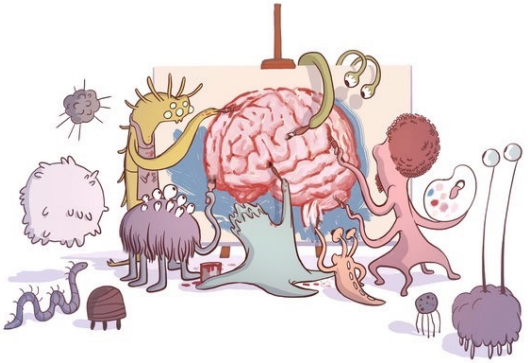
Annual meeting of the Nutritional Leadership Network, Oakland, April 10-11, 2024

Mental Health & the Microbiome

Emeran A. Mayer, MD



emeranmayer.com
UCLACNS.org

Disclosures

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- Axial Biotherapeutics
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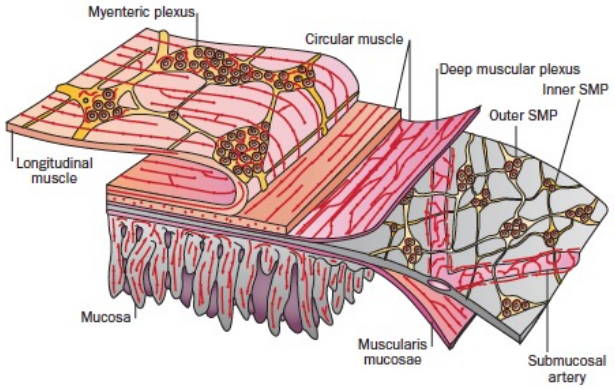
- Seed

My presentation does not endorse any of the listed companies or promote any of their products

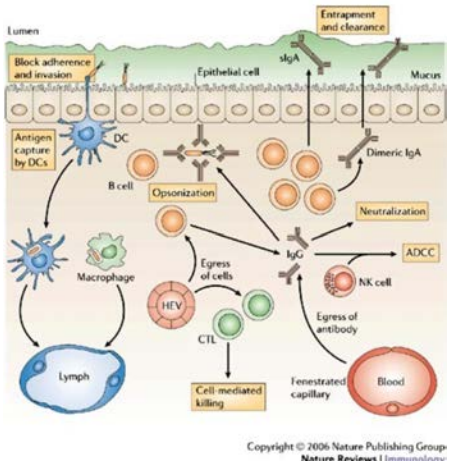
Overview

- The Gut and Brain Connectomes 101
- The bidirectional communication within the Brain Gut Microbiome (BGM) system
- Diet and Lifestyle in BGM Interactions
- Role of altered BGM system in brain disorders

The 3 Components of the Gut Connectome

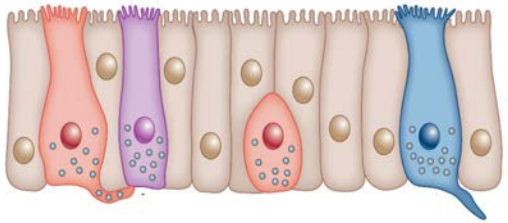


The Enteric Nervous System – The "Second Brain"



The Gut-Based Immune System

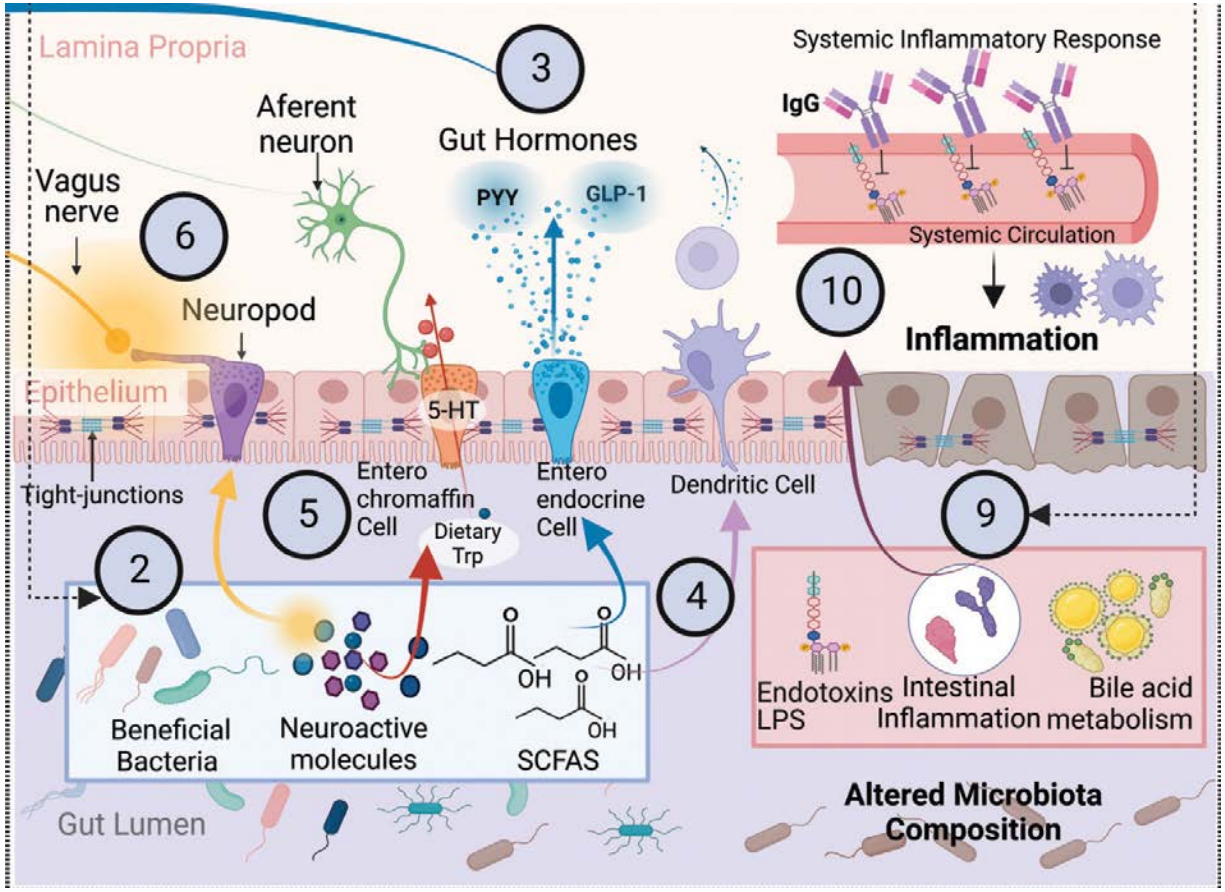
Hormone producing Cells in the Gut



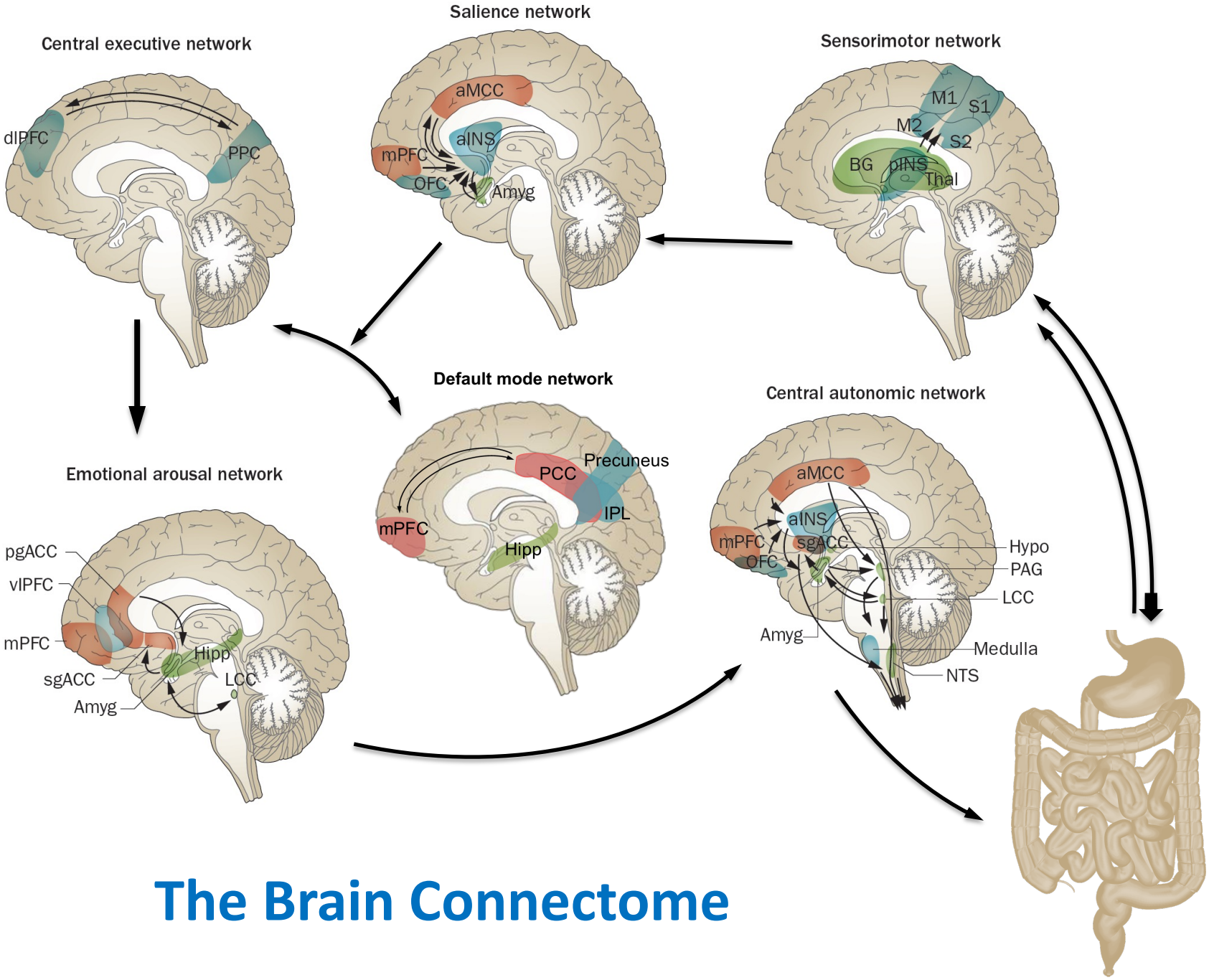
The Gut Endocrine System

The Gut Connectome – The Second Most Complex Organ in the Body

- 70% of immune system
- Enteric nervous system: 150 M neurons
- Glial and epithelial cells
- Extrinsic innervation
- Endocrine system
- Inhabitated by 100 T microbes



The Healthy Gut:
Coordinated interactions of neurons, immune cells, endocrine cells and luminal microbial organisms (”the gut connectome”)

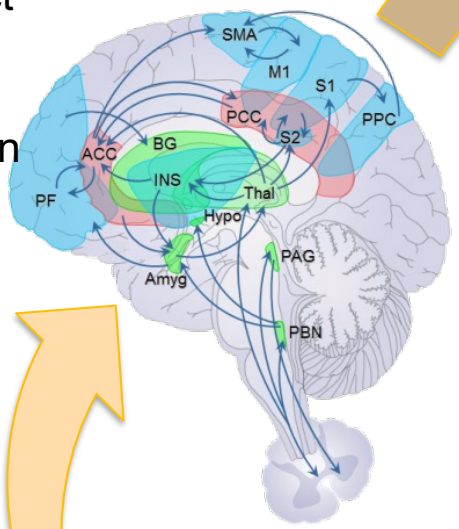


The Brain Connectome

Bidirectional Communication in the BGM System

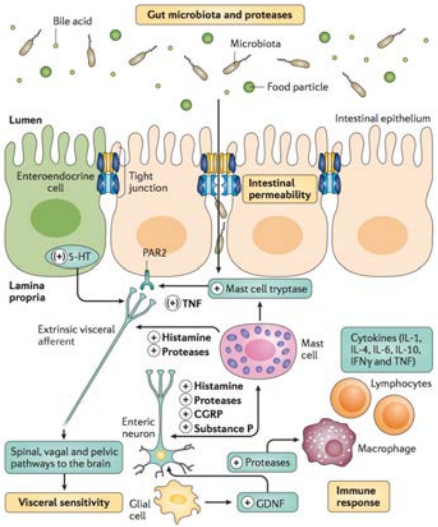
Alterations in brain networks:

- Stress react
- Anxiety
- Sensory perception



Stress:

- Chronic stress
- Early adverse life events
- Trauma



Stress- induced alterations of gut connectome

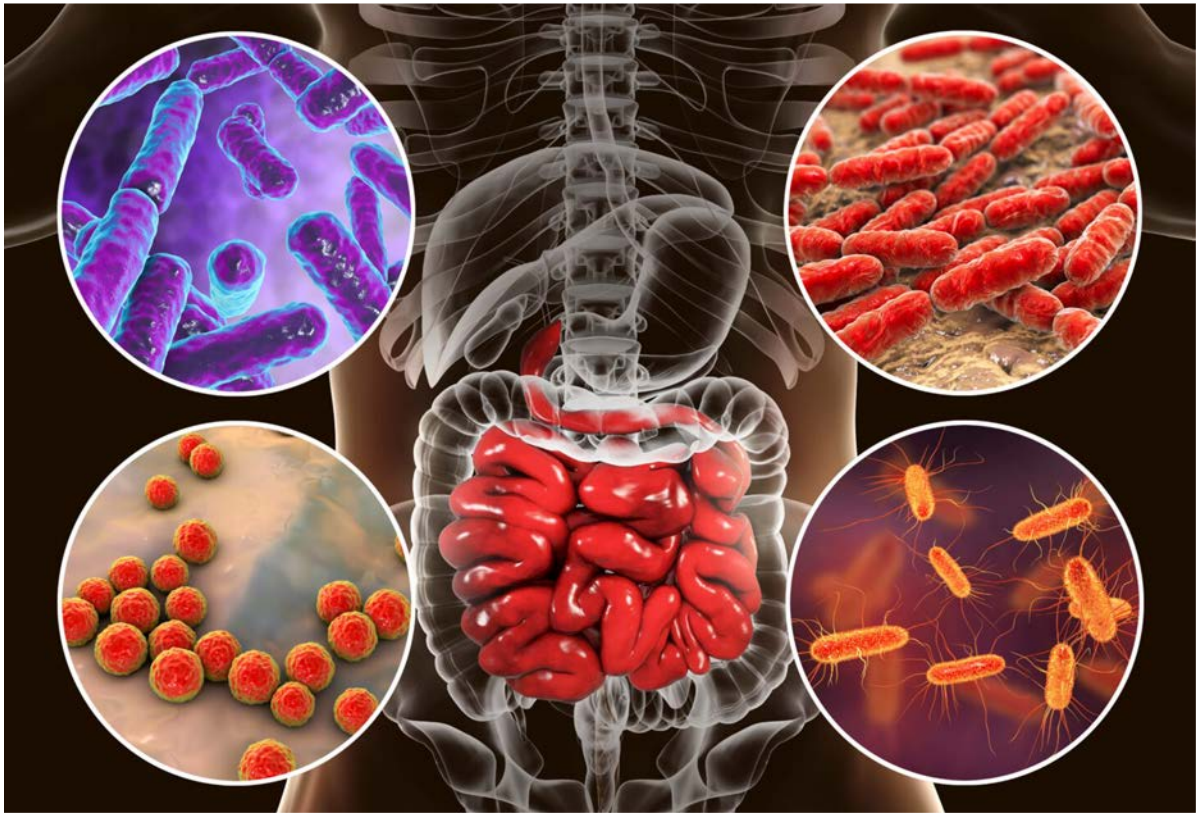
- Dysbiosis
- Increased gut permeability
- Immune activation

