

# Dietary Needs of the Cognitively Impaired

Gut-brain axis and the microbiome  
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# Presentation Outline

- The Role of Nutrition in Dementia
- The Microbiome and bacteria in the gut
- Impact on the immune system
  - Gut-Brain axis and hypothalamic–pituitary–adrenal axis (HPA axis)
- Microbiota and cognitive health
  - Psychobiotics

## Presentation Outline Cont'd

- Learnings from Germ-free mice
- Role and potential of Prebiotics
- The Gut-Makeover diet
- Leaky gut and drug addiction
- Limitations to altering gut-brain function

# Nutrition and Dementia

- The Role of Nutrition in Dementia Prevention and Management
- Sponsored by the Sackler Institute for Nutrition Science
- Hosted by the New York Academy of Sciences
- 26-27-March-2015

# Cognitive decline in older adults

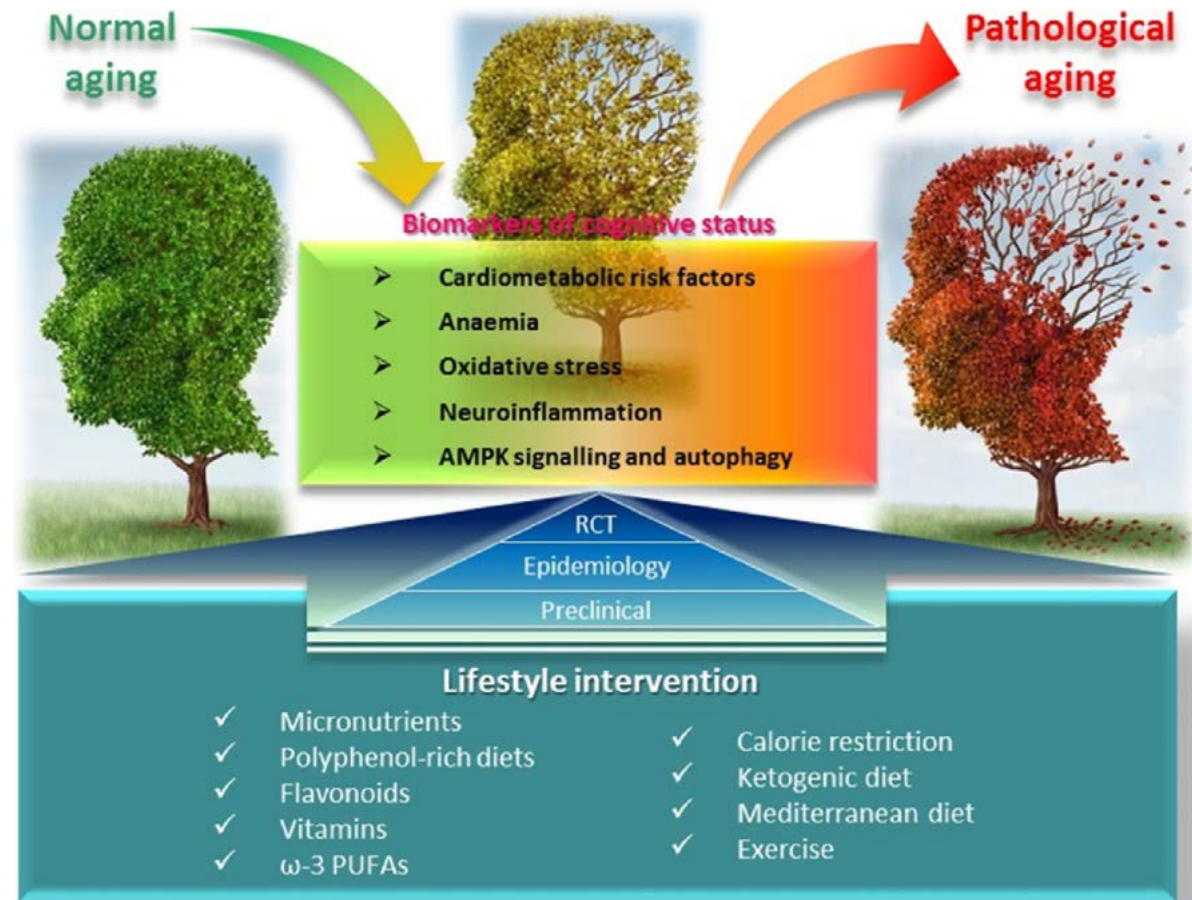


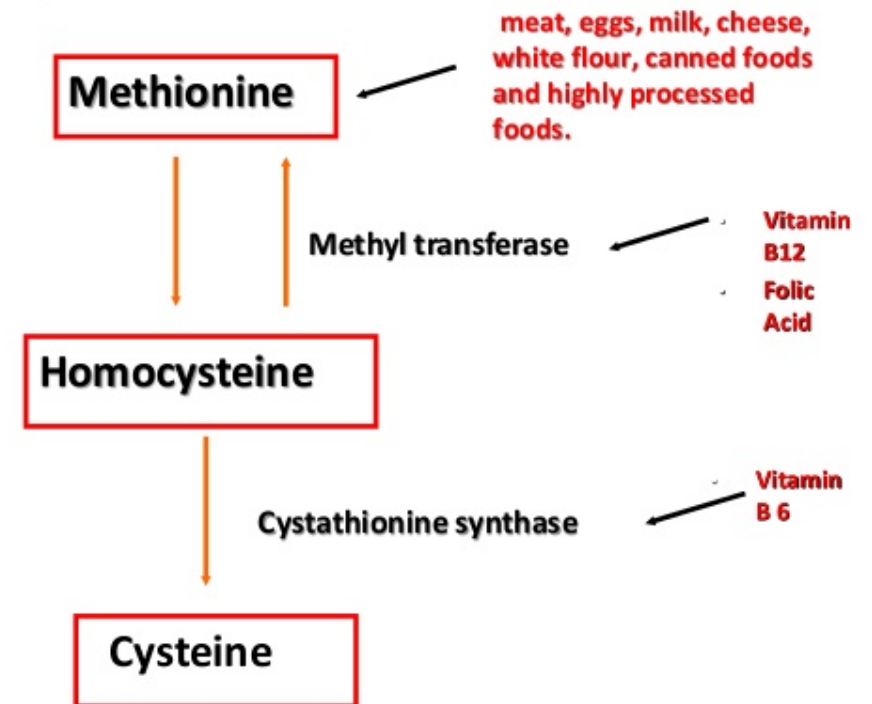
Fig. 1. Overview of links between lifestyle interventions on cognition and healthy brain function during ageing.

# Nutrients needed for cognitive health

## Vitamin B12, Folic Acid, Vitamin B6

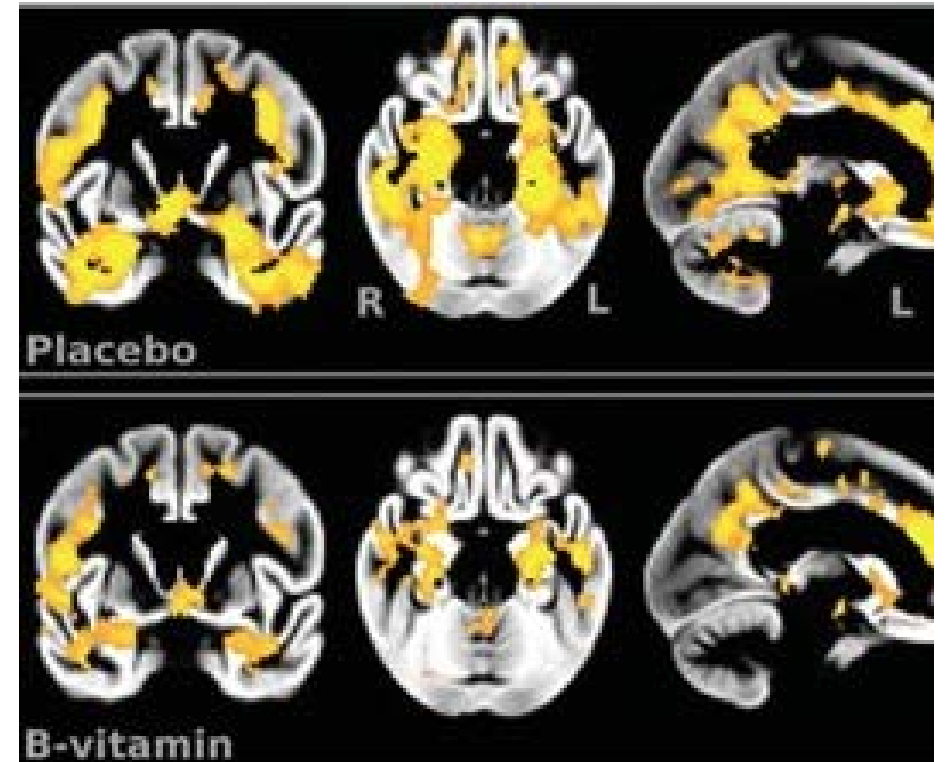
- Dr. Irwin Rosenberg
  - Inverse relationship between homocysteine levels, which are regulated by B vitamins, and dementia, heart disease, stroke, and osteoporosis

