Mood & Microbes

Jane A. Foster, Ph.D.

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About the speaker…

The University of Western Ontario

Queen's University

UNIVERSITY of TORONTO

EXPERTISE - PhD Scientist

- ★ Behavioural Neuroscience
- ★ Molecular Neuroscience
- ★ Mood & Microbes

POND network

CAN-BIND

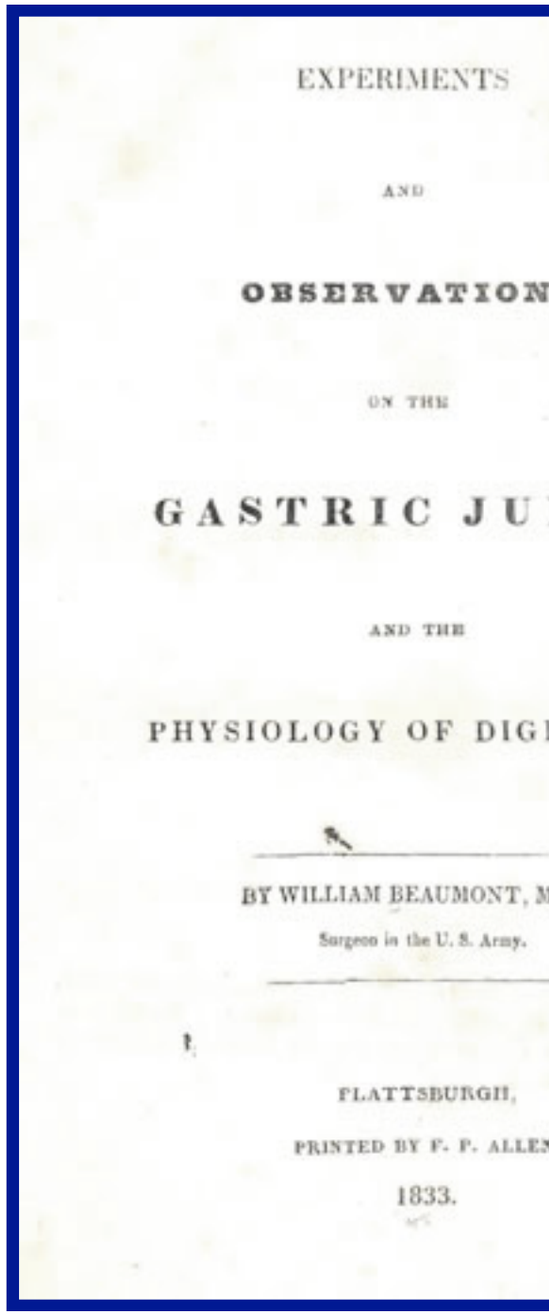
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

“All diseases begin in the gut.”

–Hippocrates

Gut-brain Axis

1833 - Beaumont



EXPERIMENTS

AND

OBSERVATIONS

ON THE

GASTRIC JUICE,

AND THE

PHYSIOLOGY OF DIGESTION.

BY WILLIAM BEAUMONT, M. D.

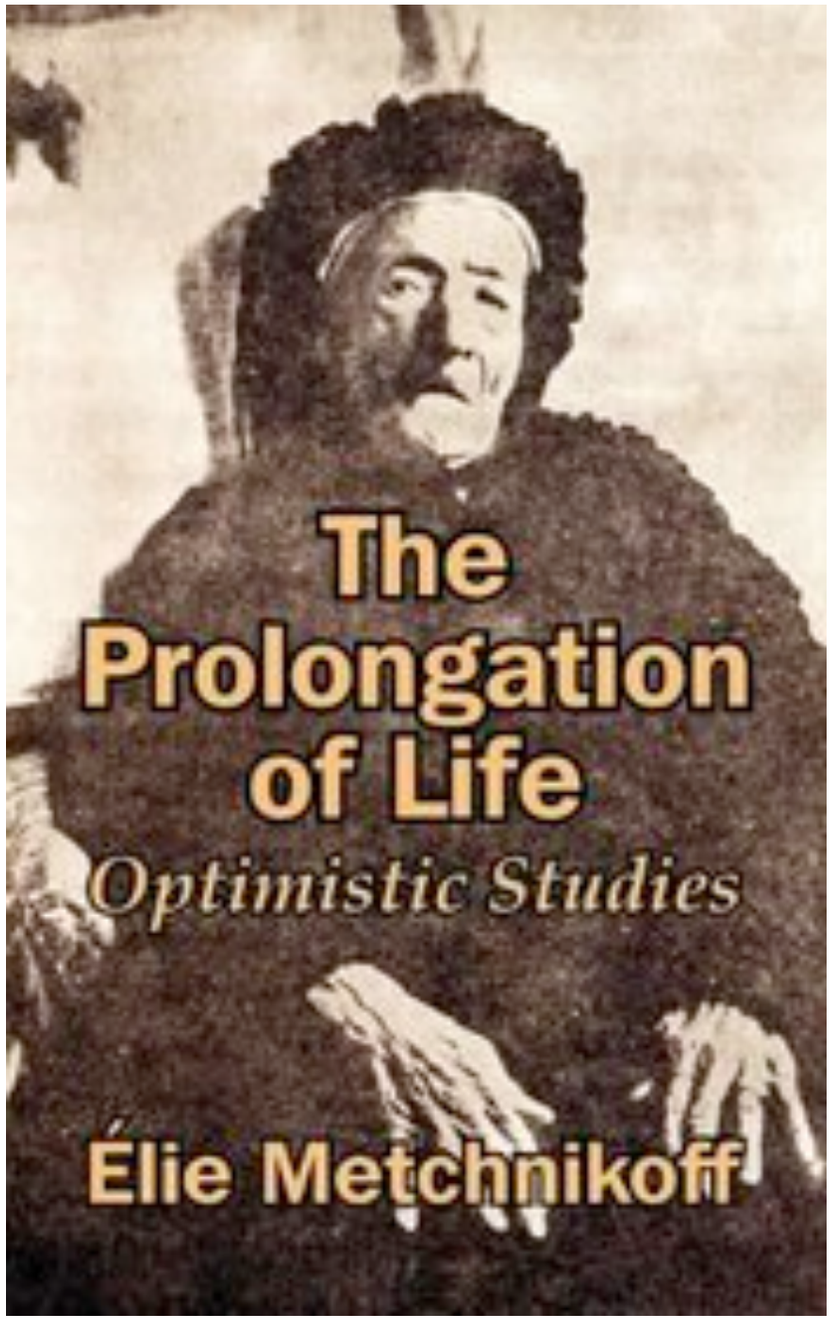
Surgeon in the U. S. Army.

FLATTSBURGH,

PRINTED BY F. P. ALLEN.

1833.

1907 - Metchnikoff



Fermented Foods to probiotics…

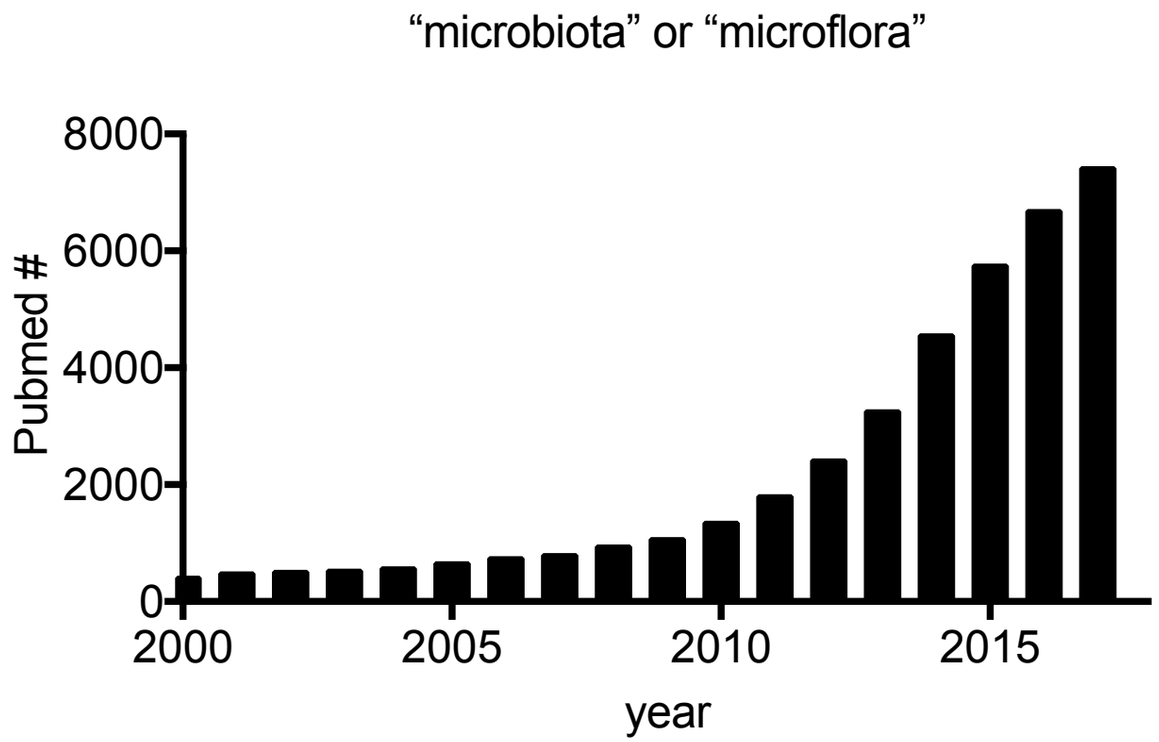
- Metchnikoff inspired Minoru Shirota to investigate the connection between bacteria and good GI health
- Shirota is the inventor of Yakult - the yogurt-like probiotic drink containing *Lactobacillus casei* strain Shirota - 1930

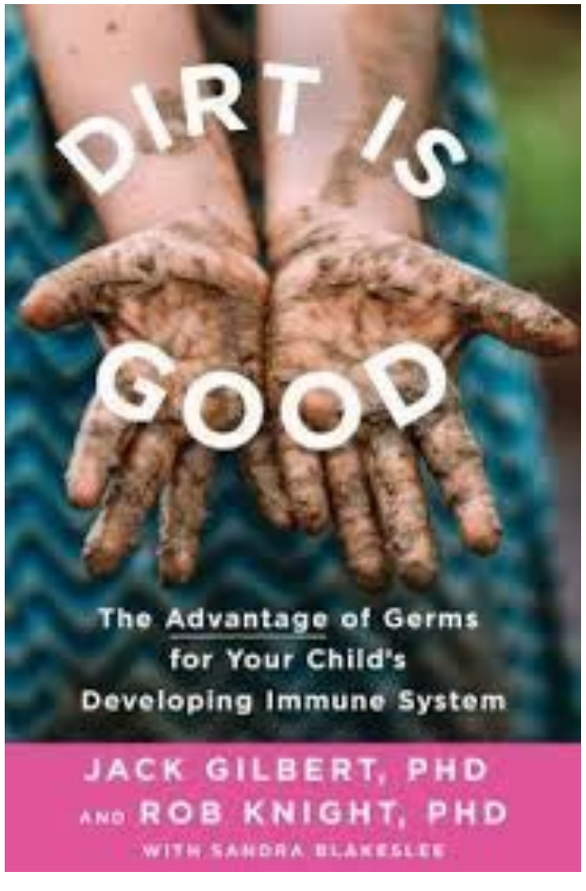
Probiotics are “live micro-organisms that when administered in adequate amounts, confer a health benefit on the host”

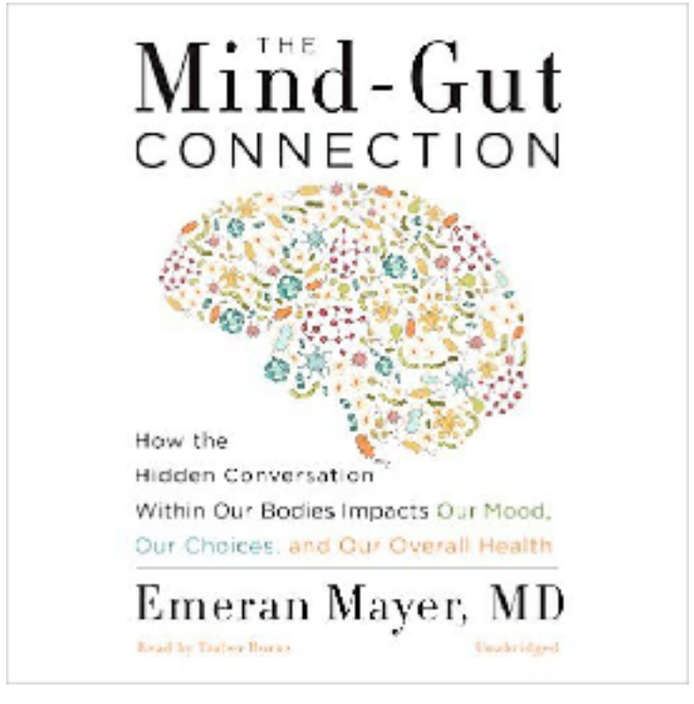
World Health Organization (WHO), Food and Agricultural Organization (FAO) 2015

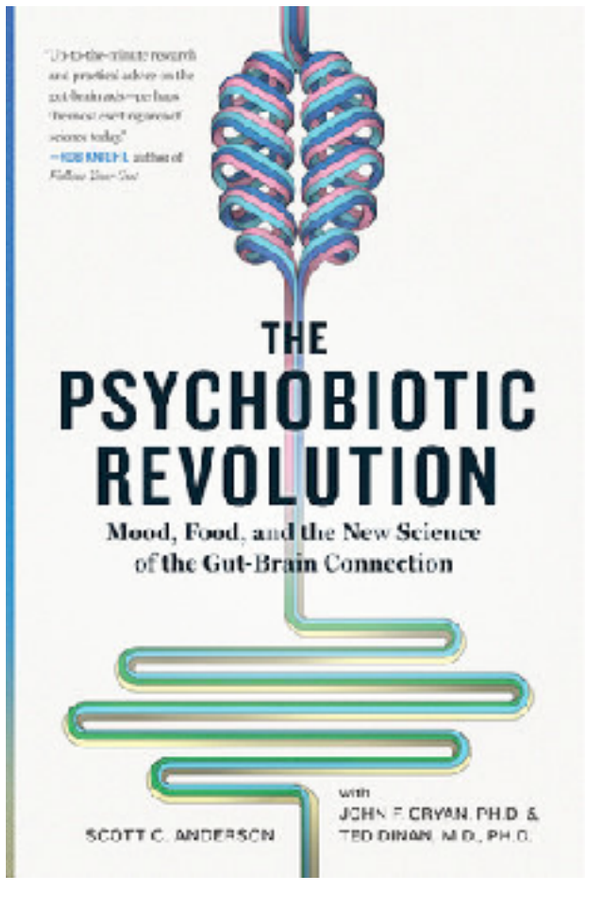
🔥HOT TOPIC🔥

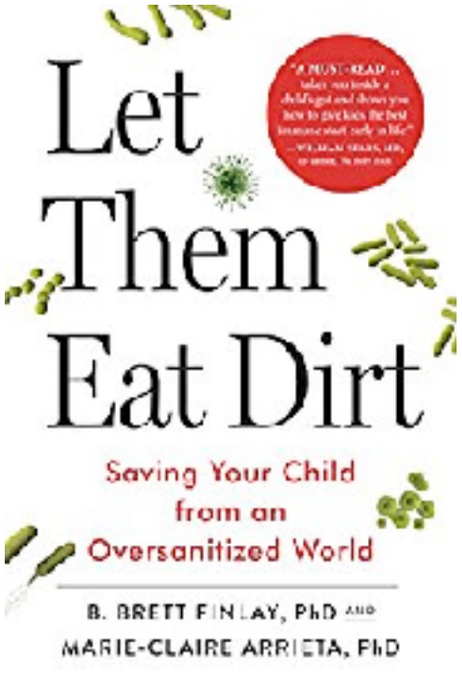
Microbiome in health and disease











Biological Psychiatry

Commentary

Targeting the Microbiome for Mental Health: Hype or Hope?

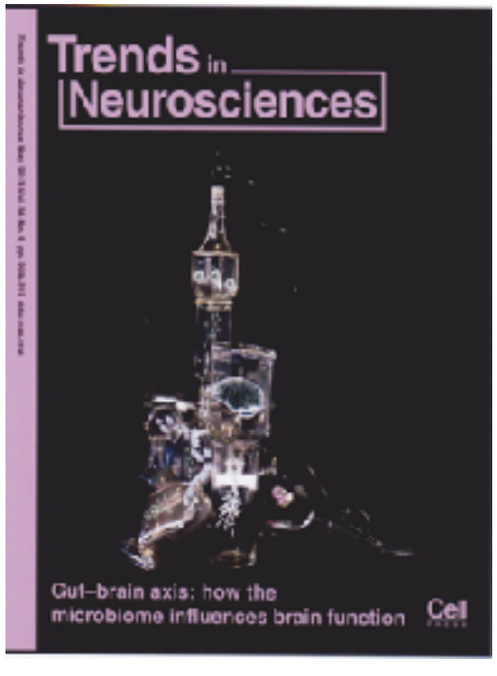
Jane A. Foster

Key Questions for Today :

- What do we know about the microbiome?
- How do microbes communicate with the brain?
- What is the evidence that microbes influence mood?
- What are the opportunities for therapeutic development and precision medicine approaches?