Alterations in gut brain signaling

- Microbioal neuroactive metabolites
- Immune mediators

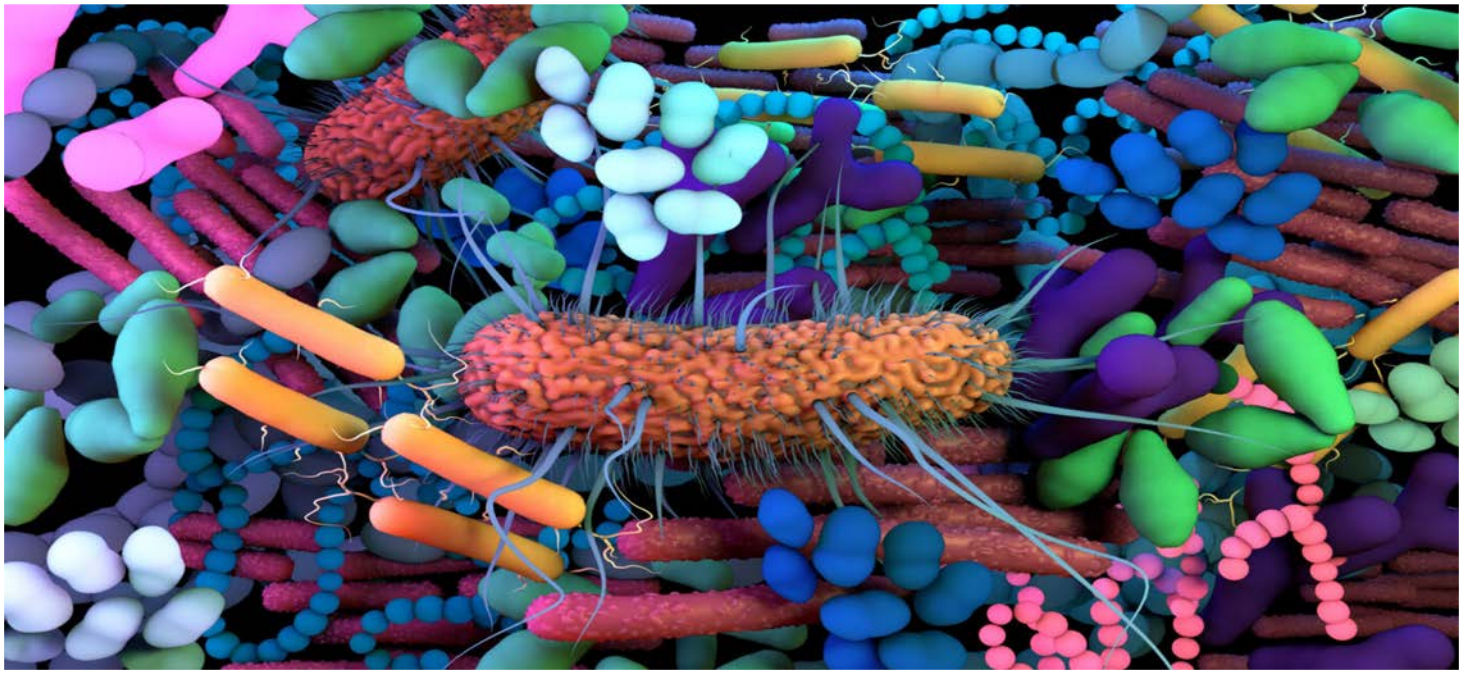
Brain Gut Microbiome 101

The Microbiome Revolution



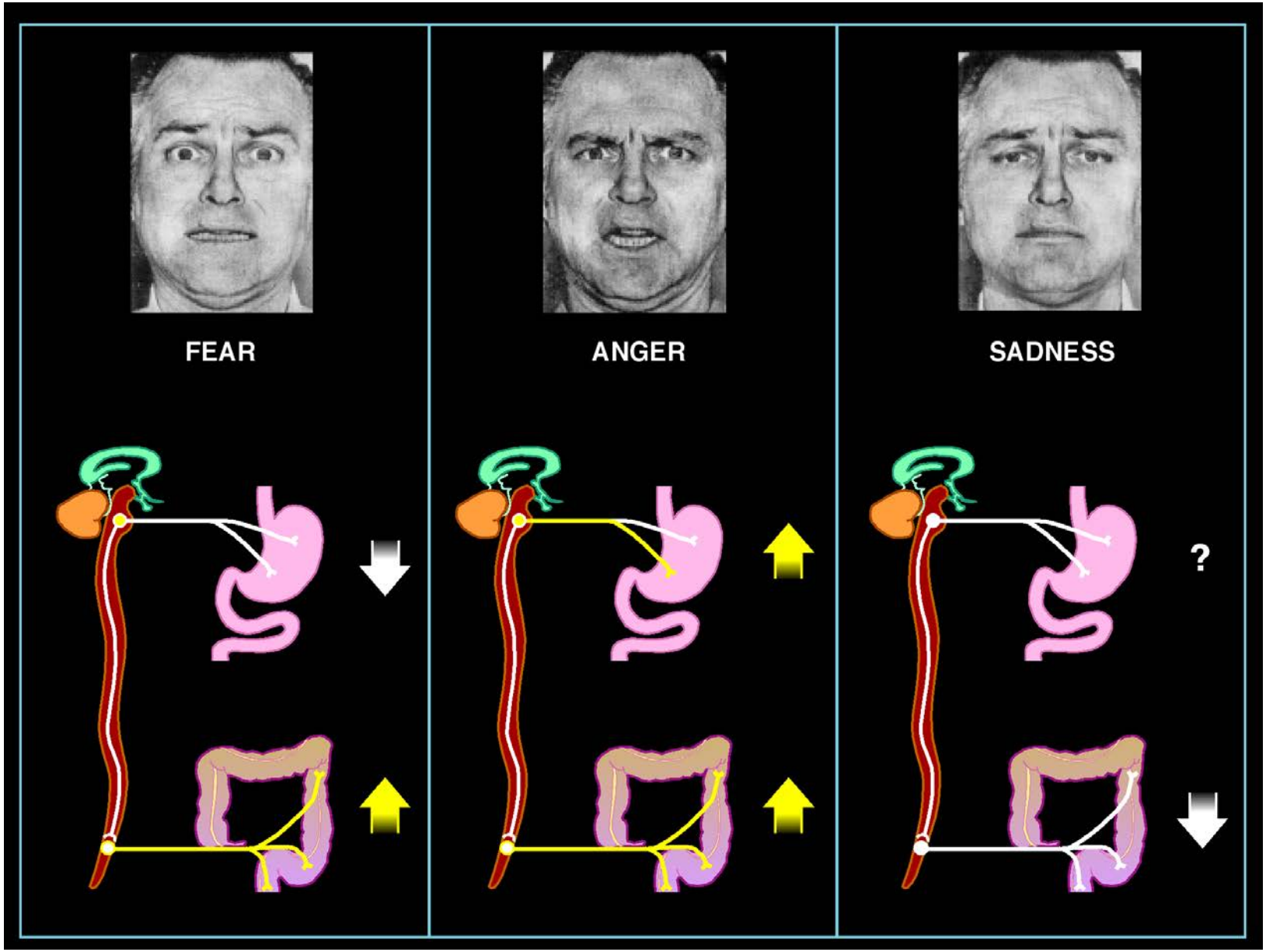
- There are five nonillion (1 followed by 54 zeros) bacteria in the Earth's ecosystem, including the ones found in living beings
- Microbes are the oldest and most abundant lifeform on the planet (>4 B years)
- Microbes are the second biggest biomass on earth (70 G tons, 15% of global) only surpassed by plants
- Microbes make up 70% of marine biomass

The Human Gut Microbiome



- Highest density of microbes in the human colon
- 100 trillion microorganisms (bacteria, archae, fungi), 40% of number of human cells; 10x > than neurons in the brain
- Holobiont – Human organism and microbial species have lived in symbiosis for a million years
- Mutually beneficial interactions between host and gut microbiome influence human physiology, metabolism, nutrition and immune function

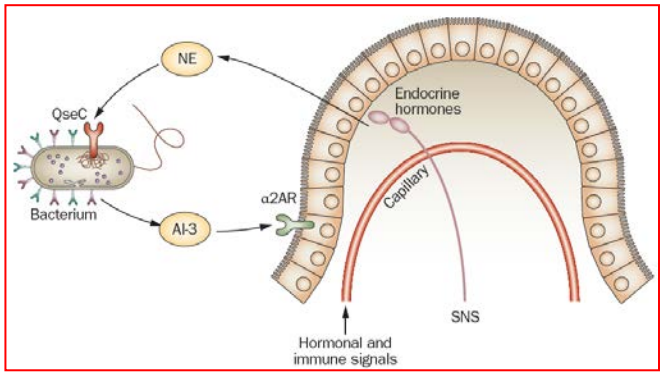
The Brain Talks to the Gut



Stress and Emotion Modulation of Gut Microbial Behavior

Psychosocial Stress

Anxiety, fear
Anger
Sadness



Stress-induced changes of gut microbes and their environment:

- GI motility (regional alterations in intestinal transit)
- Intestinal fluid and mucus secretion (biofilm?)
- Gastric/bile acid secretion
- Paneth cell secretion (antimicrobials)
- **Enteroendocrine cell function**
- Intraintestinal pH
- **Immune modulation**
- Epithelial and blood brain barrier permeability

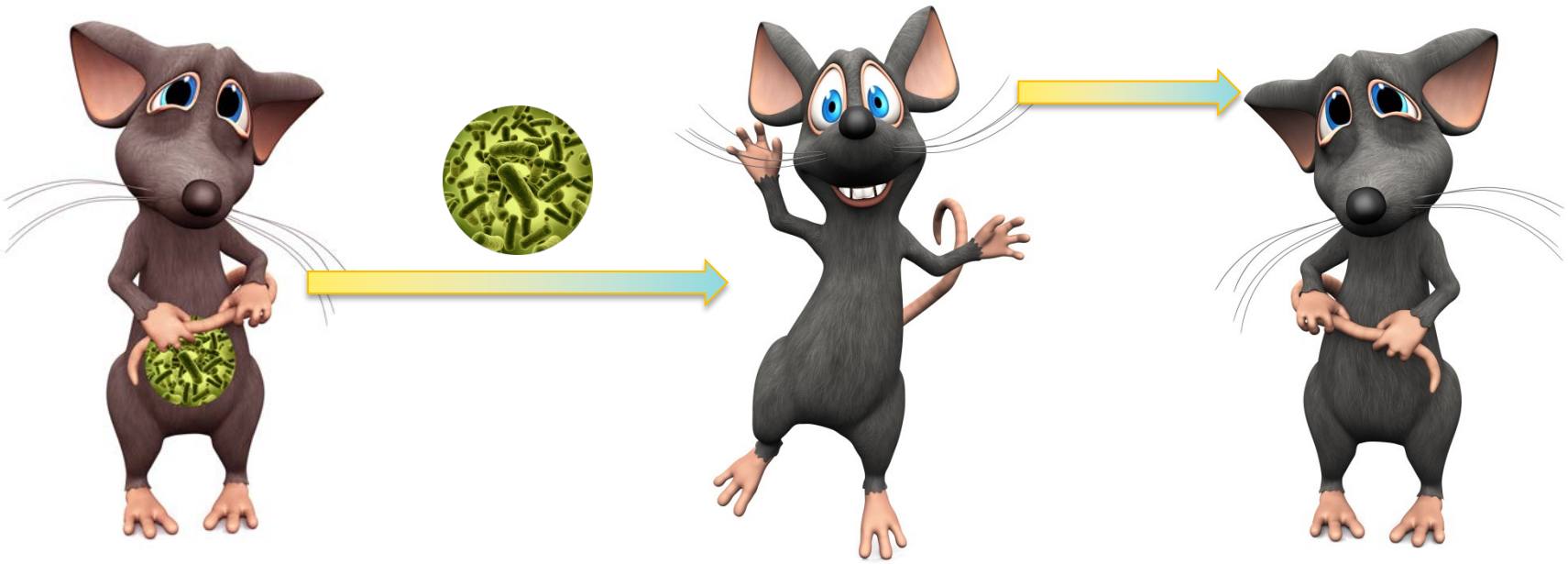
Rhee et al. NRGH 2009

The Gut Talks to the Brain

Timid "Introvert"

Outgoing "Extrovert"

Timid "Introvert"

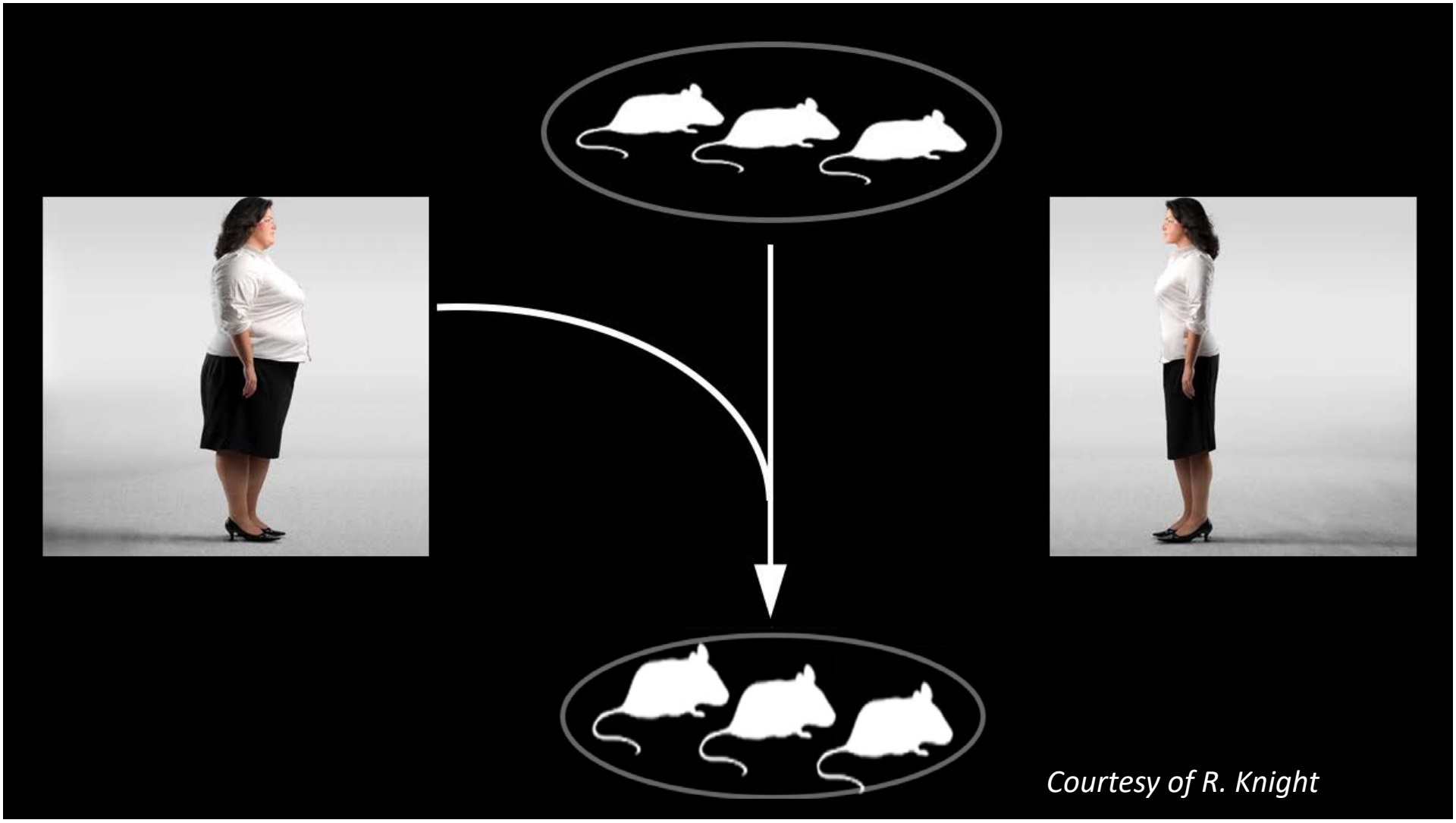


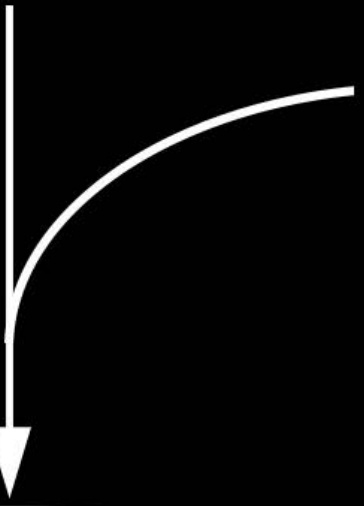
Normal gut microbes

Germ-free

Transplanted

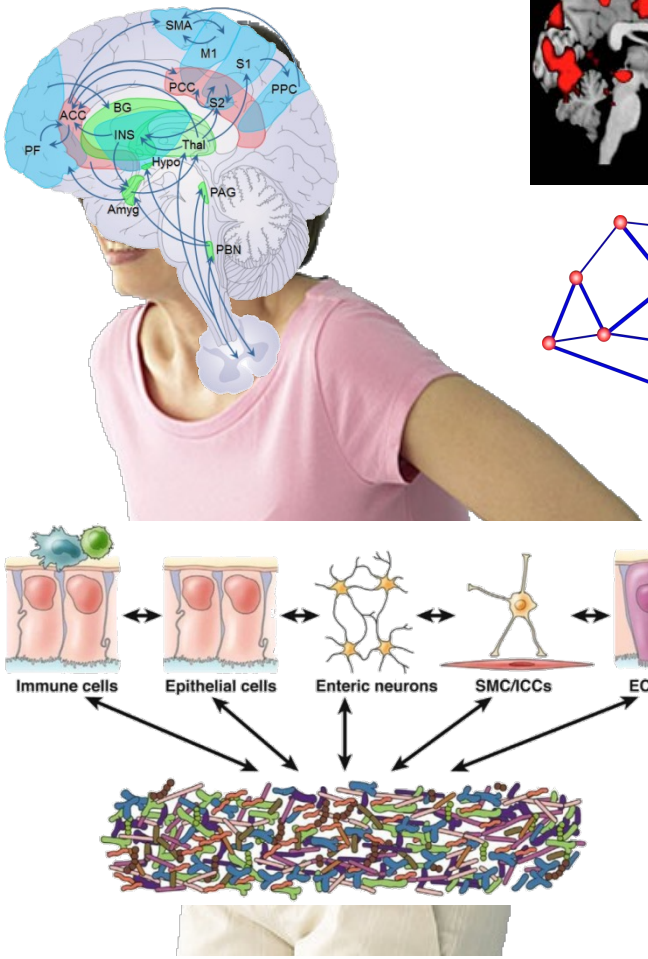
Cryan & Dinan, Nat reviews 13:701-12, 2012

