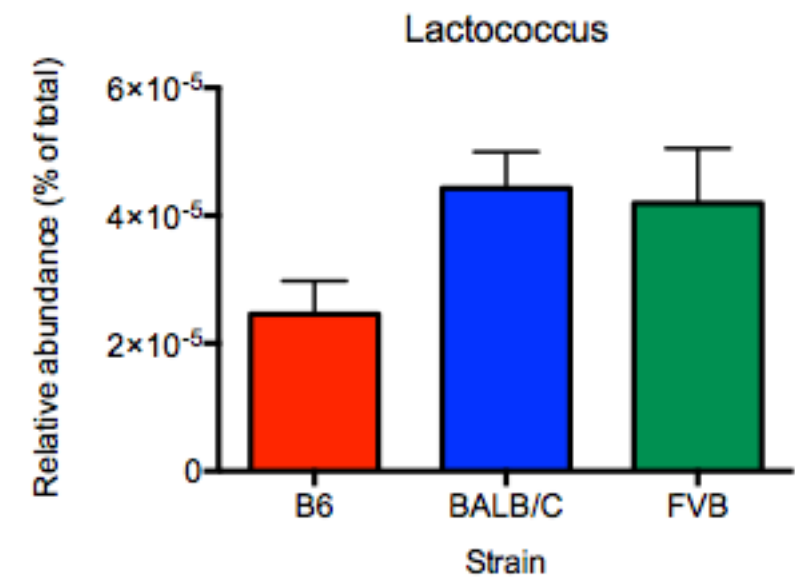
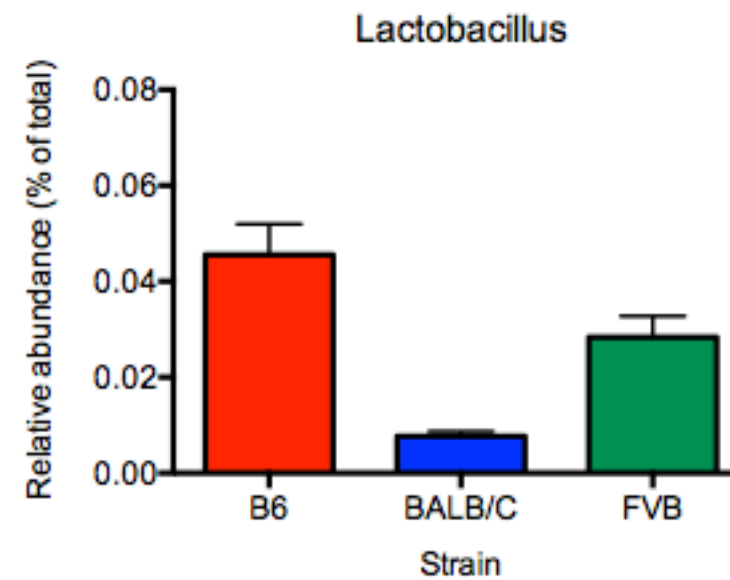
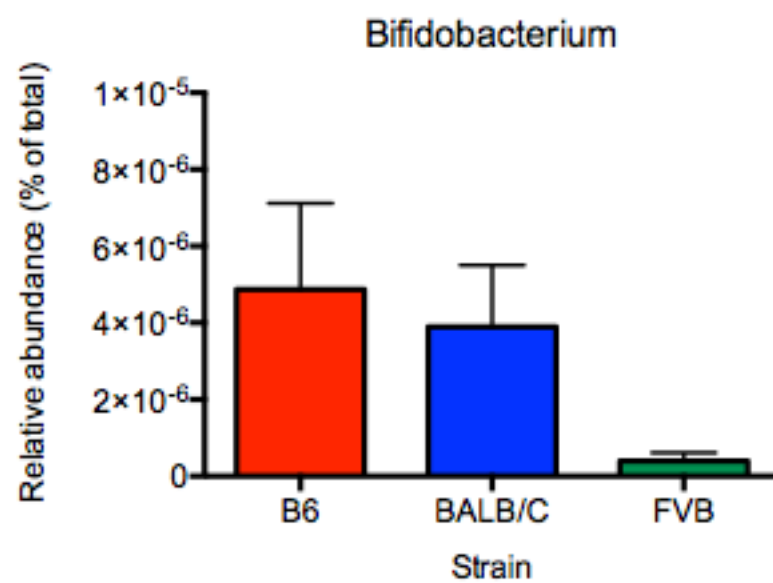
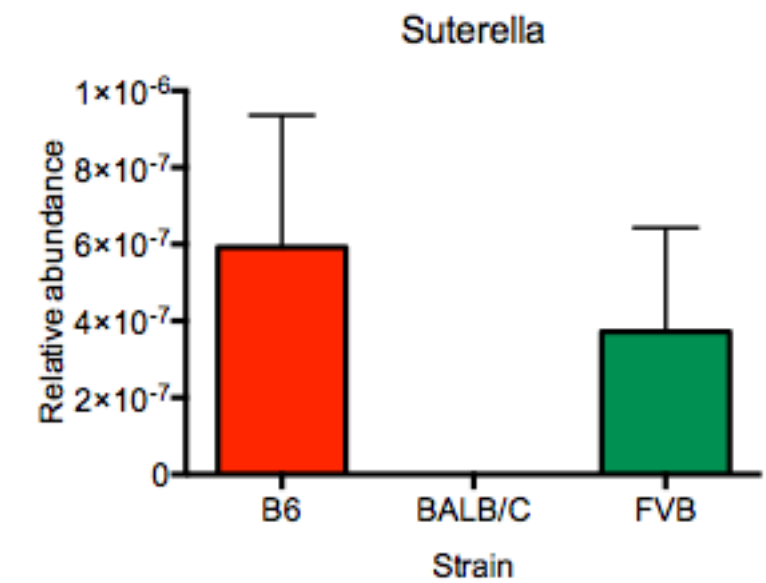
