



Interactions Among Diet, Gut Microbiome, and the Brain: Implications for Mood and Behavior.

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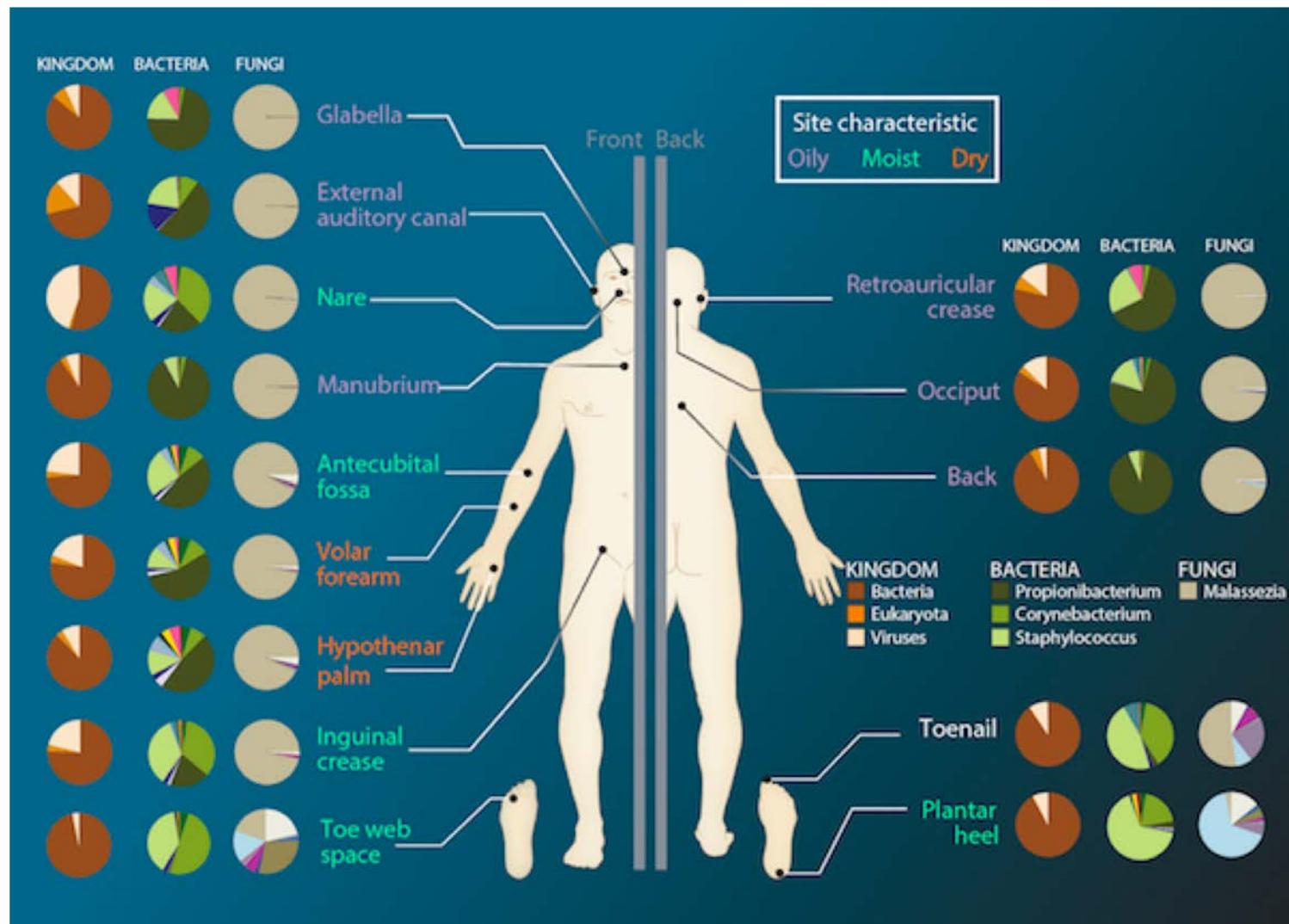
Today's Talk

- What is the microbiome?
- Factors that impact gut microbiome
- Gut microbiome interactions with brain
- Clinical associations

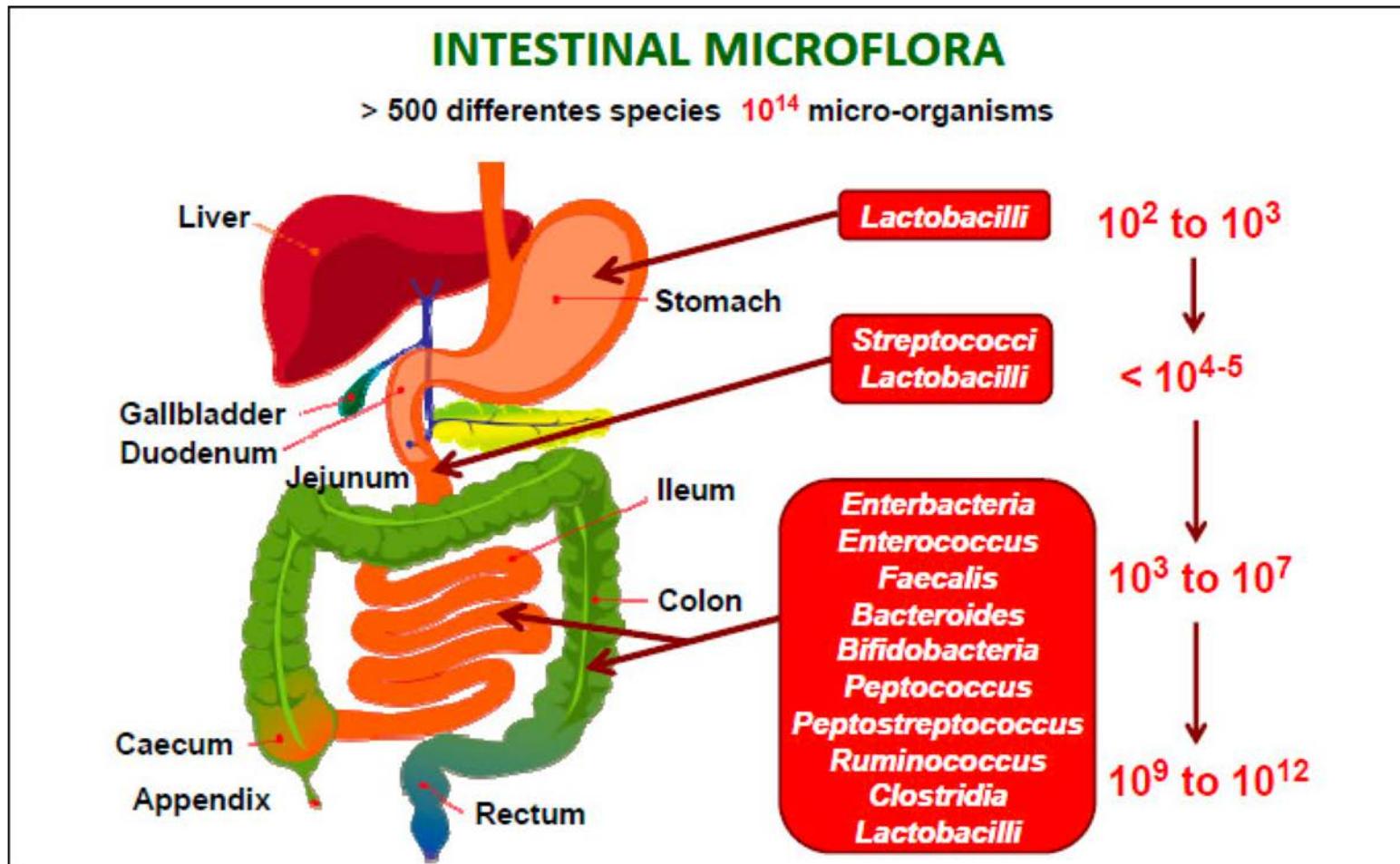
The Microbiome

- What is it?
 - Bacteria (Fungi, Archea, Virus) that live on and in our bodies.
 - considered commensal or symbiotic
- How big of a deal is this?
 - Sexy estimates ca 2014
 - 1:10 (10 trillion human cells and 100 trillion bacteria)
 - More recent (37.2 trillion cells, probably not due to obesity)
 - 1:3
 - 1:1
- Now referred to as an “organ”

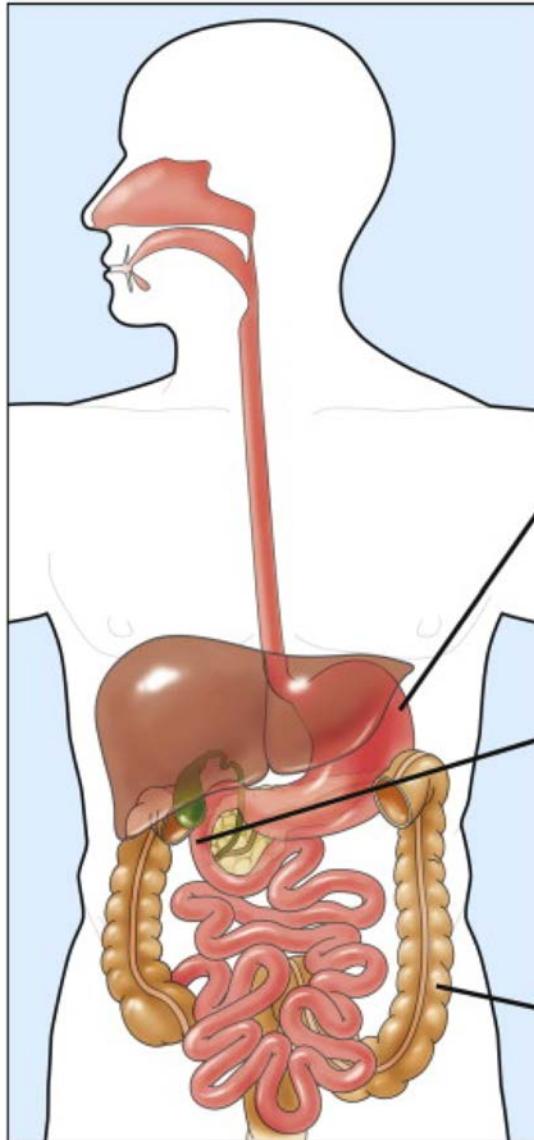
Location Specific



Specificity Across GI Tract



Regional diversity and function



Stomach

Host factors

- High pH
- Oxygenated

Microbiota characteristics

- Sparse bacterial load ($10^1/g$)
- Low-moderate diversity
- Firmicutes, Actinobacteria predominate

Duodenum

Host factors

- Neutral pH
- Low O_2
- Bile
- Mucus
- Mono- and disaccharides

Microbiota characteristics

- Increased bacterial load ($10^3/g$)
- Low diversity
- Firmicutes, Proteobacteria predominate

Colon

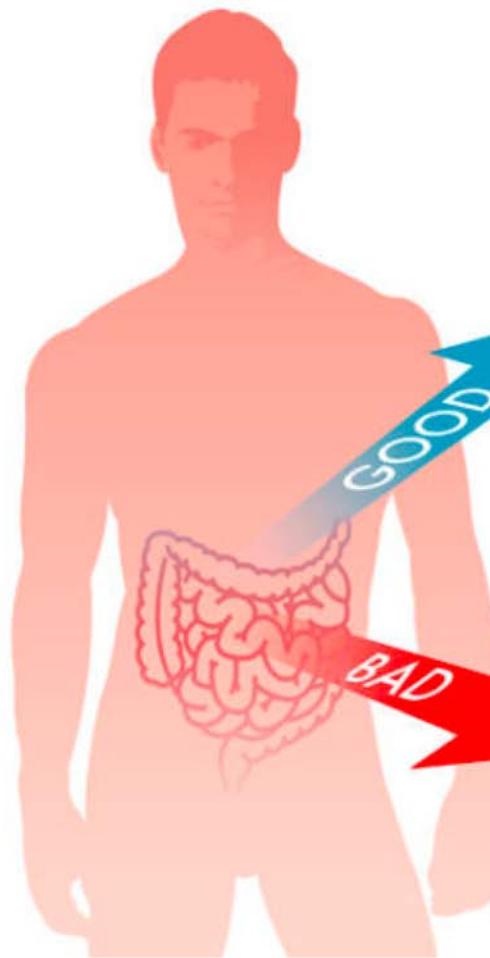
Host factors

- Neutral pH
- Low O_2
- Mucus
- Host-indigestible polysaccharides

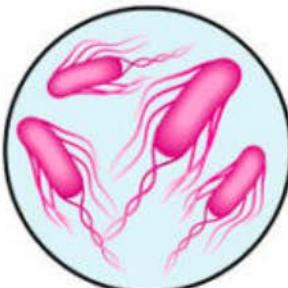
Microbiota characteristics

- High bacterial load ($10^{12}/g$)
- High diversity
- Firmicutes, Bacteroidetes predominate

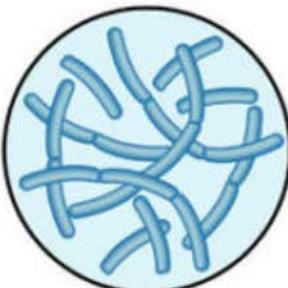
Good and Bad Bacterial Flora



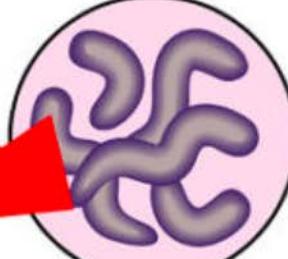
BIFIDOBACTERIA
The various strains help to regulate levels of other bacteria in the gut, modulate immune responses to invading pathogens, prevent tumour formation and produce vitamins.