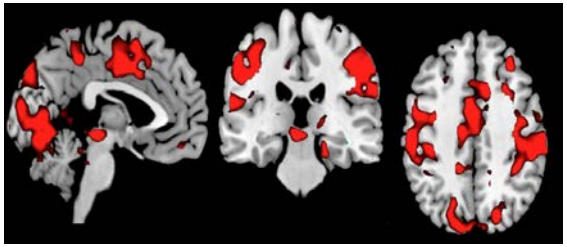

Courtesy of R. Knight

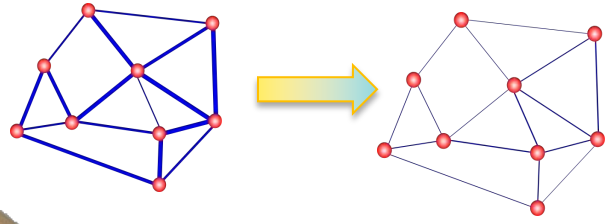


Courtesy of R. Knight

Microbes in the Gut Can Talk to the Human Brain

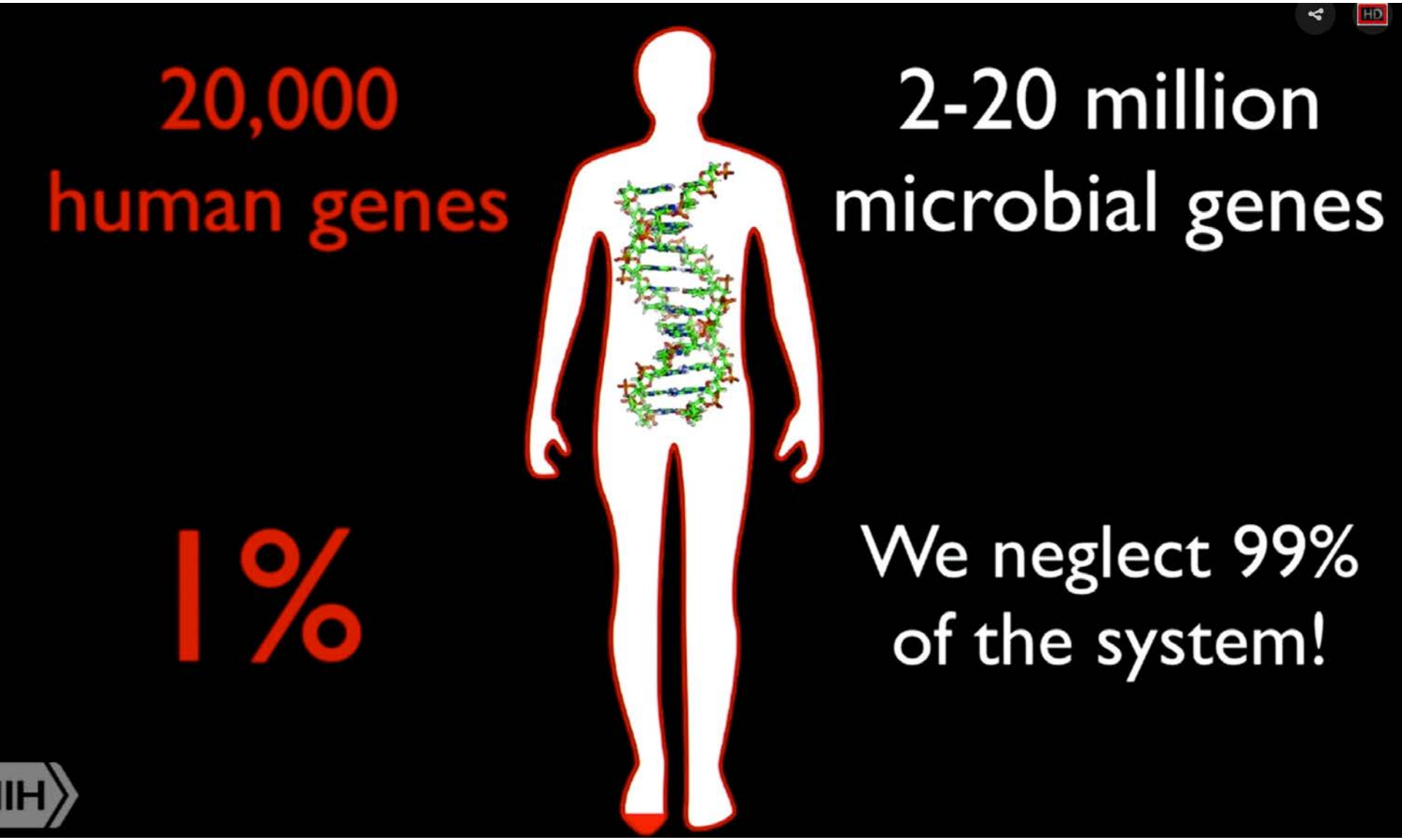






Tillisch, Mayer et al, Gastroenterology 2013

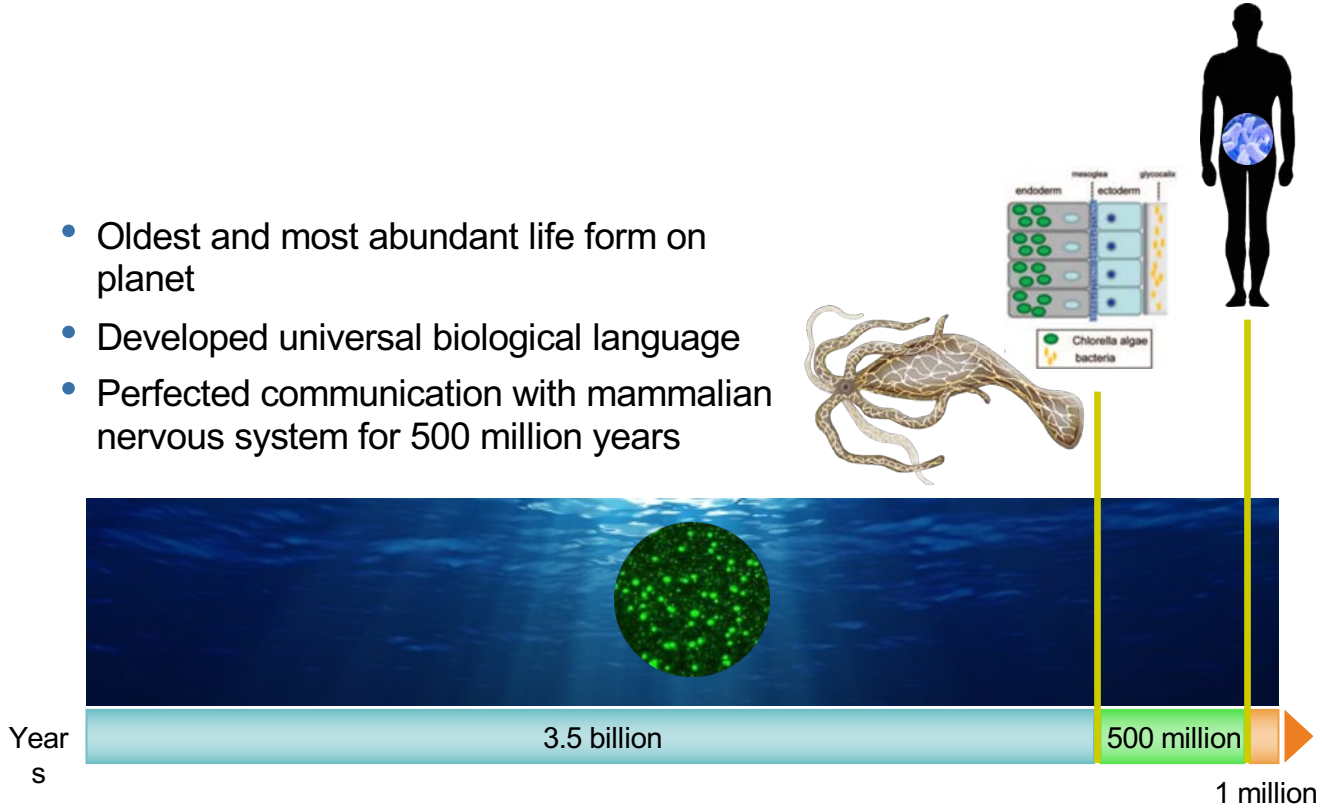
The Human Microbiome – We Are Only Scratching On the Surface



Presented by Dr. R. Knight at NIH Emerging Themes symposium, August 16-18, 2017

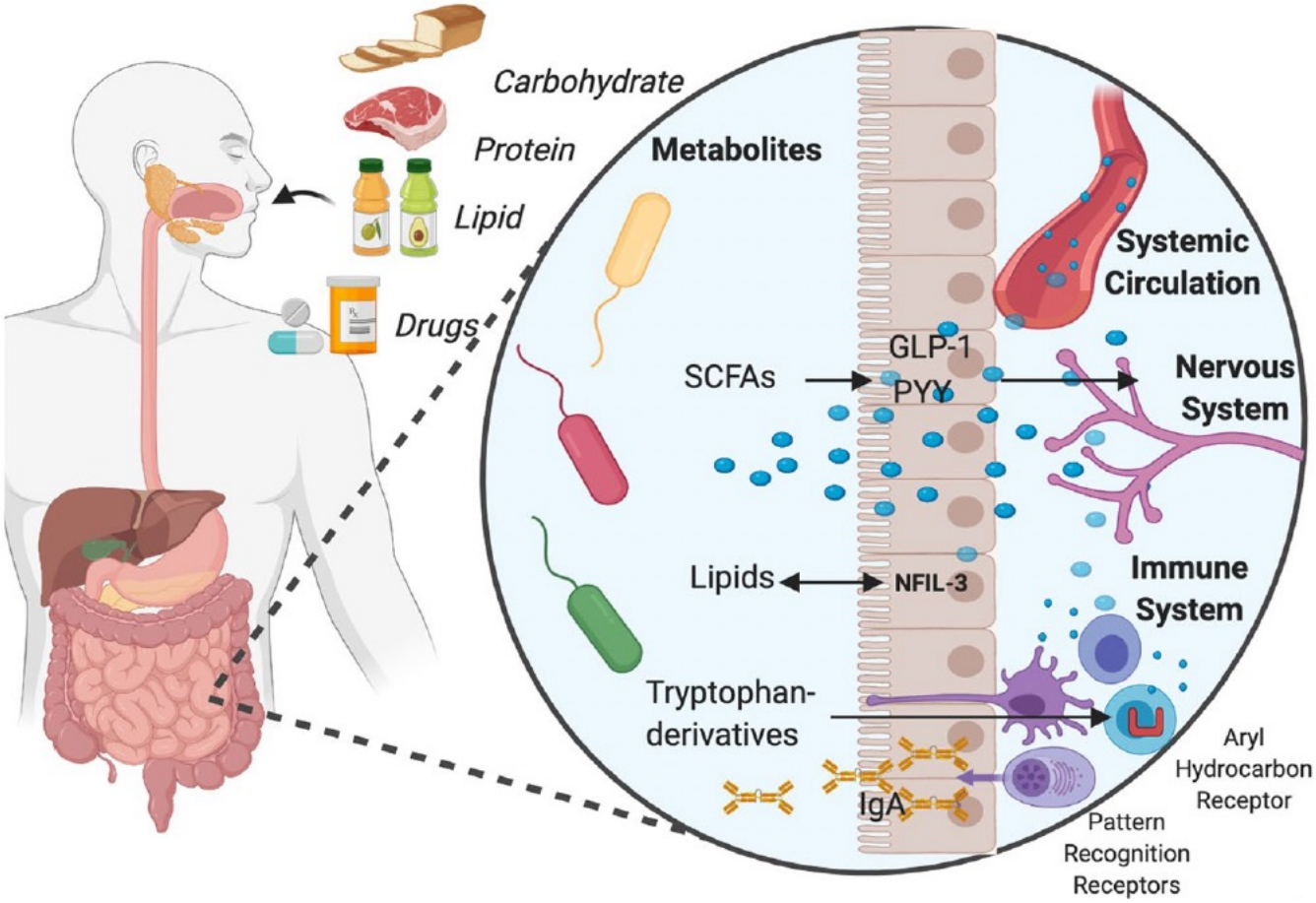
Why is there Communication Between the Gut Microbes and the Brain?

- Oldest and most abundant life form on planet
- Developed universal biological language
- Perfected communication with mammalian nervous system for 500 million years

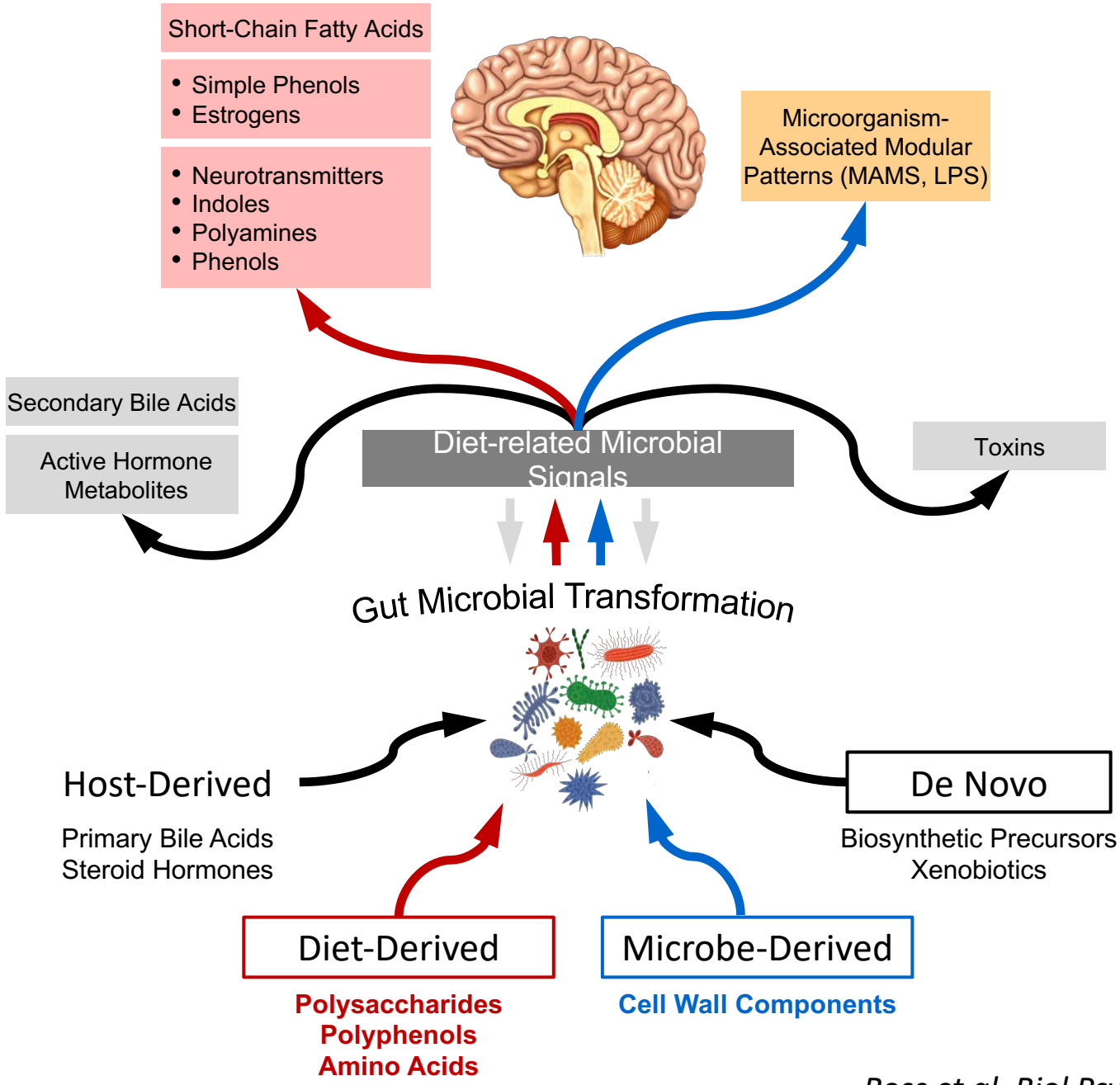


Emeran Mayer TEDx 2015

Biological Language 2.0: The Microbiome Translates Food Components into Thousands of Biologically Active Metabolites

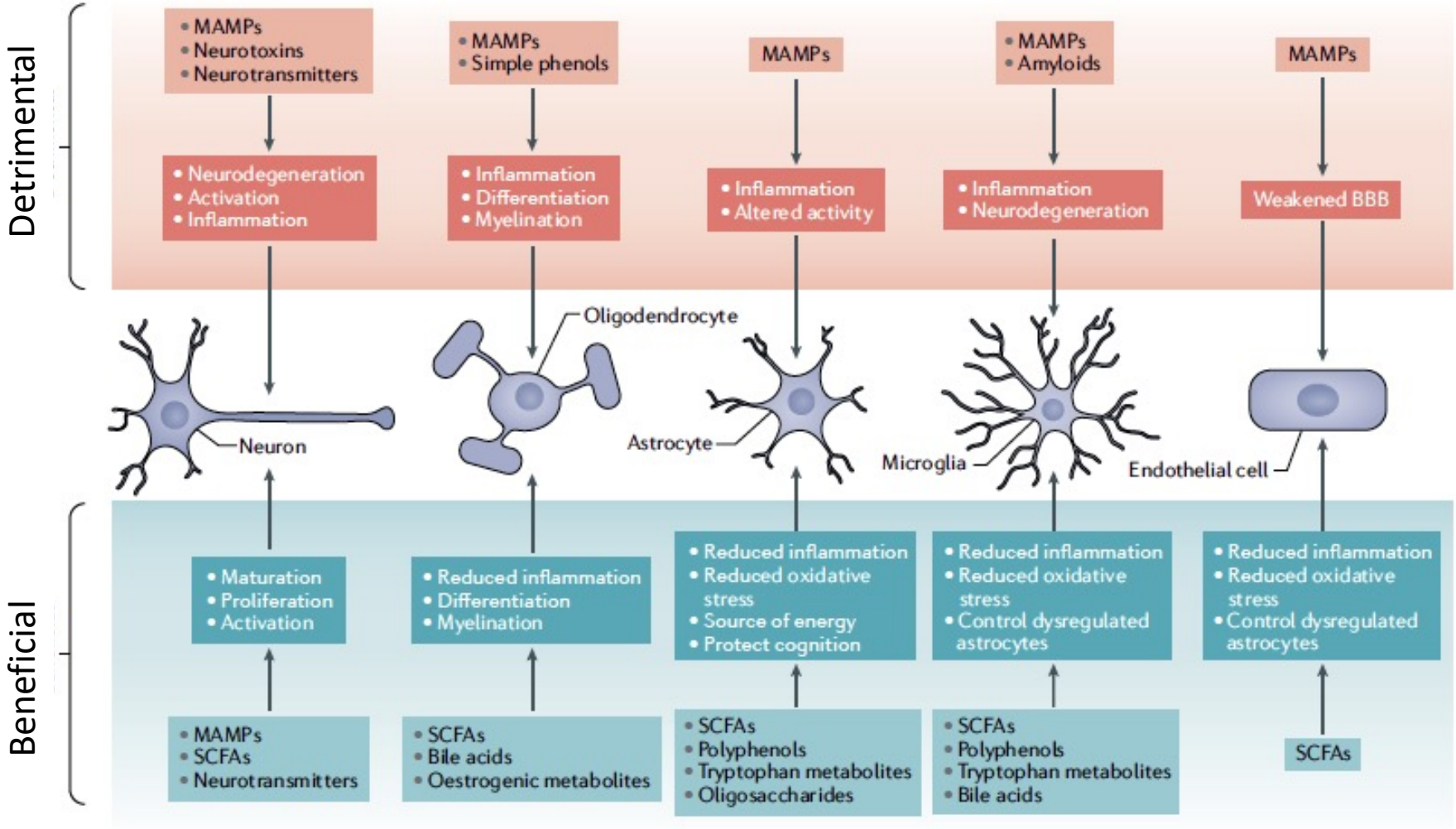


Cox et al. Genome Medicine 2022



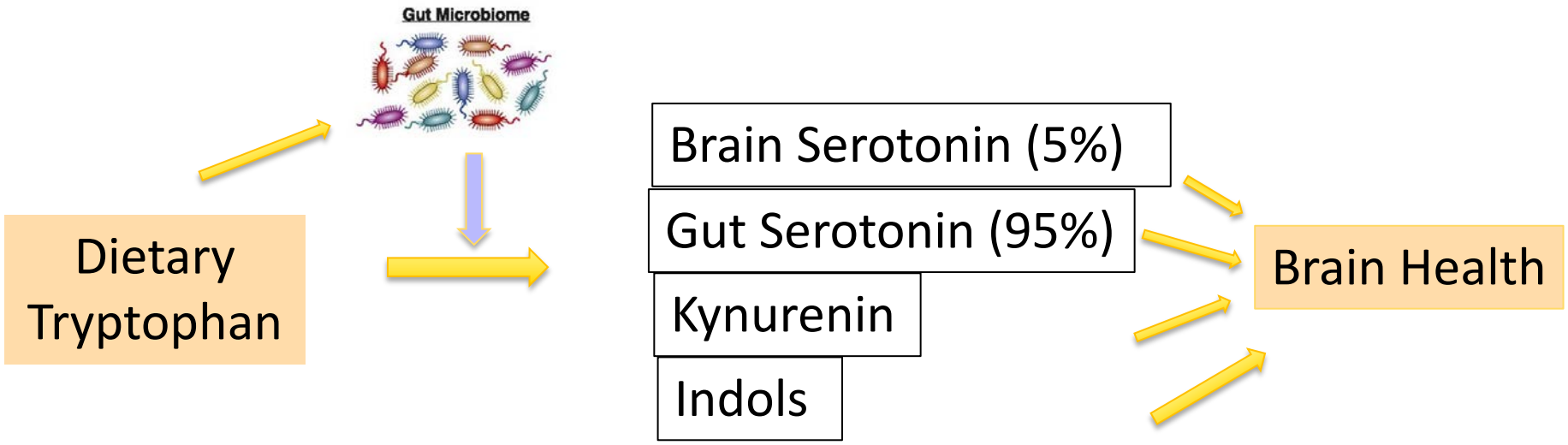
Ross et al. Biol Psychiatry 2024

The Yin and Yang of Gut Microbe to Brain Signaling - Inflammatory and Antiinflammatory Influences on the Brain