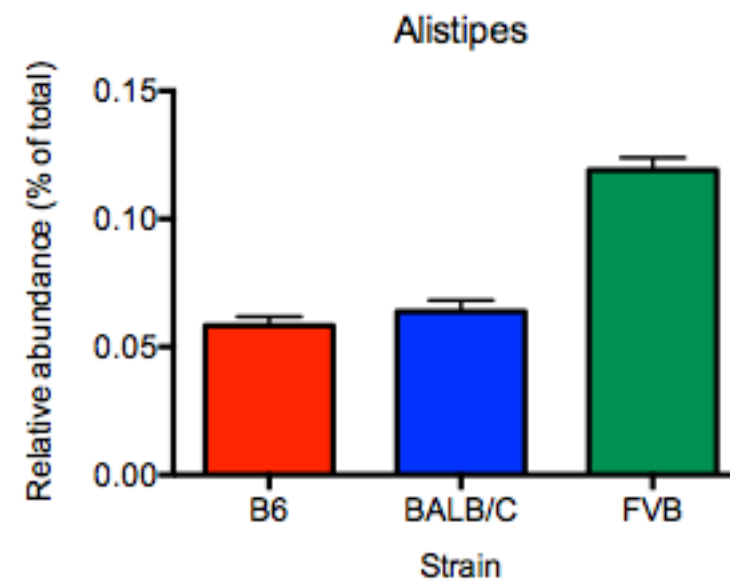
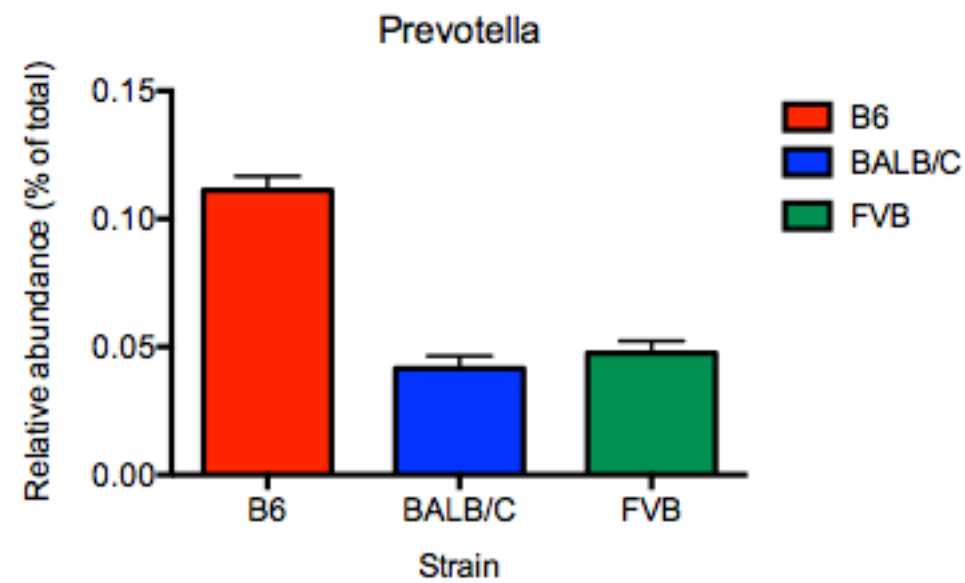
Are specific taxa associated with different strains of mice?