ESCHERICHIA COLI
Several types inhabit the human gut. They are involved in the production of vitamin K2 (essential for blood clotting) and help to keep bad bacteria in check.
But some strains can lead to illness.



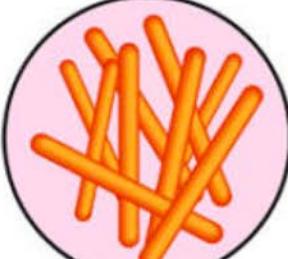
LACTOBACILLI
Beneficial varieties produce vitamins and nutrients, boost immunity and protect against carcinogens.



CAMPYLOBACTER
C. Jejuni and C. coli are the strains most commonly associated with human disease. Infection usually occurs through the ingestion of contaminated food.

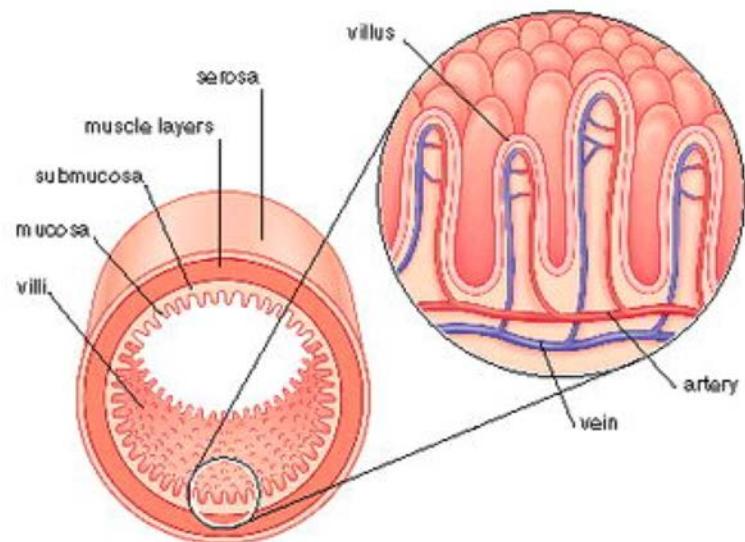


ENTEROCOCCUS FAECALIS
A common cause of post-surgical infections.

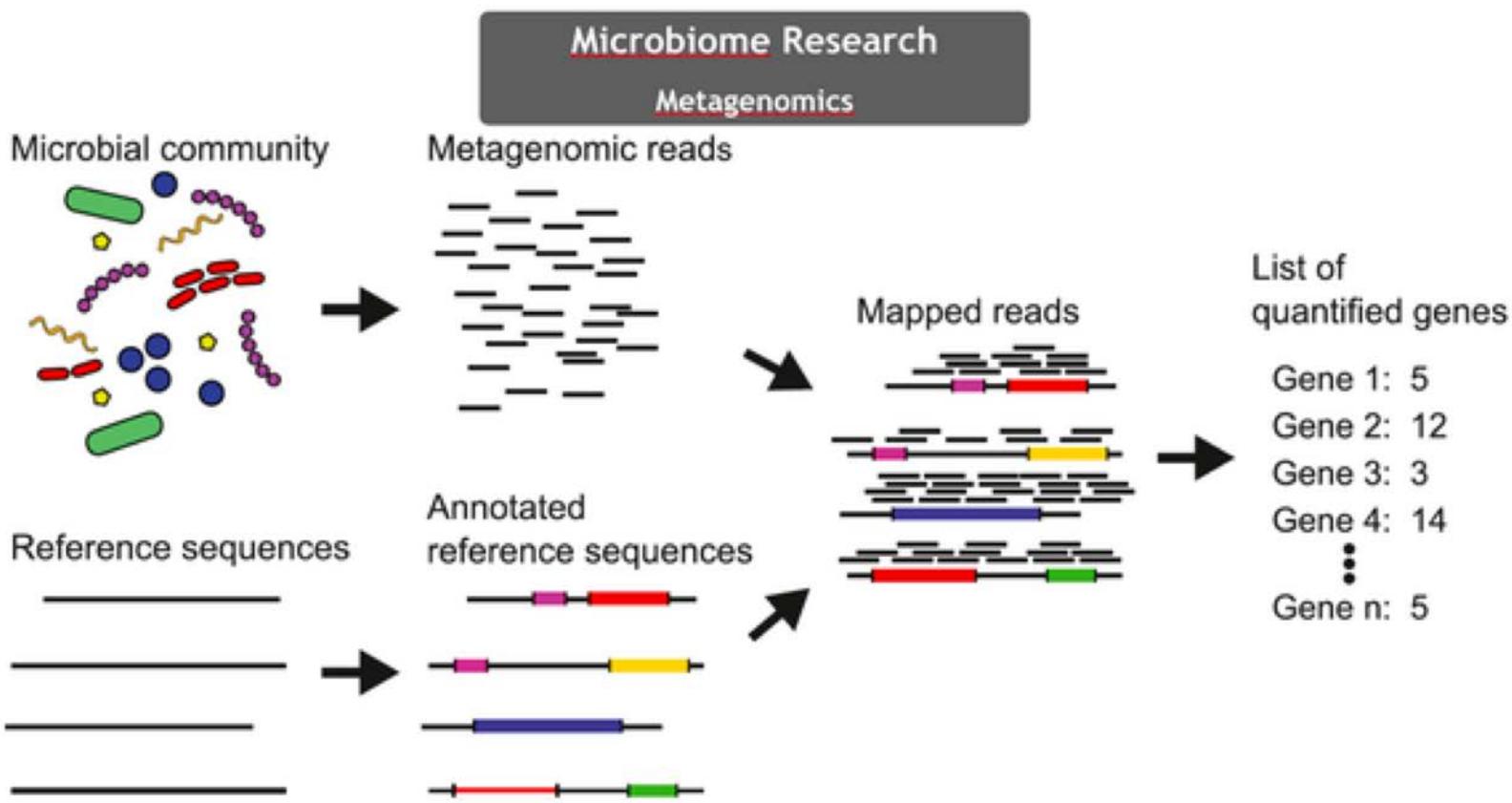


CLOSTRIDIUM DIFFICILE
Most harmful following a course of antibiotics when it is able to proliferate.

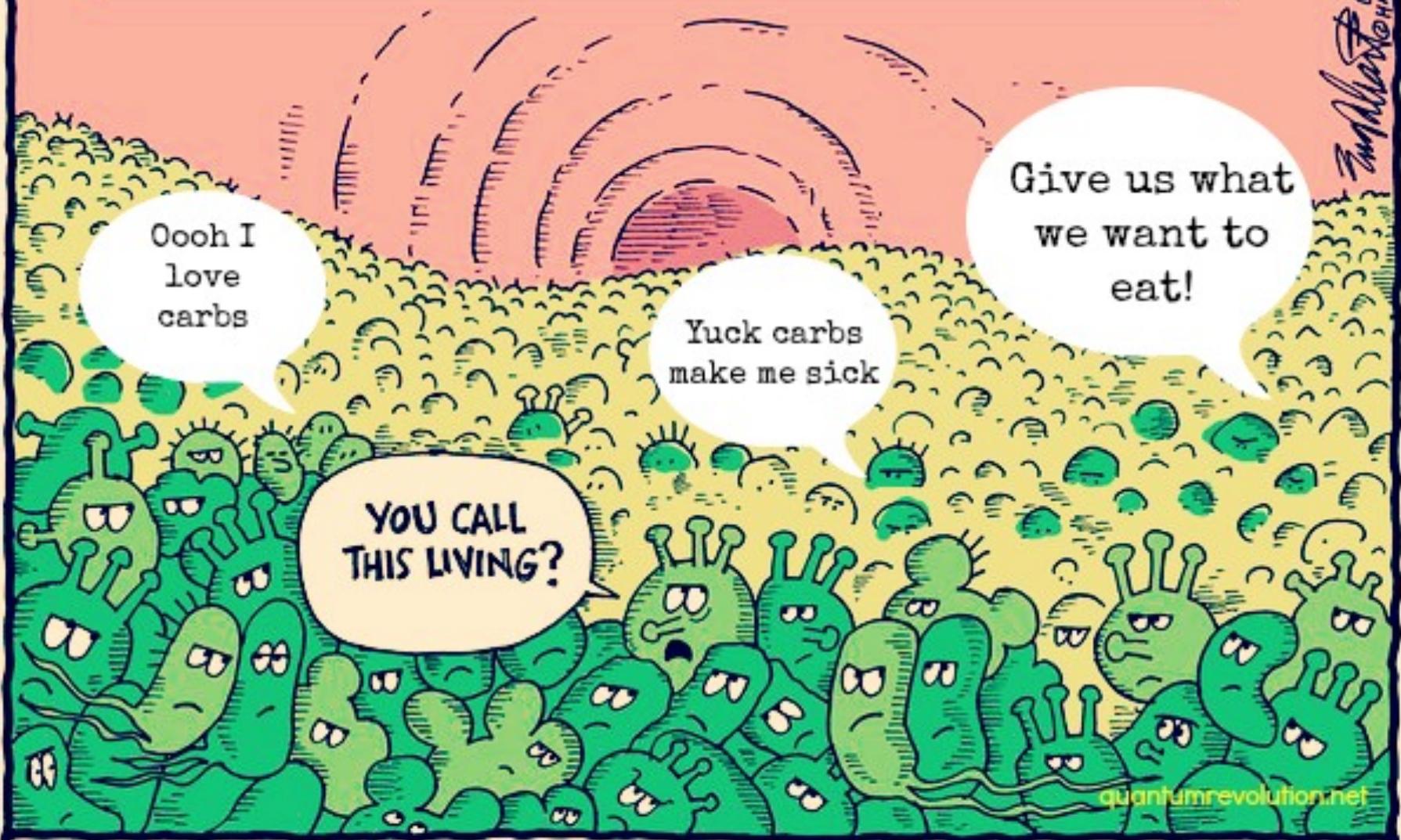
- A large proportion of anaerobic bacteria
 - Difficult to culture
- Low-abundance/rare species
- What is the current tool(s) for measuring?







THE HUMAN MICROBIOME PROJECT SAYS THE HUMAN BODY HAS 100 TRILLION MICROSCOPIC LIFE FORMS LIVING IN IT.



Zimkowitz 6/15/12
©HARTEFORD GAZETTE

What we know

- Many of these findings are descriptive/associative
 - Complex system
- Diversity appears to be good as it associates with health

Dietary and Lifestyle Choices Impact Metabolism

Physical Activity 2000 vs. 1950 (*Brownson, 2005*)

- Time spent watching TV increased 61.4%
- Number of people walking to work dropped 71%
- Low physical activity occupations increased 83%



However, during 2007–2010, half of the total U.S. population consumed <1 cup of fruit and <1.5 cups of vegetables daily; 76% did not meet fruit intake recommendations, and 87% did not meet vegetable intake recommendations (2).

Helps manage body weight. Water consumed in place of more

energy-dense foods (1). Adults who engage in <30 minutes of moderate physical activity daily should consume 1.5–2.0 cup equivalents of fruit and 2–3 cups of vegetables daily.* However, during 2007–2010, half of the total U.S. population consumed <1 cup of fruit and <1.5 cups of vegetables daily; 76% did not meet fruit intake recommendations, and 87% did not meet vegetable intake recommendations (2).

>18 years residing in the United States. BRFSS collects data

on health risk behaviors and conditions, chronic diseases and conditions, access to health care, and use of preventive health services and practices related to the leading causes of death and disabilities in the United States (4). BRFSS asks respondents how many times per day, week, or month they consumed 100% fruit juice, whole fruit, dried beans, dark green vegetables, orange vegetables, and other vegetables over

Environment has changed rapidly in last 150 years, what is the interaction with our microbiome?