Biological Psychiatry October 1, 2017; 82:456–457 www.sobp.org/journal

Microbes - microbiome - microbiota



- All of the surfaces of your body are covered with microbes
- Microbes include bacteria, viruses, fungi, protozoa, and parasites
- “Microbiome" refers to all of the microbes and their related genetic material
- “Microbiota” refers to the microbes themselves
- Much of the research focused on gut microbiota - also referred to as commensal bacteria

What do we know about gut microbiota?

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

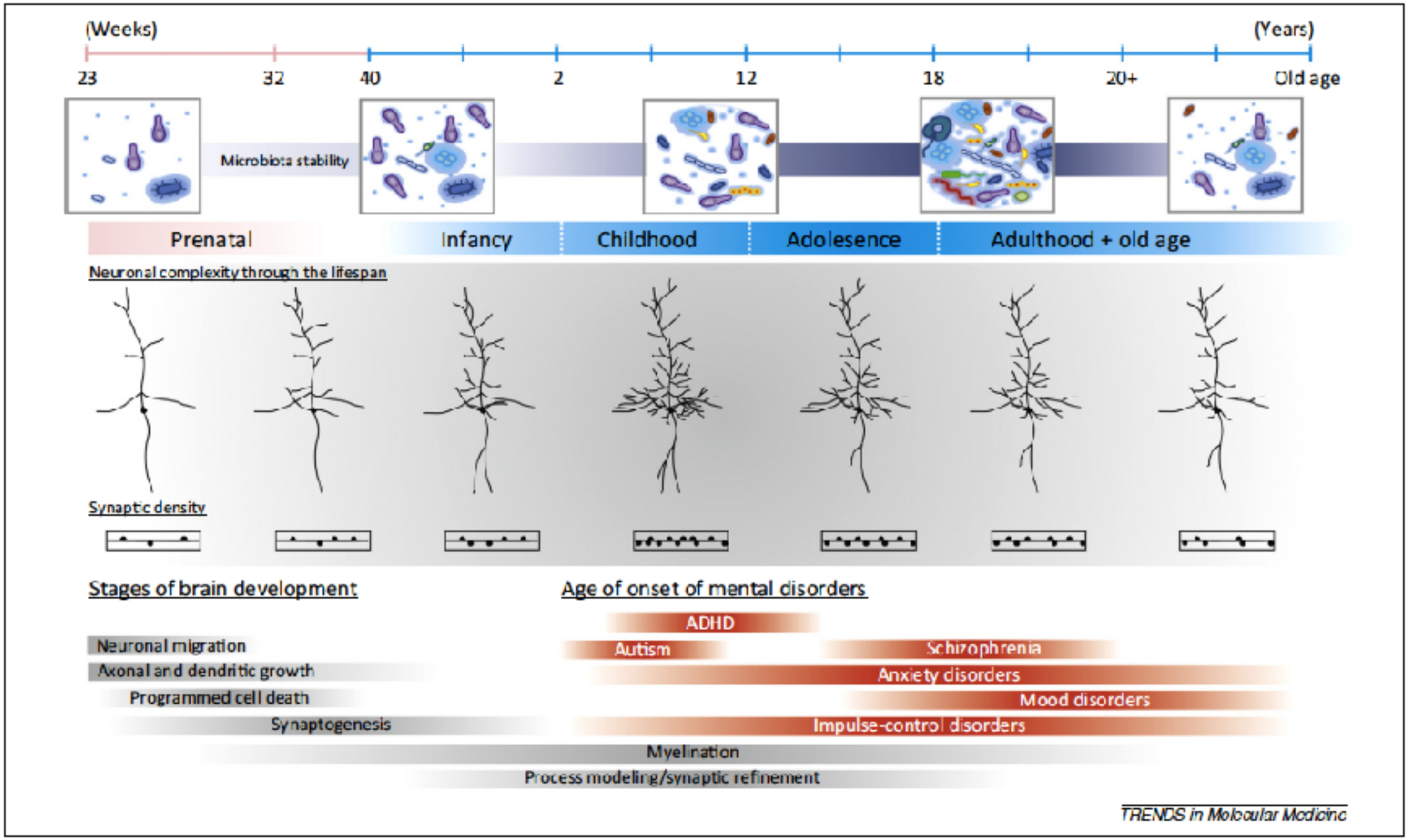
- Exposure to microbes and colonization occurs primarily at birth and continues through development

- Microbiota are essential to pathogen defence, nutrient uptake, and metabolism

- Microbiota are essential to the development and function of the immune system

- Recent evidence shows that microbiota-brain communication is important to healthy brain 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)



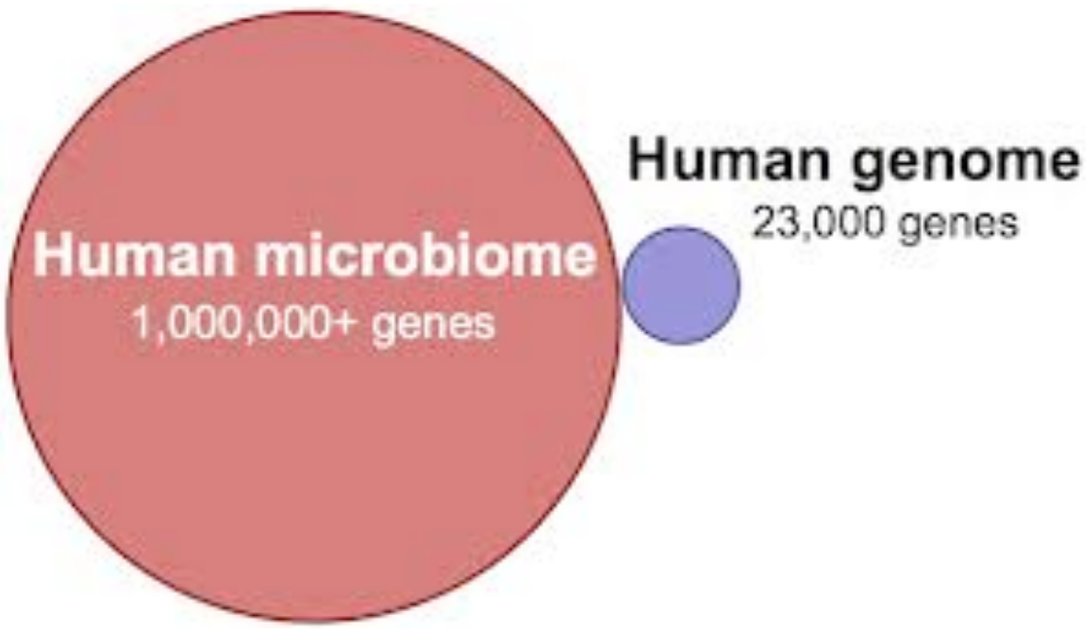
Borre et al 2014

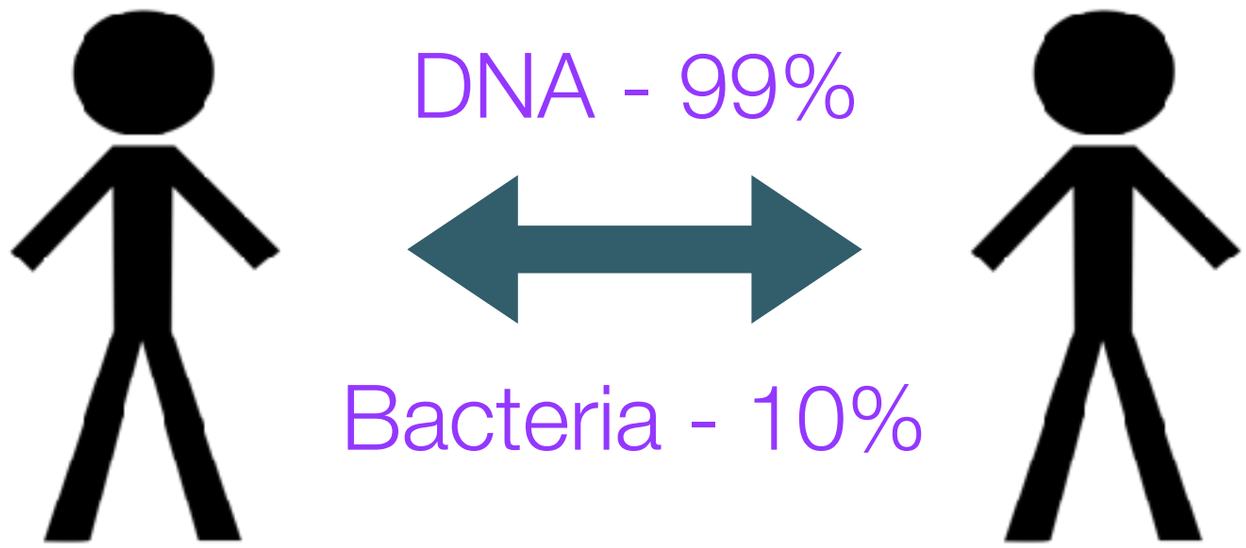
Leading Edge
Commentary

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,*]

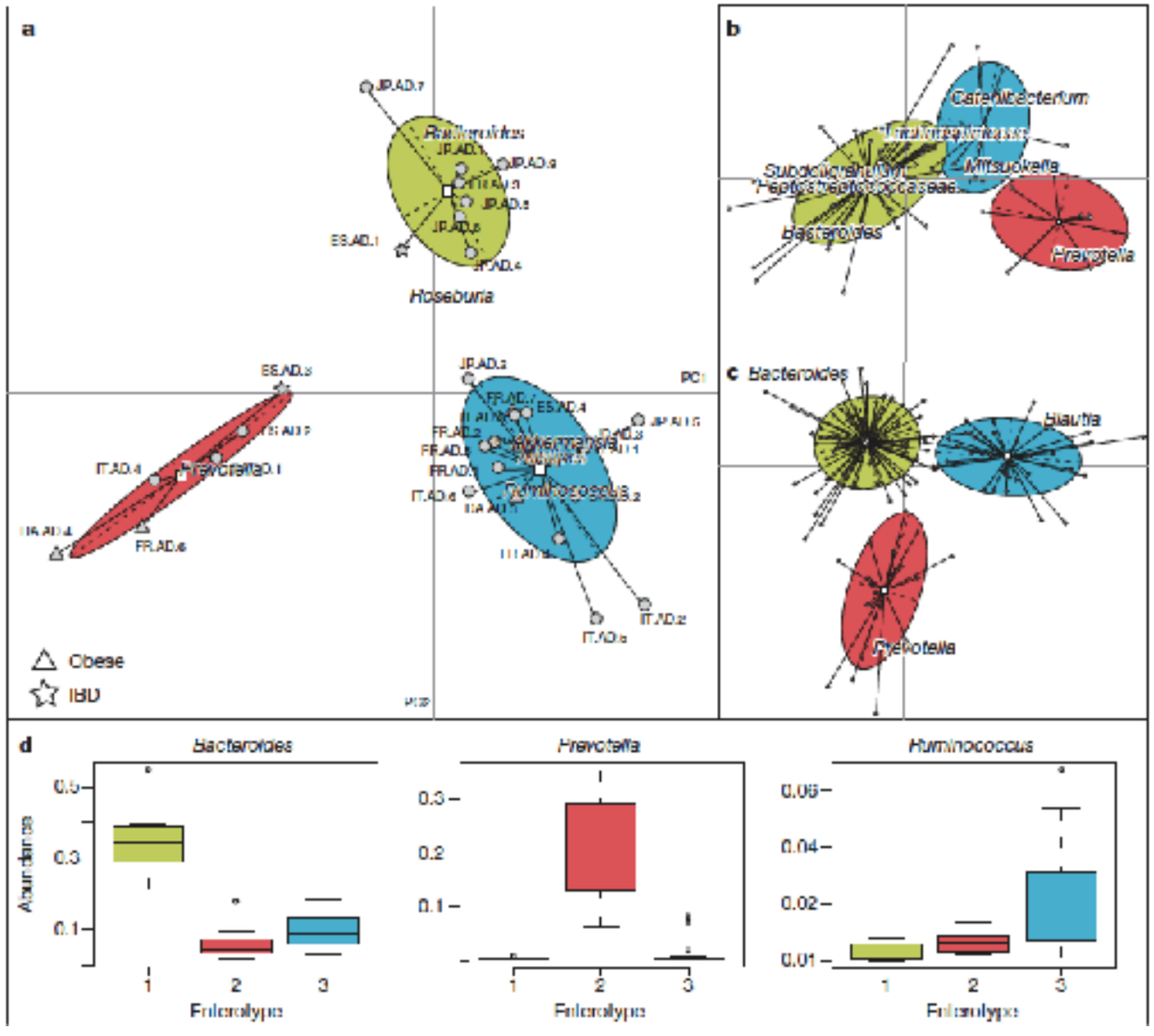




in healthy adults…

Enterotypes of the human gut microbiome

Manimozhiyan Arumugam[1]*, Jeroen Raes[1,2]*, Eric Pelletier[3,4,5], Denis Le Paslier[3,4,5], Takuji Yamada[1], Daniel R. Mende[1], Gabriel R. Fernandes[1,6], Julien Tap[1,7], Thomas Bruls[3,4,5], Jean Michel Batto[7], Marcelo Bertalan[8], Natalia Borruel[9], Francesc Casellas[9], Leyden Fernandez[10], Laurent Gautier[8], Torben Hansen[11,12], Masahira Hattori[13], Tetsuya Hayashi[14], Michiel Kleerebezem[15], Ken Kurokawa[16], Marion Leclerc[7], Florence Levenez[7], Chaysavanh Manichanh[9], H. Bjørn Nielsen[8], Trine Nielsen[11], Nicolas Pons[7], Julie Poulain[3], Junjie Qin[17], Thomas Sicheritz-Ponten[8,18], Sebastian Tims[15], David Torrents[10,19], Edgardo Ugarte[3], Erwin G. Zoetendal[15], Jun Wang[17,20], Francisco Guarner[9], Oluf Pedersen[11,21,22,23], Willem M. de Vos[15,24], Søren Brunak[8], Joel Doré[7], MetaHIT Consortium†, Jean Weissenbach[3,4,5], S. Dusko Ehrlich[7] & Peer Bork[1,25]



Key points to consider

- Inter-individual differences in healthy human gut microbiota can be reduced by clustering individuals into subgroups, referred to as enterotypes, based on enrichment of specific taxa at the genus level

- Several tools available to examine the microbiome (composition, function, and active gene expression)

Arumugam et al 2011 Nature 473, 174-180

Human Microbiome Project

- Human microbiome project - Phase I HMP, Phase II iHMP

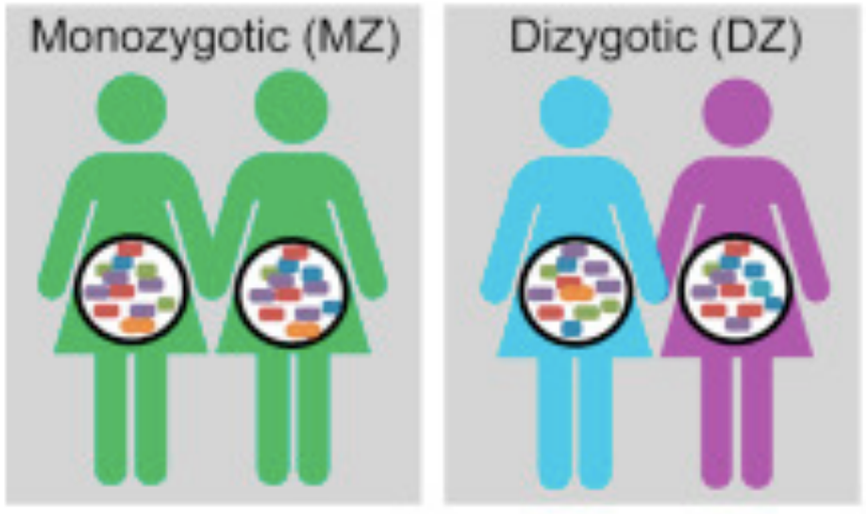
- Phase I HMP examined diversity and composition of the human microbiome in healthy individuals

- Phase 2 iHMP examines the role of the microbiome in human health and disease - longitudinal (3 y) studies on pregnancy, gut disease onset (IBD), and respiratory viral infection and onset of type 2 diabetes

- information and publications to data at https://www.hmpdacc.org/hmp/

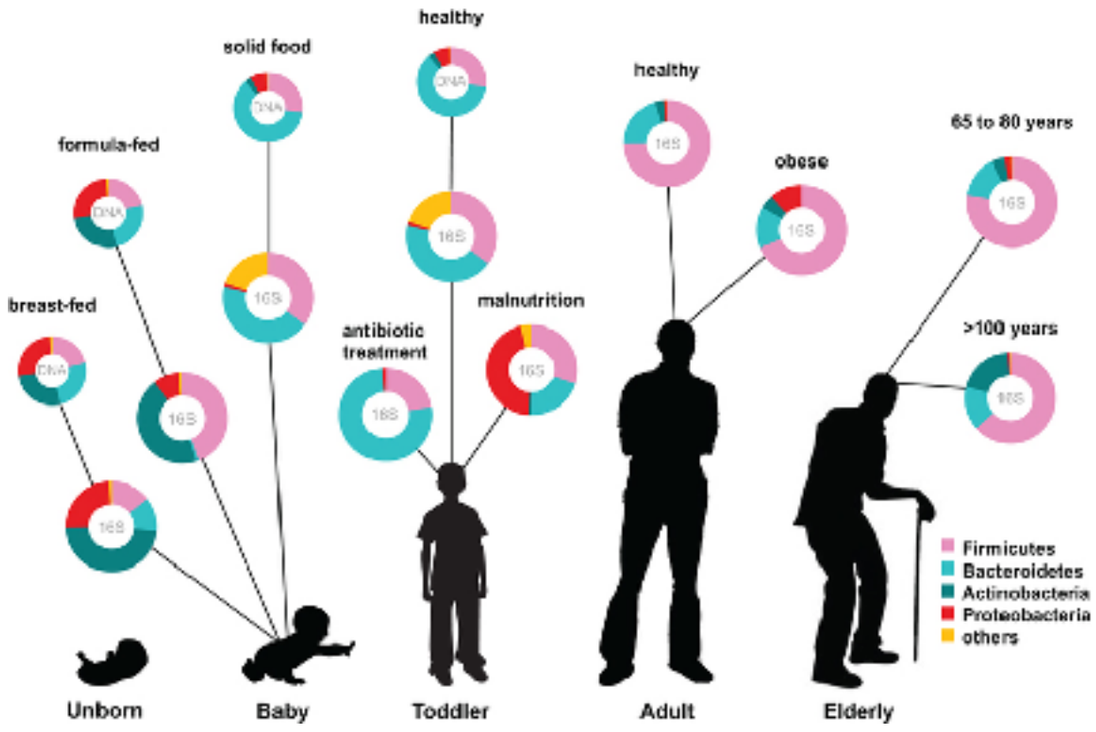
Many factors are important to gut health and the composition of gut bacteria?