PCoA Comparing B6, BALBC, and FVB
Bray Curtis Dissimilarity



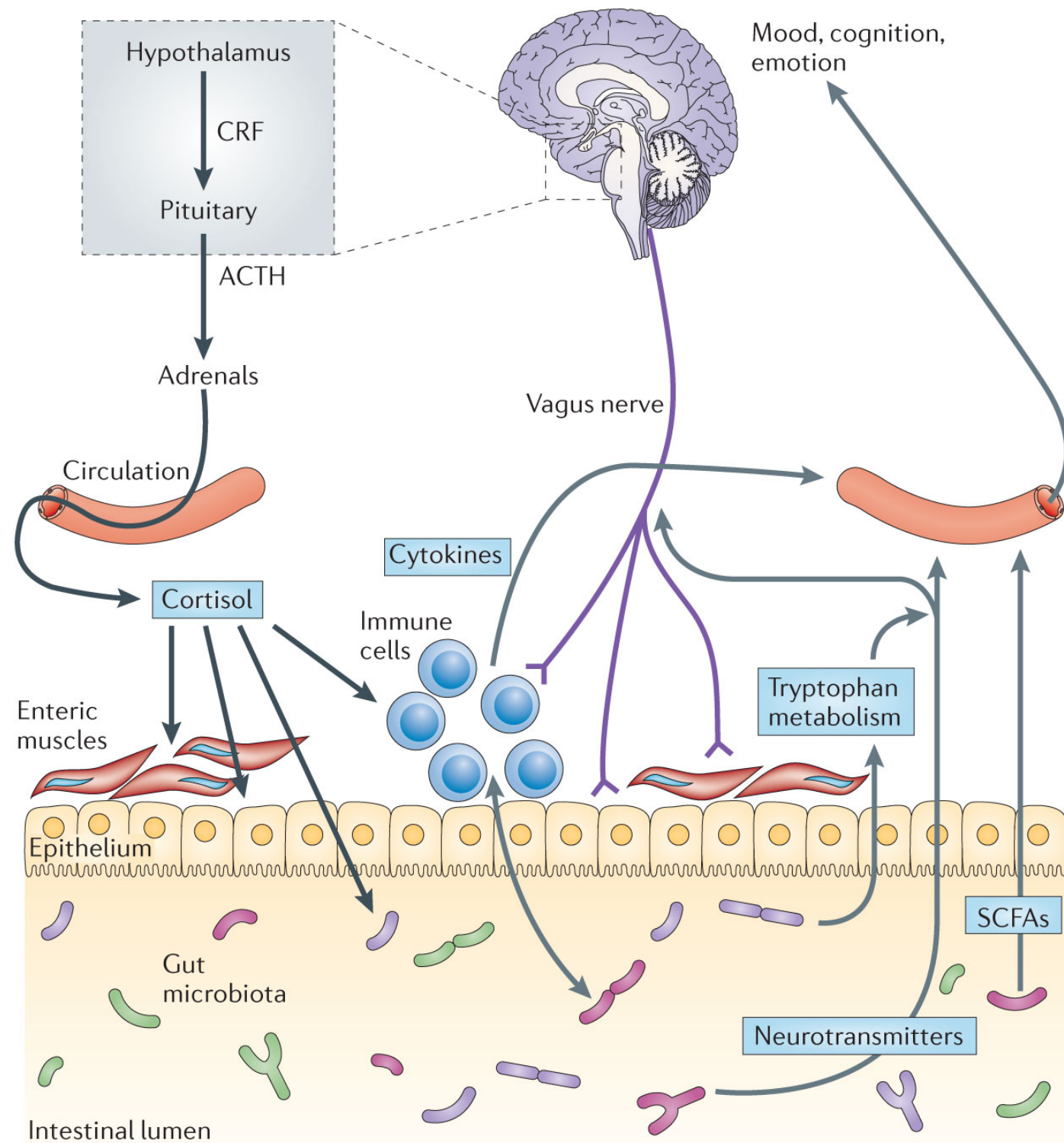
PCo Analysis
with
count-weighted ave
for top 20 taxa