Environmental, Dietary, and Behavioral Impacts on Microbiome

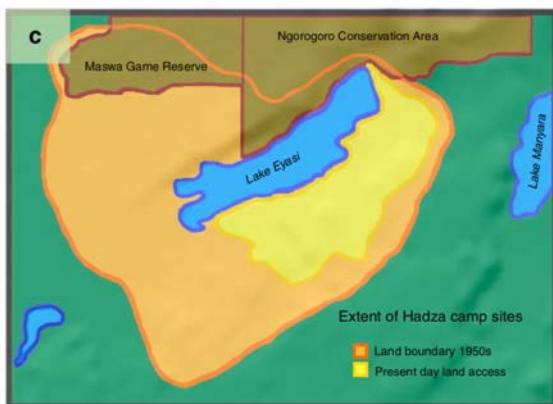
Have very interesting insights from a study on Hadza tribe that live in Tanzania



Schnorr, 2014; *Nature Commun*

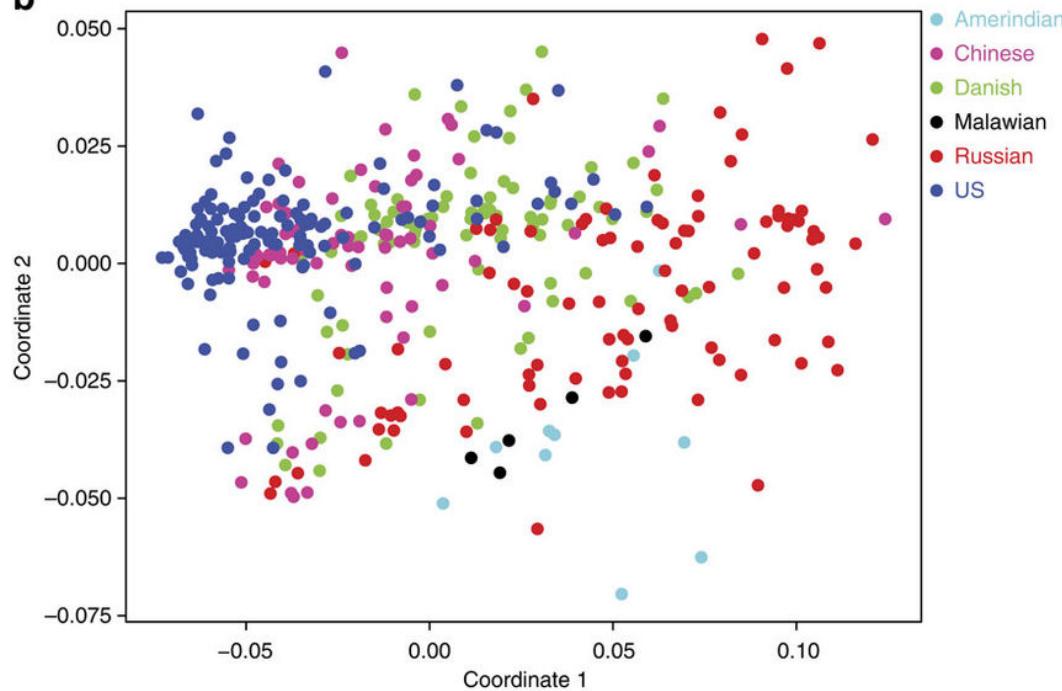


Hunting and Gathering
make up majority (>90%)
of subsistence



Hadza Tribe Microbiome

- Hadza have higher levels of microbial richness and biodiversity than Italian urban controls
- comparisons with two rural farming African groups illustrate other features unique to Hadza that can be linked to a foraging lifestyle
- Bifidobacterium and differences in microbial composition between the sexes that probably reflect sexual division of labor → although a number of studies have identified sex differences in microbiome
- Seasonal variation in microbiome (*Smits, 2017*)

a**b**

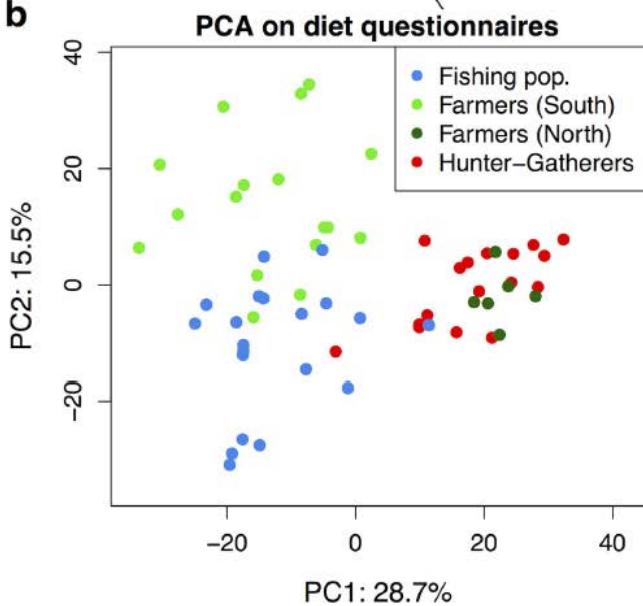
- Differences between rural and urban populations
- Urban more western looking
- Rural had increased diversity and proportions of bacteria involved in resistant starch and oligosaccharide degradation

Rural African gut microbiome correlates with feeding practices and parasites

a



b

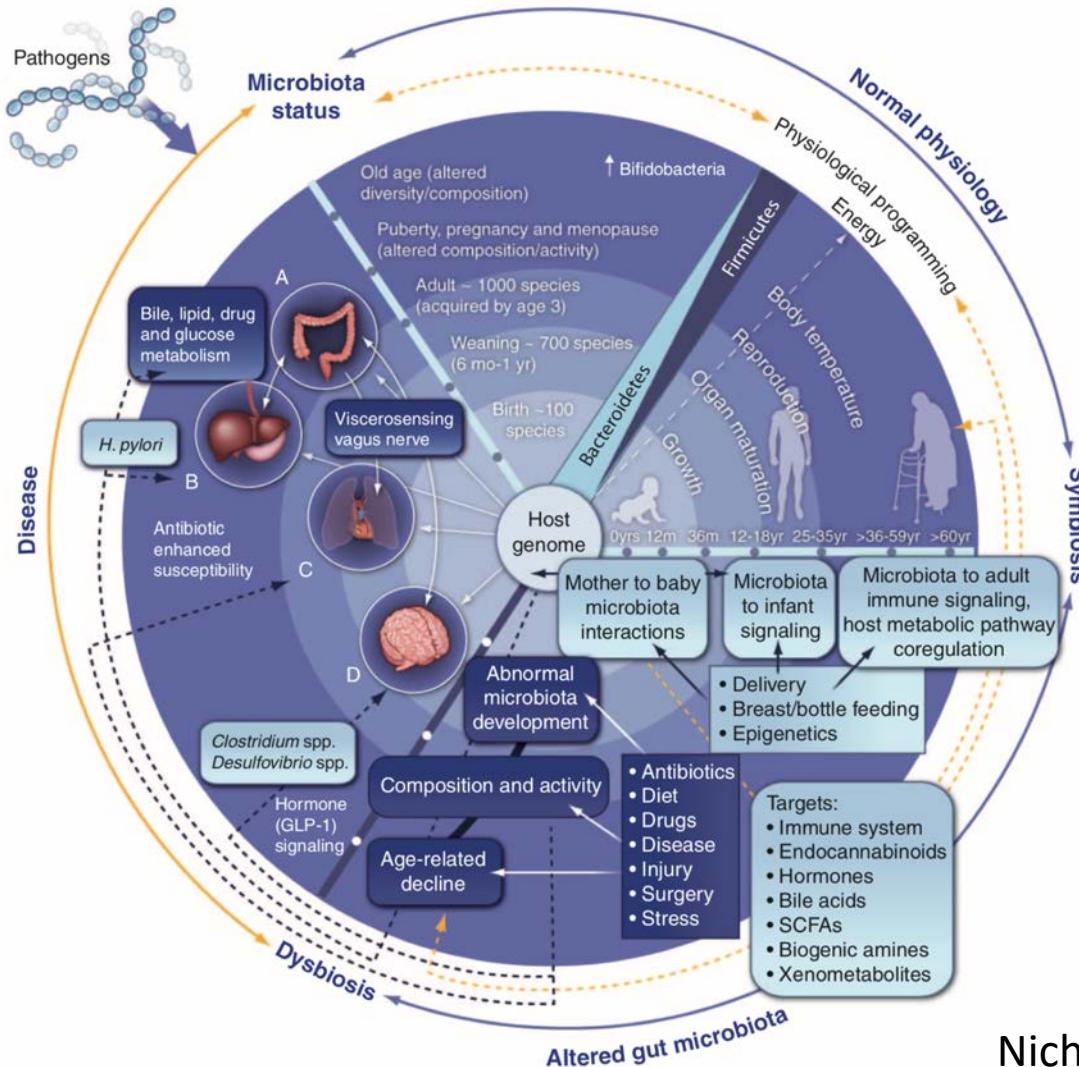


Fishing population (N=20)	Bantu
Farmers (South) (N=17)	
Farmers (North) (N=7)	
Hunter-gatherers (N=20)	Pygmy

Having a Parasite (Entamoeba)

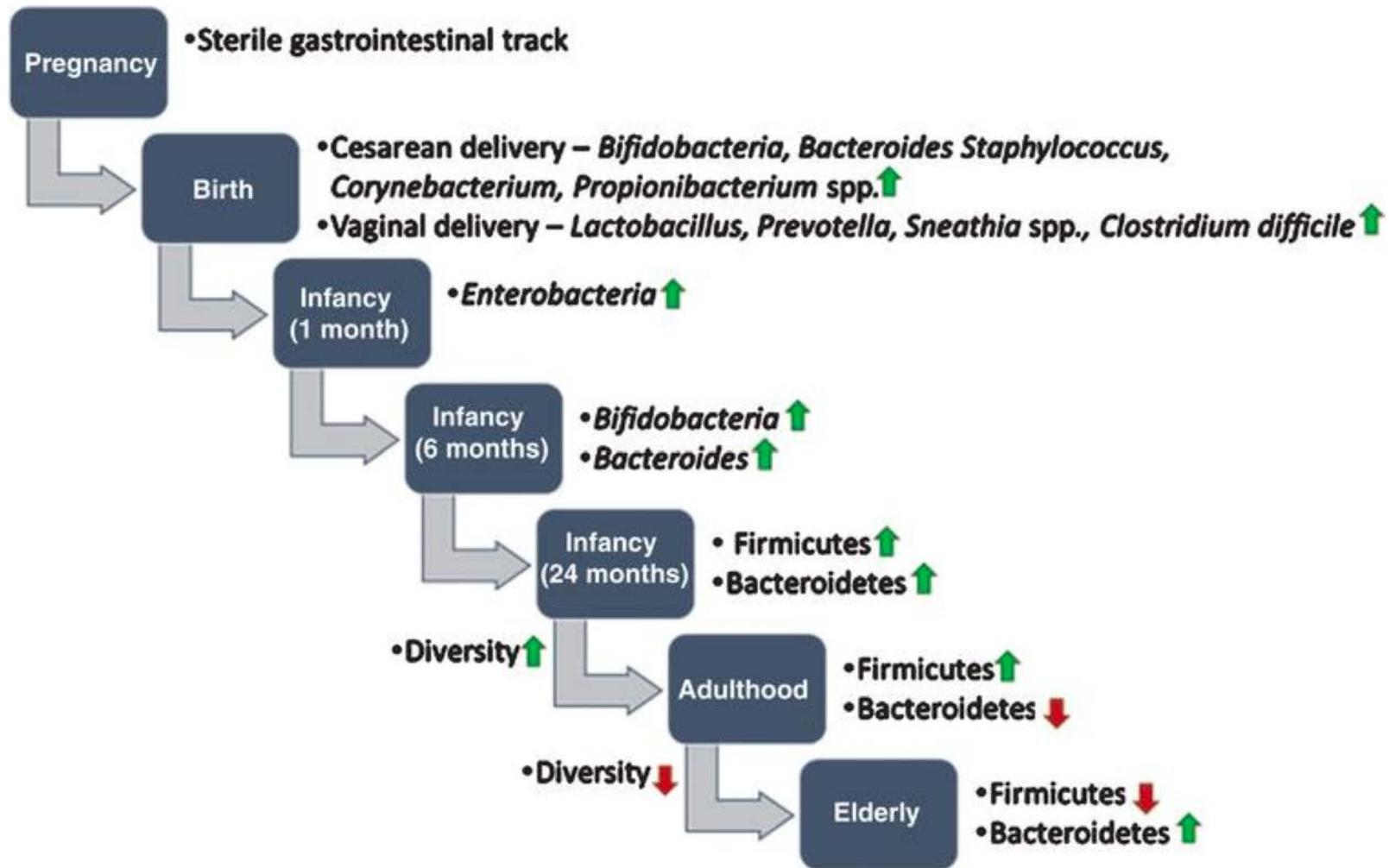
- Enriches microbiome for Ruminococcaceae (uncl)
 - Also seen in Hadza
 - Part of the Termite gut microbiome