Genetics **Diet** **Exercise** **Drugs** **Stress**



MZ twins have a more similar microbiota than DZ twins

Goodrich et al 2015 Cell 159, 789-799

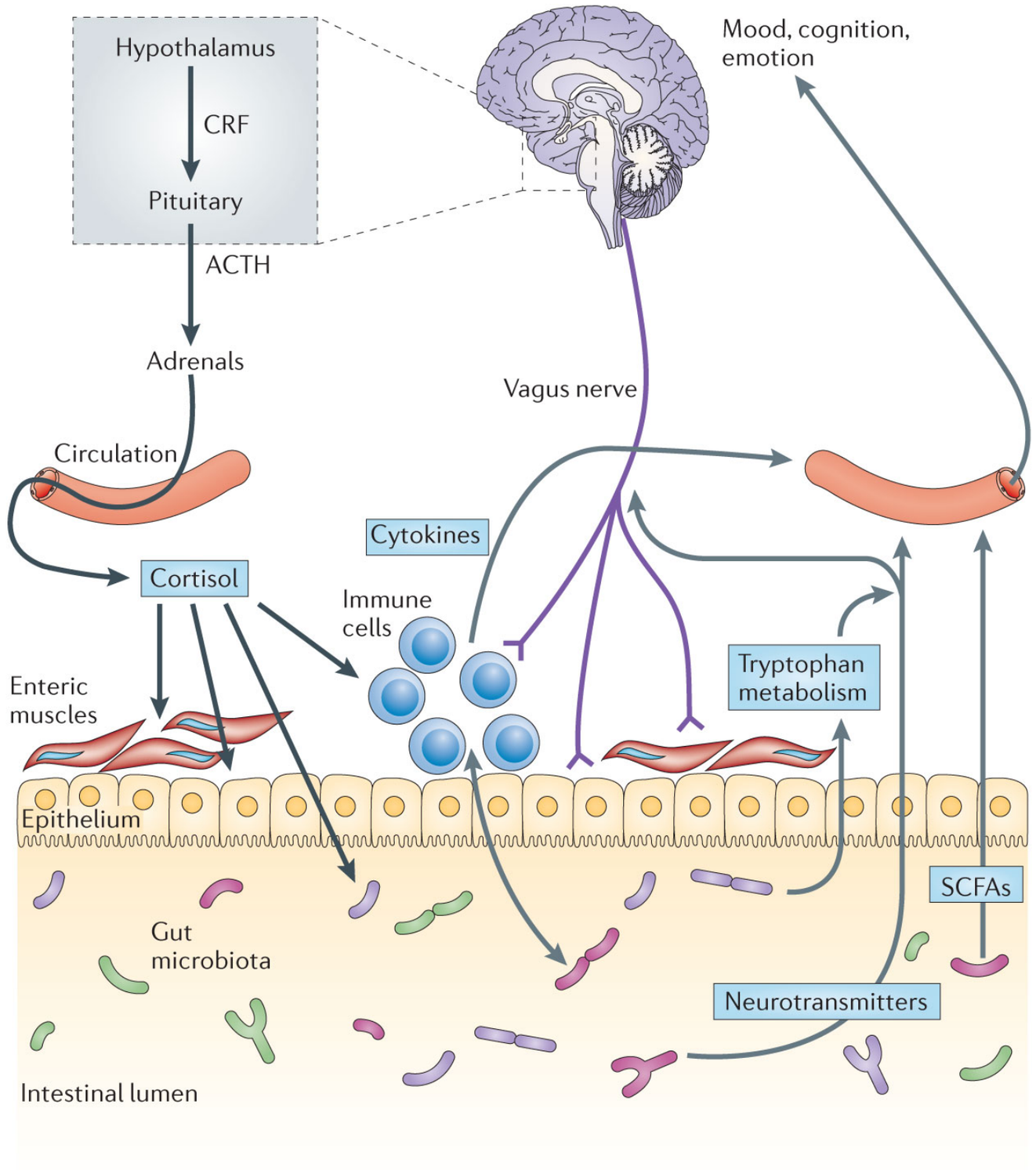


Age **Sex**

Ottman et al 2012 Front. Cell. Infect. Microbiol. 2, 1-11

How do microbiota communicate with the brain?

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



Nature Reviews | Neuroscience

Cryan and Dinan 2012 Nat Rev Neurosci 701-712

What is the benefit of looking at microbes and mental health?

- Identification of biomarkers that will help understand individual biological differences and help subgroup clinical populations to predict best treatment

- Identify individuals at risk for early intervention

- Provide novel targets for drug development

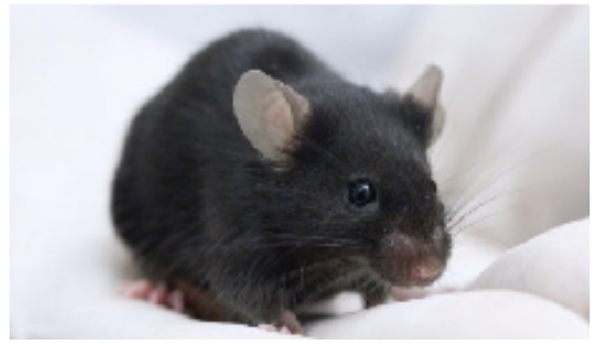
- Expansion and development of diet, prebiotic, probiotic, or other intervention strategies for psychiatric illness

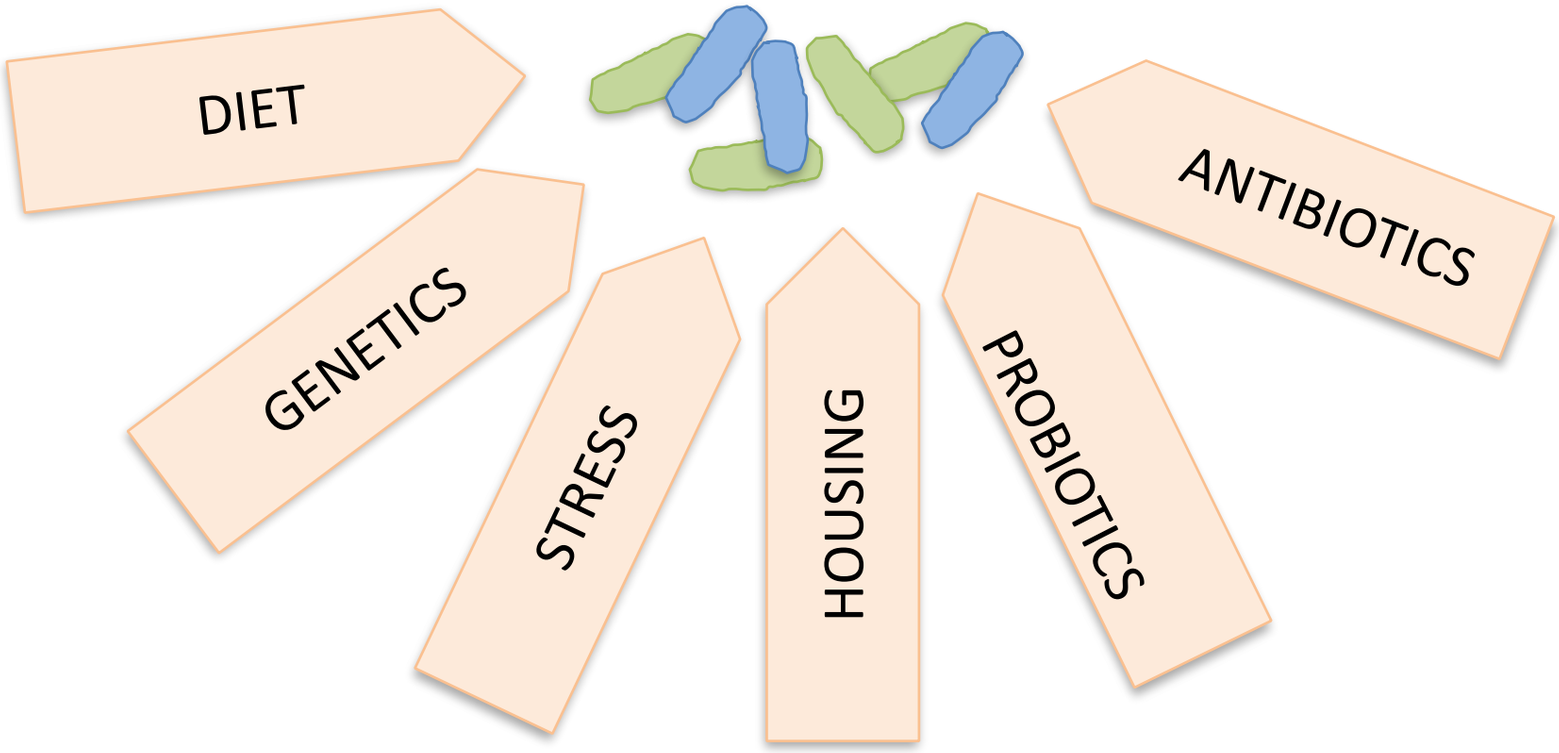
FOSTER LAB

BEHAVIOUR

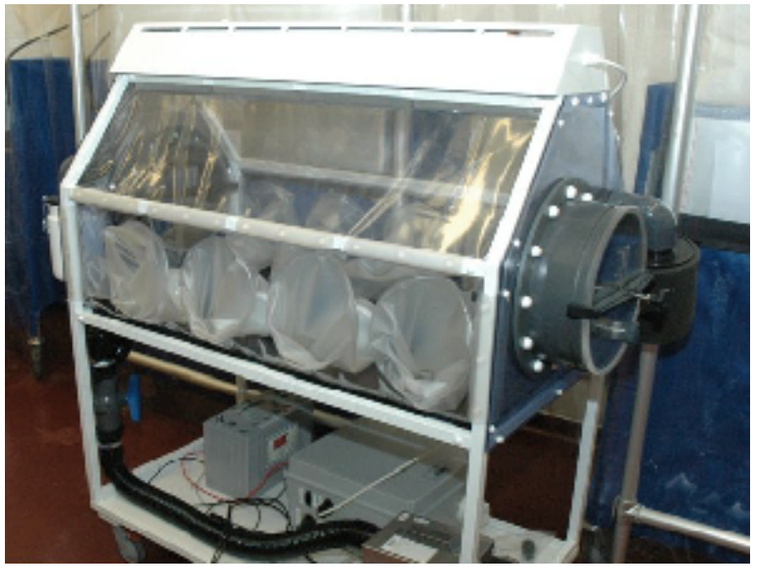
BRAIN

MICROBIOTA





The starting point…

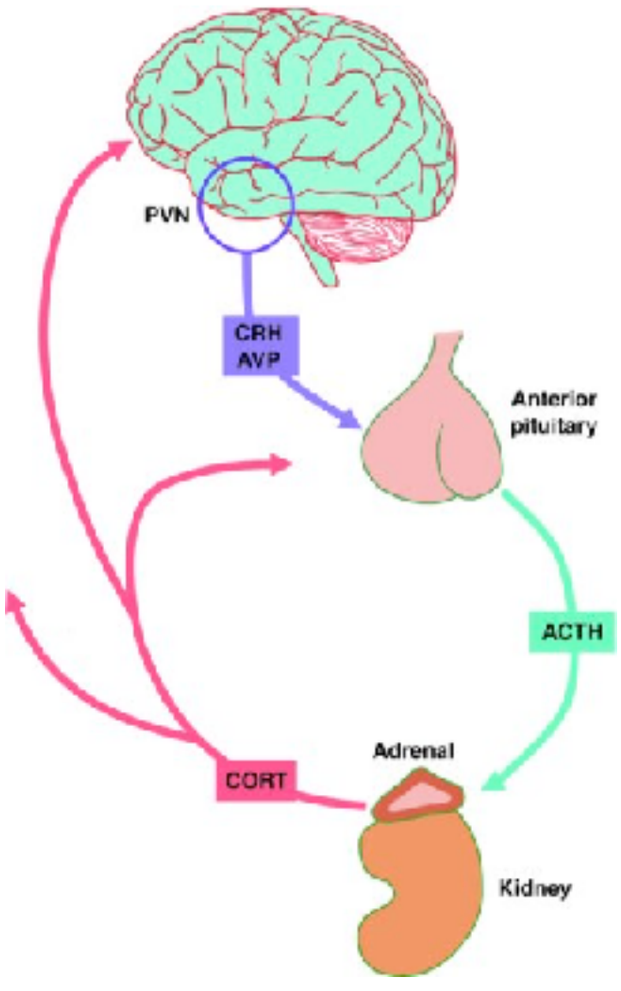


Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice

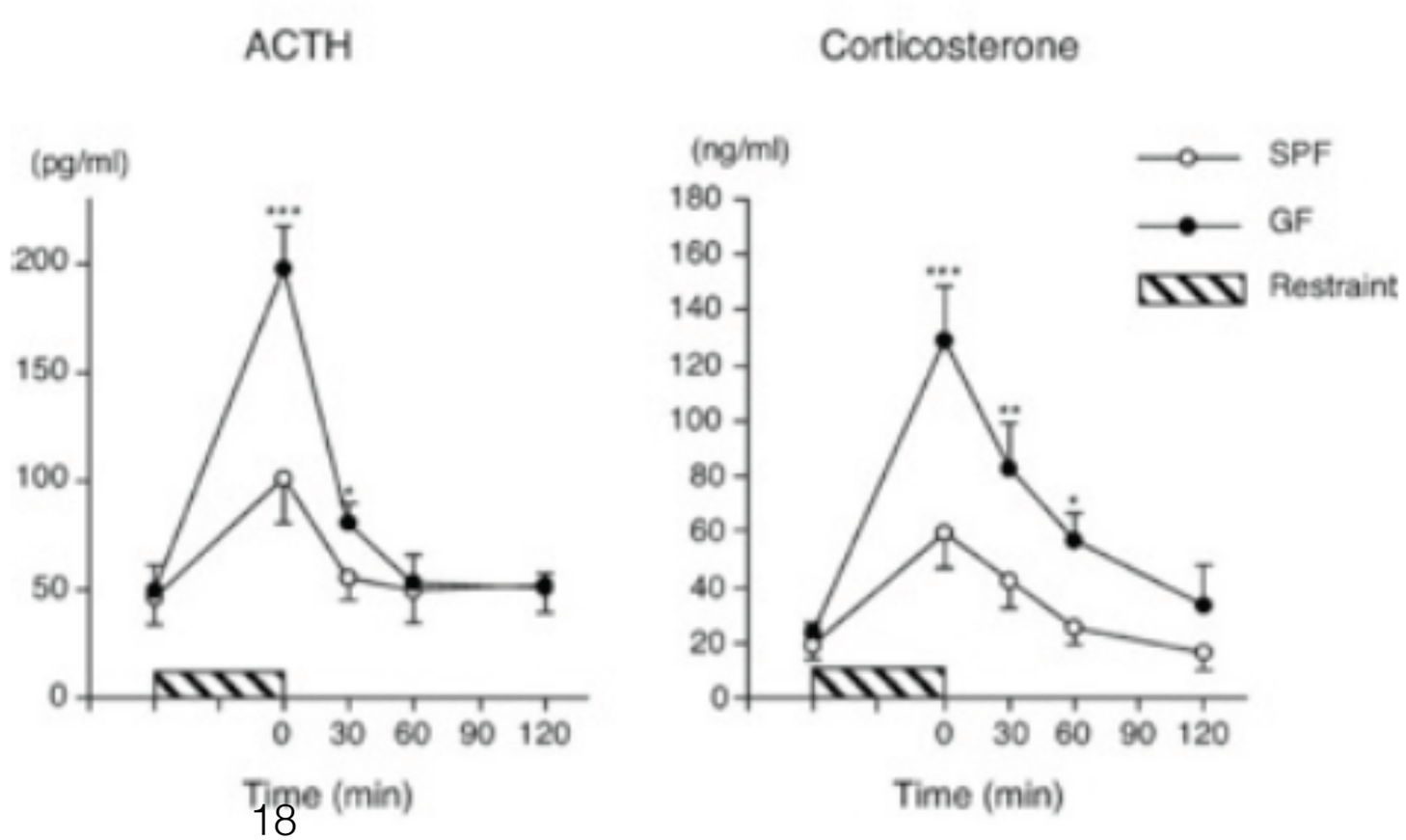
Sudo et al 2004 J Physiol 558: 263-275

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 Scienc Kyushu University, Fukuoka, Japan,* [3]*Department of Infectious Diseases, Tokai University School of Medicine, Isehara, Kanagawa, Japan and* [4]*Wakam Pharmaceutical Co. Ltd, Oji-machi, Kanagawa, Japan*