Commensals linked to brain and behaviour vary by strain



How do microbiota communicate with the brain?

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



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

News Feature: Microbes on the mind

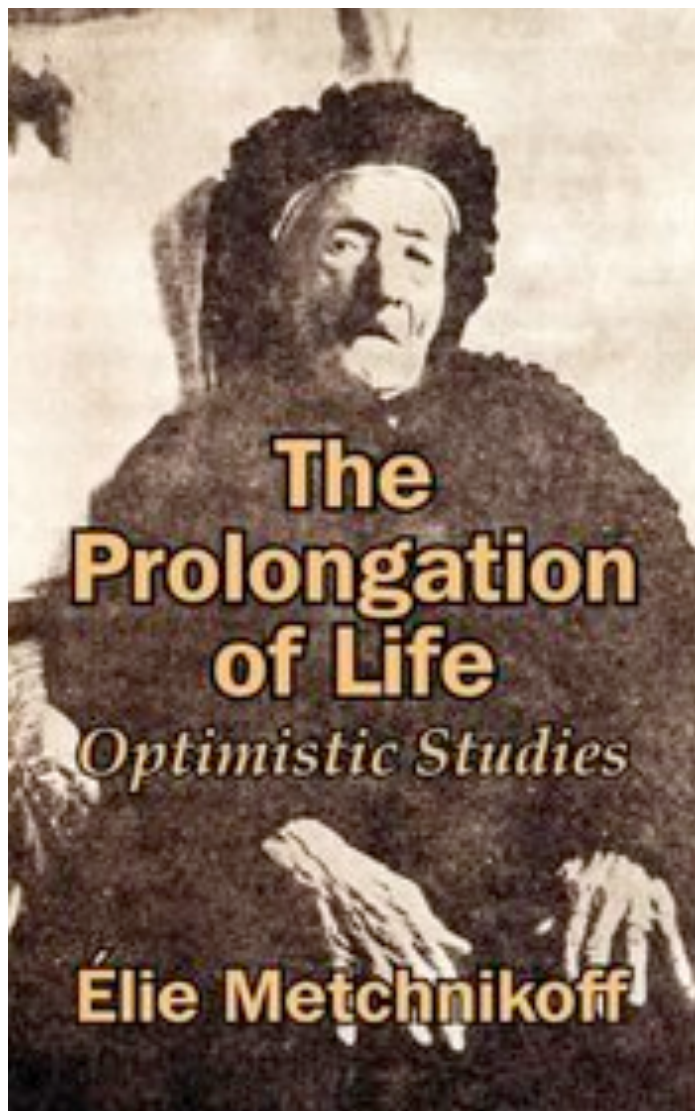
Could the gut microbiome have a critical role in brain and behavior? The notion is starting to gain acceptance amongst both researchers and funders.