Nicholson, 2012; Science

Changes across the lifespan



Hospitalized Elderly with Higher Diversity have Longer Survival

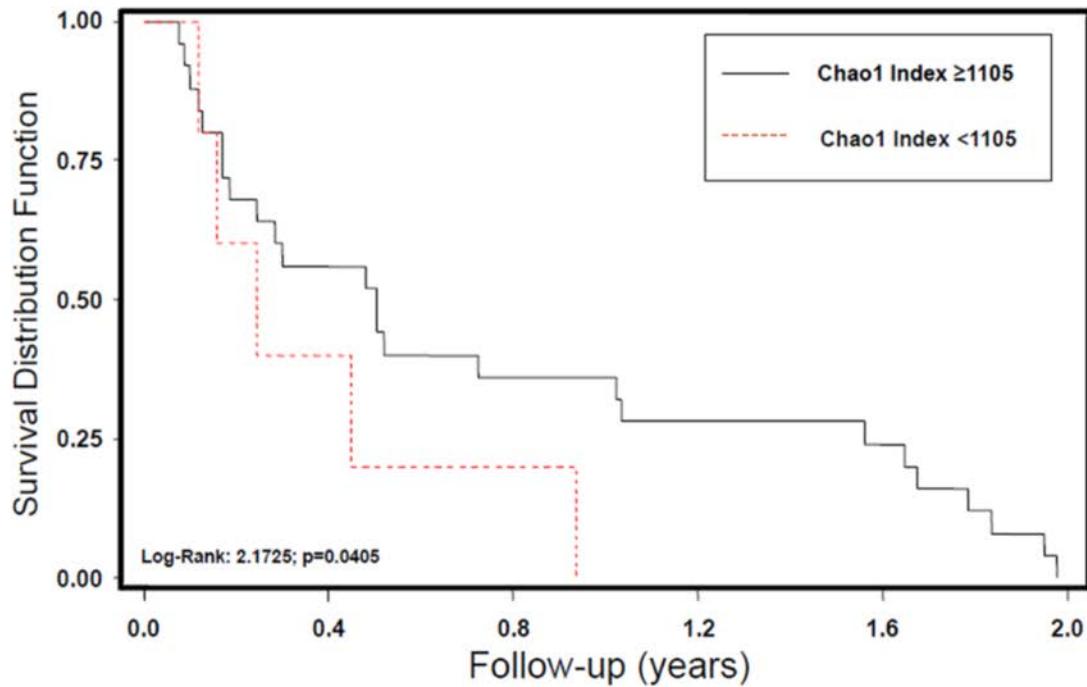
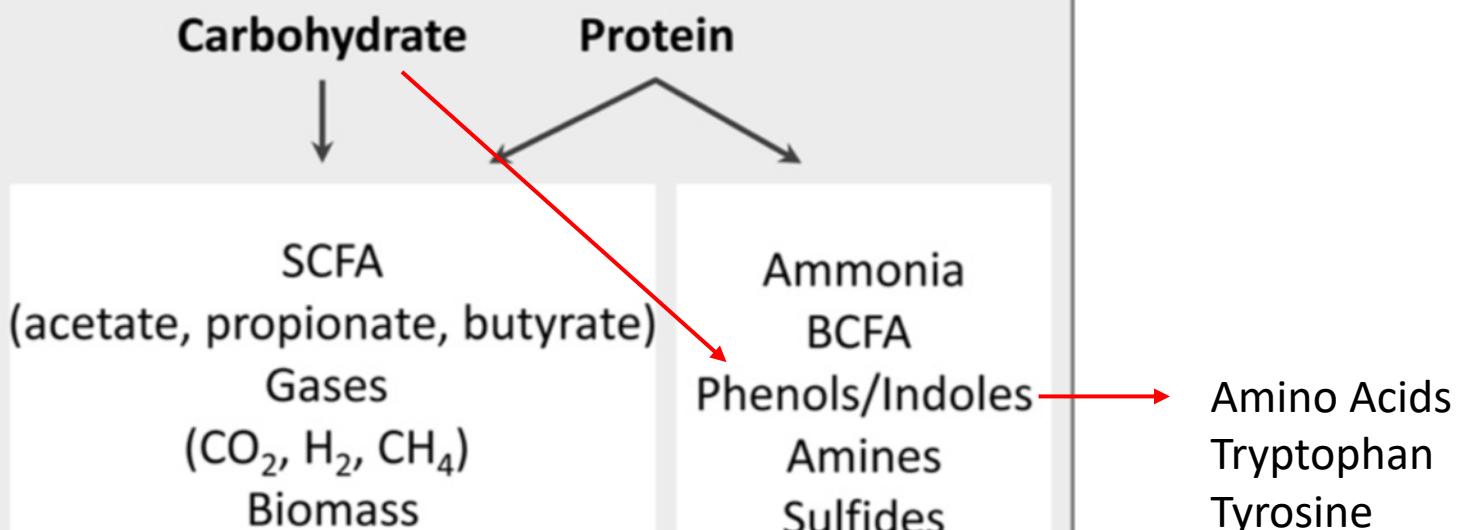


Figure 5. Fecal microbiota biodiversity and survival in hospitalized patients. Survival distribution function of 76 hospitalized patients categorized according to values of Chao1 Index of biodiversity in fecal microbiota. Subjects with higher biodiversity (upper tertile of Chao1 Index, values ≥ 1105) have a statistically longer survival than patients with deeper dysbiosis after a 2-year follow-up.

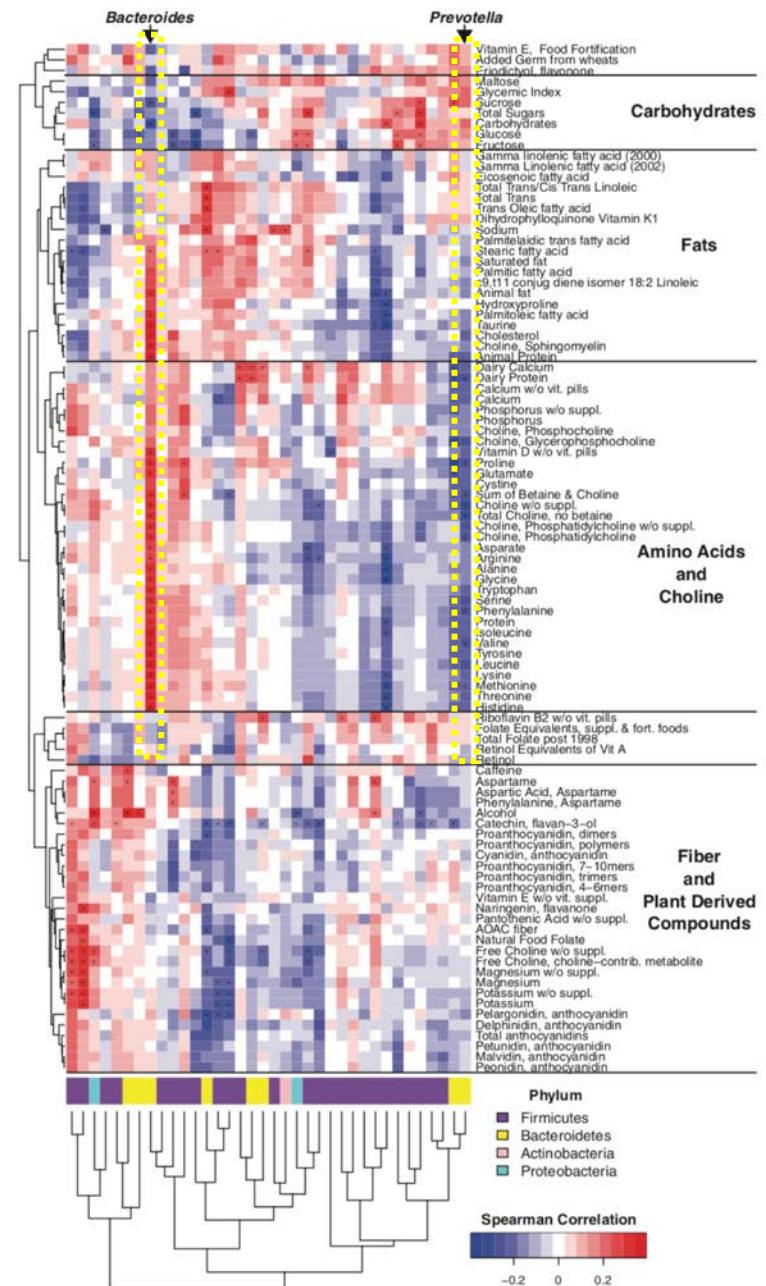
Diet and Microbiome

Bacterial fermentation products

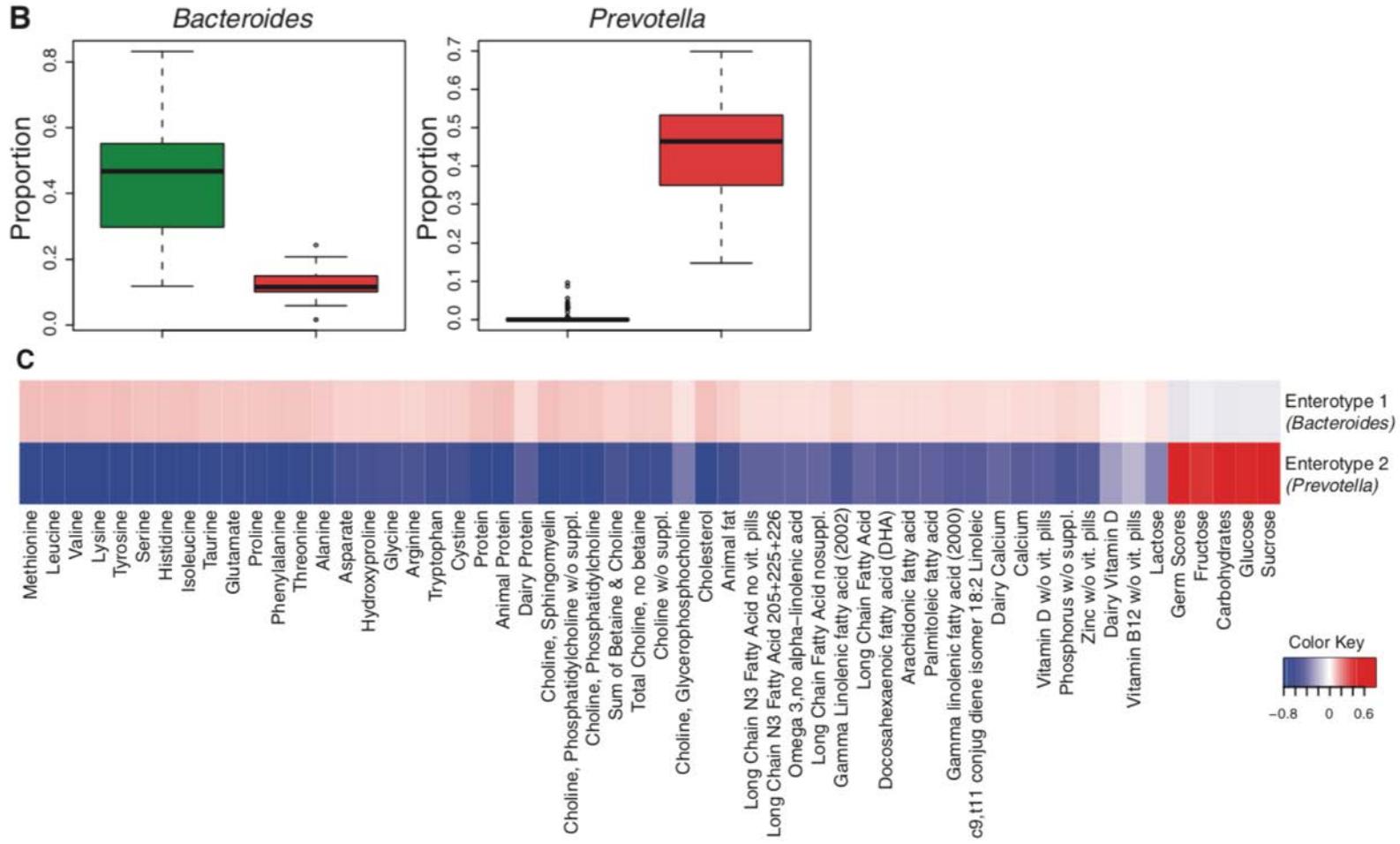


Linking Long-Term Dietary Patterns with Gut Microbial Enterotypes

Gary D. Wu,^{1*} Jun Chen,^{2,3} Christian Hoffmann,^{4,5} Kyle Bittinger,⁴ Ying-Yu Chen,¹ Sue A. Keilbaugh,¹ Meenakshi Bewtra,^{1,2} Dan Knights,⁶ William A. Walters,⁷ Rob Knight,^{8,9} Rohini Sinha,⁴ Erin Gilroy,² Kernika Gupta,¹⁰ Robert Baldassano,¹⁰ Lisa Nessel,² Hongzhe Li,^{2,3} Frederic D. Bushman,^{4*} James D. Lewis^{1,2,3*}