Germ-free mice showed exaggerated stress response



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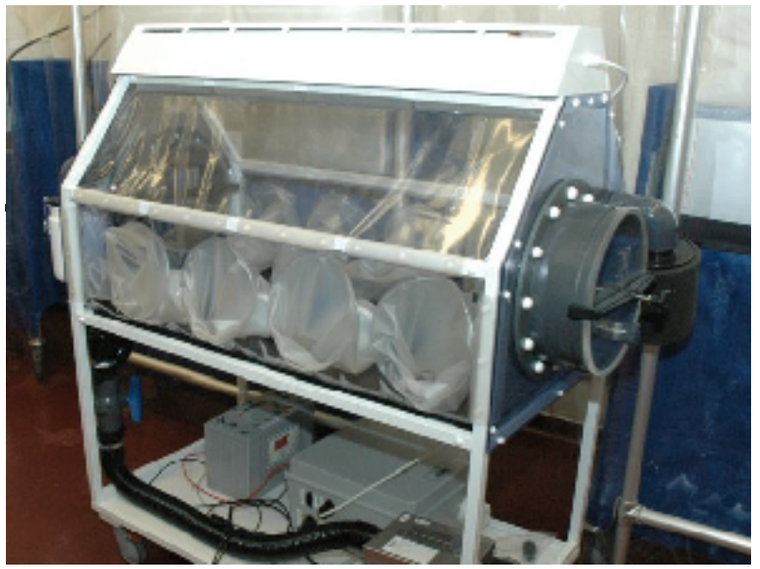
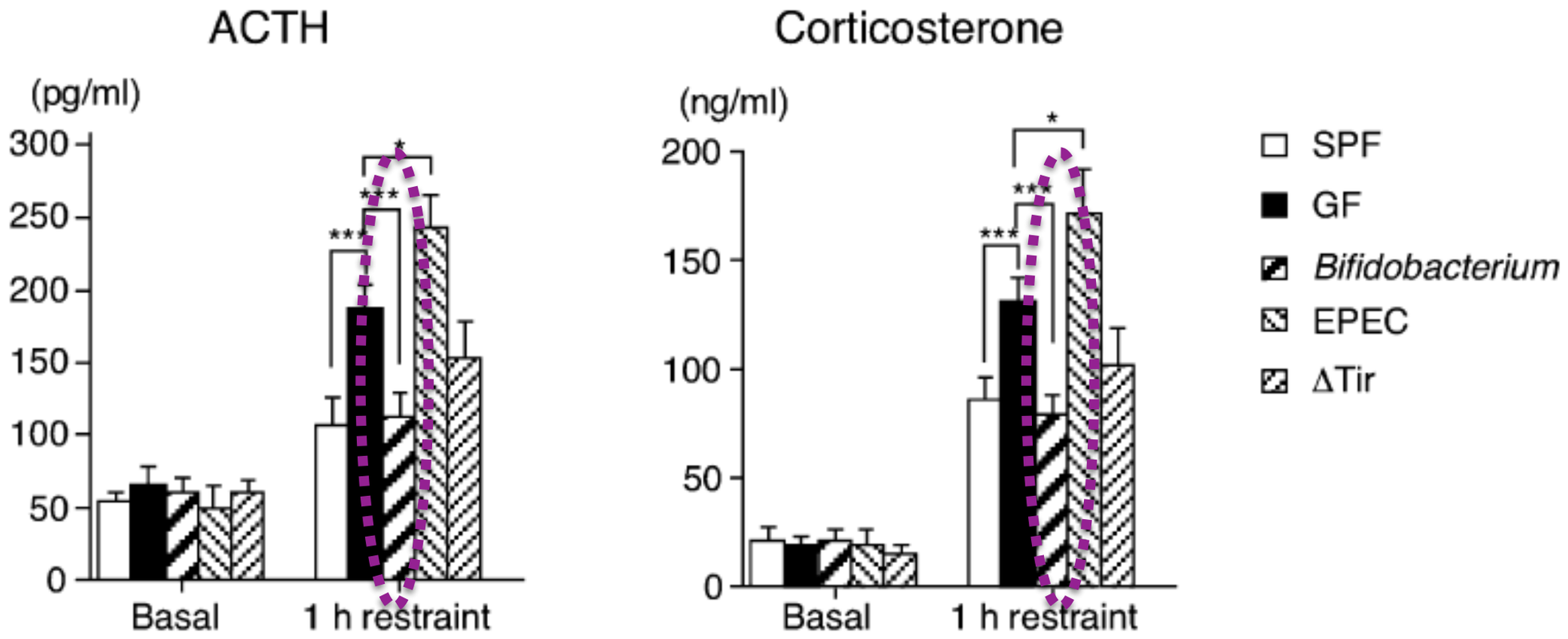
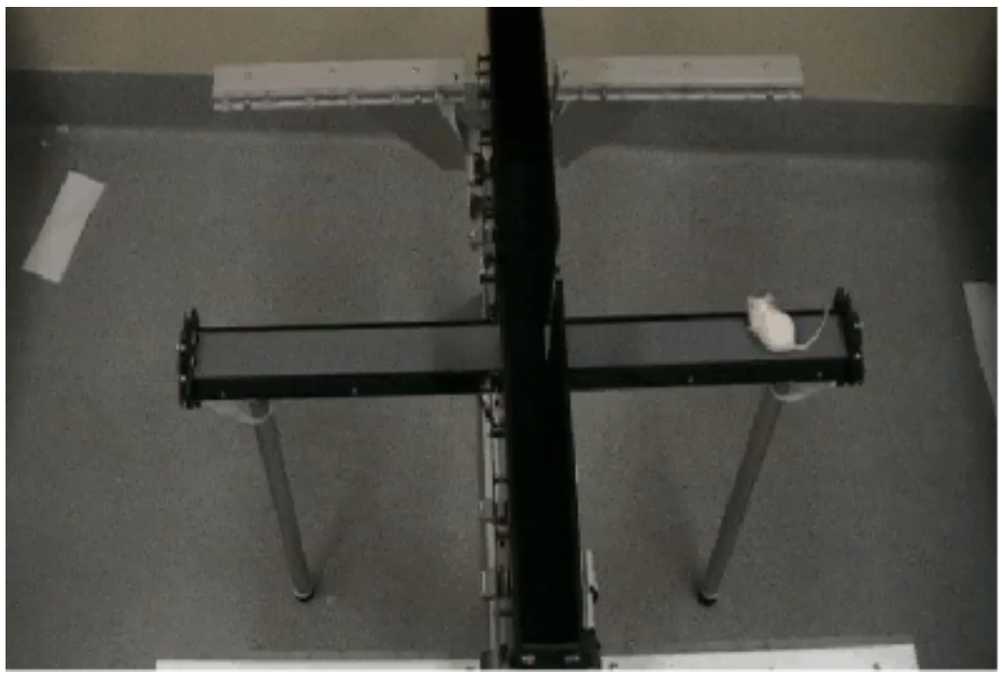


Colonization with *Bifidobacterium* normalized stress response





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]

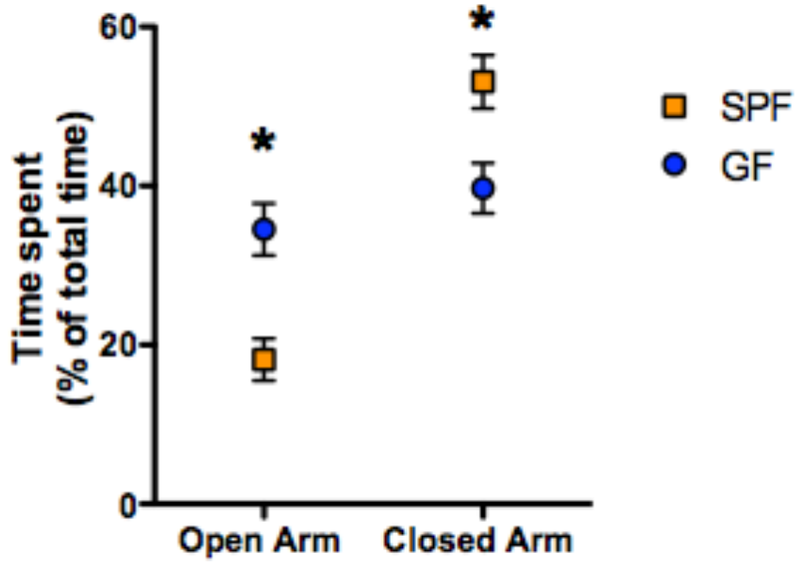
Molecular Psychiatry (2012), 1–8

www.nature.com/mp

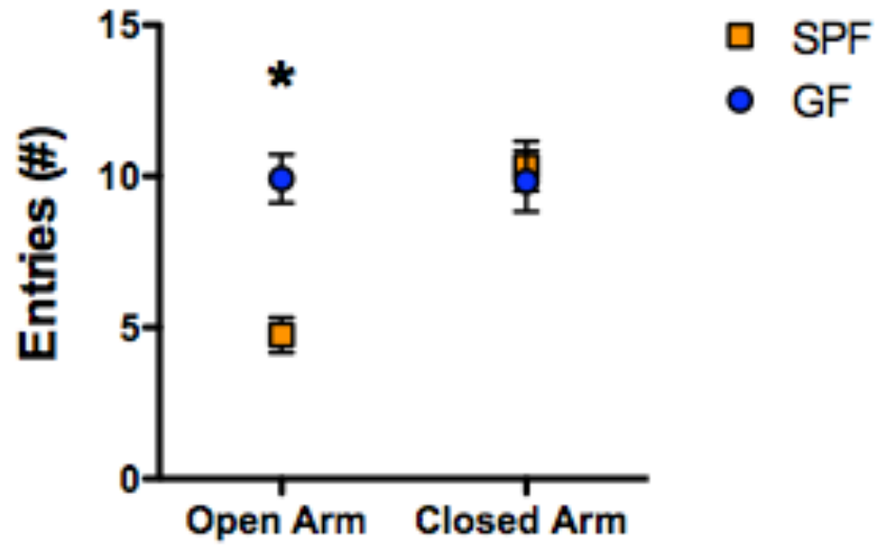
ORIGINAL ARTICLE

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]

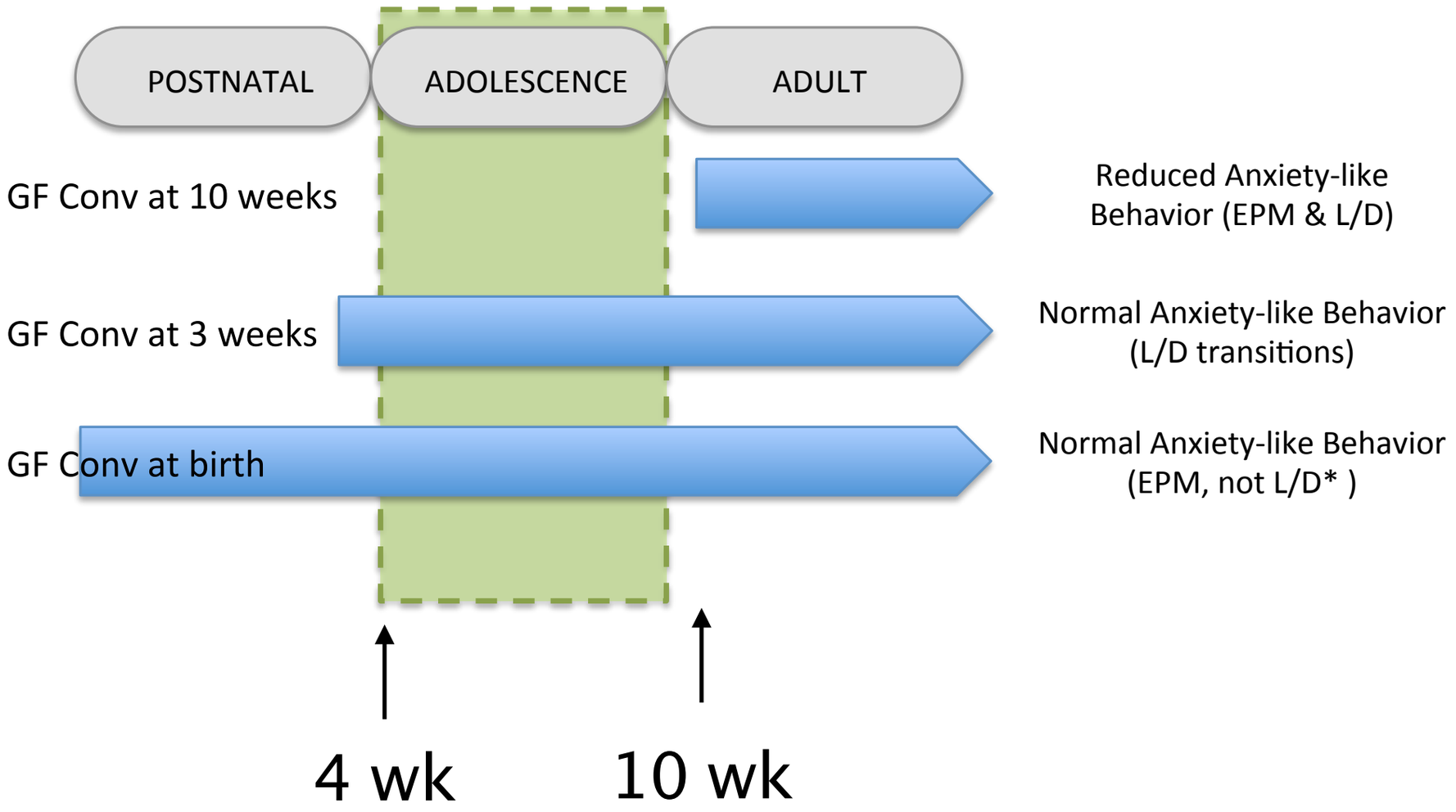


GF mice spent more time in the open arms of the EPM



GF mice showed increased open arm entries

Adolescence is a key window for microbiota-brain interactions that influence anxiety