Helen H. Shen
Science Writer

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

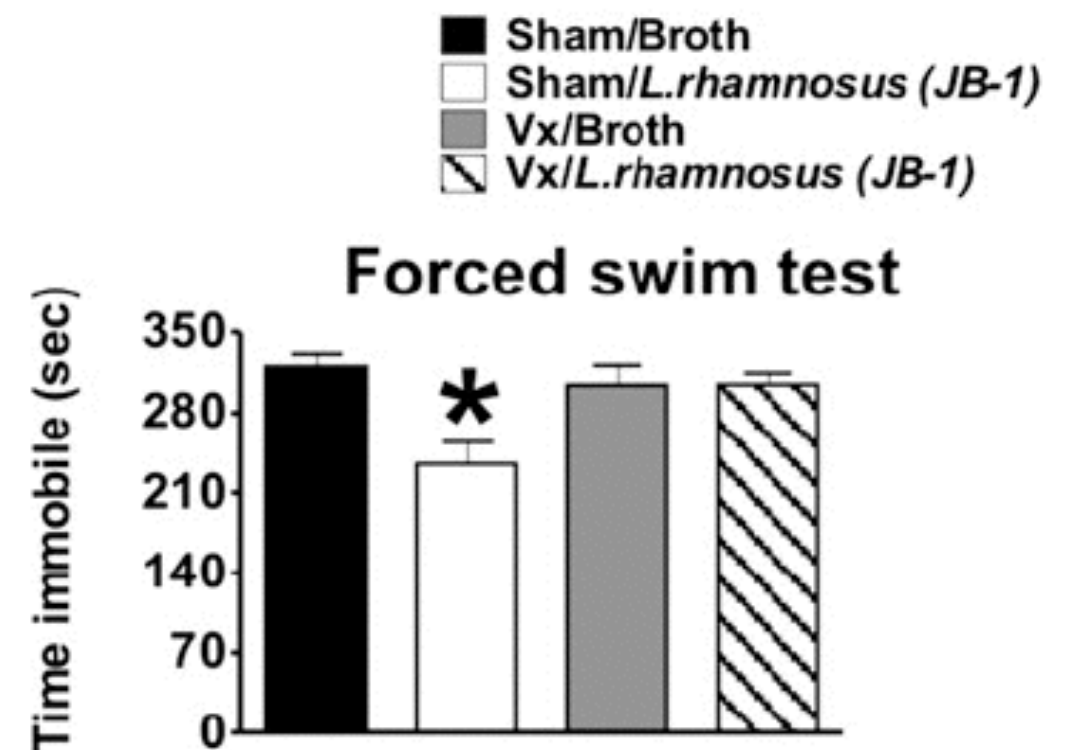
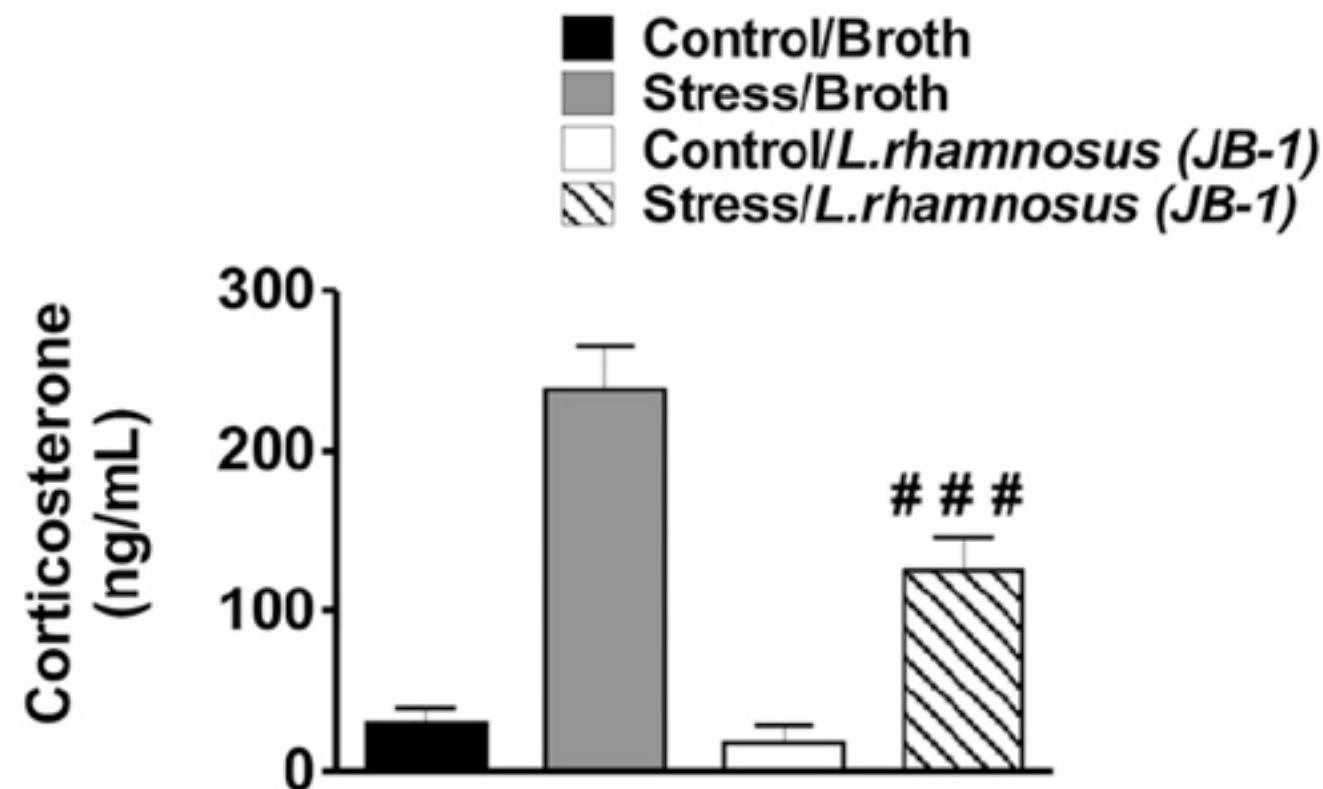