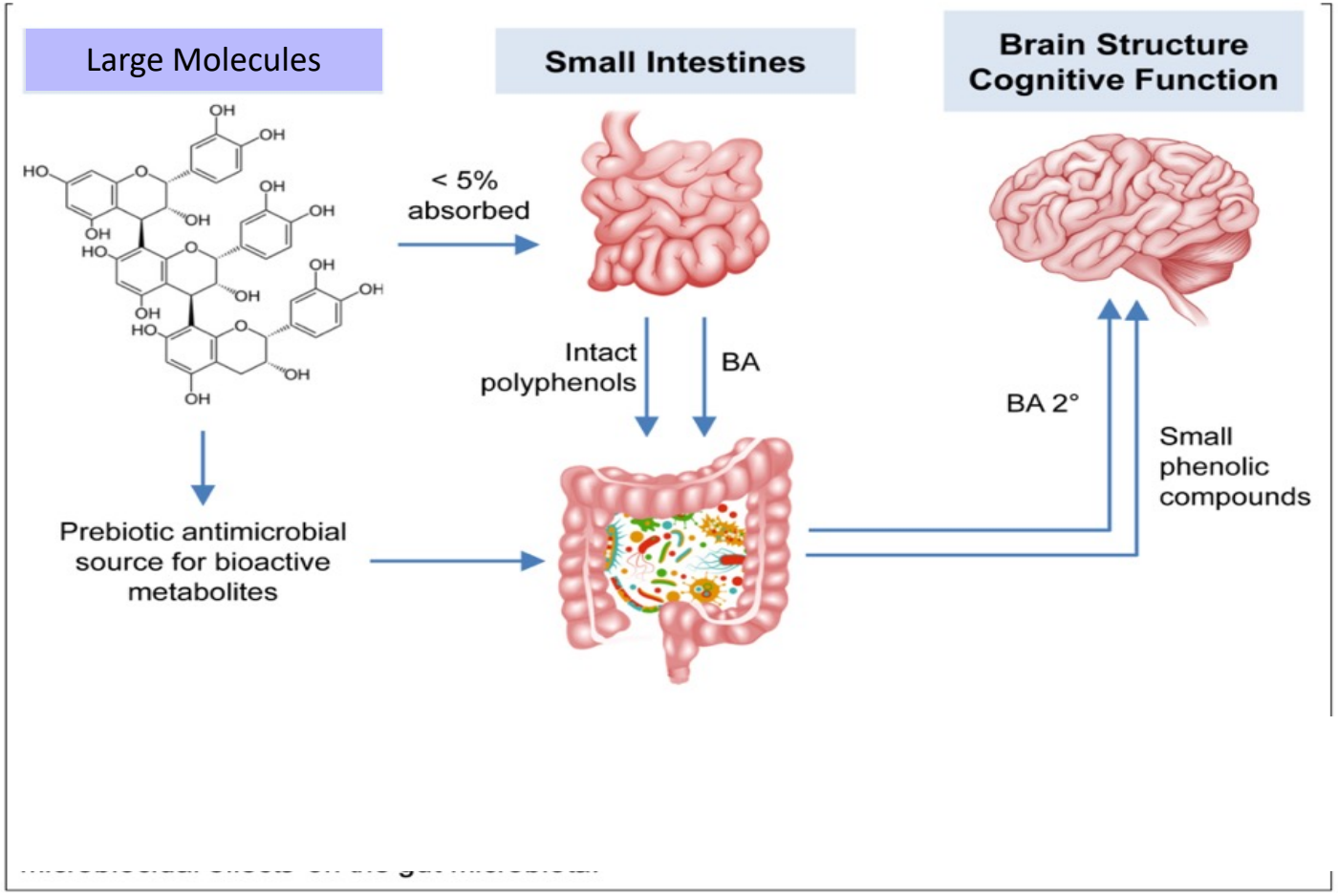
Needham BD et al, Nature Reviews Neurosci, 2020

Example Tryptophan: The Microbiome Turns Dietary Tryptophan into Brain Modulating Molecules



The Microbiome Turns Large, Unabsorbable Molecules Into Brain Modulating Signals

- Many herbal compounds;
- Fiber
- Polyphenols



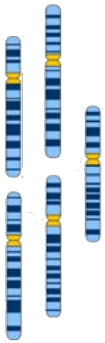
Early Programming

The Brain Gut Microbiome Axis is Programmed Throughout Life by Interactions between Genes & Environment

Maternal Child Interactions

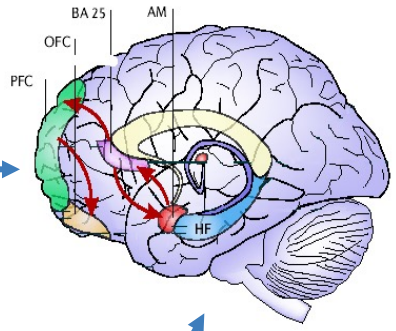
Clinical Phenotype

Sex



Race

Gene Expression



Wellness vs Chronic Disease

Exposome (Diet, microbes)

Early Programming of Gut Microbiome

Contents lists available at ScienceDirect

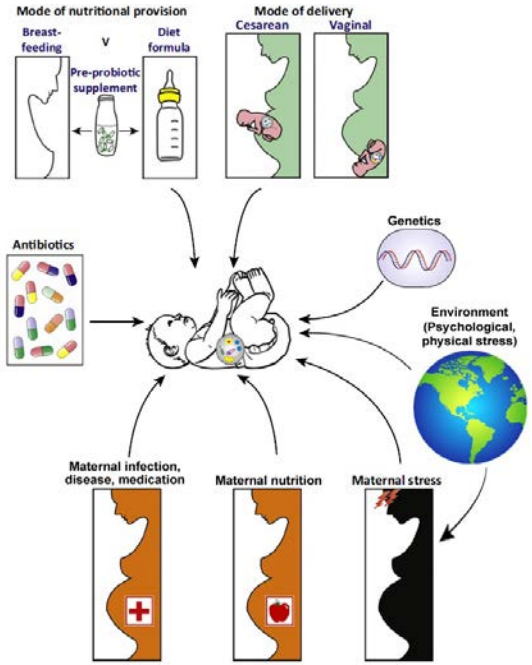
Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

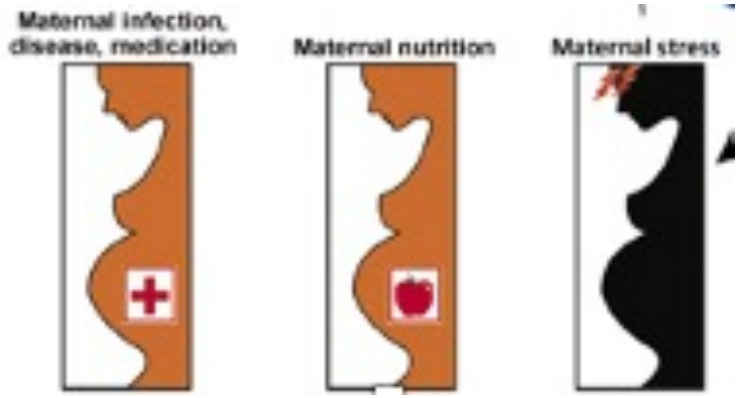
Prenatal and postnatal contributions of the maternal microbiome on offspring programming

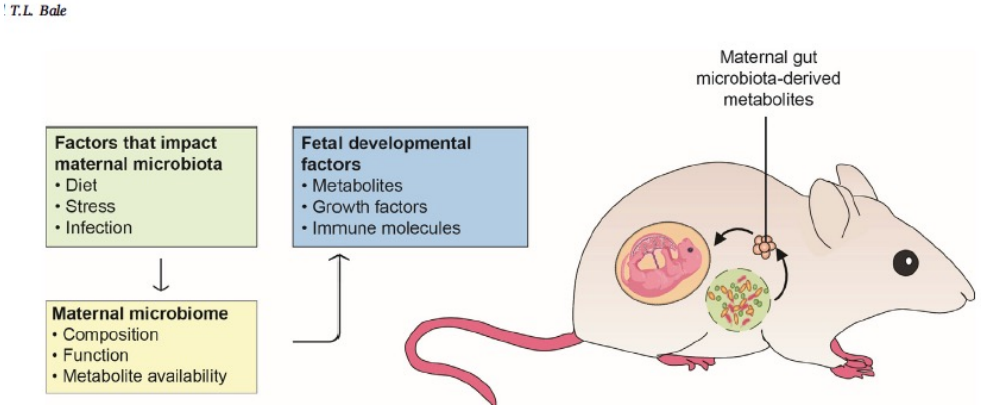
Eldin Jašarević, Tracy L. Bale*

Center for Epigenetic Research in Child Health and Brain Development, Department of Pharmacology, University of Maryland School of Medicine, Baltimore, MD 21230, United States



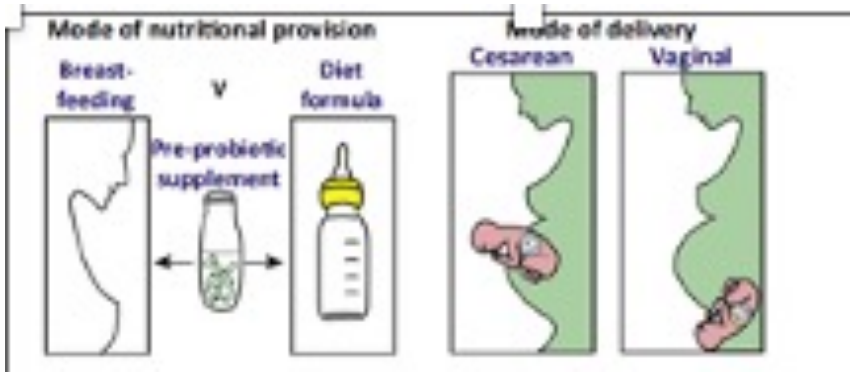
Prenatal Programming of Gut Microbiome

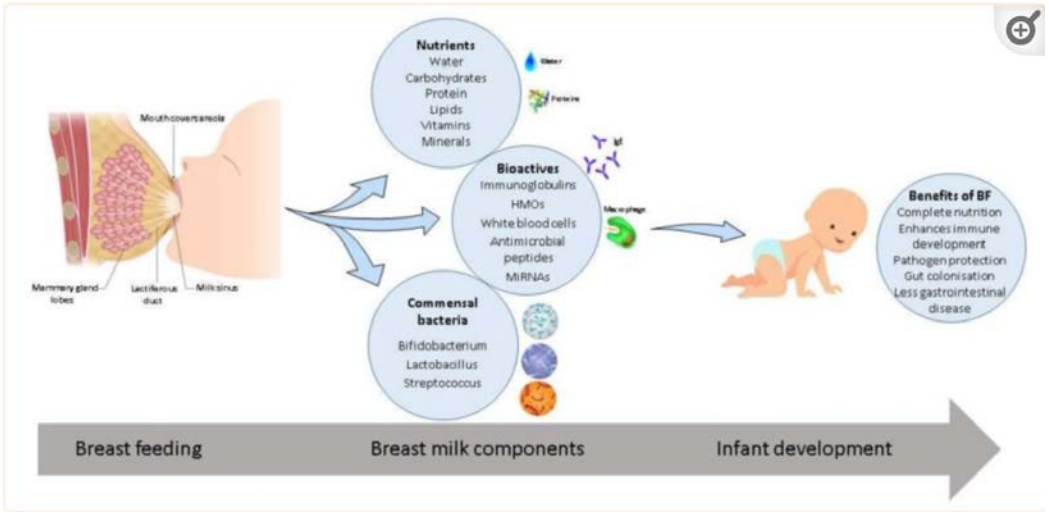




Jasarevic & Bale, Front Neuroendocrinol 2019

Postnatal Programming of Gut Microbiome





Lyons et al, Nutrients 2020

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-26634-9 OPEN

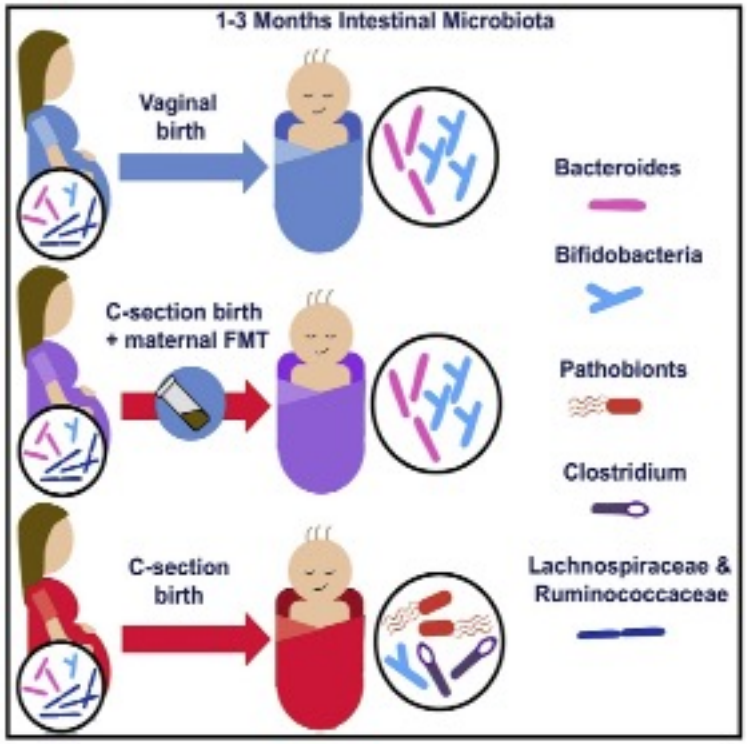
The composition of human vaginal microbiota transferred at birth affects offspring health in a mouse model

Eldin Jašarević[1,2,6], Elizabeth M. Hill[1,2], Patrick J. Kane[1,2], Lindsay Rutt[3,4], Trevonn Gyles[1,2], Lillian Folts[1,2], Kylie D. Rock[1,2], Christopher D. Howard[1,2], Kathleen E. Morrison[1,2], Jacques Ravel[3,4] & Tracy L. Bale[1,2,5]✉

Cell

Maternal Fecal Microbiota Transplantation in Cesarean-Born Infants Rapidly Restores Normal Gut Microbial Development: A Proof-of-Concept Study

Graphical Abstract



Authors

Katri Korpela, Otto Helve, Kaija-Leena Kolho, ..., Anne Salonen, Sture Andersson, Willem M. de Vos

Correspondence

willem.devos@wur.nl

In Brief

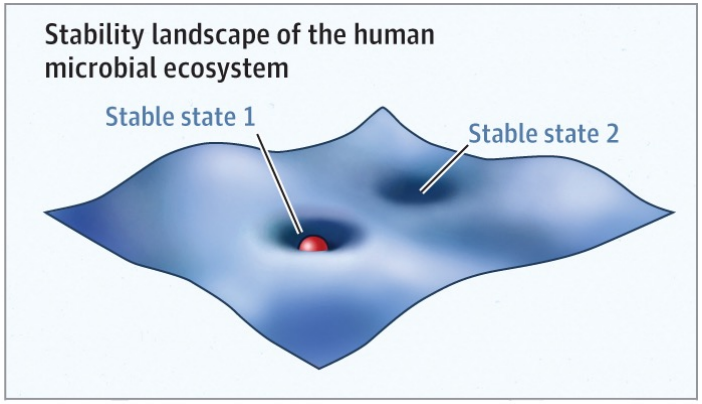
A proof-of-concept safety study shows that oral fecal transplantation can shift the microbiome composition of infants who are born via cesarean section to a profile that is more similar to those born via vaginal delivery.

The Influence of Lifestyle on BGM Interactions

Perturbations of the Gut Microbial Ecosystem Throughout Life

Mind
Connectedness
Eudaimonia
Compassion
Empathy

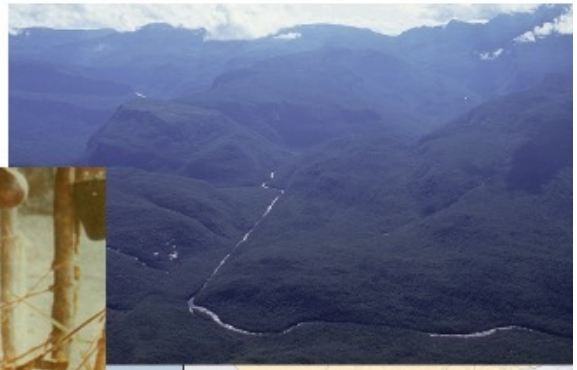
Diet
Plant based
Minimally processed
Sustainably produced

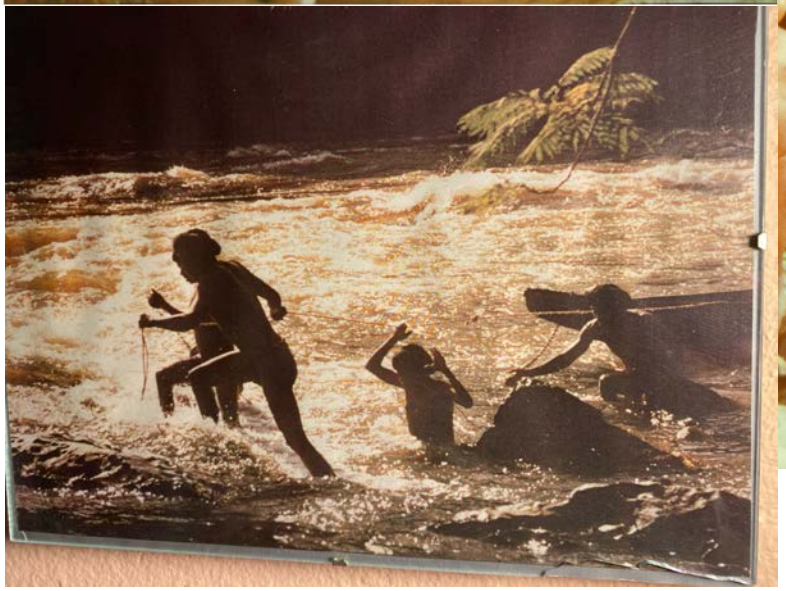


Brain
Psychological stress,
Emotions
Wellness
Sleep

Lifestyle
Physical Exercise
Social connectedness
Hygiene

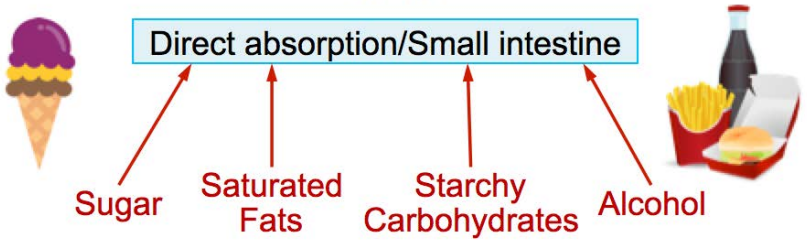
What we have learned from the Yanomami





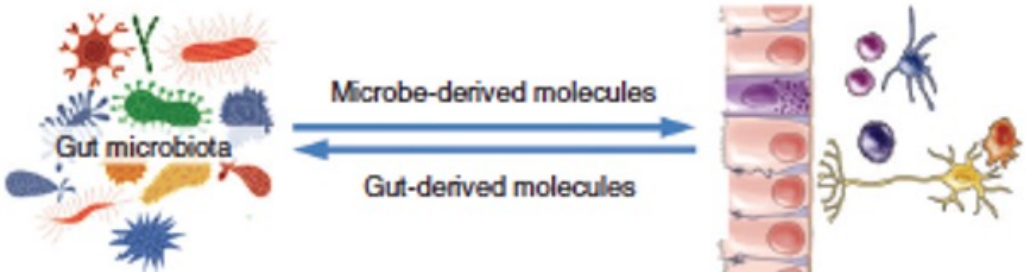
Film Expedition to the Yanomami on the Upper Orinoco River 1977