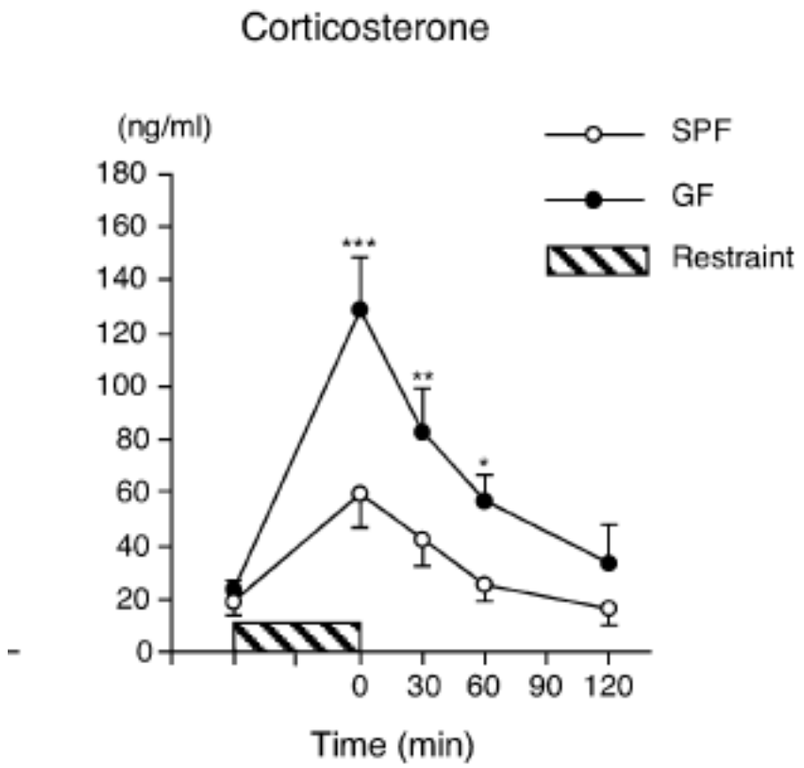


Foster & McVey Nefeld, 2013 TINS

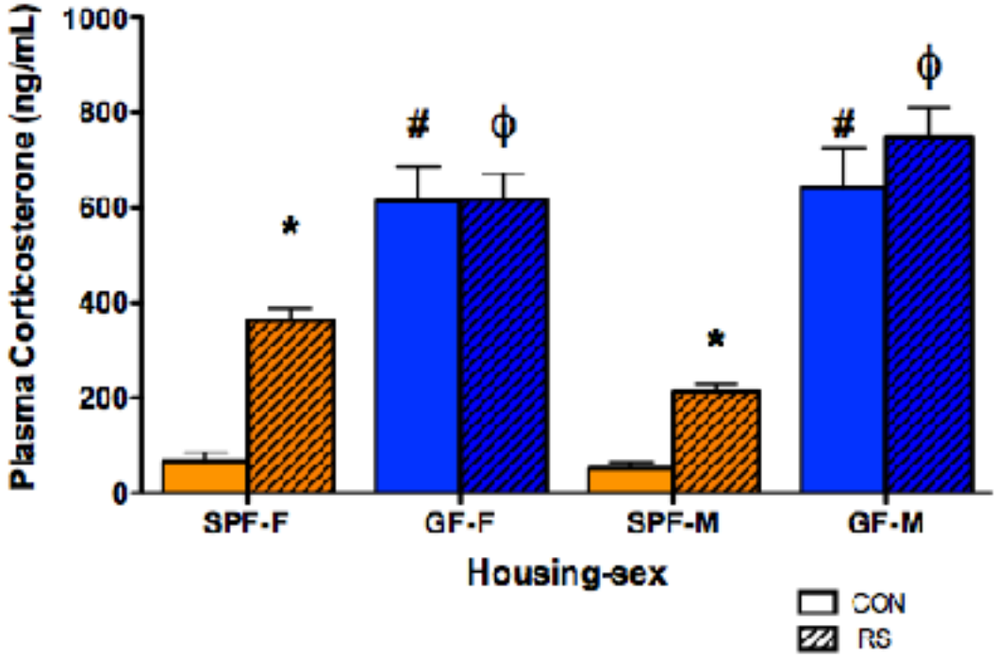
Male Balb/C Mice

↑Stress Reactivity

Sudo et al, 2004, J Phsyiol 558:263.



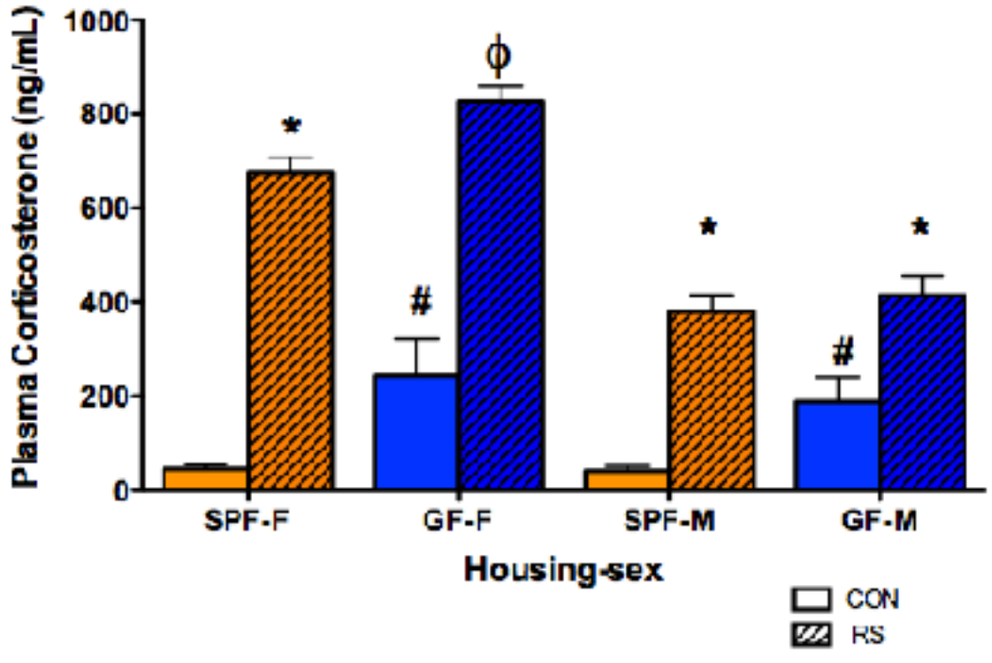
Swiss Webster Mice



significant basal increase in GF compared to SPF

*significant RS increase compared to CON

ϕ significant increase compared to SPF RS



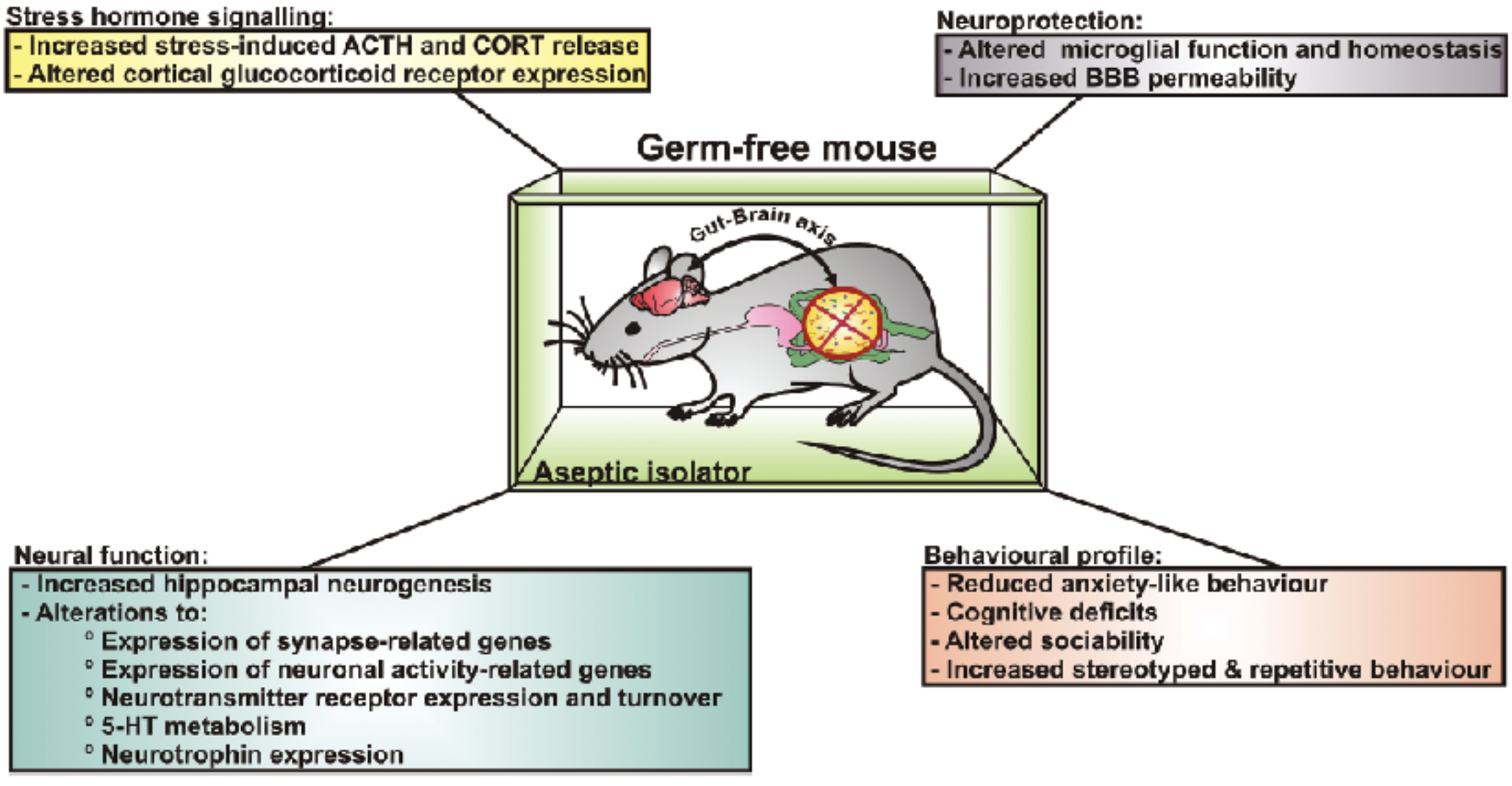
significant basal increase in GF compared to SPF

*significant RS increase compared to CON

ϕ exaggerated RS response compared to SPF-F

Lessons learned from germ free mice

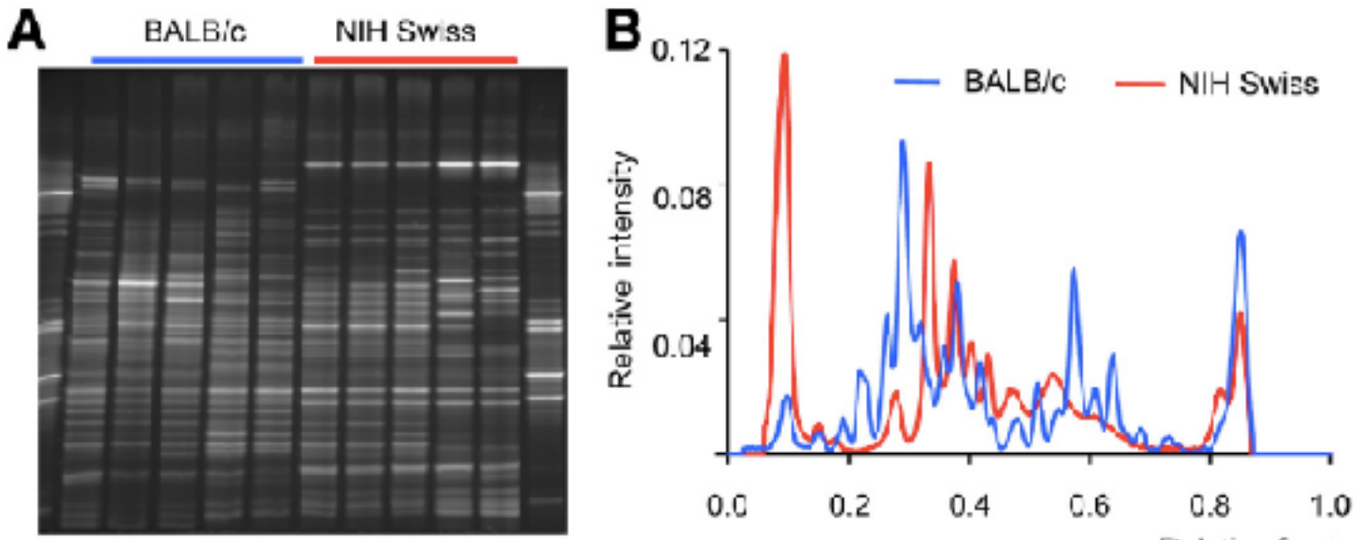
- microbiota influence behaviour, stress circuitry, stress responsively, and brain structure



Luczynski et al 2016; Int J Neuropsychopharm

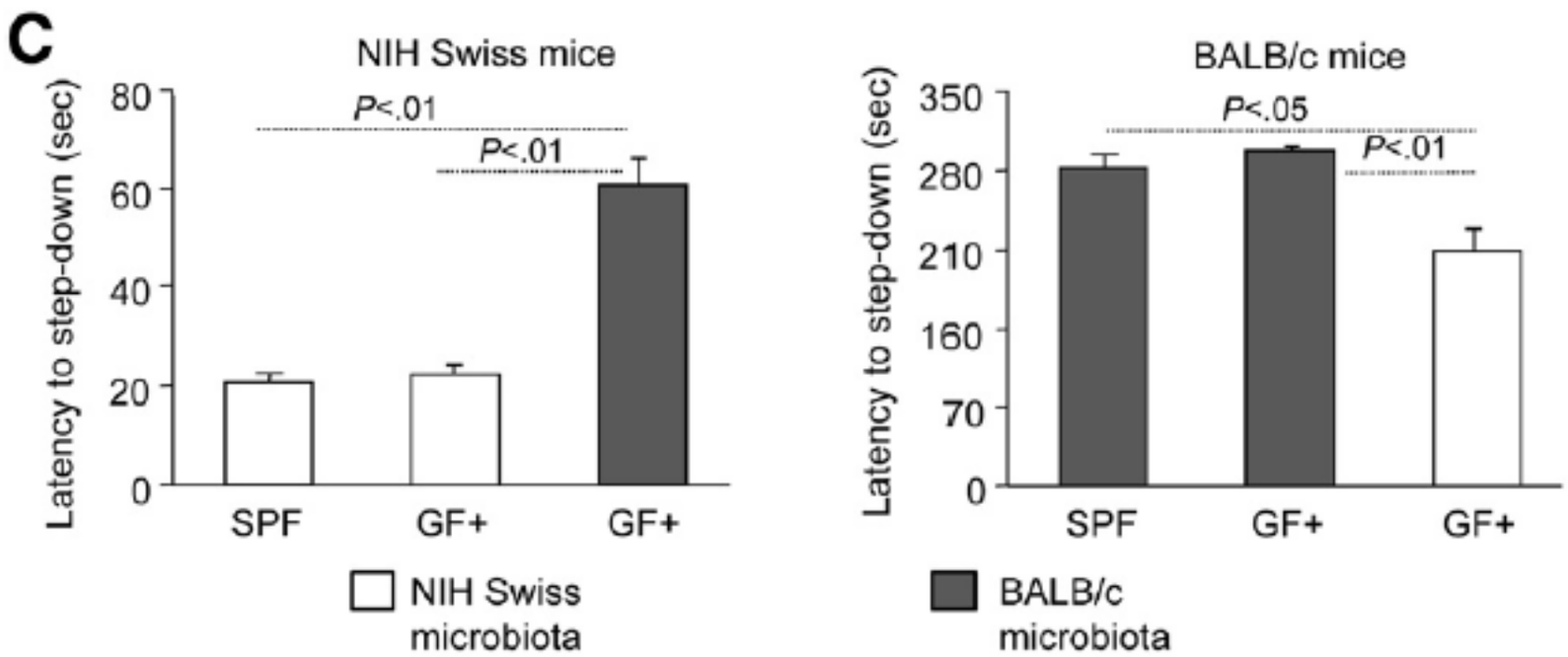
IMPORTANCE OF ENTERIC NERVOUS SYSTEM
West et al, 2016; McVey Neufeld et al, 2013

The host microbiota contributes to anxiety-like phenotype



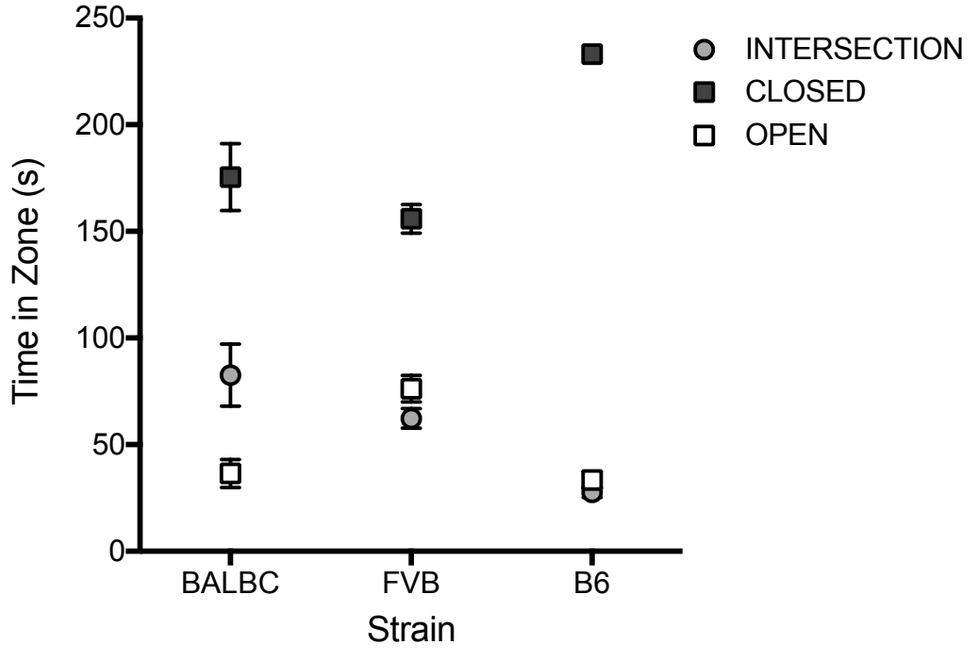
Bercik et al 2011

Relative fron:

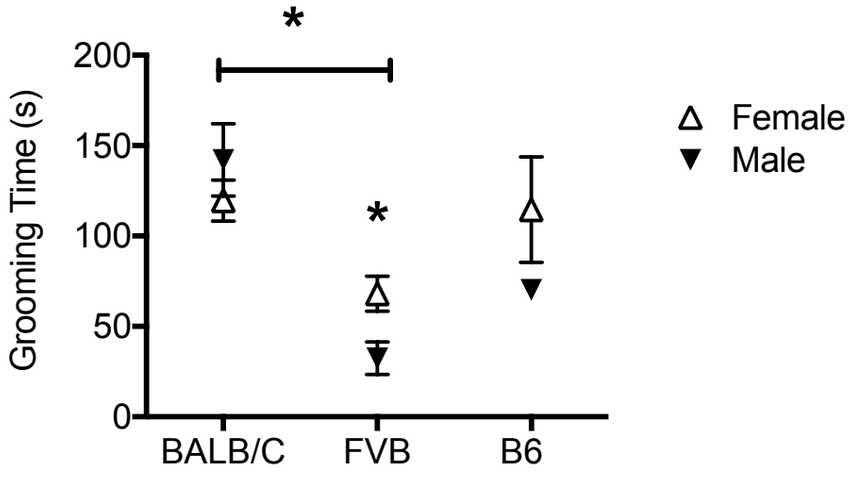


Host Genetics influences Behaviour

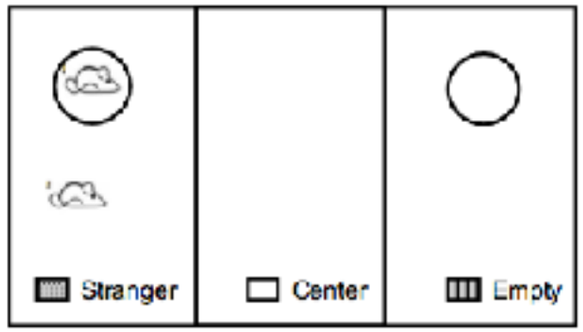
Elevated Plus Maze behaviour

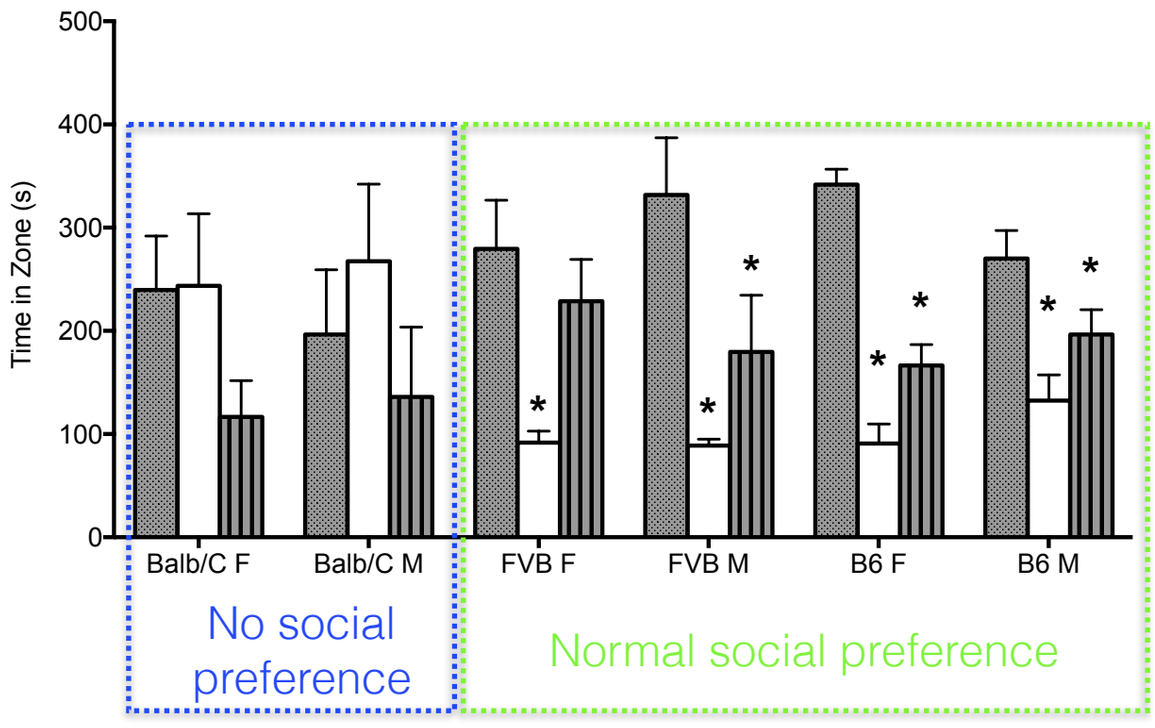


Self-grooming behaviour

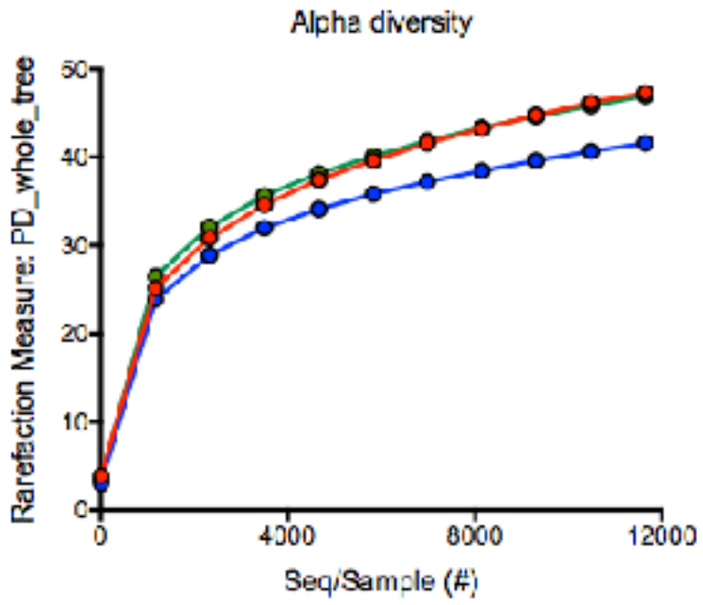


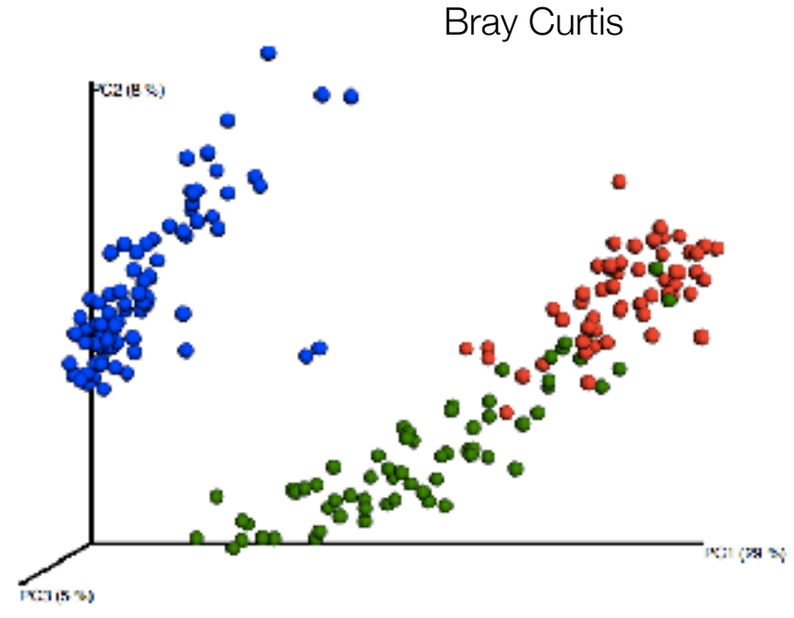
Social behaviour

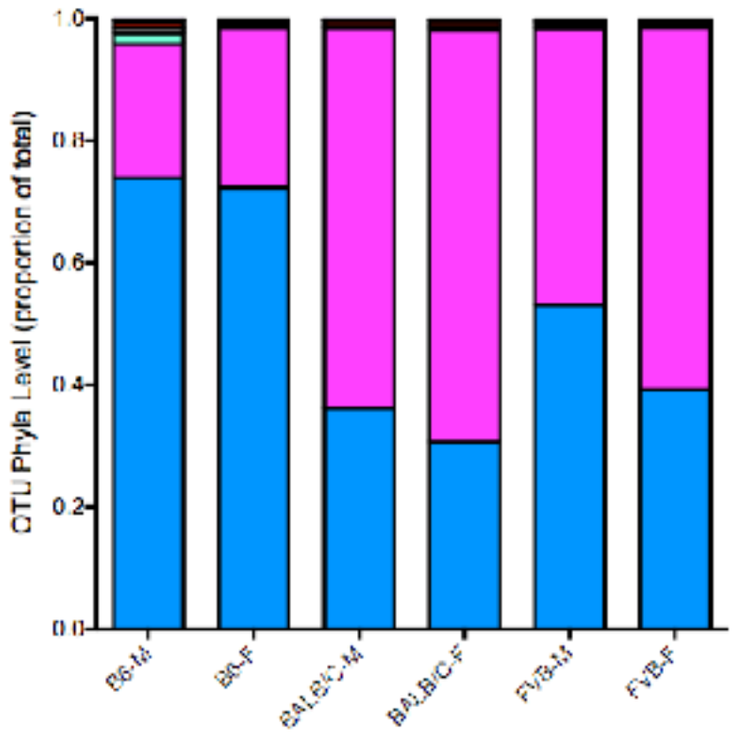


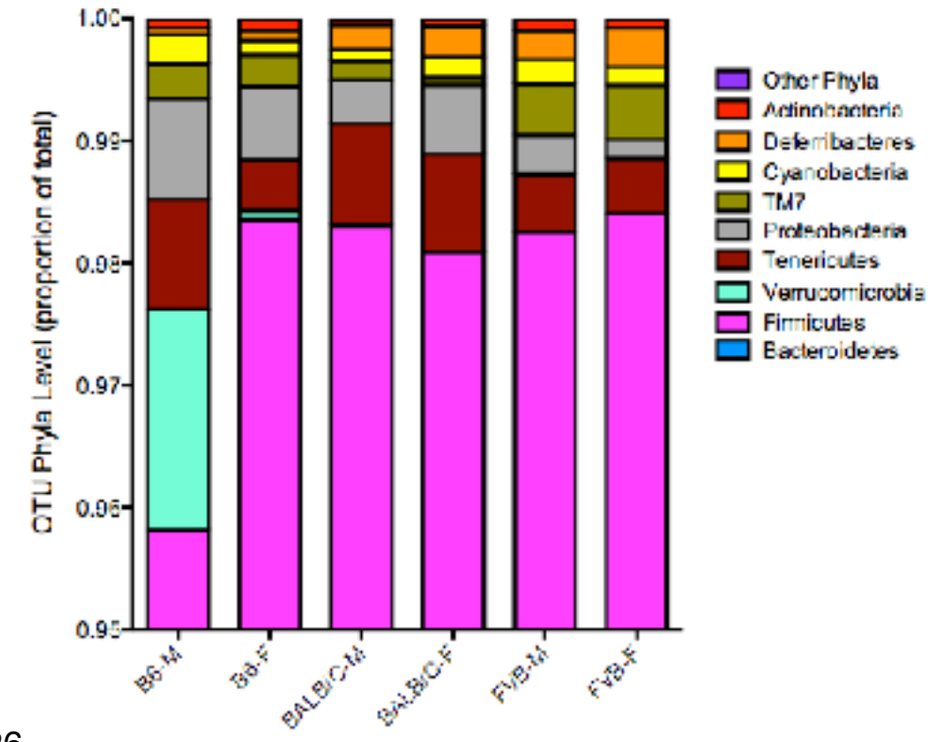


16s rRNA analysis of bacterial composition



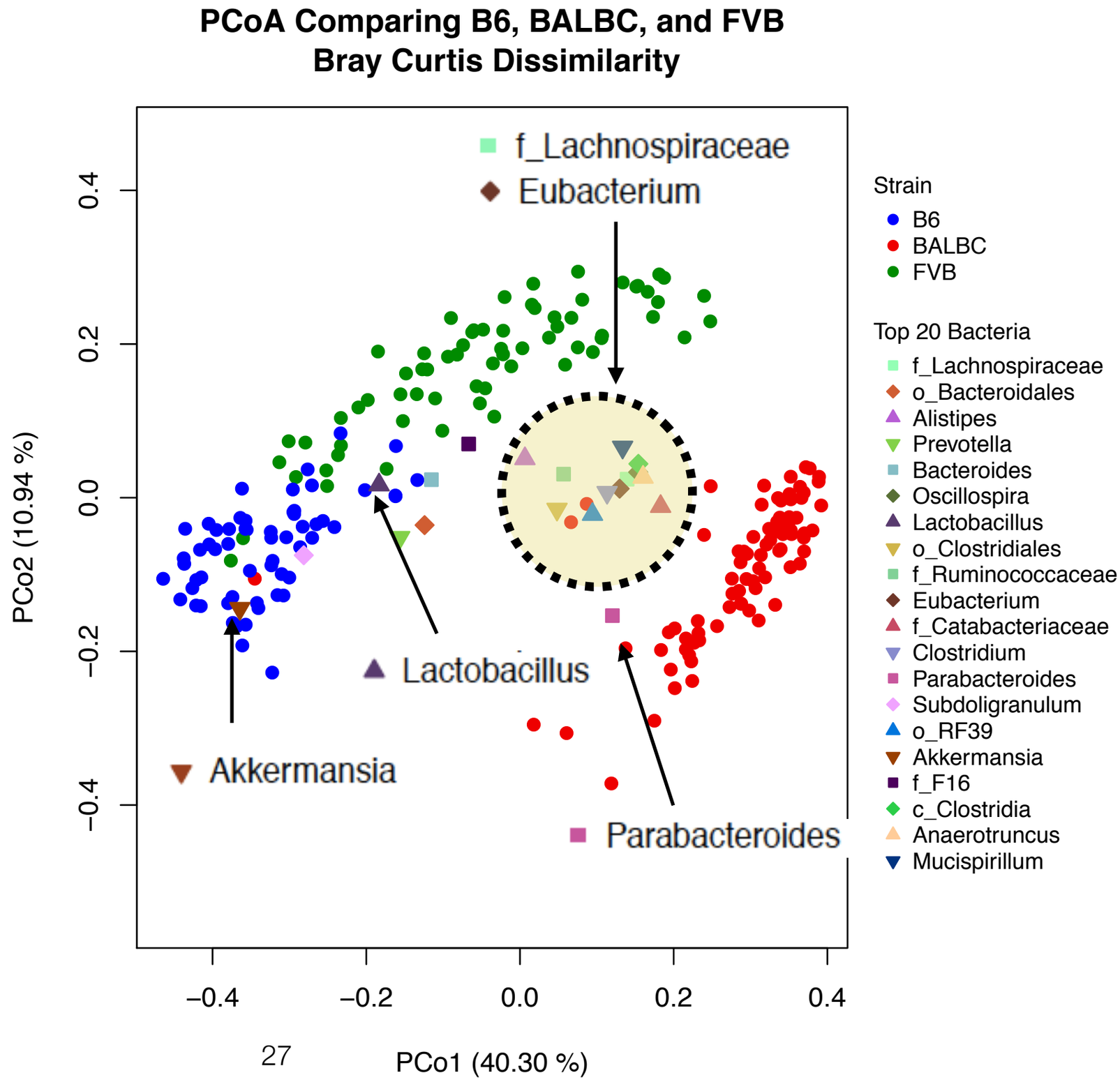




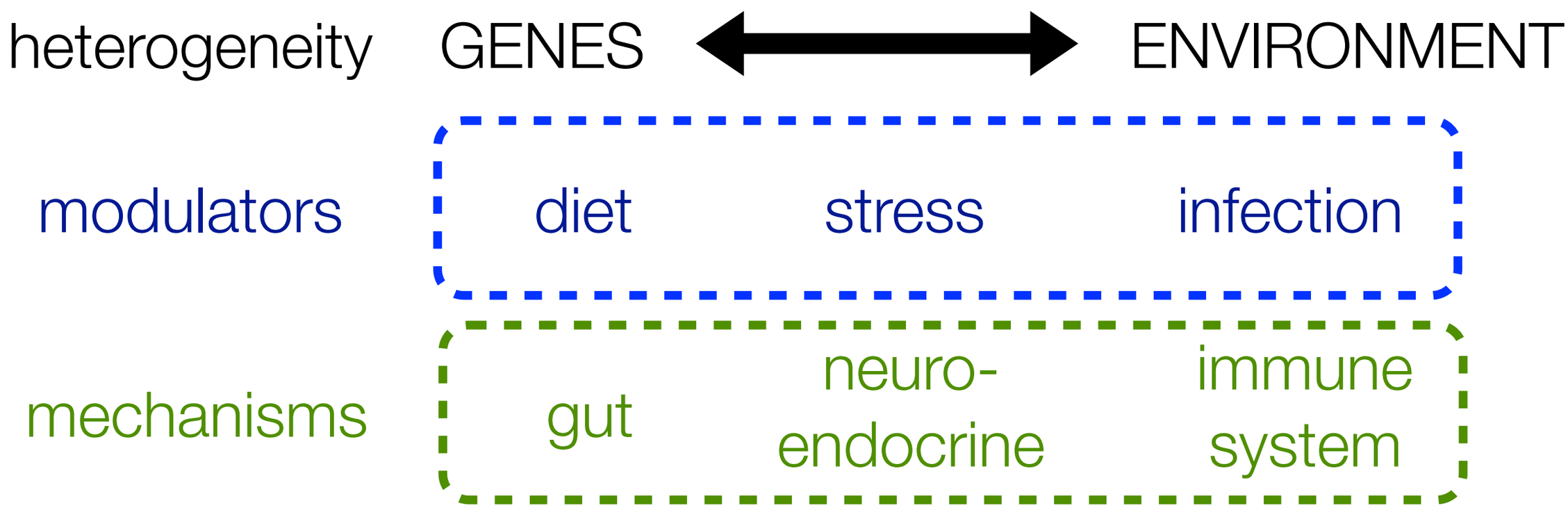


Are specific taxa associated with different strains of mice?