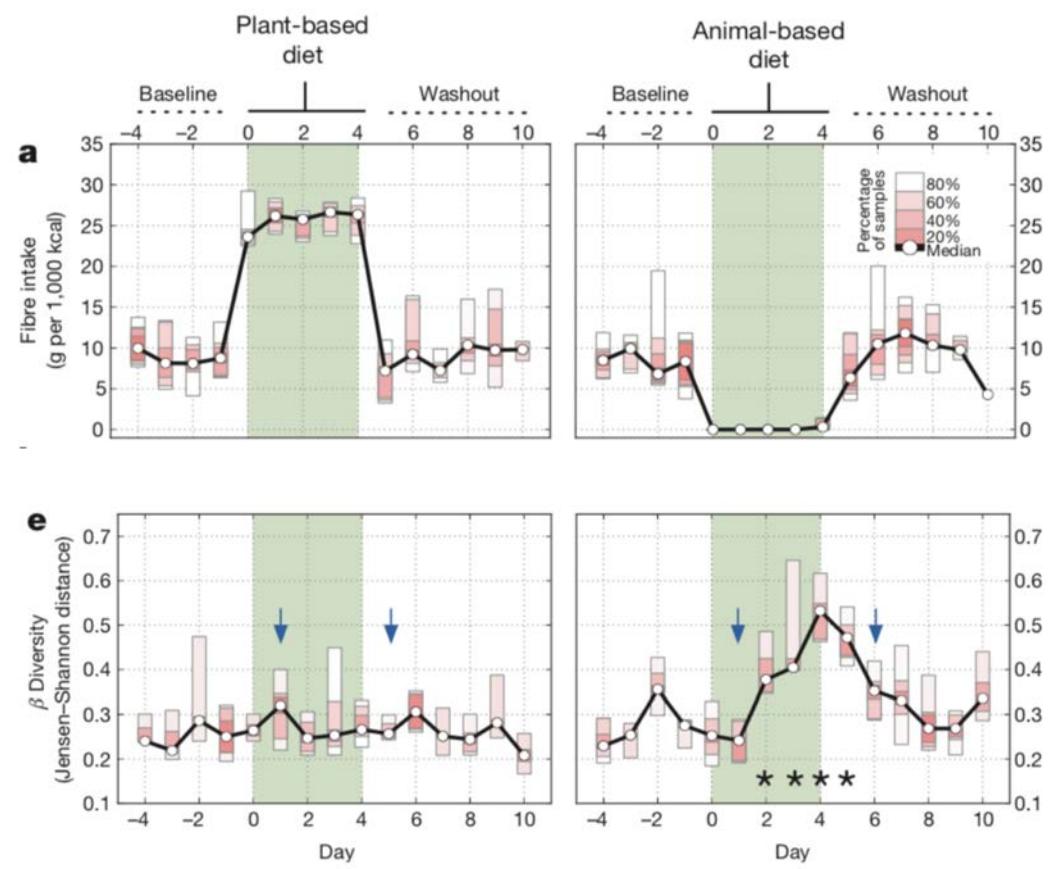
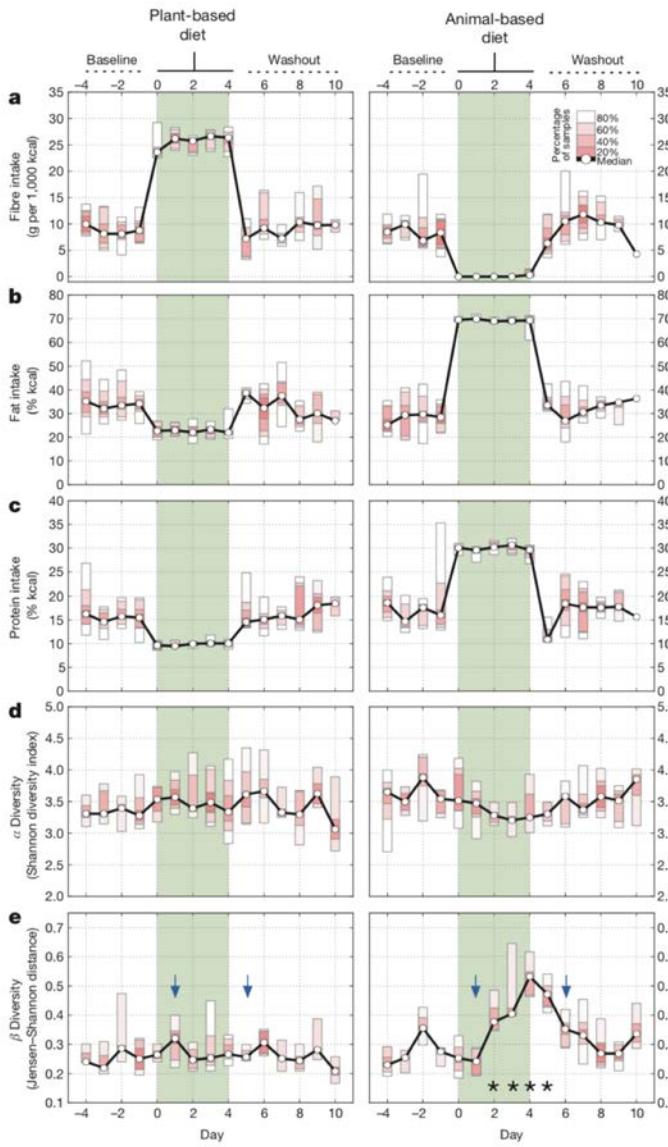


Proportions of these bacteria associate with dietary intake

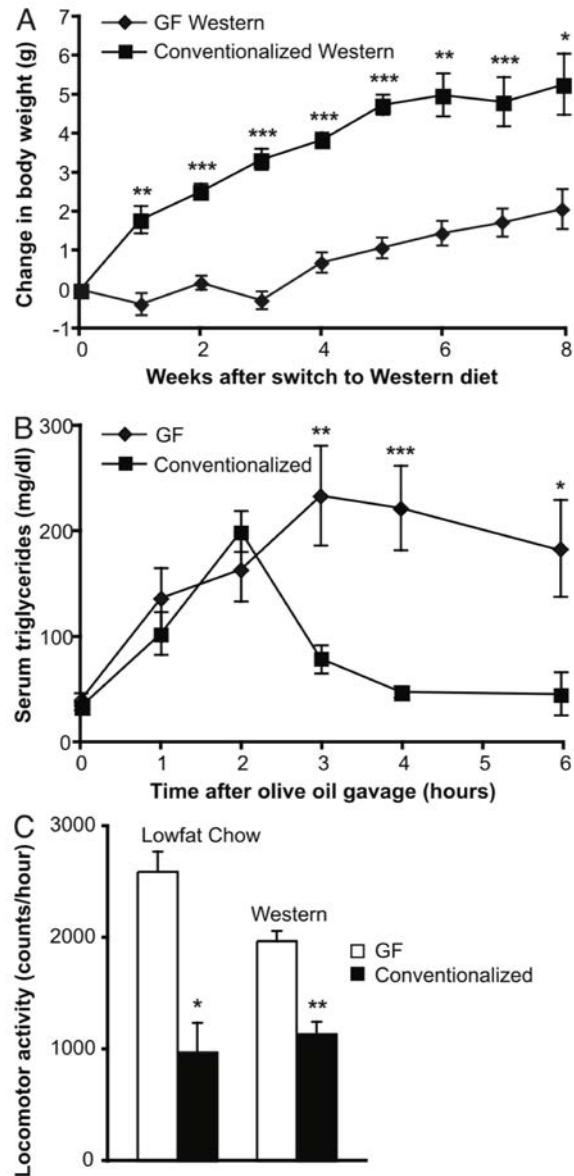


Diet rapidly and reproducibly alters the human gut microbiome

Lawrence A. David^{1,2†}, Corinne F. Maurice¹, Rachel N. Carmody¹, David B. Gootenberg¹, Julie E. Button¹, Benjamin E. Wolfe¹, Alisha V. Ling³, A. Sloan Devlin⁴, Yug Varma⁴, Michael A. Fischbach⁴, Sudha B. Biddinger³, Rachel J. Dutton¹ & Peter J. Turnbaugh¹



Microbiome impacts metabolic response to “Western” diet

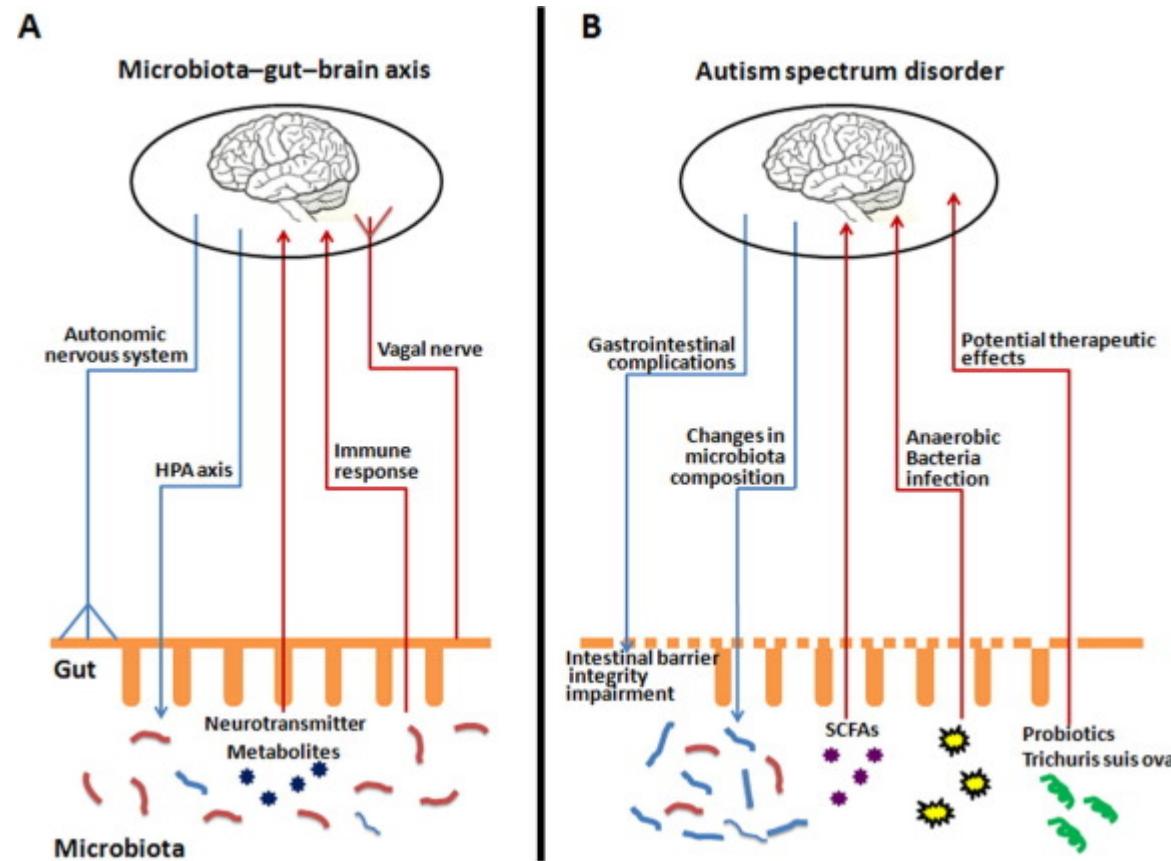


Backhed, 2006; PNAS

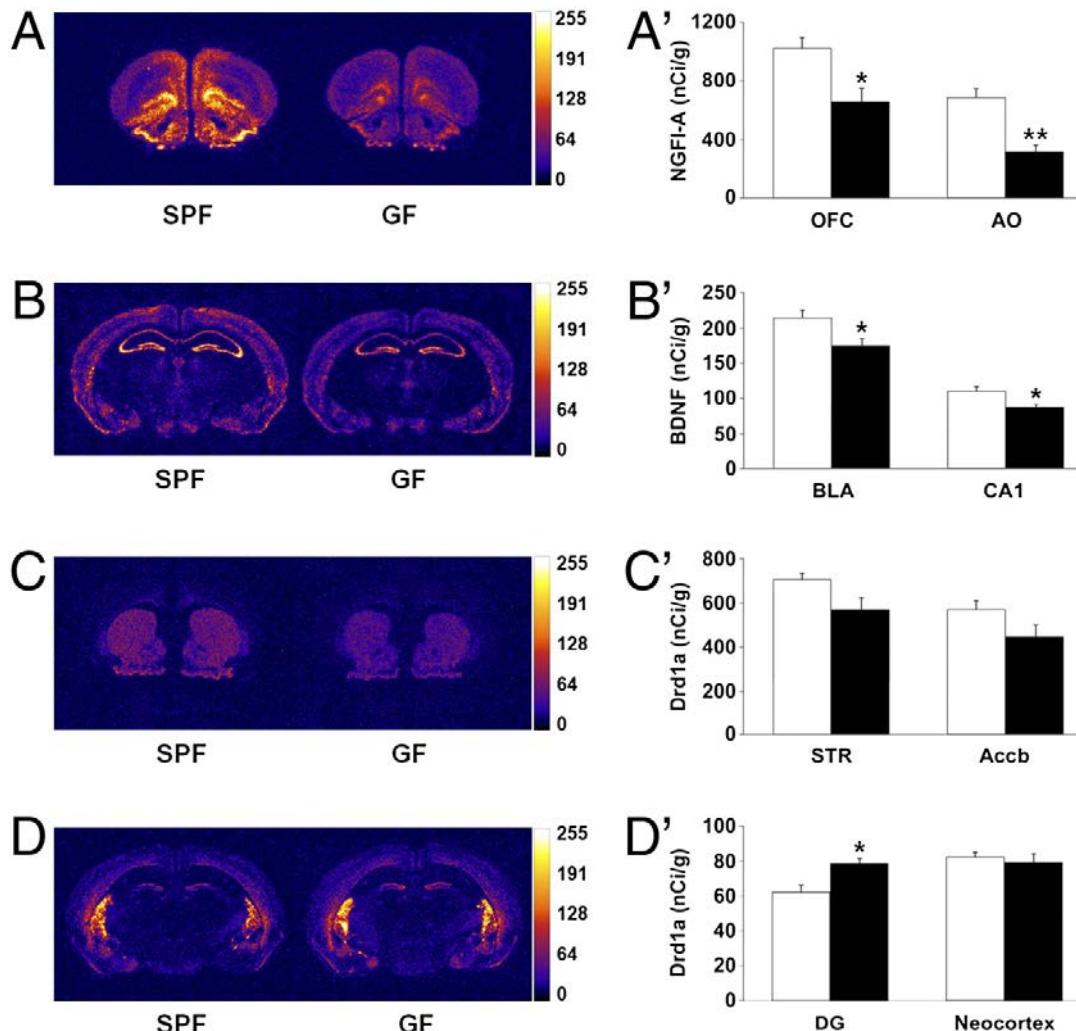
Microbiome and the Brain

Current Concepts

- Bidirectional relationship between brain and gut
- This is mediated by microbial communities
- This may be manifested through:
 - Developmental alterations in CNS
 - Vagal stimulation
 - Hormones
 - Changes in neurotransmitter precursors



GF mice show altered expression of anxiety and synaptic plasticity-related genes.