Welcome to the Standard American Diet



The Standard American Diet

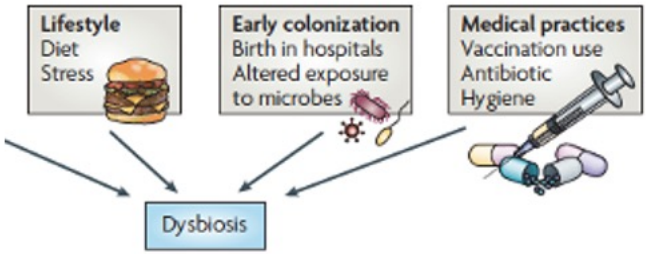
Traditional Symbiotic Relationship of Gut Microbiome and Gut Connectome

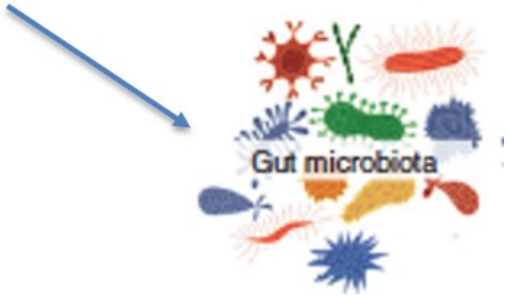


Symbiotic relationship between ancient gut microbiome with human GI tract

Rapid Adaptation of Microbiome to Changing Environment

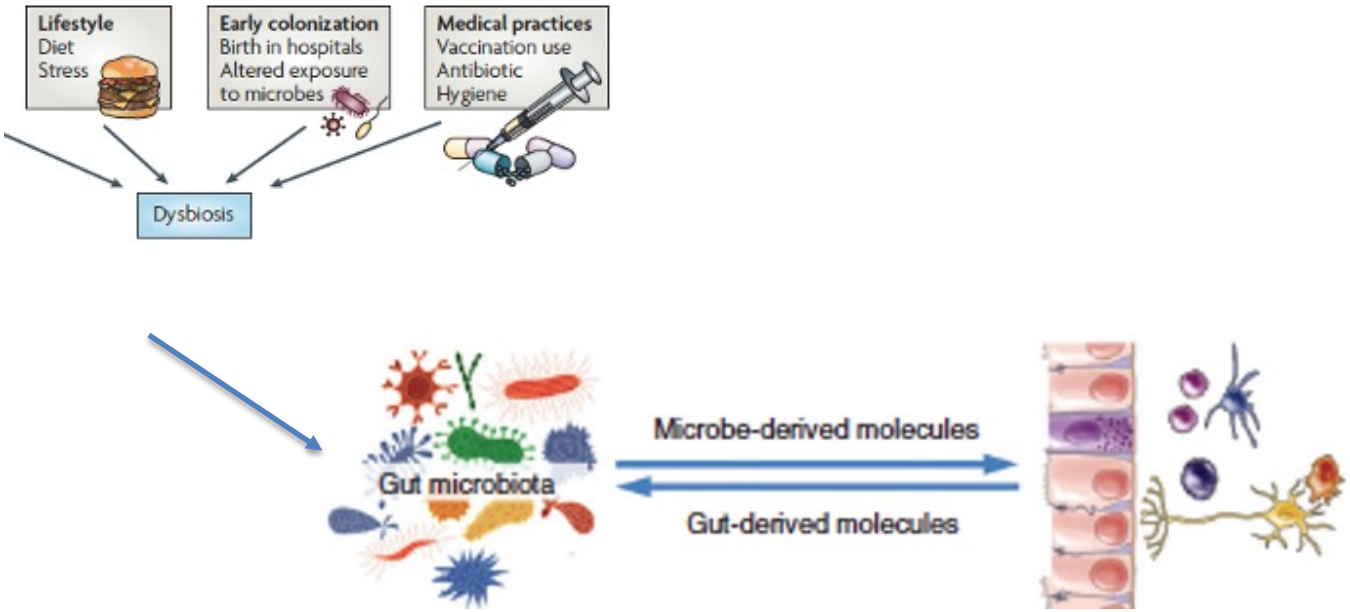
Dramatic changes of exposome during past 75 years





Rapid (days) adaptation of relative abundances, diversity and function to changing influences (2 M genes, epigenetics)

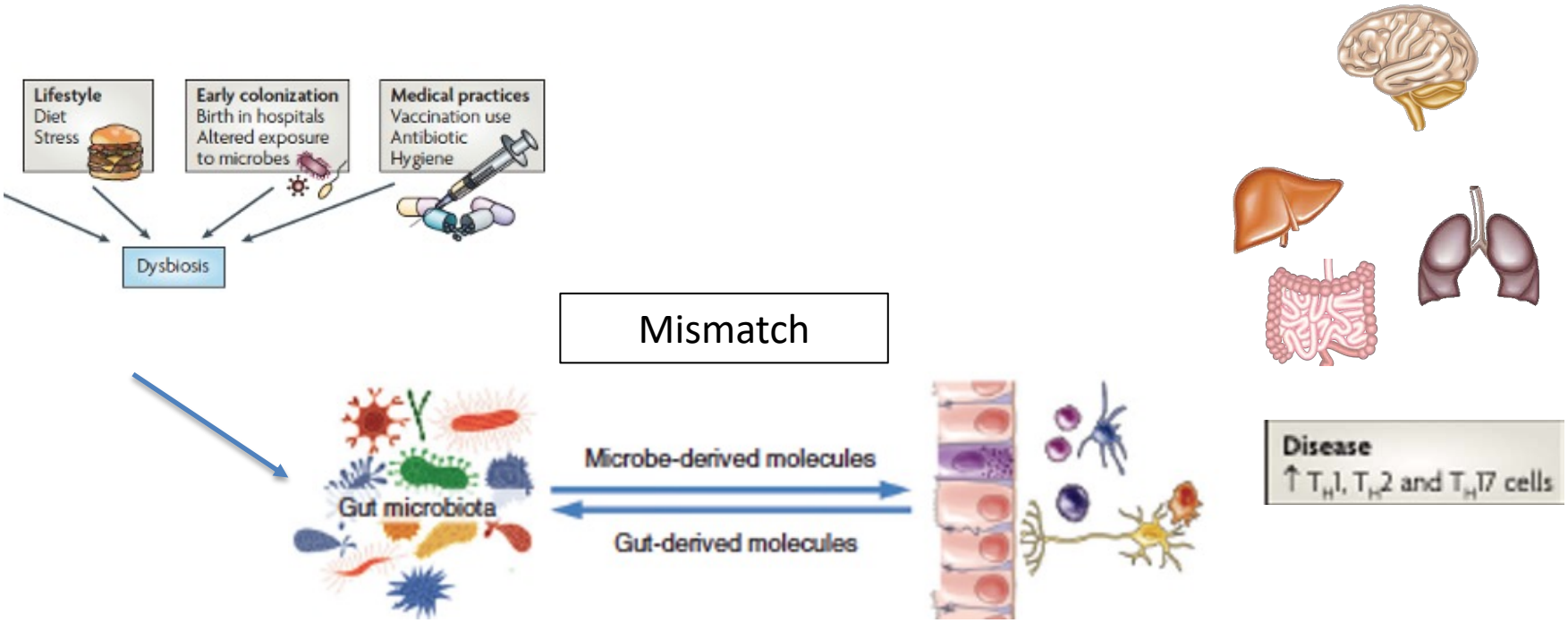
Poor Gut Health Can Have Widespread Effects on the Body



Immune system activation, metabolic endotoxemia

Slow (10-15,000 years) adaptation) of gut to altered microbiome (20,000 genes)

Poor Gut Health Can Have Widespread Effects on the Body



Immune system activation, metabolic endotoxemia; disease in vulnerable individuals

Healthy Diet

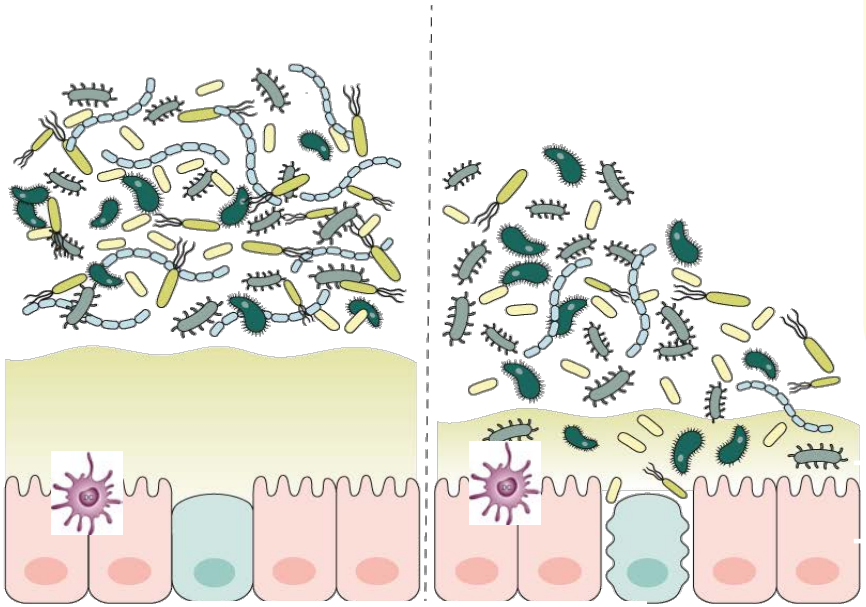
- Complex carbohydrates
- High fiber
- ↑ Fiber degradation
- ↑ Gut microbiome diversity
- ↑ Abundance of mucus-stimulating microorganisms
- ↑ Prevotella abundance

↑ Mucus thickness

Intact gut barrier

Healthy Gut

"Leaky" Gut



Chronic Stress

Western diet

- Refined carbohydrates, sugar
- High fat
- Low fiber
- ↓ Fiber degradation
- ↓ Gut microbiome diversity
- ↓ Abundance of mucus-stimulating microorganisms
- ↓ Prevotella abundance

↓ Mucus thickness

↓ Gut barrier

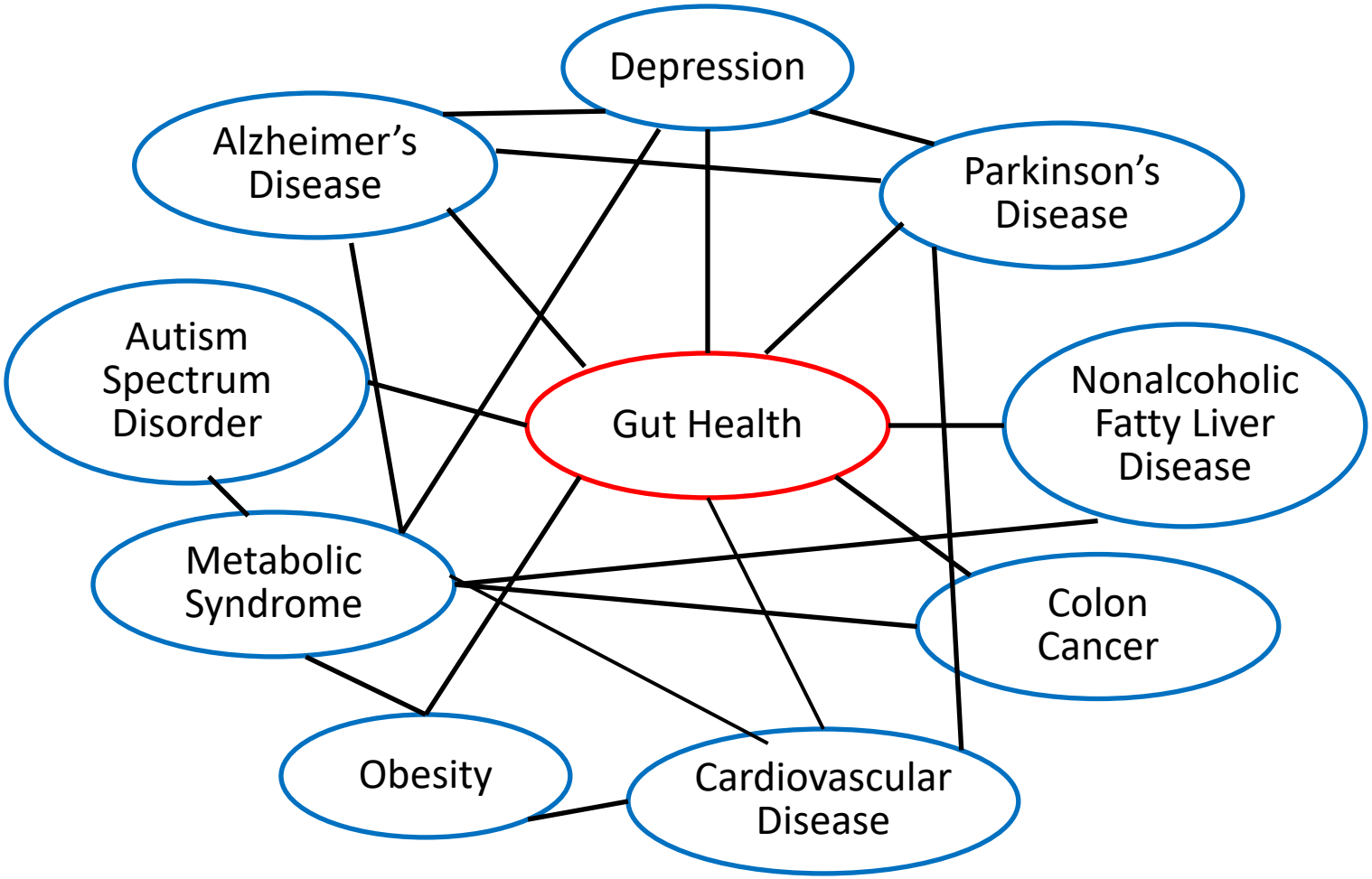
- Metabolic endotoxemia

Increased genetic risk

Depression | NAFLD | Colon cancer | Cognitive decline (AD) | Parkinson's Disease | Metabolic syndrome

Mayer, Osadchyi, Gupta, Nature Rev Gastro Hepatol 2020

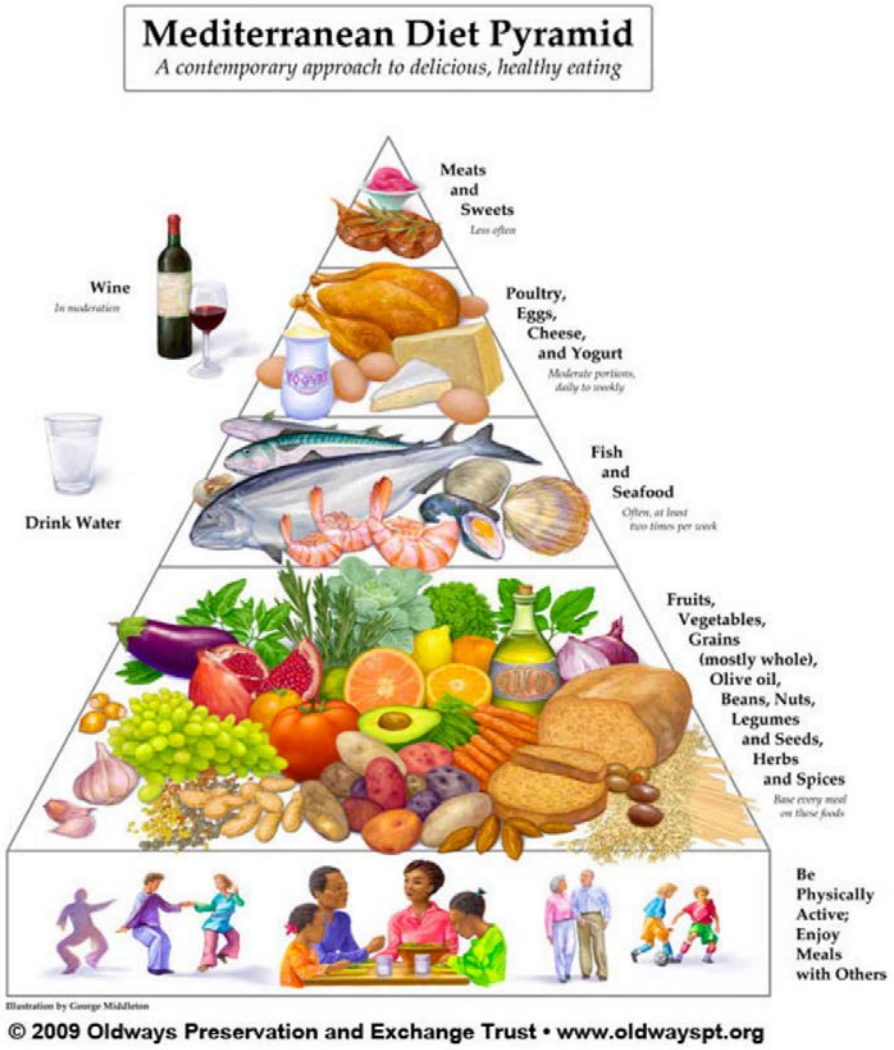
Gut Health is at the Center of the Chronic Non-Communicable Disease Network