### Homocysteine metabolism



# Nutrients needed for cognitive health

- Dr. David Smith and Dr. Helga Refsum
  - B vitamin supplementation (folate, B6 and B12) reduce the rate of brain atrophy by lowering total homocysteine levels.



# Nutrients needed for cognitive health

- Clarke et al 2014 Meta Analysis, Effects of homocysteine lowering with B vitamins on cognitive aging
  - Possible reasons for poor correlation
    - Was the requirement for cognitive changes in the placebo group necessary?
    - Is the Mini Mental State Examination (MMSE) test rigorous enough?
    - Test groups were not stratified according to B-vitamin status.



# Correlation between thiamine (Vitamin B1) and Alzheimer's disease

*Nutrients* 7 (2015) 2415–2439

- Thiamine is an essential nutrient involved in brain metabolic and cellular functions, including carbohydrate metabolism and neurotransmitter production, notably acetylcholine and gamma-amino butyric acid (GABA).
- Thiamine shields the body from the harmful effects of advanced glycation end products (AGEs).
- Thiamine deficiency can be treated with Benfotiamine, a synthetic S-acyl derivative of thiamine (vitamin B1).
- Insufficient evidence to draw conclusions regarding the role of thiamine on cognitive function in older adults. Requires large-scale clinical trials

# Cognitive Health and Vitamin D

- Cédric Annweiler, Katherine Tucker
  - Vitamin D levels correlate with reduced incidence of dementia, Alzheimer's disease and stroke.
  - Dr. Tucker cited the outcome of a Health Study focused on Puerto Rican adults living in the Greater Boston area.
    - Vitamin B6, Omega-3 fatty acids and **vitamin D** levels correlate with improved cognitive abilities.
    - High sugar consumption and reduced fruit and vegetable consumption correlate with cognitive impairment.

# Omega-3 PUFA and cognitive health

Ann Nutr Metab 60 (2012) 272-292

- Omega-3 fatty acids have been associated with decreased brain inflammation
- More than 30 studies have shown a beneficial correlation
  - Improved executive functioning
  - MRI
    - Reduced gray matter atrophy
    - Improved white matter microstructural integrity

# Antioxidants and cognitive health

Aging Research Reviews 35 (2017) 222-240

- Polyphenols: Fruits (grapes, apples, pears, cherries, and other berries), coffee, tea, red wine, chocolate, cinnamon, legumes and nuts
  - InCHIANTI study-Participants who consumed a diet rich in polyphenols reduced the risk of all-cause mortality and the risk of cognitive decline
    - No association between consumption vs urinary polyphenol levels
      - Improved biomarkers and detection methods will provide further clarity

# Antioxidants and cognitive health

Aging Research Reviews 35 (2017) 222-240

- Flavonoids: Berries, cocoa, chocolate, grapes, apples, citrus fruit, acerola cherry, elderberry, cabbage, soybeans
  - Strong correlation with improved cognitive function
  - Putative mechanisms
    - Stimulate pro-survival signaling pathways
    - Increase anti-oxidant gene expression
    - Potently inhibit beta and gamma secretase activity\*\*
    - Improve peripheral vascular function and blood flow
      - Increase NO bioavailability via eNOS
    - Basic mechanism for cognitive improvement is unclear, detection of metabolites is limited due to poor bioavailability of flavonoids

# Magnesium and brain health

- Associated with muscle cramps and heart health
- Magnesium and the Brain: The Original Chill Pill: Emily Deans M.D.
  - Case studies: anxiety, apathy, depression, headaches, insecurity, irritability, restlessness, talkativeness, and sulkiness
  - Mechanism: Improved control of HPA axis, reduced stress hormone production