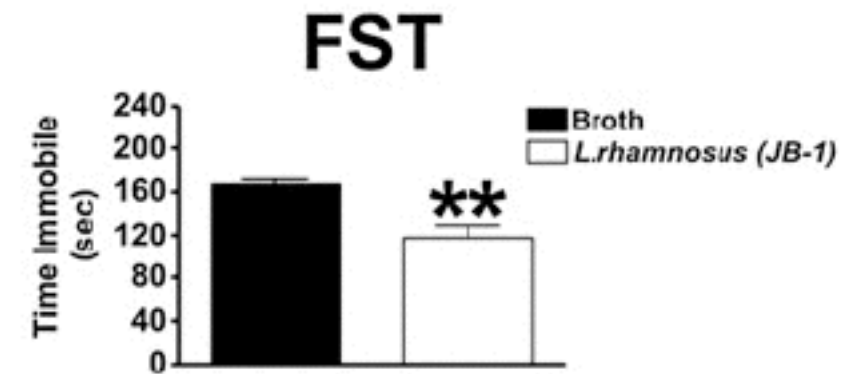
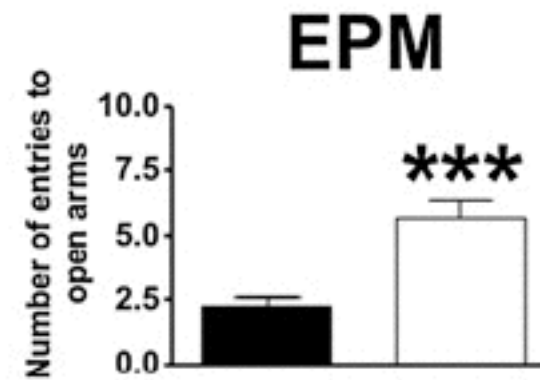
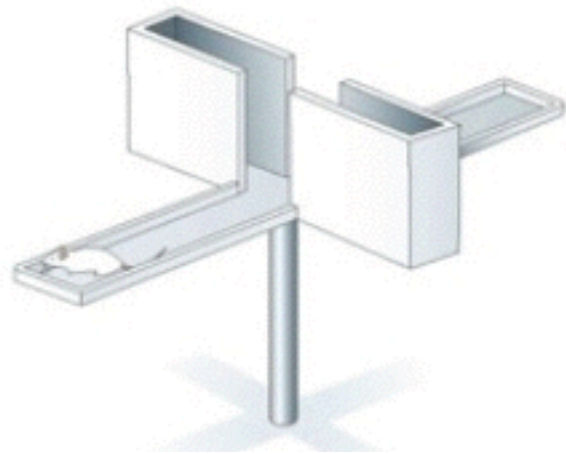
Can Probiotics Improve Your Mood?