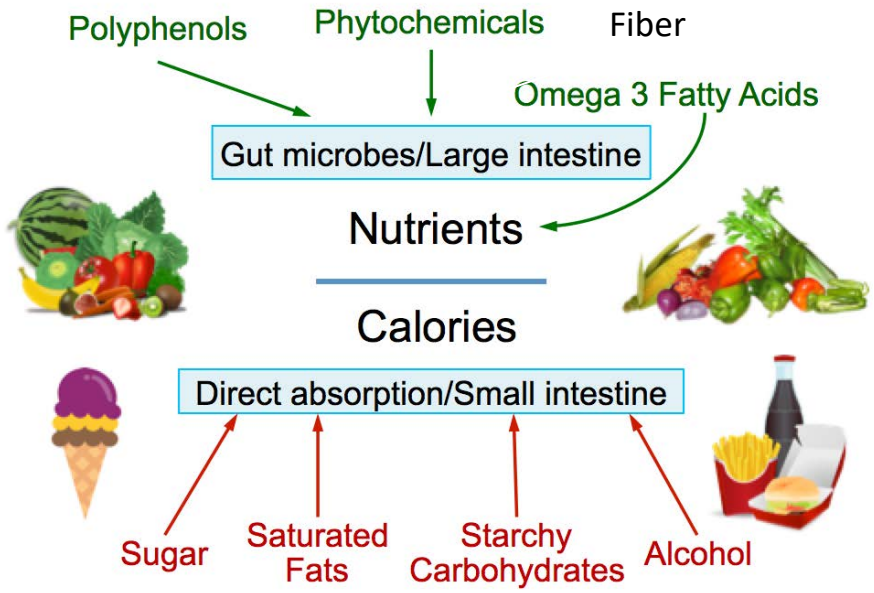
The Mind Gut Immune Connection, 2021

Diet and BGM Interactions

The Healthy Diet Pyramid and Gut Health

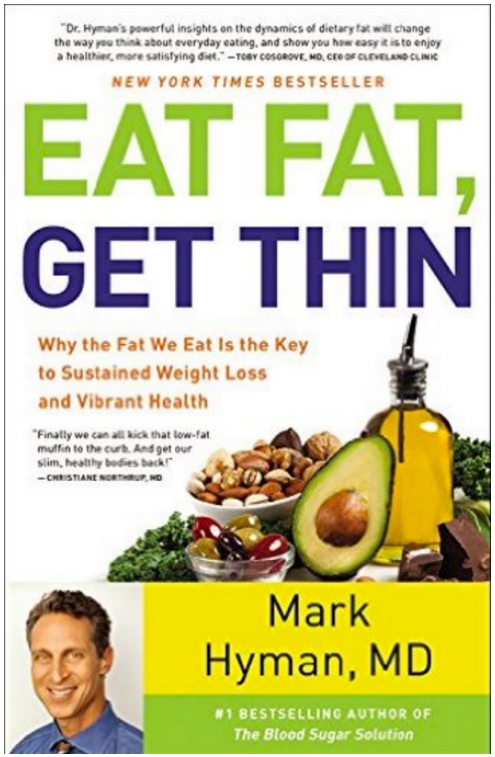


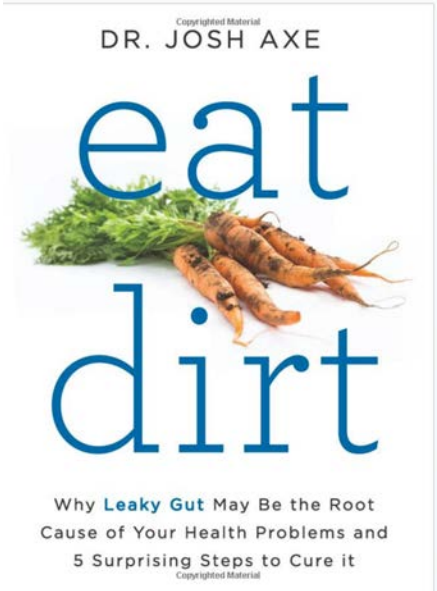
The Gut Healthy Diet

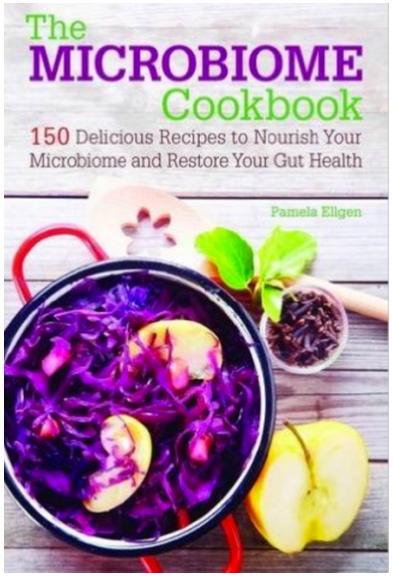


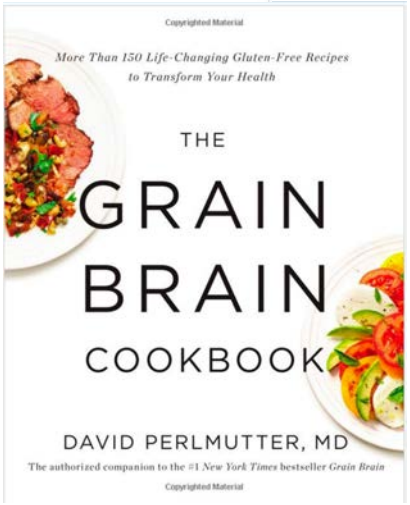
The Standard American Diet

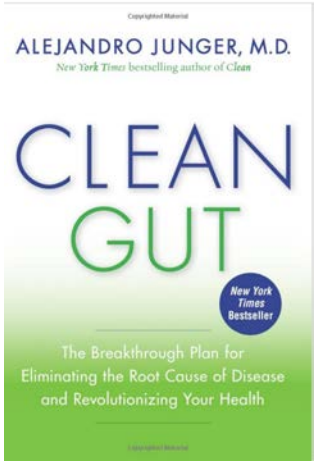
“Lessons” from Today’s Diet Gurus –
Non-scientific Media Are Dominating the Conversation



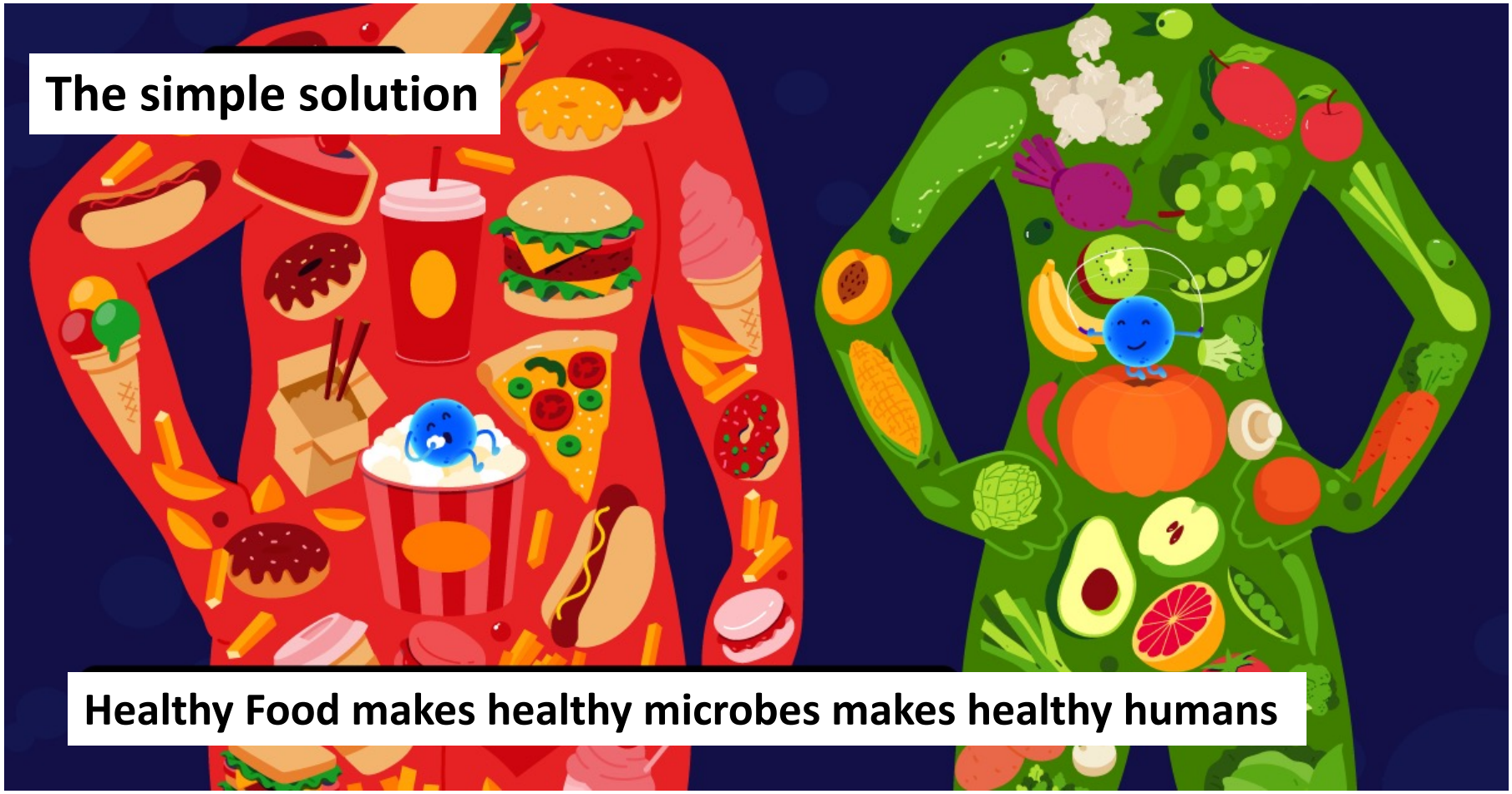








The best Approach to Improve the Gut Microbiome



Picture from article: Is There A Link Between Gut Bacteria And Weight Loss? By Leanne Edermaniger

Courtesy from H. Hirt

Best Dietary Strategy for Optimal Gut Health: High Consumption of a Large Variety of Fruits & Vegetables

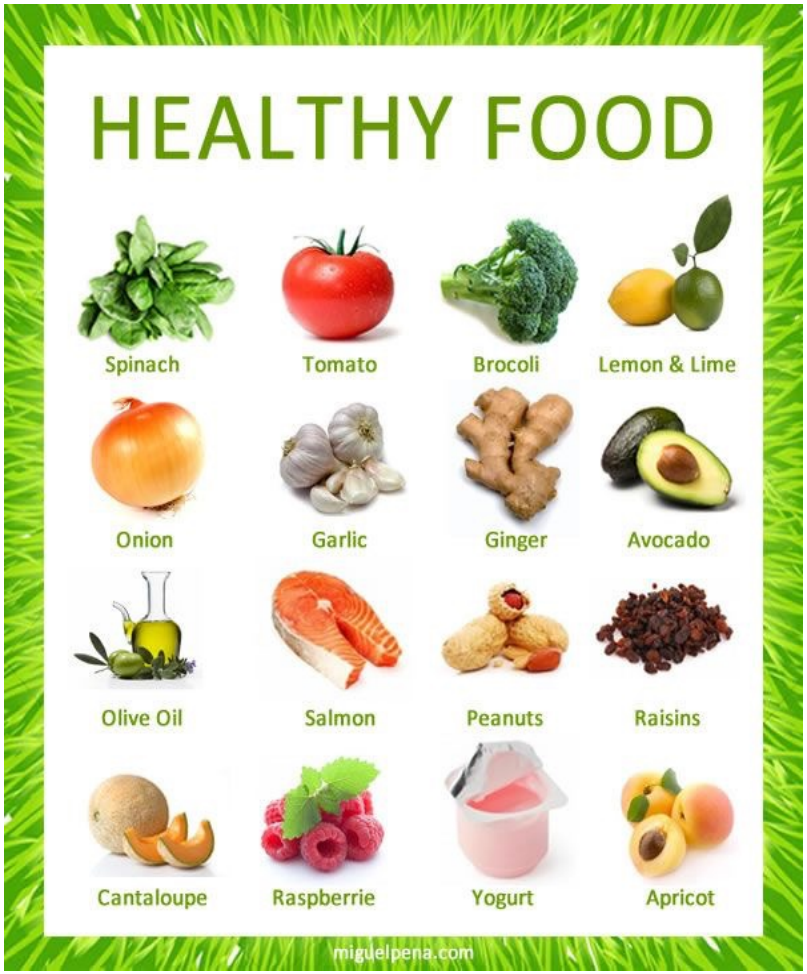
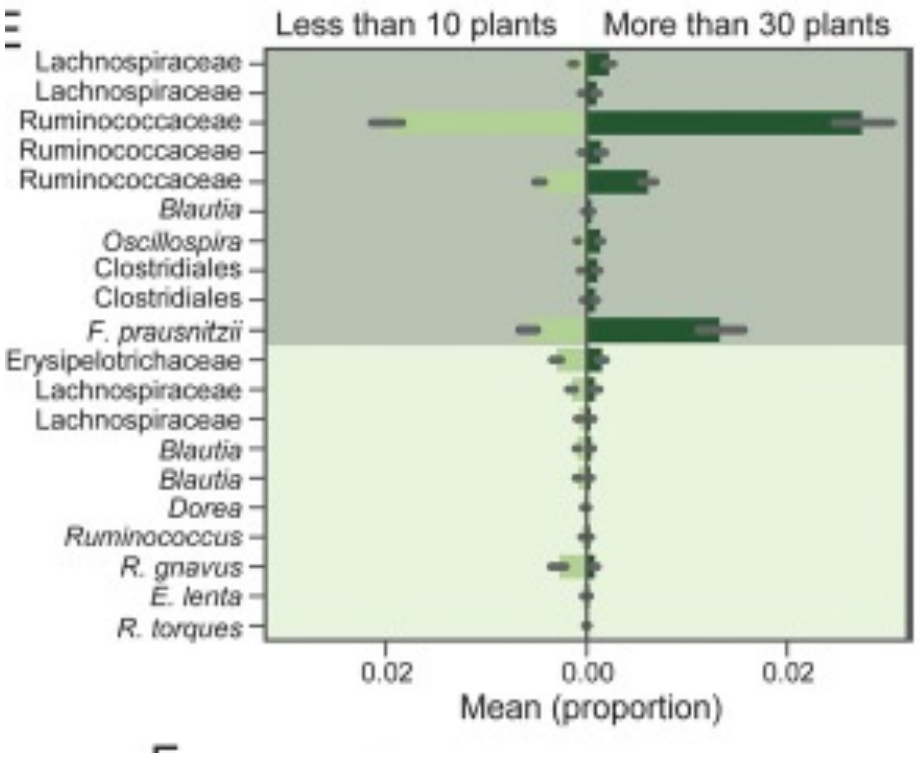


Image from Comida: 16 productos sanos | Miguel Pena Roma - Pasando por la cocina



D. McDonald et al. mSystems 2018

The Traditional Korean Diet –

Variety of Naturally Fermented Foods

The Traditional Mediterranean Diet

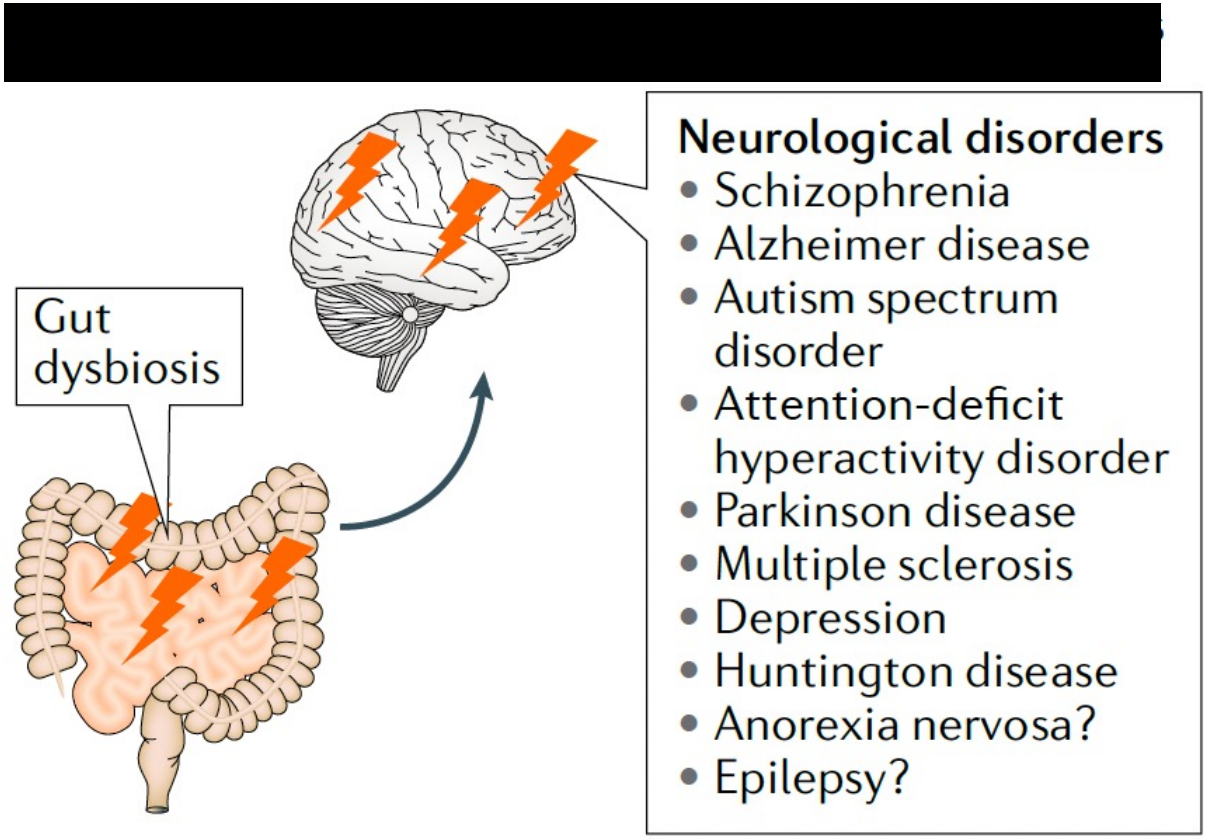
Our Food in the Anthropocene: Healthy Diets From Sustainable Food Systems

Prof. Walter Willett MD
Harvard T.H. Chan School of Public Health

"Transformation to healthy diets by 2050 will require substantial dietary shifts. Global consumption of fruits, vegetables, nuts and legumes will have to double, and consumption of foods such as red meat and sugar will have to be reduced by more than 50%. A diet rich in plant-based foods and with fewer animal source foods confers both improved health and environmental benefits."

EAT Lancet Commission Report, 2019

Reported Association of Brain Disorders With Gut Dysbiosis



Needham, Kaddurah-Daouk, Mazmanian, Nat Rev Neurosci 21:717. 2020

nature communications

Article

https://doi.org/10.1038/s41467-022-34504-1

The gut microbiota and depressive symptoms across ethnic groups

Received: 27 May 2021

Accepted: 27 October 2022

Published online: 06 December 2022

Jos A. Bosch[1,2] ✉, Max Nieuwdorp[3], Aeilko H. Zwinderman[4], Mélanie Deschasaux[4,5], Djawad Radjabzadeh[6], Robert Kraaij[6], Mark Davids[3], Susanne R. de Rooij[4,8] & Anja Lok[7,8]

nature communications

Article

https://doi.org/10.1038/s41467-022-34502-3

Gut microbiome-wide association study of depressive symptoms

Received: 28 May 2021

Accepted: 26 October 2022

Published online: 06 December 2022

Djawad Radjabzadeh[1], Jos A. Bosch[2,3], André G. Uitterlinden[1,4], Aeilko H. Zwinderman[5], M. Arfan Ikram[4], Joyce B. J. van Meurs[1], Annemarie I. Luik[4], Max Nieuwdorp[6], Anja Lok[7], Cornelia M. van Duijn[4,8], Robert Kraaij[1] ✉ & Najaf Amin[4,8] ✉

Parkinson's Disease

"a disordered state of the stomach and bowels may induce a morbid action in a part of the medulla spinalis"

"there appears to be sufficient reason for hoping that some remedial process may ere long be discovered, by which, at least, the progress of the disease may be stopped."