Rochellys Diaz Heijtz et al. PNAS 2011;108:7:3047-3052

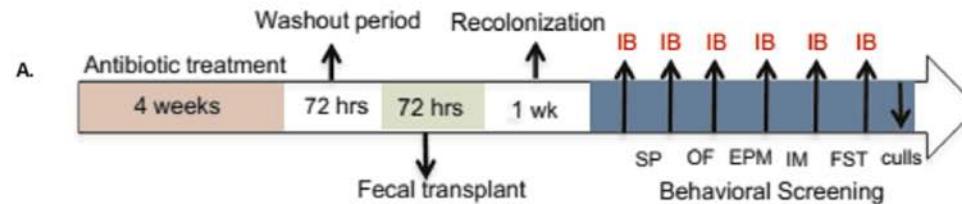
PNAS

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

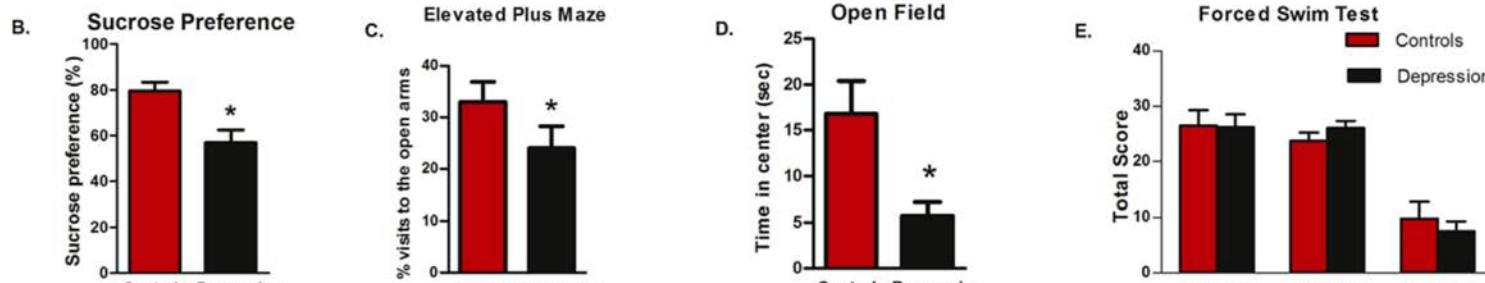


John R. Kelly ^{a, b}, Yuliya Borre ^a, Ciaran O' Brien ^{a, c}, Elaine Patterson ^{a, c}, Sahar El Aidy ^{a, d}, Jennifer Deane ^c, Paul J. Kennedy ^a, Sasja Beers ^a, Karen Scott ^a, Gerard Moloney ^a, Alan E. Hoban ^a, Lucinda Scott ^b, Patrick Fitzgerald ^a, Paul Ross ^c, Catherine Stanton ^c, Gerard Clarke ^{a, b}, John F. Cryan ^{a, e}, Timothy G. Dinan ^{a, b, *}

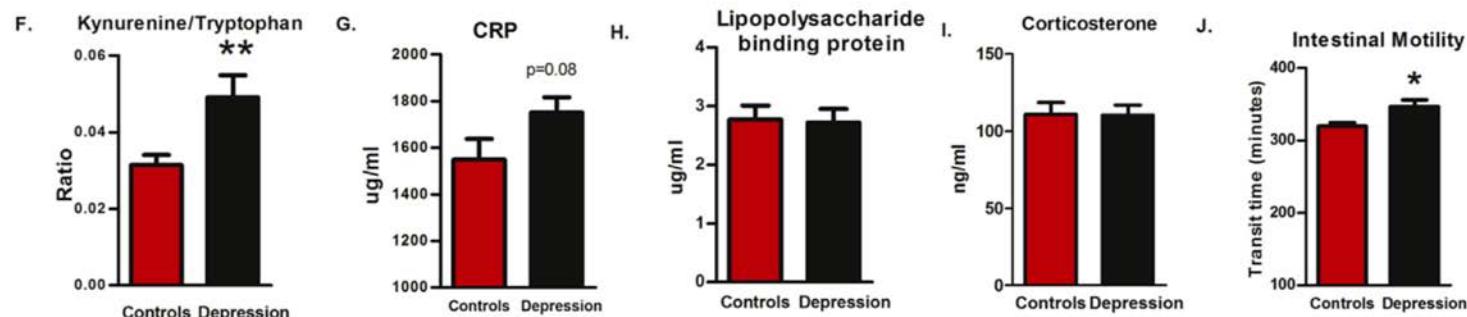
Experimental Design



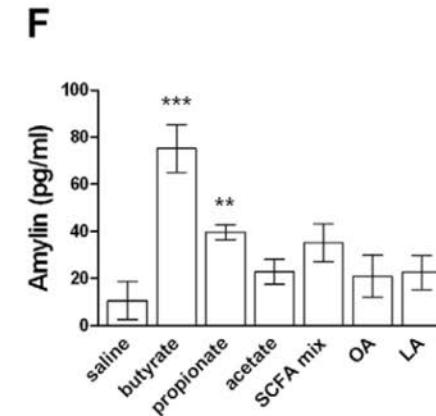
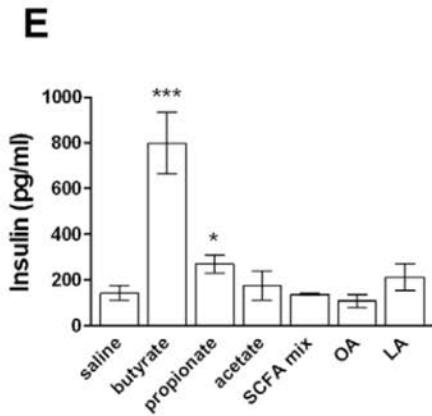
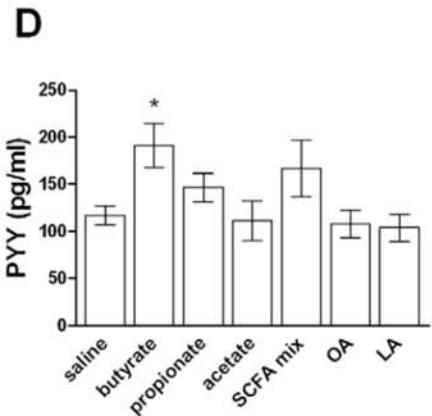
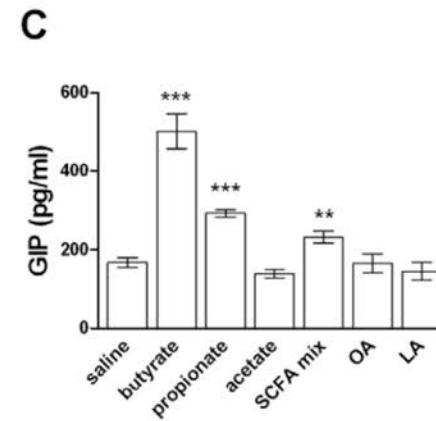
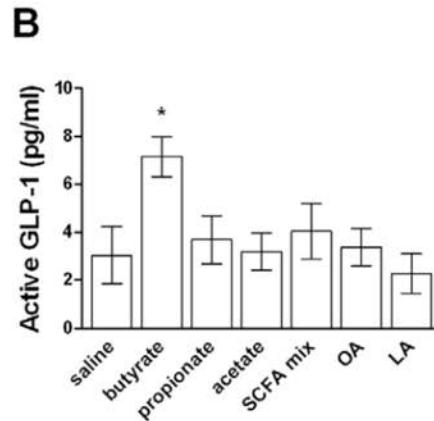
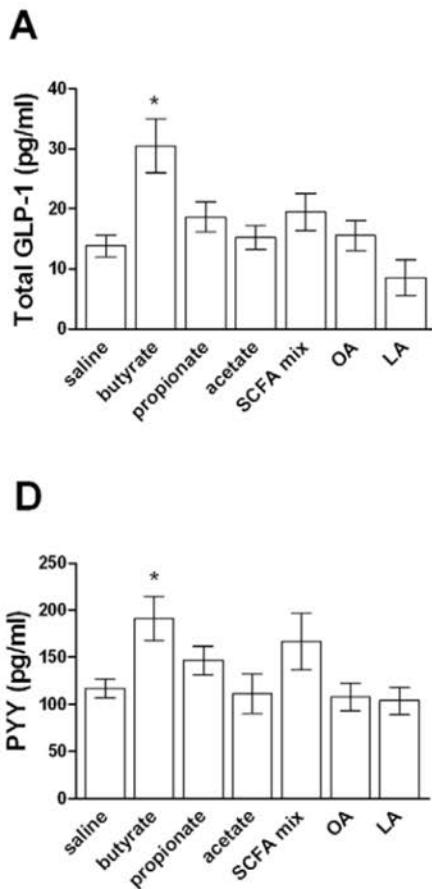
Behavioural Profile



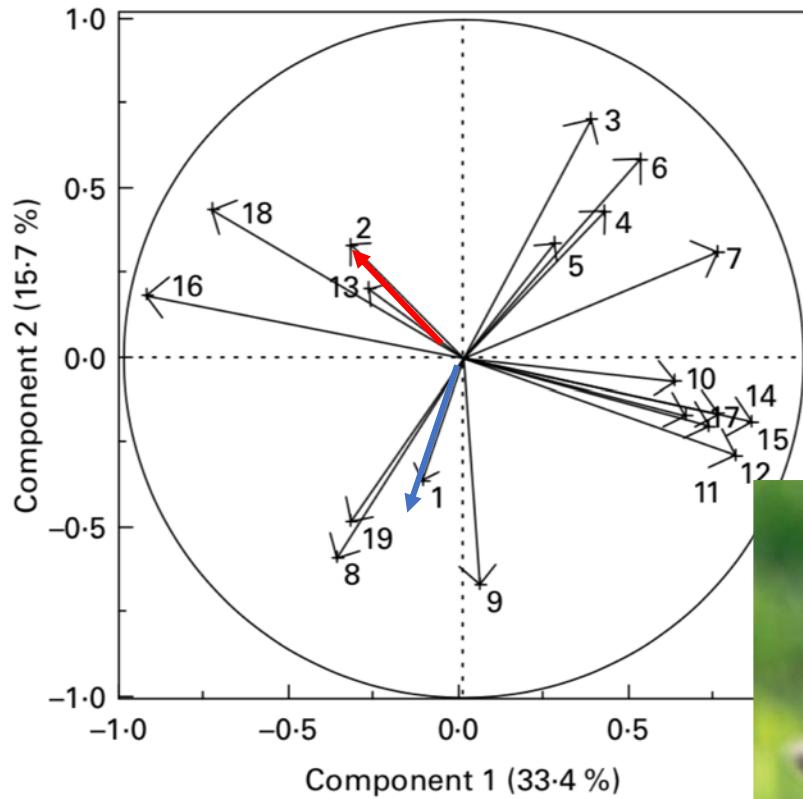
Physiological Profile



SCFA (Butyrate & Propionate) Increase Hormones that Reduce Food Intake



Hormonal response to microbiome and diet



Leptin
Ghrelin
Hooda, 2013; BDN



Humans



“Humans are a poor model of
mouse physiology”

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

- Supplementation with Fermented Milk Probiotic Product (FMPP)
- Reductions in negative affect
- Brain response to emotional faces task is reduced following FMPP (*Tillisch, 2013; Gastroent*)
- Structural alterations following FMPP (*Tillish, 2017; Psychosom Med*)

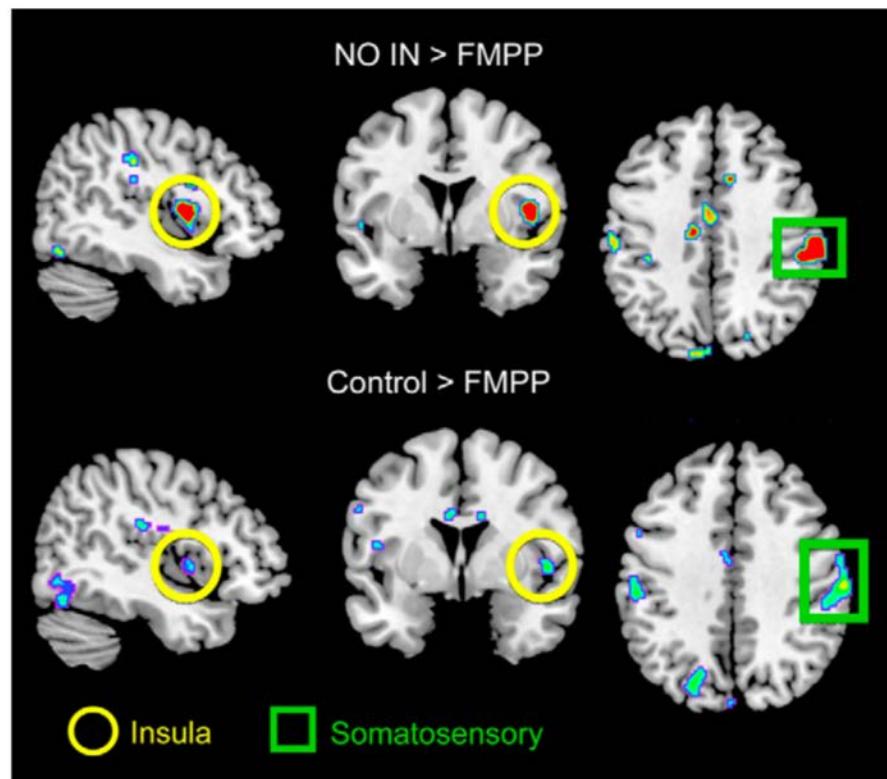
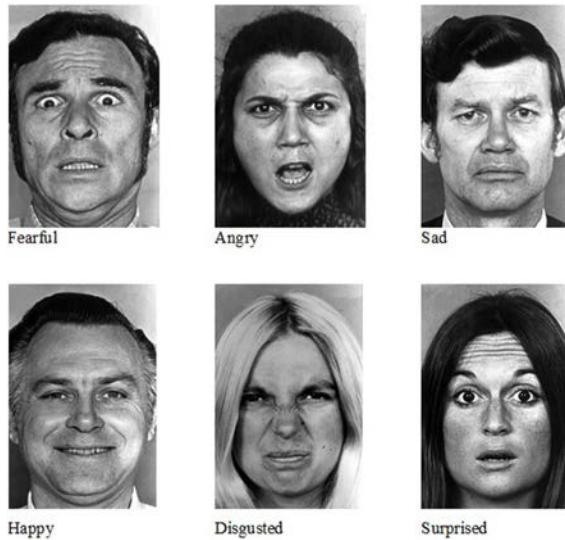
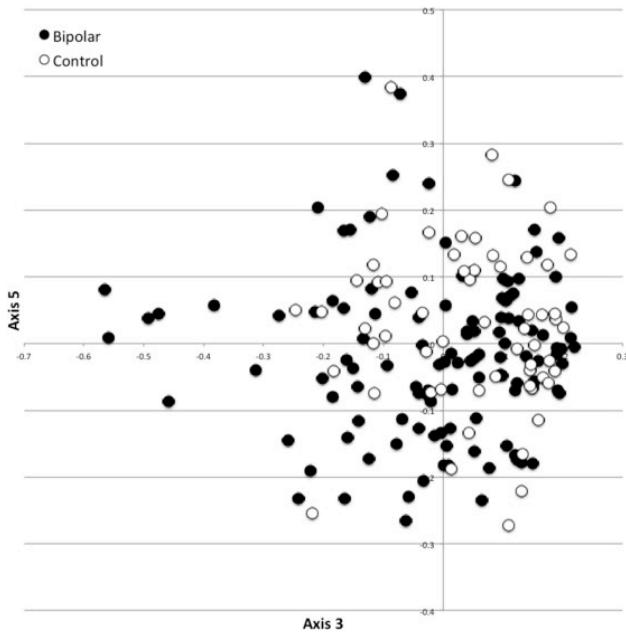