PCo Analysis
with
count-weighted ave
for top 20 taxa



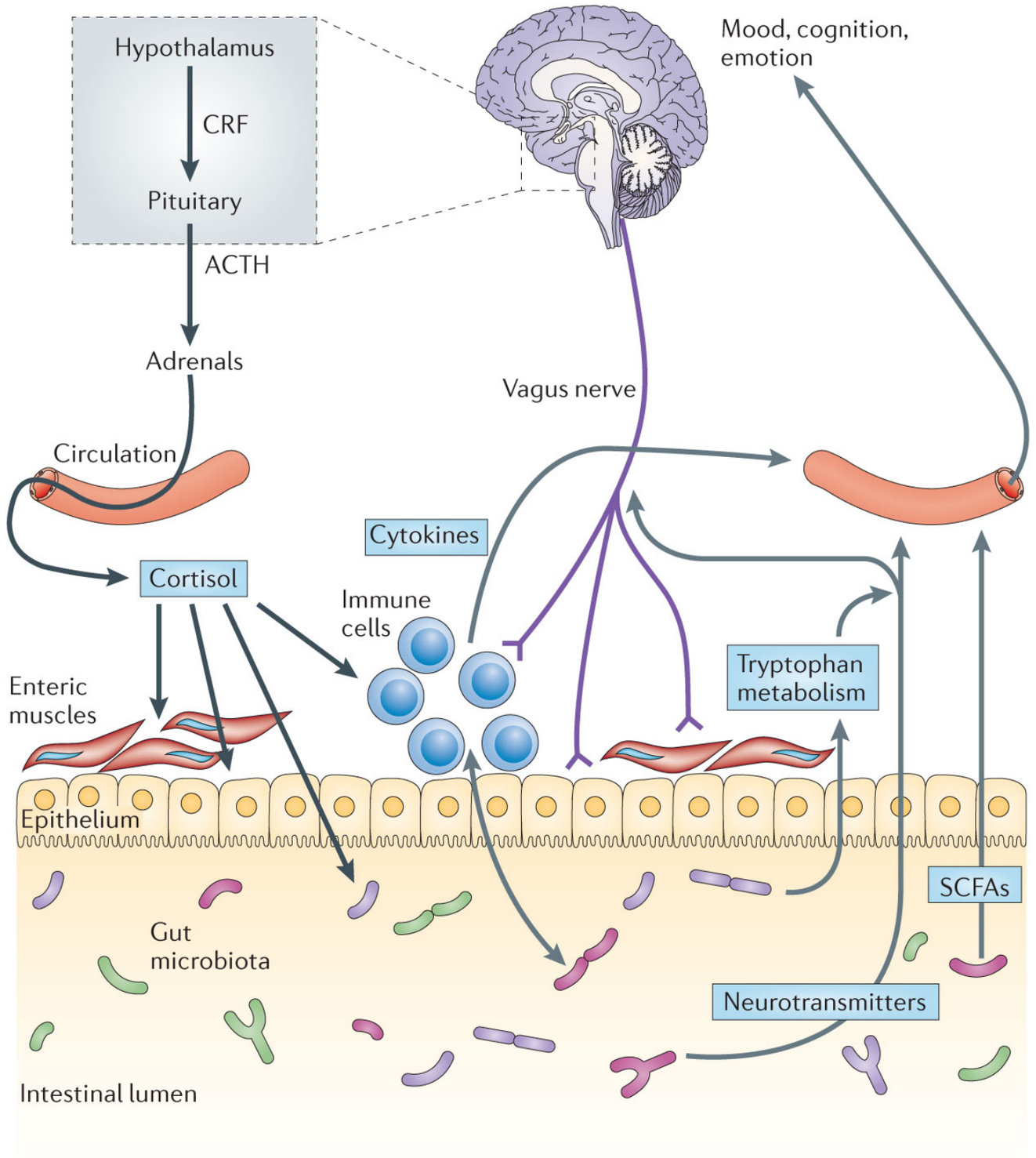
Can peripheral measures such as microbiota explain heterogeneity in health and disease?



POND network

CAN-BIND

Can peripheral measures such as microbiota explain heterogeneity in health and disease?



Cryan and Dinan 2012 Nat Rev Neurosci 701-712

Nature Reviews | Neuroscience

Do microbes influence brain function and behaviour in people?

Brain Structure and Response to Emotional Stimuli as Related to Gut Microbial Profiles in Healthy Women

Kirsten Tillisch, MD, Emeran A. Mayer, MD, PhD, Arpana Gupta, PhD, Zafar Gill, BSc, Rémi Brazeilles, MSc, Boris Le Nevé, PhD, Johan E.T. van Hylckama Vlieg, PhD, Denis Guyonnet, PhD, Muriel Derrien, PhD, and Jennifer S. Labus, PhD

- In healthy women, identified two enterotypes/clusters, a *Bacteroides* cluster and a *Prevotella* cluster

- Using functional MRI, structural MRI and diffusion tensor imaging, the investigators identified association between these 2 groups and emotional response, white matter connectivity, and brain volume

Tillisch et al 2017 Psychosomatic Med 79, 905-913

What is the evidence that microbes influence mood in people?

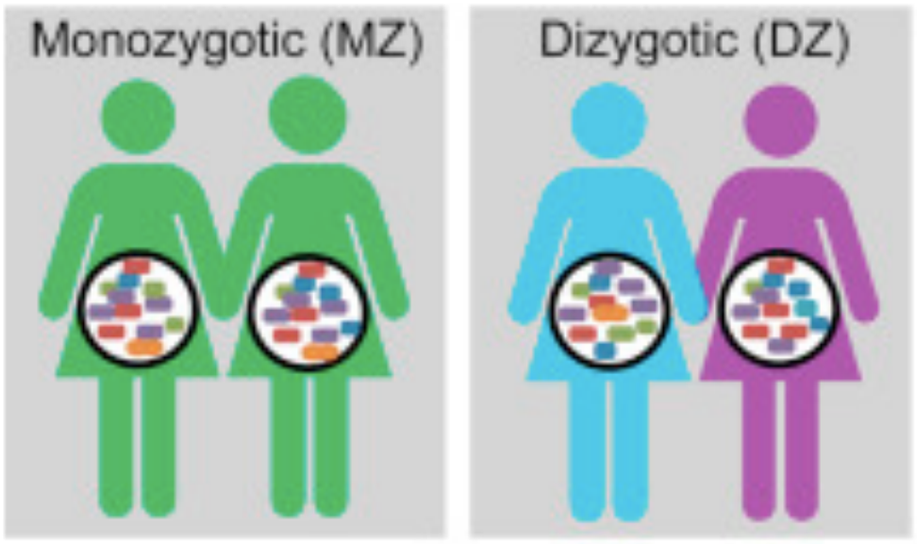
- Several studies have shown that the gut-brain axis may play an important role in brain development, behaviour, and mood
- In particular, studies have examined the impact of probiotics on stress systems in healthy individuals
- Several studies have show benefit of probiotic consumption in healthy individuals
  - 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)
  - showed reduction in cognitive reactivity to sad mood, specifically ruminative thoughts (Steenbergen et al 2015)

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,[1] Rob Knight,[1,5,6] 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

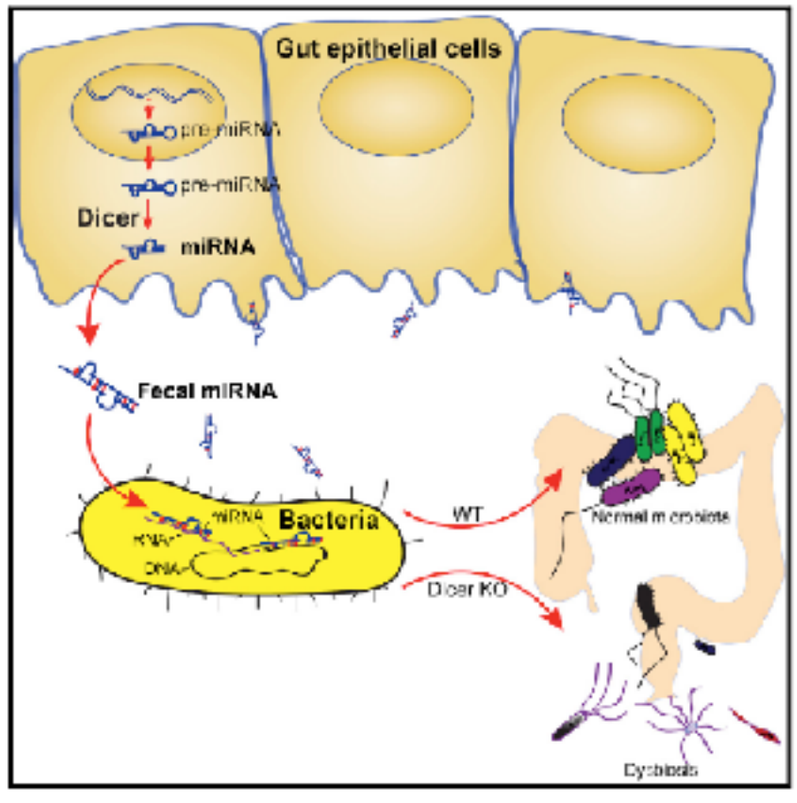
Authors

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

Cell Host & Microbe

The Host Shapes the Gut Microbiota via Fecal MicroRNA

Graphical Abstract



Gut bacteria and depression

Correlation between the human fecal microbiota and depression

Neurogastroenterol Motil (2014) 26, 1155–1162

A. L[illegible]

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,*]

Possible association of *Bifidobacterium* and *Lactobacillus* in the gut microbiota of patients with major depressive disorder

Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat

Journal of Psychiatric Research 82 (2016) 109–118

John R. Kelly [a, b], Yuliya Borre [a], Ciaran O' Brien [a, c], Elaine Patterson [a, c], Sahar El Aidy [a, d], Jennifer Deane [c], Paul J. Kenned[illegible] Alan E. Hoban [a], Lucinda Scott [b] Gerard Clarke [a, b], John F. Cryan

Prevotella and Klebsiella proportions in fecal microbial communities are potential characteristic parameters for patients with major depressive disorder

Journal of Affective Disorders 207 (2017) 300–304

Ping Lin[a,1], Bingyu Ding[b,c,1], Chunyan Feng[d], Shuwei Yin[b], Ting Zhang[b], Xin Qi[b], Huiying Lv[b], Xiaokui Guo[c], Ke Dong[c], Yongzhang Zhu[c,1], Qingtian Li[b,*,1]

Gut bacteria and depression

Table 1. Bacterial taxa differences observed in individuals with major depressive disorder

Experimental Design				
Reference	MDD Sample (n)	Comparison Group (n)	OTU Picking	Taxon Assignment
Naseribafrouei et al 2014	mild to severe MDD (37)	neurological outpatient (18)	Closed Reference, UClust modified	RDP database
Jiang et al 2015	mild to moderate MDD (29)	healthy volunteers (30)	Mothur ver1.25.0, custom Perl scripts	RDP database
Kelly et al 2016	MDD (34)	healthy volunteers (33)	USEARCH v7	BLAST, Silva v.111
Zheng et al 2016	MDD (58)	healthy volunteers (63)	Roche software	RDP database
Lin et al 2017	MDD (10)	healthy volunteers (10)	Mothur v.1.30	Silva v.119 in mothur

Differences in Relative Abundance

Phyla	Order	Class	Family	Genus
Naseribfrouei et al 2014 - method				
Bacteroidetes (up)		Bacteroidales (down)	Lacnopiraceae (down)	*Alistipes* (up)
				Oscillibacter (up)
Jiang et al 2015 - Mothur metastats				
Bacteroidetes (up)			Acidaminoccocaceae (up)	*Alistipes* (up)
Proteobacteria (up)			Enterobacteriaceae (up)	*Blautia* (up)
Firmicutes (down)			Fusobacteriaceae (up)	*Clostridibum XIX* (up)
			Porphyromonadaceae (up)	*Lachnospiacea* (up)
			Rikenellaceae (up)	*Megamonas* (up)
			Bacteroidaceae (down)	*Parabacteroides* (up)
			Erysipelotrichaceae (down)	*Parasutterella* (up)
			Lacnopiraceae (down)	*Phascolarctobacterium* (up)
			Prevotellaceae (down)	*Oscillibacter* (up)
			Ruminococcaceae (down)	*Roseburia* (up)
			Veillonellaceae (down)	*Bacteroides* (down)
				Dialister (down)
				Faecalibacterium (down)
				Prevotella (down)
				Ruminococcus (down)
Jiang et al 2015 - LefSe LDA; alpha leve = 0.05, effect size threshold = 2				
	Enterobacteriales (up)		*Polphyromonadaceae* (up)	*Alistipes* (up)
			Eneterobacteriaceae (up)	*Parabacteroides (up)*
			Rikenellaceae (up)	*Butyricimonas* (up)
			Erysipelotrichaceae (up)	*Flavonifractor* (up)
			Peptostreptococcaceae (down)	*Haemophilus (down)*
			Pasterueliaceae (down)	*Dialister* (down)
			Ruminococcaceae (down)	*Faecalibacterium* (down)
				Escherichia shigella (down)
				Ruminococcus (down)
Kelly et al 2016 - Mann-Whitney U test, FDR adjusted 10%				
			Prevoellaceae (down)	*Prevotella* (down)
			Thermoanaerobacteriaceae (up)	*Dialister* (down)
				Eggerthella (up)
				Holdemania (up)
				Gelria (up)
				Turicibacter (up)
				Paraprevotella (up)
				Anaerofilum (up)

			Anaerostipes (up)
Lin et al 2017 - Student's t-test (Phyla) and Wilcoxon's Sign Rank Test (Genus)			
	Bacteroidetes (down)		*Prevotella*
	Firmicutes (up)		*Klebsiella*
			Steptococcus
			Clostridibum XIX
Zheng et al 2016 - Random Forest Classifier			
		Actinomycineae (up)	*Parvimonas* (up)
		Coriobacterineae (up)	*Anerostipes* (up)
		Lactobacillaceae (up)	*Blautia* (up)
		Streptococcaceae (up)	*Dorea* (up)
		Clostridales incertae sedis XI (up)	*Lachnospiraceae incertae sedis* (up)
		Eubacteriaceae (up)	*Clostridium IV* (up)
		Lachnospiraceae (up)	*Alistipes* (down)
		Ruminococcaceae (up)	*Coproccus* (down)
		Erysipelotrichaceae in certae sedis (up)	*Clostridium XIVa* (down)
		Bacteroidaceae (down)	*Phascolarctobacterium* (down)
		Rikenellaceae (down)	*Megamonas (down)*
		Lachnospiraceae (down)	*Lachnospiraceae incertae sedis* (down)
		Acidaminococcaceae (down)	*Roseburia* (down)
		Vellonellaceae (down)	*Faecalibacterium* (down)
		Sutterellaceae (down)	