James Parkinson, 1817

Gastrointestinal manifestations of Parkinson's Disease

- Dysphagia
- Gastroparesis
- Slow transit constipation
- Dyschezia
- Visceral hypersensitivity

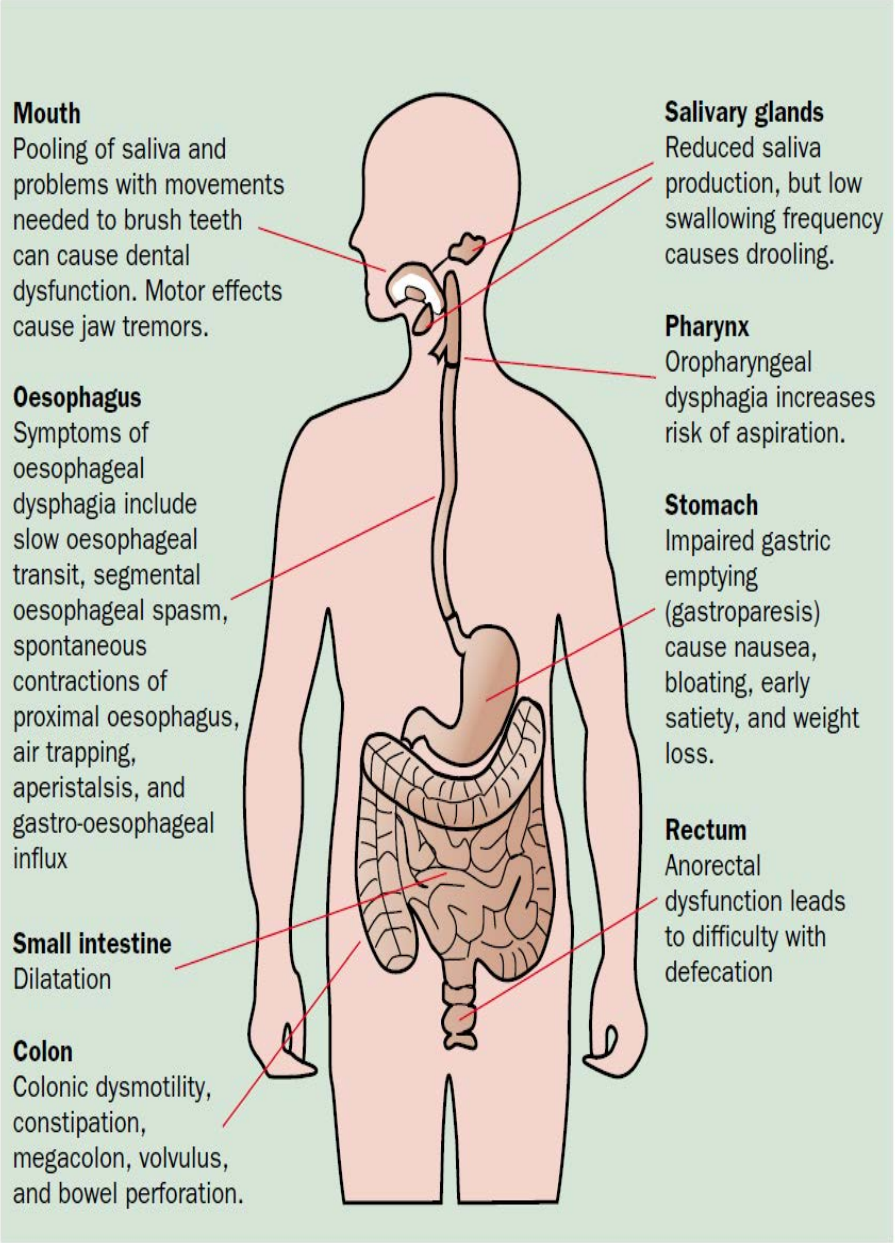
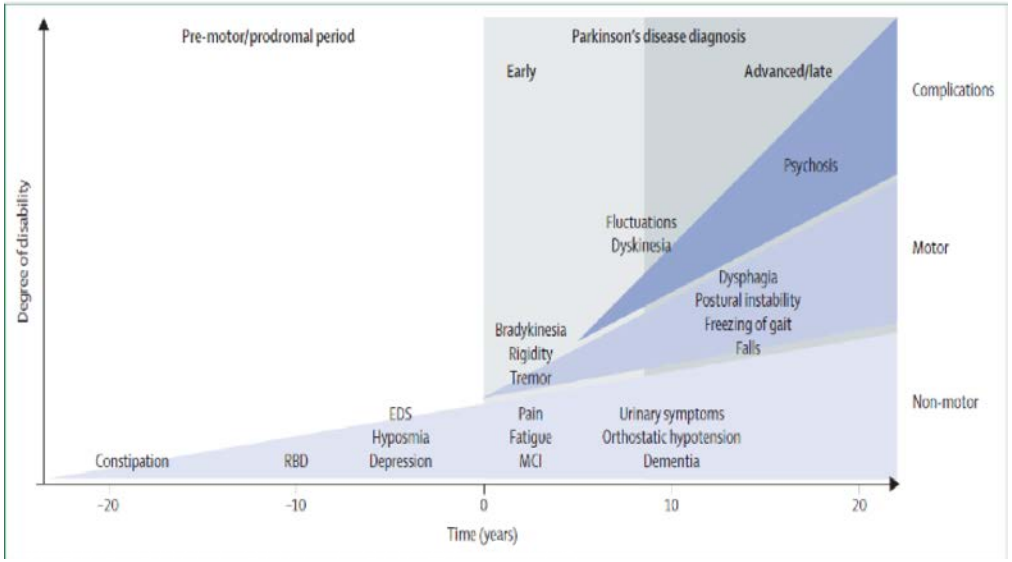


Figure 1. Overview of gastrointestinal dysfunction in PD.

Pfeiffer, Lancet Neurol. 2003 Feb;2(2):107-16.

Parkinson's Disease

Putative Role of Gut Microbial Brain Communication



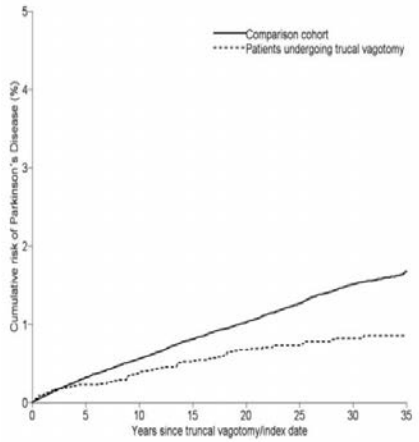


FIGURE 1: Cumulative incidence curves of Parkinson's disease for patients who underwent truncal vagotomy compared to a matched general population cohort.

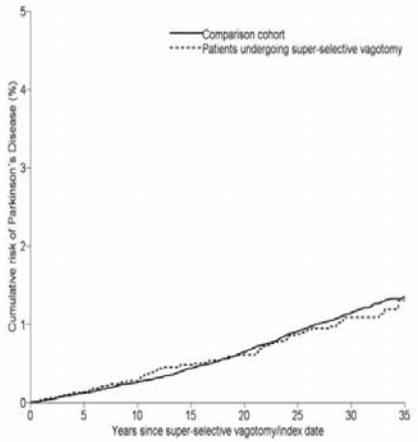
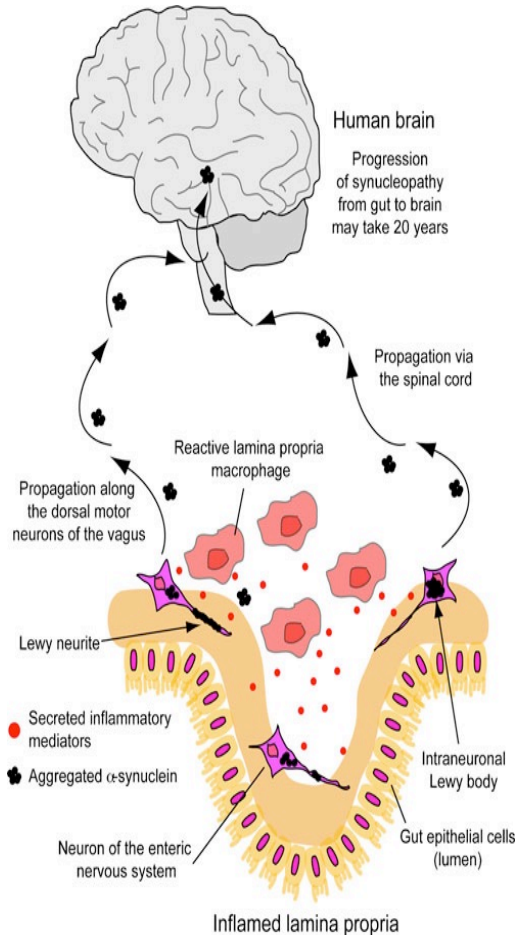


FIGURE 2: Cumulative incidence curves of Parkinson's disease for patients undergoing superselective vagotomy compared to a matched general population cohort.

Svensson et al. Ann Neurol. 2015 Oct;78(4):522-9.



Courtesy of F. Schepperjans

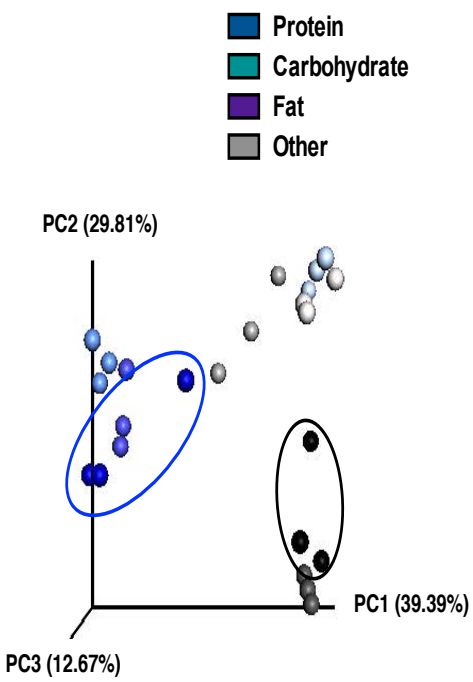
Epilepsy:

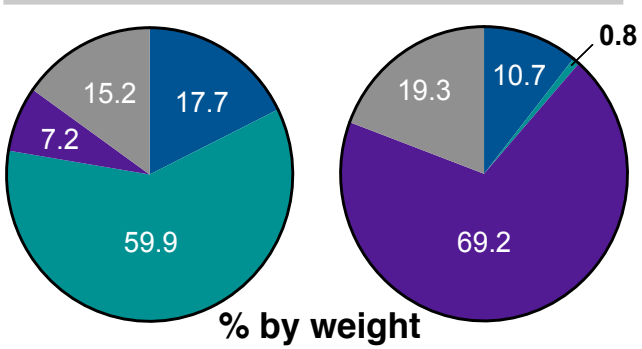
Gut Microbiome Brain Interactions and Diet

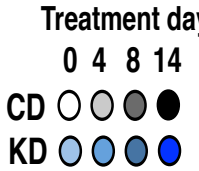
The Gut Microbiota Mediates the Anti-Seizure Effects of the Ketogenic Diet

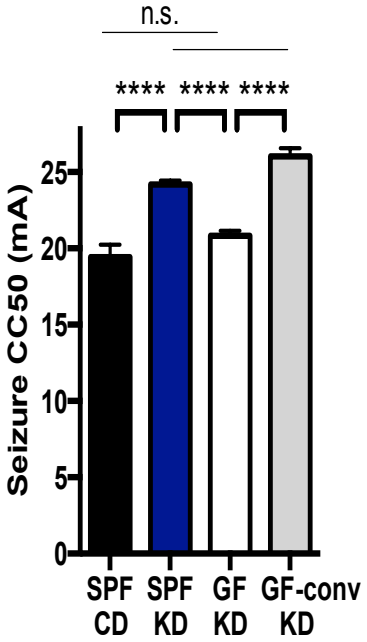
Christine A. Olson,[1] Helen E. Vuong,[1] Jessica M. Yano,[1] Qingxing Y. Liang,[1] David J. Nusbaum,[1] and Elaine Y. Hsiao[1,2,*]
[1]Department of Integrative Biology and Physiology, University of California, Los Angeles, Los Angeles, CA 90095, USA
[2]Lead Contact
*Correspondence: ehsiao@ucla.edu
https://doi.org/10.1016/j.cell.2018.04.027

Cell 2018

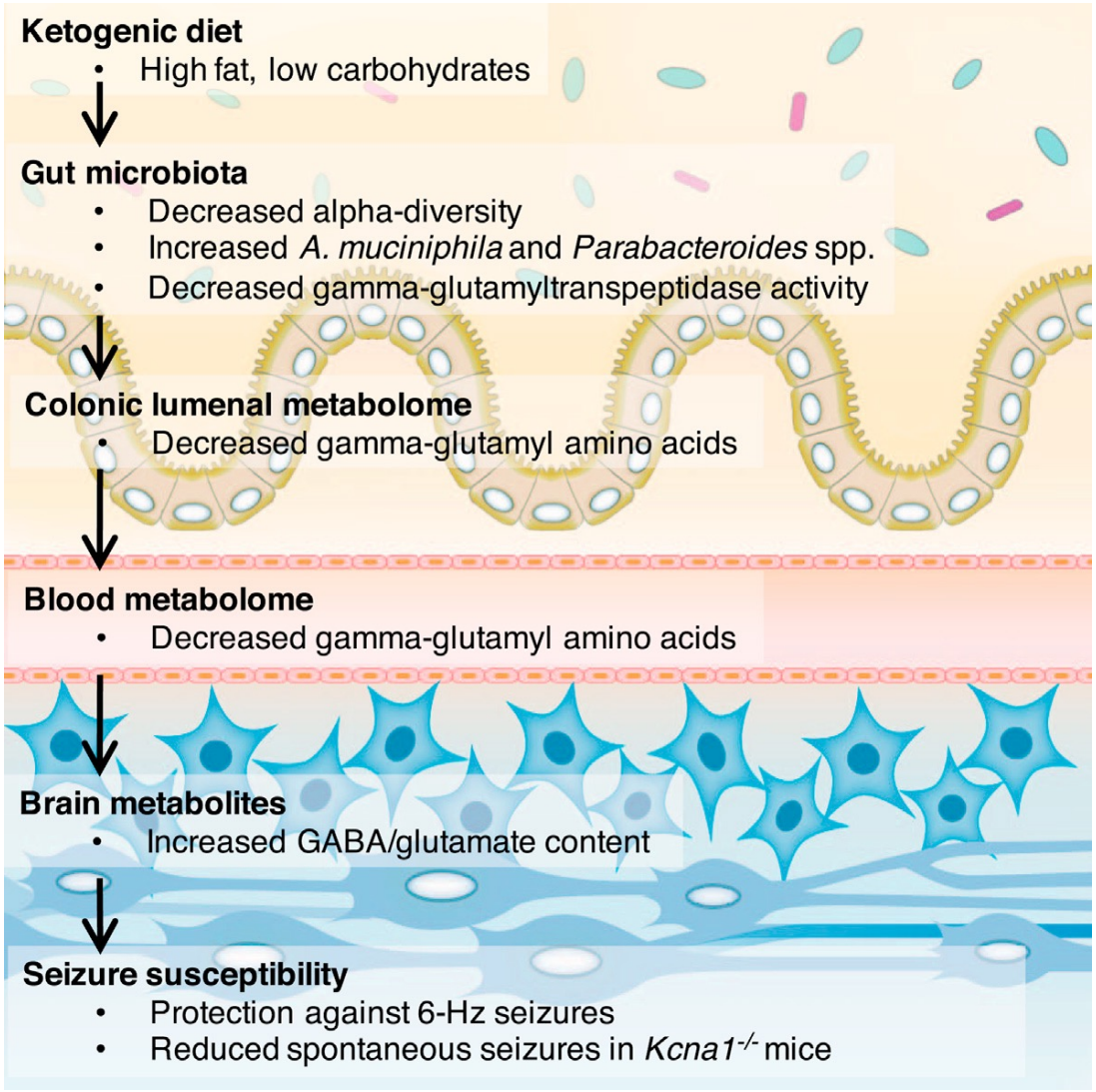








Ketogenic Diet and Seizure Susceptibility in the Mouse



Olson, Hsiao et al. 2018

nature reviews gastroenterology & hepatology

https://doi.org/10.1038/s41575-023-00857-1

Review article

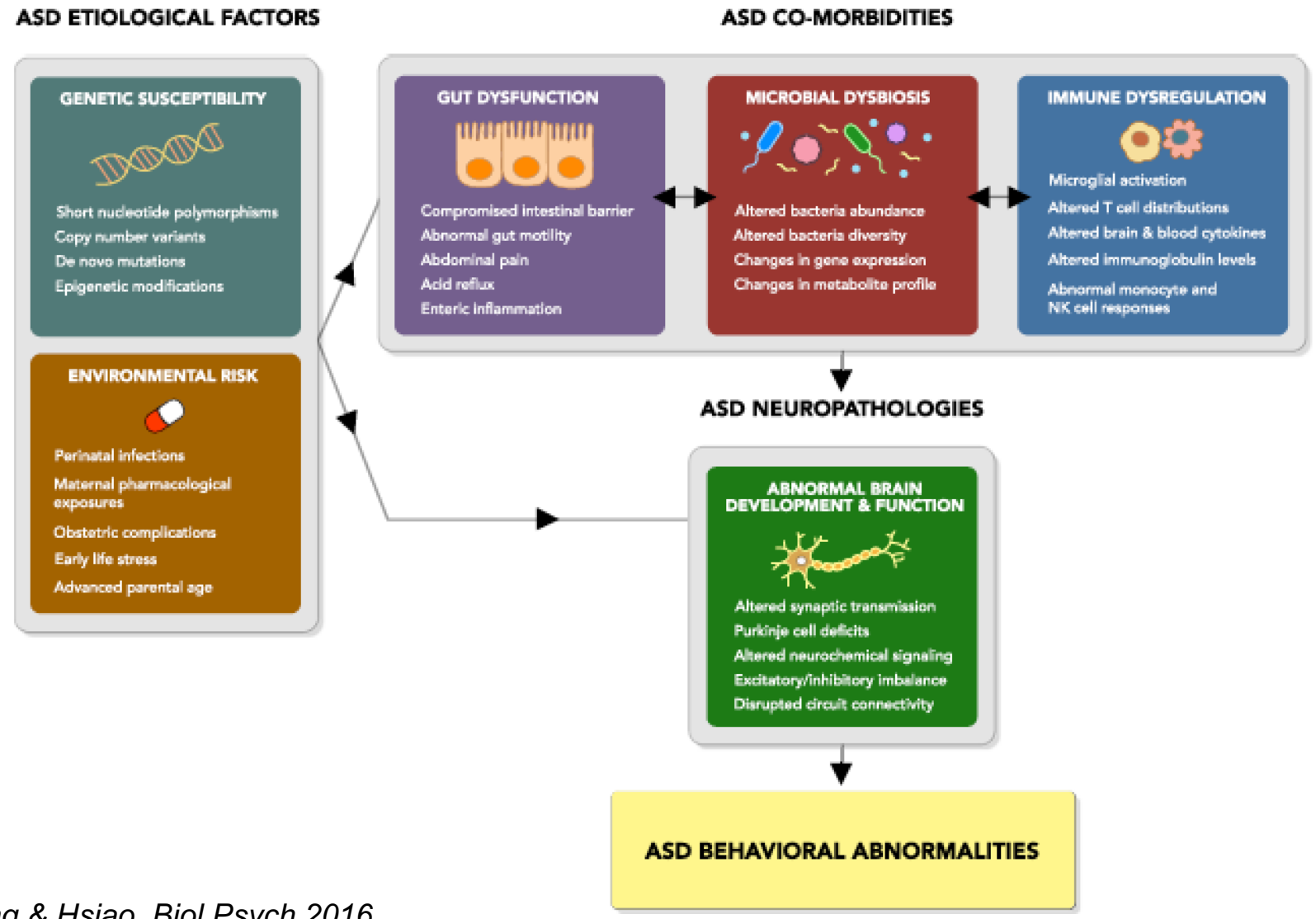
Check for updates

Autism spectrum disorders and the gastrointestinal tract: insights into mechanisms and clinical relevance