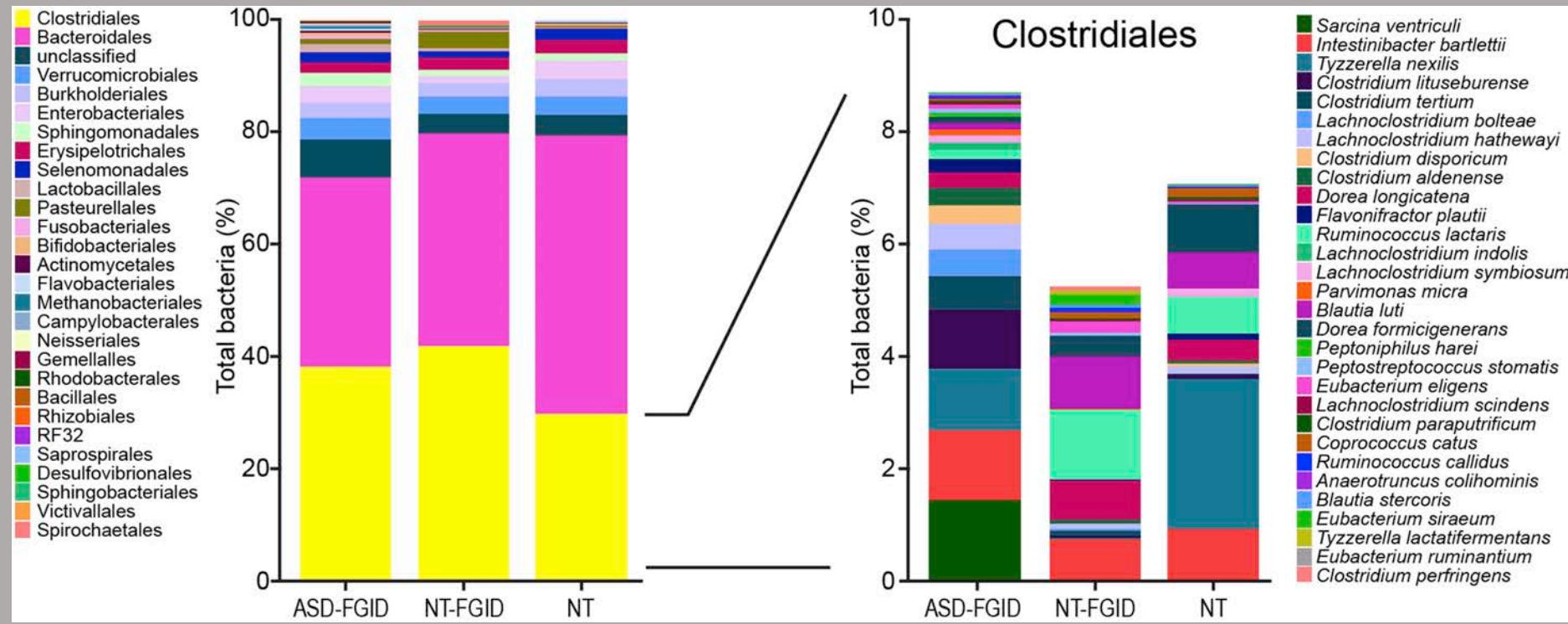
Figure 2. Regions showing reduced activity in response to an emotional faces attention task after FMPP intervention are shown, with significant regions demarcated.

Clinical Relevance – Bipolar Disorder



- All of the daily stool samples from the child with autism contained four organisms that earlier research had associated with autism. These included *Sarcina ventriculi*, *Barnesiella intestihominis*, *Clostridium bartletti*, and *Clostridium bolteae*. By contrast, none of these bacteria appeared in the stool of the unaffected sibling.

Clinical Relevance – Autism Spectrum Disorder



Luna, 2017; Cell Mol Gastro Hepat

Changing the Diet

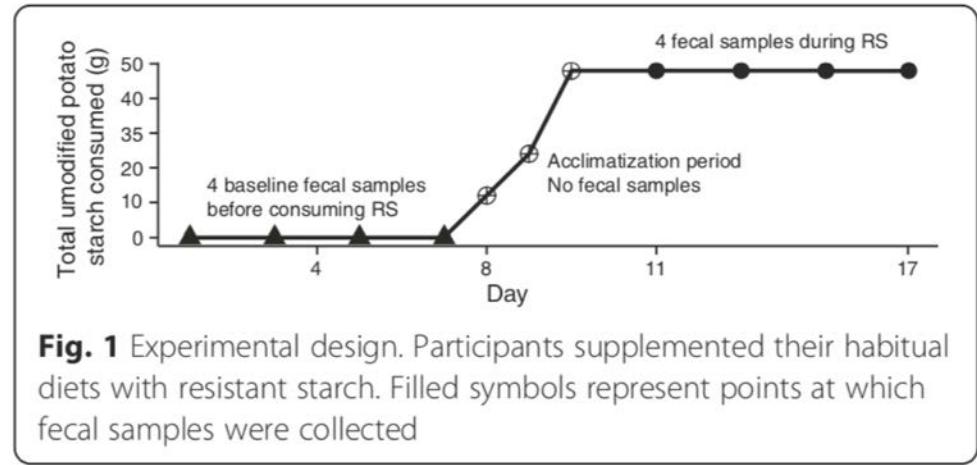
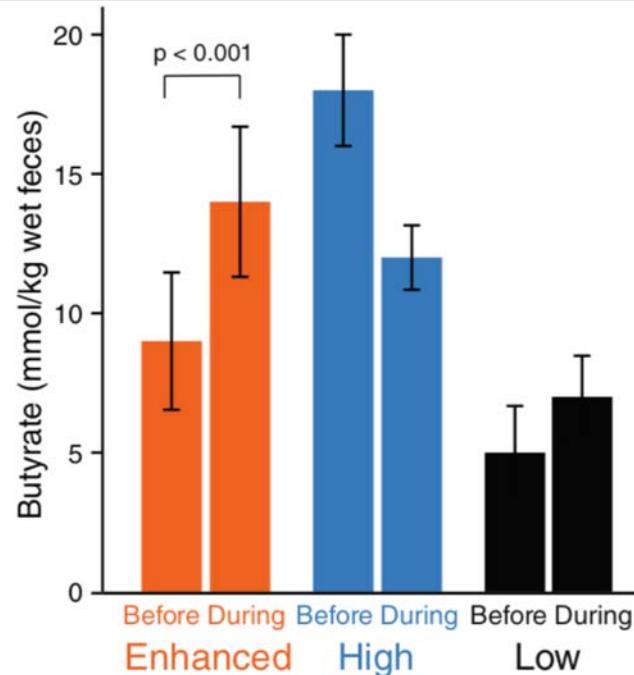
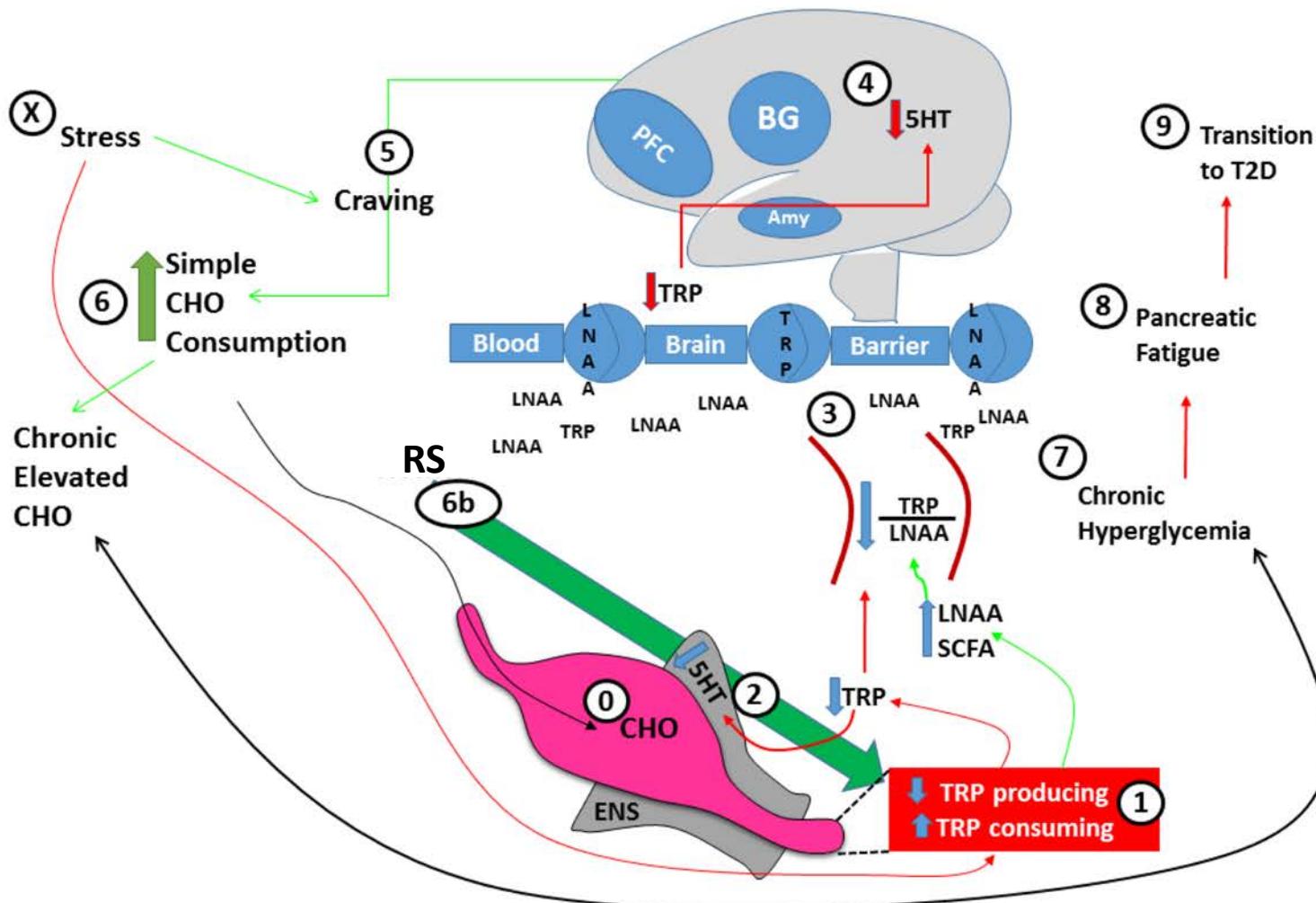