Mandy Oaklander @mandyoaklander | April 10, 2015



- 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



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

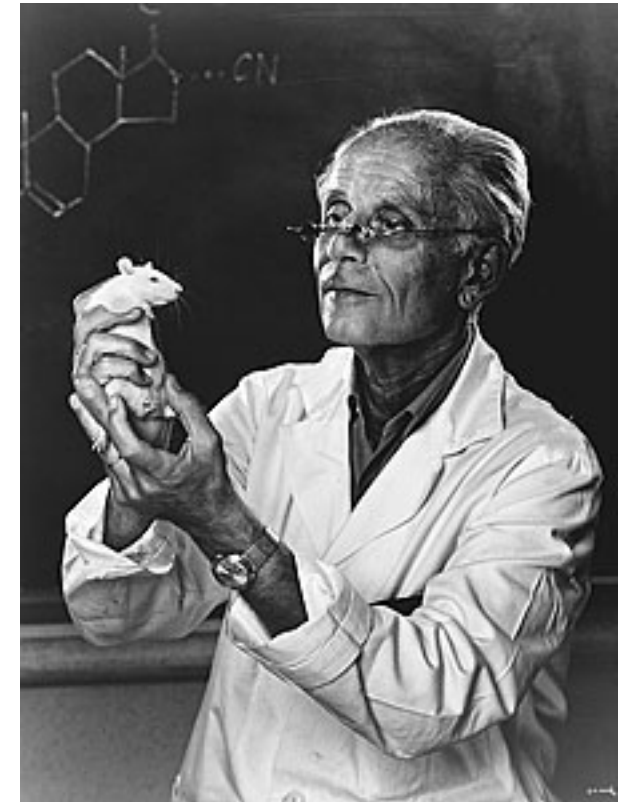
- *Messoudi et al 2011*
 - *Lactobacillus helveticus* (R0052) and *Bifidobacterium longum* (R0175) or placebo administered to healthy volunteers for 30 days
 - Reduced self-report psychological stress levels
- Steenbergen et al 2015
 - 28 days administration of “Ecologic Barrier” containing *B. bifidum* 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

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

- Randomized, placebo-controlled trial in MDD
- Probiotic capsule (*Bifidobacterium bifidum*, *Lactobacillus casei*, *L. acidophilus*) for 8 weeks
- reduced Beck Depression Inventory total score in probiotic group
- Reduced insulin levels in probiotic group
- Reduced c-reactive protein levels in probiotic group

“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



Current Lab Members

Sarra Bahna
 Shawna Thompson
 Rachael Horne
 Daiana Pogacean
 James St. Pierre
 Tess McGurn
 Cassandra Francesca
 Gavin Lifman
 Owen Luo

Collaborators

Aadil Bharwani
 Jason Lerch
 Jacob Ellegood
 OBI POND research group
 CAN-BIND research group

Former Lab Members

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

Trends in Neurosciences



'Brain Gut Axis', depicts a reconceptualization of the brain as part of an interconnected system, in contrast to the more traditional view of the brain as superior to, or in control of, all other processes. TINS May 2013 cover image designed by Renee Jackson, in collaboration with Jane A. Foster, Suzanne McCullagh, and Dominic Letarte.