Lin Y. Hung [1] & Kara Gross Margolis [1,2,3]

Autism Spectrum Disorder

Putative Role of Brain Gut Microbiome Interactions

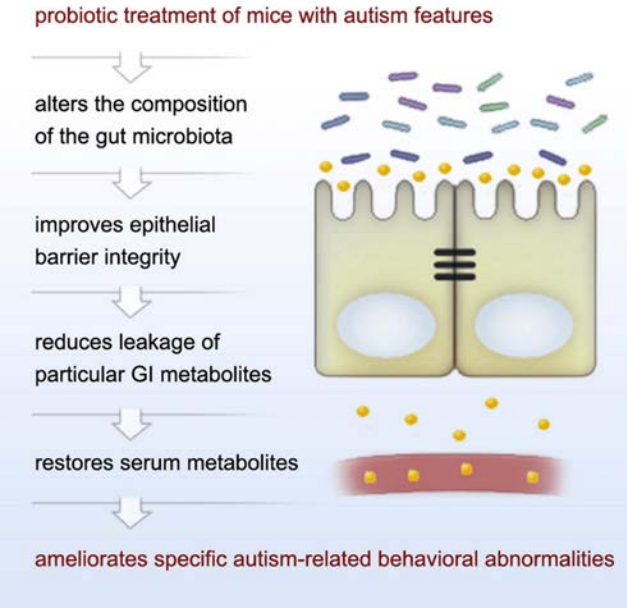


Vuong & Hsiao, Biol Psych 2016

Autism Spectrum Disorders

Microbiota Modulate Behavioral and Physiological Abnormalities Associated with Neurodevelopmental Disorders

Elaine Y. Hsiao,[1,2,*] Sara W. McBride,[1] Sophia Hsien,[1] Gil Sharon,[1] Embriette R. Hyde,[3] Tyler McCue,[3] Julian A. Codelli,[2] Janet Chow,[1] Sarah E. Reisman,[2] Joseph F. Petrosino,[3] Paul H. Patterson,[1,4,*] and Sarkis K. Mazmanian[1,4,*]
[1]Division of Biology and Biological Engineering, California Institute of Technology, Pasadena, CA 91125, USA
[2]Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, USA
[3]Alkek Center for Metagenomics and Microbiome Research, Baylor College of Medicine, Houston, TX 77030, USA
[4]These authors contributed equally to this work
*Correspondence: ehsiao@caltech.edu (E.Y.H.), php@caltech.edu (P.H.P.), sarkis@caltech.edu (S.K.M.)
http://dx.doi.org/10.1016/j.cell.2013.11.024

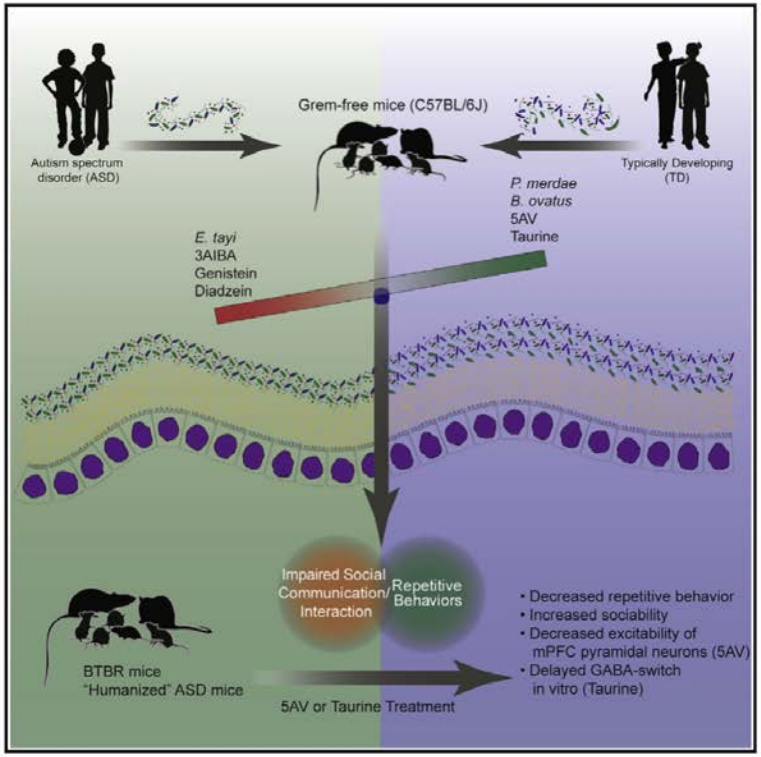


"Our findings…raise the exciting prospect that probiotics could be a safe and effective treatment for…autism"

Cell

Human Gut Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice

Graphical Abstract



Authors

Gil Sharon, Nikki Jamie Cruz, Dae-Wook Kang, ..., Daniel H. Geschwind, Rosa Krajmalnik-Brown, Sarkis K. Mazmanian

Correspondence

gsharon@caltech.edu (G.S.), sarkis@caltech.edu (S.K.M.)

In Brief

Repetitive and social behavioral abnormalities in mice with microbiomes from patients with autism spectrum disorder can be corrected by the administration of specific metabolites.

Highlights

- Mice harboring human ASD, but not TD, microbiomes exhibit ASD-like behaviors
- ASD and TD microbiota produce differential metabolome profiles in mice
- Extensive alternative splicing of risk genes in brains of mice with ASD microbiota
- BTBR mice treated with 5AV or taurine improved repetitive and social behaviors

Kang et al. Microbiome (2017) 5:10
DOI 10.1186/s40168-016-0225-7

Microbiome

RESEARCH Open Access

Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study

Dae-Wook Kang[1†], James B. Adams[2†], Ann C. Gregory[3,15†], Thomas Borody[4], Lauren Chittick[5,15], Alessio Fasano[6], Alexander Khoruts[7,8,9], Elizabeth Geis[2], Juan Maldonado[1], Sharon McDonough-Means[10], Elena L. Pollard[2], Simon Roux[5,15], Michael J. Sadowsky[8,11], Karen Schwarzberg Lipson[12], Matthew B. Sullivan[3,5,15,16*], J. Gregory Caporaso[12,13*] and Rosa Krajmalnik-Brown[1,14*]

Preliminary: open-label, 18 children, 8 weeks: improved both GI and behavioral symptoms

SCIENTIFIC REPORTS

OPEN

Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota

Received: 3 December 2018
Accepted: 5 March 2019
Published online: 09 April 2019

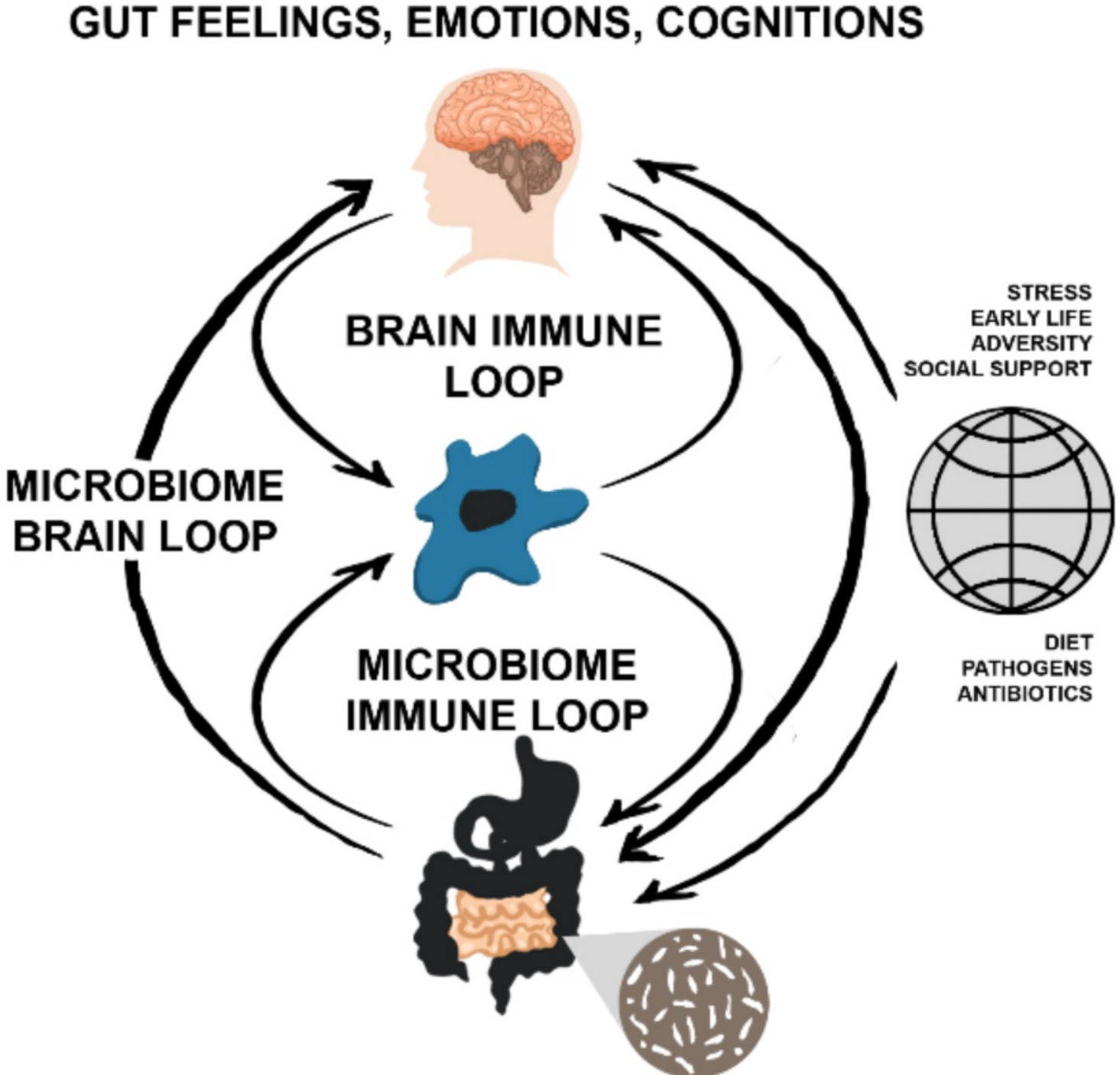
Dae-Wook Kang[1,2,8], James B. Adams[3], Devon M. Coleman[3], Elena L. Pollard[3], Juan Maldonado[1,2], Sharon McDonough-Means[4], J. Gregory Caporaso[5,6] & Rosa Krajmalnik-Brown[1,2,7]

Is Microbiome Science Causing a Fundamental Transformation of Our View of Health and Wellness?

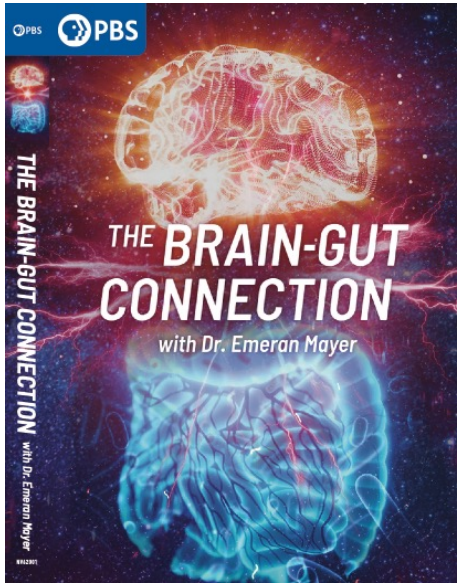
Courtesy of E. Schadt

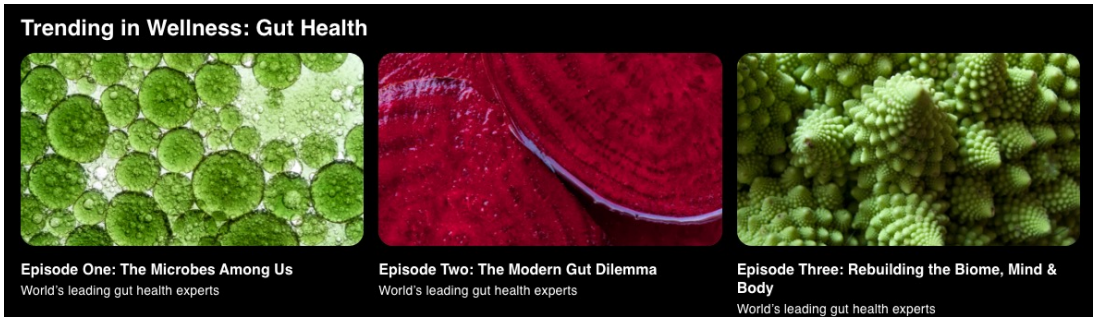
Science is a series of peaceful interludes punctuated by intellectually violent revolutions … in each of which one conceptual world view is replaced by another..

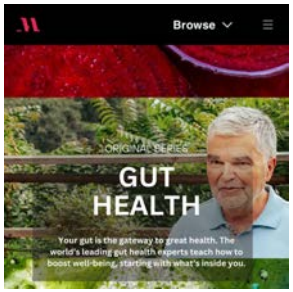
The Structure of Scientific Revolutions, Thomas S. Kuhn, 1962

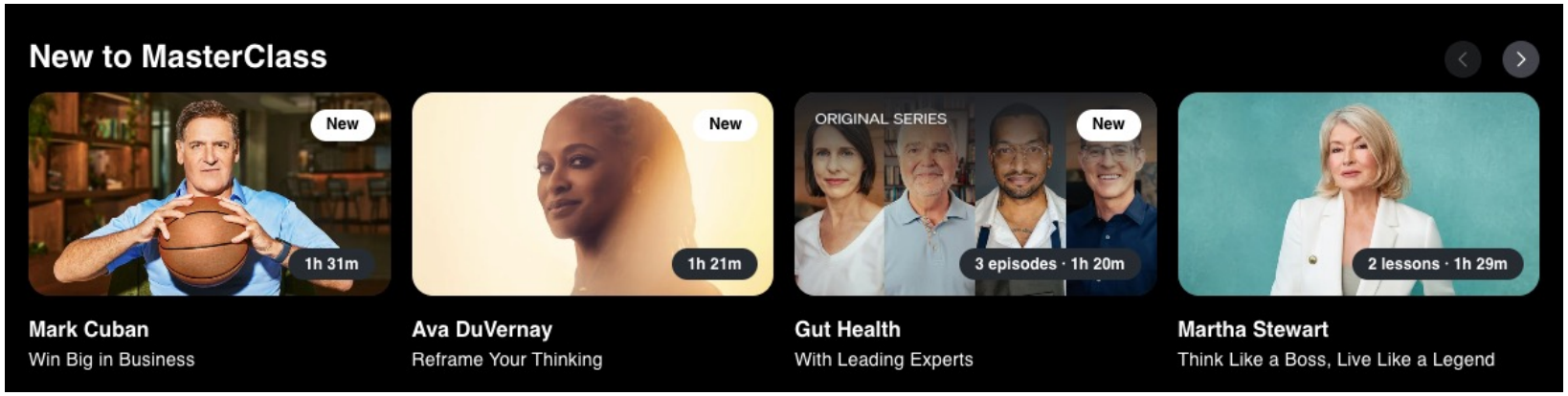

GUT FEELINGS, EMOTIONS, COGNITIONS
BRAIN IMMUNE LOOP
MICROBIOME BRAIN LOOP
MICROBIOME IMMUNE LOOP
STRESS
EARLY LIFE ADVERSITY
SOCIAL SUPPORT
DIET
PATHOGENS
ANTIBIOTICS

The Brain Gut Microbioome Connection Goes Mainstream

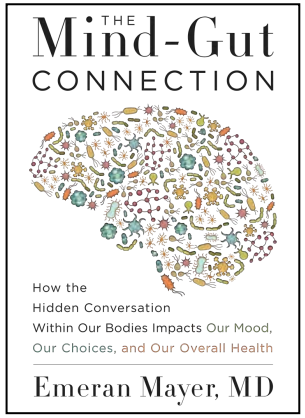


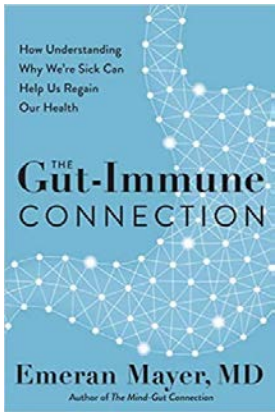


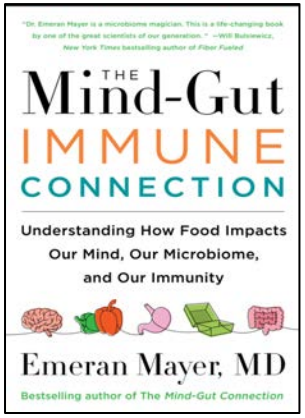


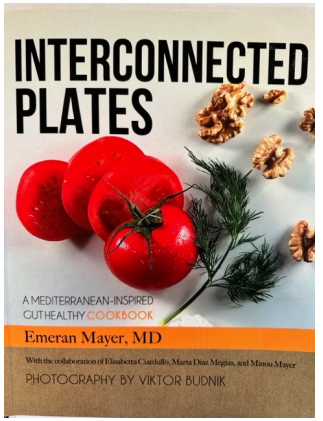


Thank You!









Learn much more about Brain Gut Microbiome Immune Interactions at:

emeranmayer.com

Sign up for:

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