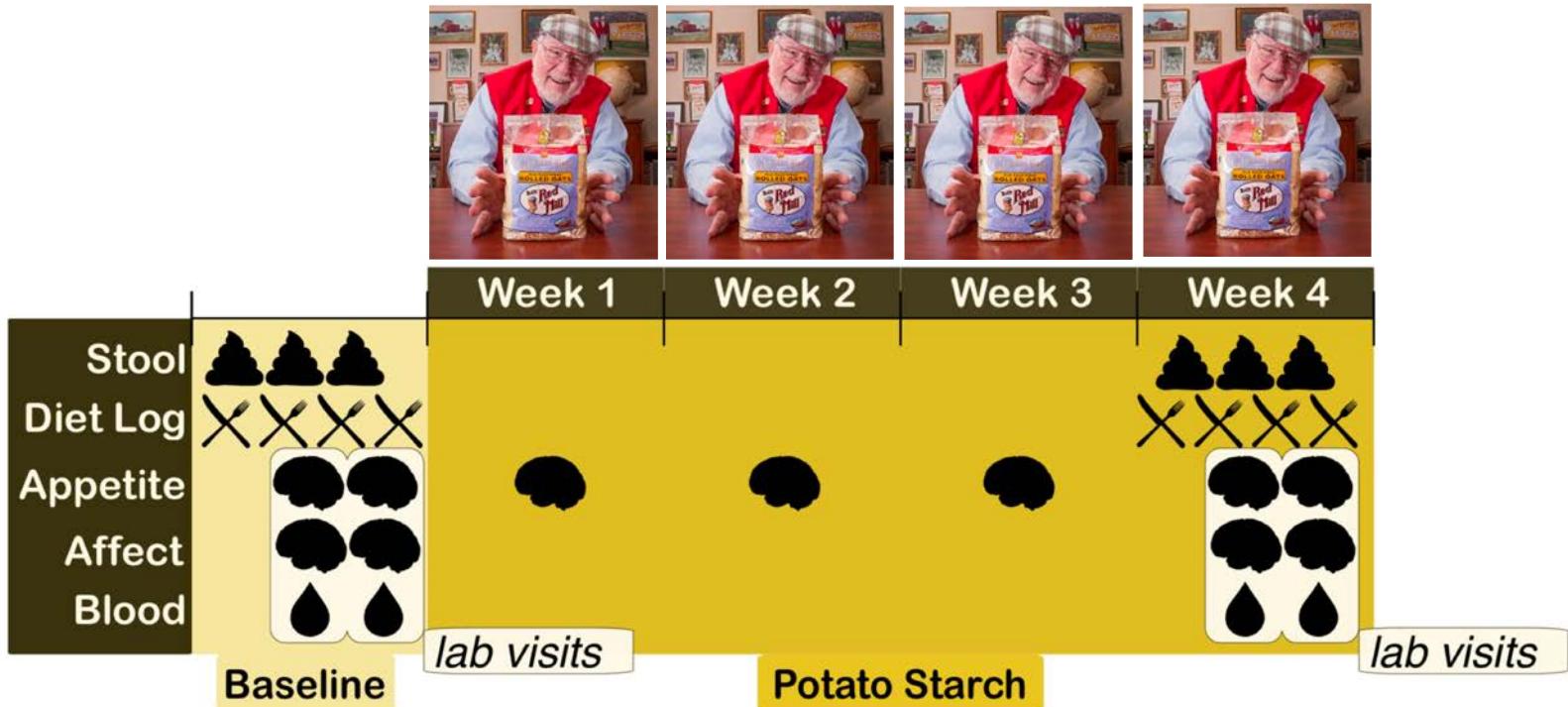
Fig. 1 Experimental design. Participants supplemented their habitual diets with resistant starch. Filled symbols represent points at which fecal samples were collected

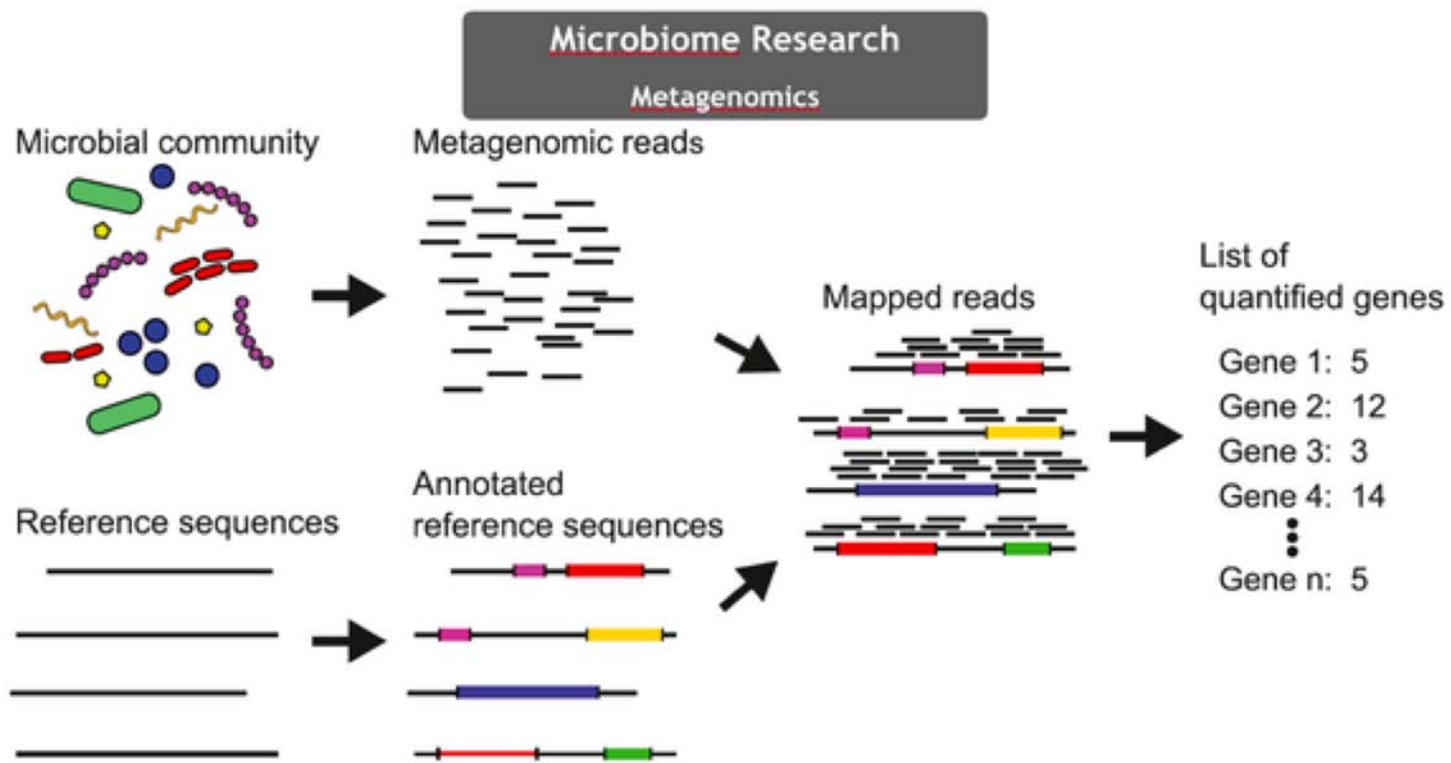


Individual's with microbiomes enhanced in *B. adolescentis* have increased Butyrate production in response to RS consumption

Venkataraman, 2016; Microbiome





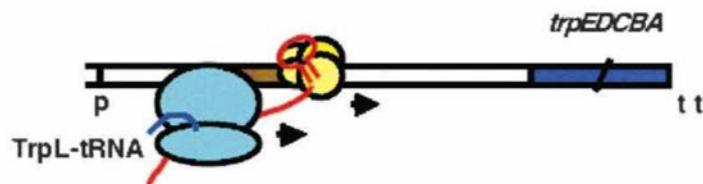


16s DNA sequencing

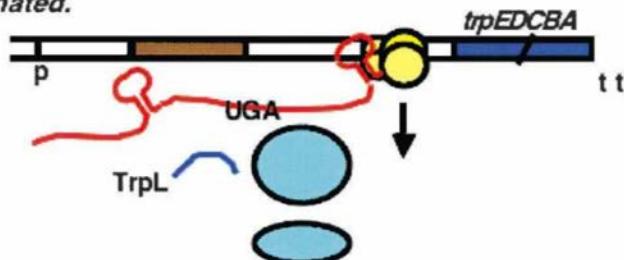
- Tells you who is there, but you have no idea what they are doing
- Can we start to understand function?

Regulation of TRP producing/sensing genes in bacteria

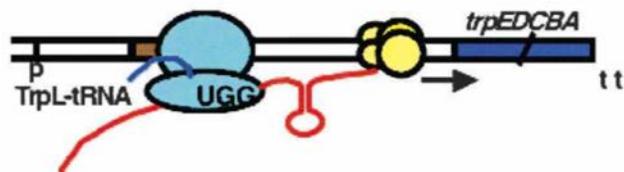
Stage 1. Transcription begins - polymerase pauses, translation begins, moving ribosome releases the paused polymerase.



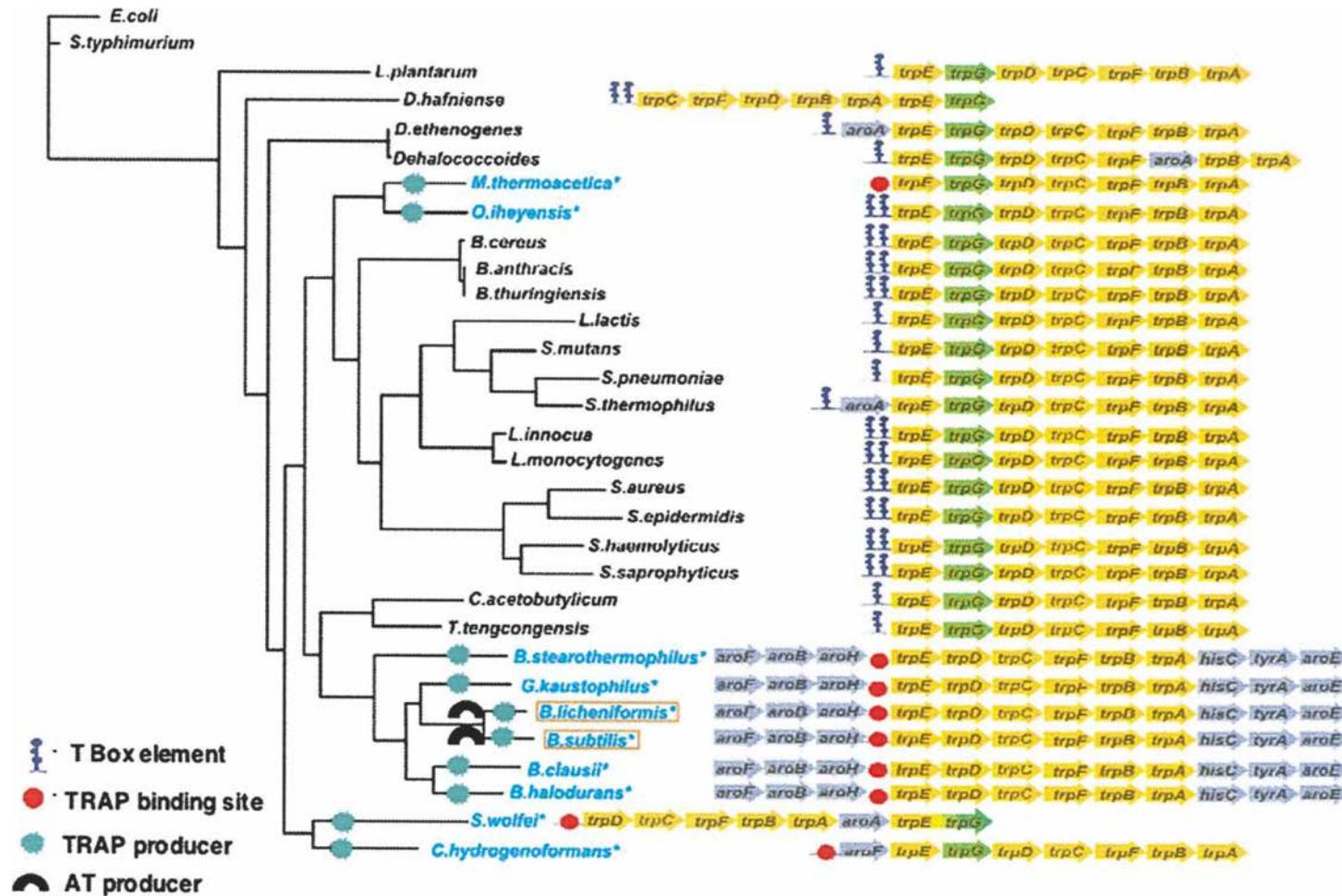
Stage 2a. Adequate charged tRNA^{Trp} - Peptide is synthesized and released, ribosome is released, anti-antiterminator and terminator form, transcription is terminated.



Stage 2b. Deficiency of charged tRNA^{Trp} - Ribosome stalls at one of two Trp codons of trpL and the antiterminator forms, preventing formation of the terminator; the polymerase resumes transcription.



Regulation of TRP producing/sensing genes in bacteria



So far....

- Dietary RS supplementation
 - Alters community
 - Influences nutrients available to host
 - Reduces IL18, and increases prolactin
 - Decreases negative affect
 - Alters gene expression in tested species

Today's Talk

- What is Microbiome
 - Definition
 - Locational Diversity
 - Gut
- Factors that impact Microbiome
 - Environment
 - Diet
 - Behavior
 - Sex
 - Life exposure/Adaptation
 - Mode of Birth
 - Germ Free as an extreme example
 - Changes in assisted living → links to frailty
- Gut microbiome and brain
 - Routes
 - Vagal stimulation
 - Neuroimmune
 - Hormonal
 - Metabolite
 - SCFA
 - Amino Acids
 - Brain to gut influence
- Clinical impacts
- Dietary intervention can influence microbiome and host-brain relationship

Thank you



- crème-lab
 - Andrew Neff
 - Katlin Chappelle
 - Kasia Nowak
 - Chelsea Schwartz
 - Armita Bahadori
 - Jyoti Saha
 - Sommer Pappas
- Collaborators
 - Jeffry Stanley, PhD
 - Kevin Theis, PhD
 - Otto Muzik, PhD



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www.creme-lab.org