Gut bacteria and depression

Nutrition 32 (2016) 315–320

Applied nutritional investigation

Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial

Ghodarz Akkasheh M.D.[a], Zahra Kashani-Poor M.D.[a], Maryam Tajabadi-Ebrahimi Ph.D.[b], Parvaneh Jafari Ph.D.[c], Hossein Akbari Ph.D.[d], Mohsen Taghizadeh Ph.D.[e], Mohammad Reza Memarzadeh Ph.D.[f], Zatollah Asemi Ph.D.[e,*], Ahmad Esmaillzadeh Ph.D.[g,h,i]

- Probiotic supplementation for 8 week compared to placebo - *Lactobacillus case, L. acidophilus, Bifidobacterium bifidum*

- Probiotic supplement was associated with
  - reduced depression scores (Beck Depression Score)
  - reduced serum insulin
  - reduce inflammatory marker - C-reactive protein

Benefits of probiotics - animal studies linked to mental health

Beneficial probiotics - single species

Bacteria	Benefits observed	Animal Model	Ref
Bifidobacteria infantis	Reduced inflammation	Sprague-Dawley rats	Desbonnet et al 2009
B.longum	Reduced anxiety-like behaviour	Balb/C mice	Savignac et al 2014
	Reduced depressive-like behaviour		
B. breve	Reduced anxiety-like behaviour	Balb/C mice	Savignac et al 2014
B.longum	Improved recognition memory	Balb/C mice	Savignac et al 2015
	Improved spatial learning		
	Reduced fear behaviour		
B. breve	Improved recognition memory	Balb/C mice	Savignac et al 2015
B. longum	Reduced infection-related anxiety-like behaviour	AKR mice	Bercik et al 2010
Lactobacillus rhamnosus	Reduced anxiety-like behaviour	Balb/C mice	Bravo et al 2011
	Reduced depressive-like behaviour		
	Reduced stress hormones		
L. helveticus	Reduced anxiety-like behaviour	Sprague-Dawley rats	Liang et al 2015
	Reduced stress hormones		
L. reuteri	Reduced stress-related infectious colonization	CD1 mice	Mackos et al 2013
L. reuteri	Reduced stress/infection-related inflammatory mediators	CD1 mice	Mackos et al 2016
L. pentosus	Improved age-related deficits in spatial memory	Fischer rats	Jeong et al 2015
	Reduced inflammation		
L. pentosus	Protected against stress-induced deficits in memory	C57Bl/6 mice	Woo et al 2014
	Reduced inflammation		
Mycobacterium vaccae	Improved spatial learning	Balb/C mice	Matthews et al 2013
M. vaccae	Reduced stress-related infectious colonization	C57Bl/6 mice	Reber et al 2016
	Reduced stress-related anxiety-like behaviour		

Benefits of probiotics - animal studies linked to mental health

Beneficial probiotics - combination

Bacteria	Benefits observed	Animal Model	Ref
Combnation: *L. helveticus, B. longum*	Reduced stress hormones	C57Bl/6 mice	Ait-Beignaoui et al 2012
	Prevented stress-related decrease in neurogenesis		
	Protected gut barrier integrity		
Combnation: *L. helveticus, L. rhamnosus*	Protected against stress-induced deficits in recognition memory	C57Bl/6 mice	Gareua et al 2011
Combination: *L, acidophilus, B. lactis, L. fermentum*	Improved spatial learning	Wistar rats	Davari et al 2013
Combination: *L. acidophilus, B. lactis, L. fermentum*	Synaptic transmission	Wistar rats	Davari et al 2013
Combination: *Streptococcus salivarius, B. breve, B. infanti, B. longum, L. acidophilis, L. planarum, L. casei, L. delbrueeki*	Reduced inflammation	C57Bl/6 mice	D'Mello et al 2015

Benefits of probiotics - animal studies linked to mental health

Beneficial probiotics - combination

Bacteria	Benefits observed	Animal Model	Ref
Combnation: *L. helveticus, B. longum*	Reduced stress hormones	C57Bl/6 mice	Ait-Beignaoui et al 2012
	Prevented stress-related decrease in neurogenesis		
	Protected gut barrier integrity		
Combnation: *L. helveticus, L. rhamnosus*	Protected against stress-induced deficits in recognition memory	C57Bl/6 mice	Gareua et al 2011
Combination: *L, acidophilus, B. lactis, L. fermentum*	Improved spatial learning	Wistar rats	Davari et al 2013
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Benefits of probiotics on mood

Table 1. Benefits of probiotics on mood

Benefit	Bacterial Taxa	Population	Dose (CFU)	Ref
Improved Mood	*Lactobacillus casei*	Healthy Individuals	$6X10^9$/day	[1]
Reduced anxiety and depressive measures	*Lactobacillus helveticus* R0052 *Bifidobacterium longum* R0175	Healthy Individuals	$3X10^9$/day	[2]
Reduced anxiety measures	*Lactobacillus casei*	Chronic fatigue syndrome	$2.4\ X10^{10}$/cay	[3]
Reduced stress hormone levels	*Lactobacillus helveticus* R0052 *Bifidobacterium longum* R0175	Healthy Individuals	$3X10^9$/day	[2]
Reduced engagement of brain network to emotion recognition task	*Streptococcus thermophilis* (CNCM I-1630) *Lactobacillus bulgaricus* (CNCM I-1632 and I-1519) *Lactococcus lactis* supsp *lactis* (CNCM I-1631) *Bifidobacterium animalis* subsp *lactis* (CNCM I-2494)	Healthy Individuals	$1.2\ X10^9$/day $1.25\ X10^9$/day	[4]
Reduction in cognitive reactivity to sad mood	*Bifidobacterium bifidum* W23 *Bifidobacterium lactis* W52 *Lactobacillus acidophilus* W37 *Lactobacillus brevis* W63 *Lactobacillus casei* W56 *Lactobacillus salivarius* W24 *Lactococcus lactis* W19 and W58	Healthy Individuals	$5X10^9$/day	[5]
Reduced depression scores	*Lactobacillus casei* *Lactobacillus acidophilus* *Bifidobacterium bifidum*	Major depression	$2\ X\ X10^9$/day	[6]
Reduced serum insulin	*Lactobacillus casei* *Lactobacillus acidophilus* *Bifidobacterium bifidum*	Major depression	$2\ X\ X10^9$/day	[6]
Reduced inflammation	*Lactobacillus casei* *Lactobacillus acidophilus* *Bifidobacterium bifidum*	Major depression	$2\ X\ X10^9$/day	[6]

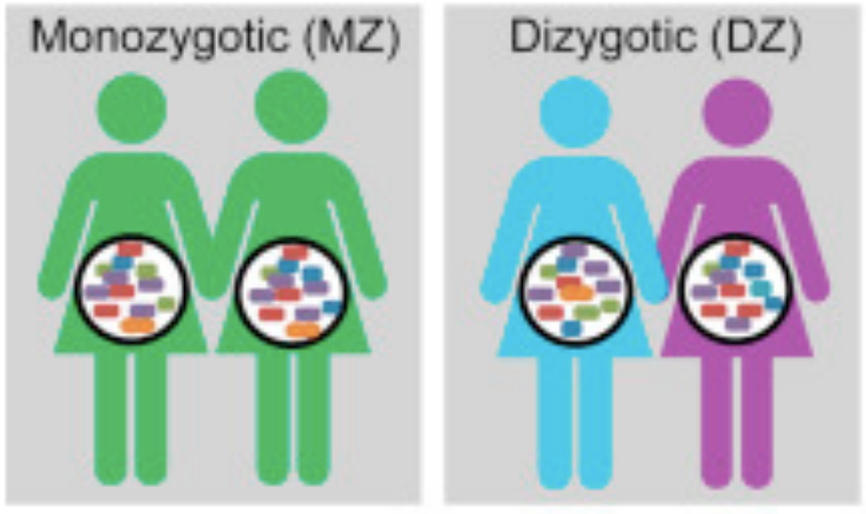
CFU – colony forming units; R – Probio'Stick: batch no. 6533308; Institut Rosell-Lallemand, Blagnac, France; CNCM – French National Collection of Cultures of Microorganisms, Paris, France; W – Ecologic Barrier, Winclove probiotics, The Netherlands

Benefits of probiotics on mood

1. Benton, D., C. Williams, and A. Brown, *Impact of consuming a milk drink containing a probiotic on mood and cognition.* Eur J Clin Nutr, 2007. **61**(3): p. 355-61.
2. Messaoudi, M., et al., *Beneficial psychological effects of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in healthy human volunteers.* Gut Microbes, 2011. **2**(4): p. 256-61.
3. Rao, A.V., et al., *A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome.* Gut Pathog, 2009. **1**(1): p. 6.
4. Tillisch, K., et al., *Consumption of fermented milk product with probiotic modulates brain activity.* Gastroenterology, 2013. **144**(7): p. 1394-401, 1401 e1-4.
5. Steenbergen, L., et al., *A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood.* Brain Behav Immun, 2015.
6. Akkasheh, G., et al., *Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial.* Nutrition, 2016. **32**(3): p. 315-20.

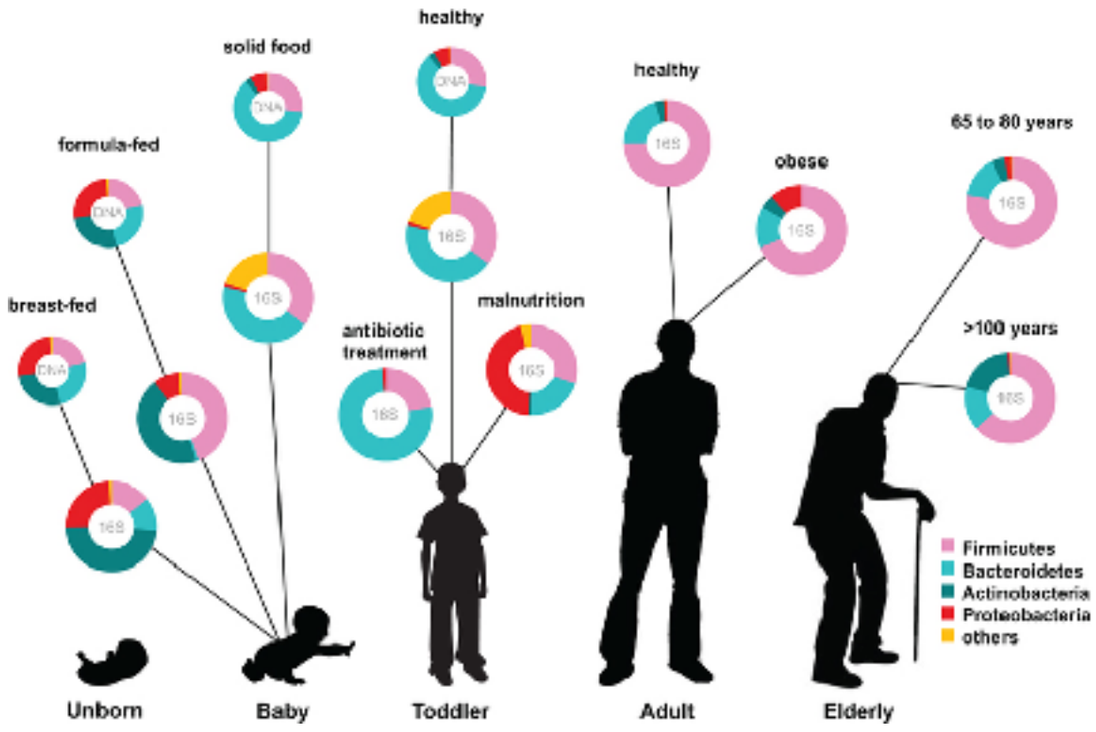
Many factors are important to gut health and the composition of gut bacteria?

Genetics **Diet** **Exercise** **Drugs** **Stress**



MZ twins have a more similar microbiota than DZ twins

Goodrich et al 2015 Cell 159, 789-799



Age **Sex**

Ottman et al 2012 Front. Cell. Infect. Microbiol. 2, 1-11

Research Funding Sources

Canada Foundation for Innovation

Fondation canadienne pour l'innovation

CIHR IRSC

Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

ONTARIO BRAIN INSTITUTE

NSERC CRSNG

Brain Canada

Lundbeck

janssen

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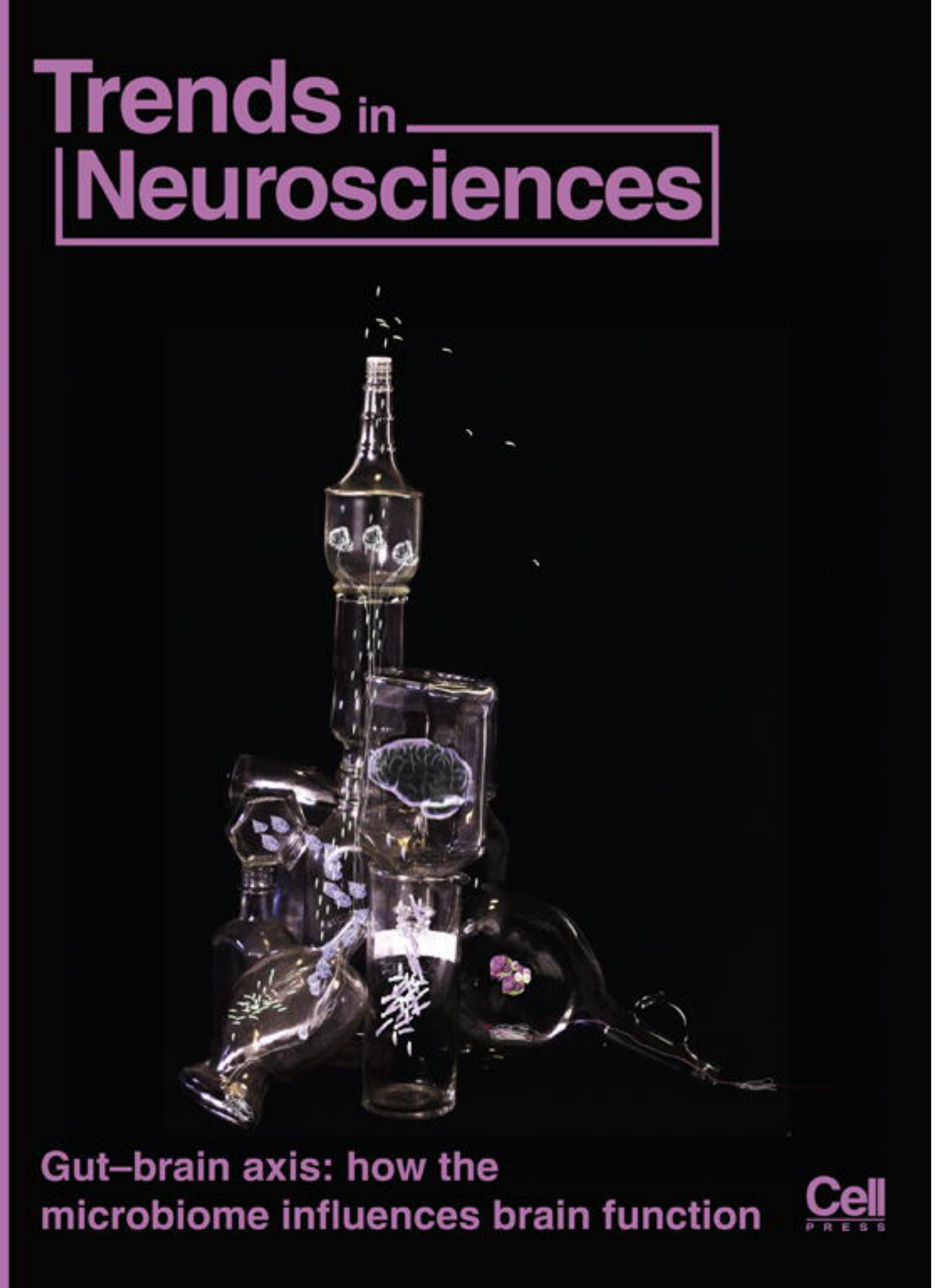
Trends in Neurosciences May 2013 Vol. 36 No. 5, pp. 259–312 ISSN 0166-2236



Using clear bottles as a metaphor for the physical inner workings of the human body, BrainGut Axis depicts the re-conception of the brain as part of an interconnected system, rather than the more traditional view of the brain as superior to, or in control of all other processes. There is movement throughout this system of various shapes and colors meant to insinuate components at work within the body such as microbiota and hormones, as well as to symbolize moods, impulses and the more abstract processes happening within us. In addition, these "inner-workings" leak outside of the system, reminding us that things are not fully contained, but are continuously moving beyond us, and wandering into us, as we maneuver our way through the world.

Thanks to:
Dr. Renee Jackson (PhD Art Education)
Dr. Suzanne McCallaugh (PhD Philosophy)
Dr. Dominic Letarte (PhD Computer Science)