# Probiotics and anxiety in elderly subjects

- Kirsten Tillisch
  - Decreased Microbiota diversity correlates with aging.
  - Anxiety and depression decrease when given probiotics
- Messaoudi et al., 2011 (*Gut Microbes* (2 [2011] 256-261)
  - Beneficial psychological effects of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in healthy human volunteers.
  - Reduction of urinary-free cortisol levels

Data  
corroboration  
from EGGLRock  
Nutrition  
Reduced mind  
and emotion  
scores following  
probiotic  
administration

**Patient Name:** \_\_\_\_\_ **Date:** \_\_\_\_\_

Rate each of the following symptoms based on your typical health profile for the specified duration:  
☐ Past month      ☐ Past week      ☐ Past 48 hours

**Point Scale:**    0—Never or almost never have the symptom    1—Occasionally have it, effect is not severe    2—Occasionally have it, effect is severe  
                          3—Frequently have it, effect is not severe    4—Frequently have it, effect is severe

I. Medical Symptoms Questionnaire (MSQ)	
<b>HEAD</b>	_____ Headaches _____ Faintness _____ Dizziness _____ Insomnia <b>TOTAL</b> _____
<b>EYES</b>	_____ Watery or itchy eyes _____ Swollen, reddened or sticky eyelids _____ Bags or dark circles under eyes _____ Blurred or tunnel vision <b>TOTAL</b> _____
<b>EARS</b>	_____ Itchy ears _____ Earaches, ear infections _____ Drainage from ear _____ Ringing in ears, hearing loss <b>TOTAL</b> _____
<b>NOSE</b>	_____ Stuffy nose _____ Sinus problems _____ Hay fever _____ Sneezing attacks _____ Excessive mucus formation <b>TOTAL</b> _____
<b>MOUTH/THROAT</b>	_____ Chronic coughing _____ Gagging, frequent need to clear throat _____ Sore throat, hoarseness, loss of voice _____ Swollen or discolored tongue, gums, lips _____ Canker sores <b>TOTAL</b> _____
<b>SKIN</b>	_____ Acne _____ Hives, rashes, dry skin _____ Hair loss _____ Flushing, hot flashes _____ Excessive sweating <b>TOTAL</b> _____
<b>HEART</b>	_____ Chest pain _____ Irregular or skipped heartbeat _____ Rapid or pounding heartbeat <b>TOTAL</b> _____
<b>LUNGS</b>	_____ Chest congestion _____ Asthma, bronchitis _____ Shortness of breath _____ Difficulty breathing <b>TOTAL</b> _____
<b>DIGESTIVE TRACT</b>	_____ Nausea, vomiting _____ Diarrhea _____ Constipation _____ Bloating feeling _____ Belching, passing gas _____ Heartburn _____ Intestinal/stomach pain <b>TOTAL</b> _____
<b>JOINTS/MUSCLE</b>	_____ Pain or aches in joints _____ Arthritis _____ Stiffness or limitation of movement _____ Feeling of weakness or tiredness _____ Pain or aches in muscles <b>TOTAL</b> _____
<b>WEIGHT</b>	_____ Binge eating/drinking _____ Craving certain foods _____ Excessive weight _____ Water retention _____ Underweight _____ Compulsive eating <b>TOTAL</b> _____
<b>ENERGY/ACTIVITY</b>	_____ Fatigue, sluggishness _____ Apathy, lethargy _____ Hyperactivity _____ Restlessness <b>TOTAL</b> _____
<b>MIND</b>	_____ Poor memory _____ Confusion, poor comprehension _____ Difficulty in making decisions _____ Stuttering or stammering _____ Slurred speech _____ Learning disabilities _____ Poor concentration _____ Poor physical coordination <b>TOTAL</b> _____
<b>EMOTIONS</b>	_____ Mood swings _____ Anxiety, fear, nervousness _____ Anger, irritability, aggressiveness _____ Depression <b>TOTAL</b> _____
<b>OTHER</b>	_____ Frequent illness _____ Frequent or urgent urination _____ Genital itch or discharge <b>TOTAL</b> _____
<b>GRAND TOTAL</b>	<b>TOTAL</b> _____

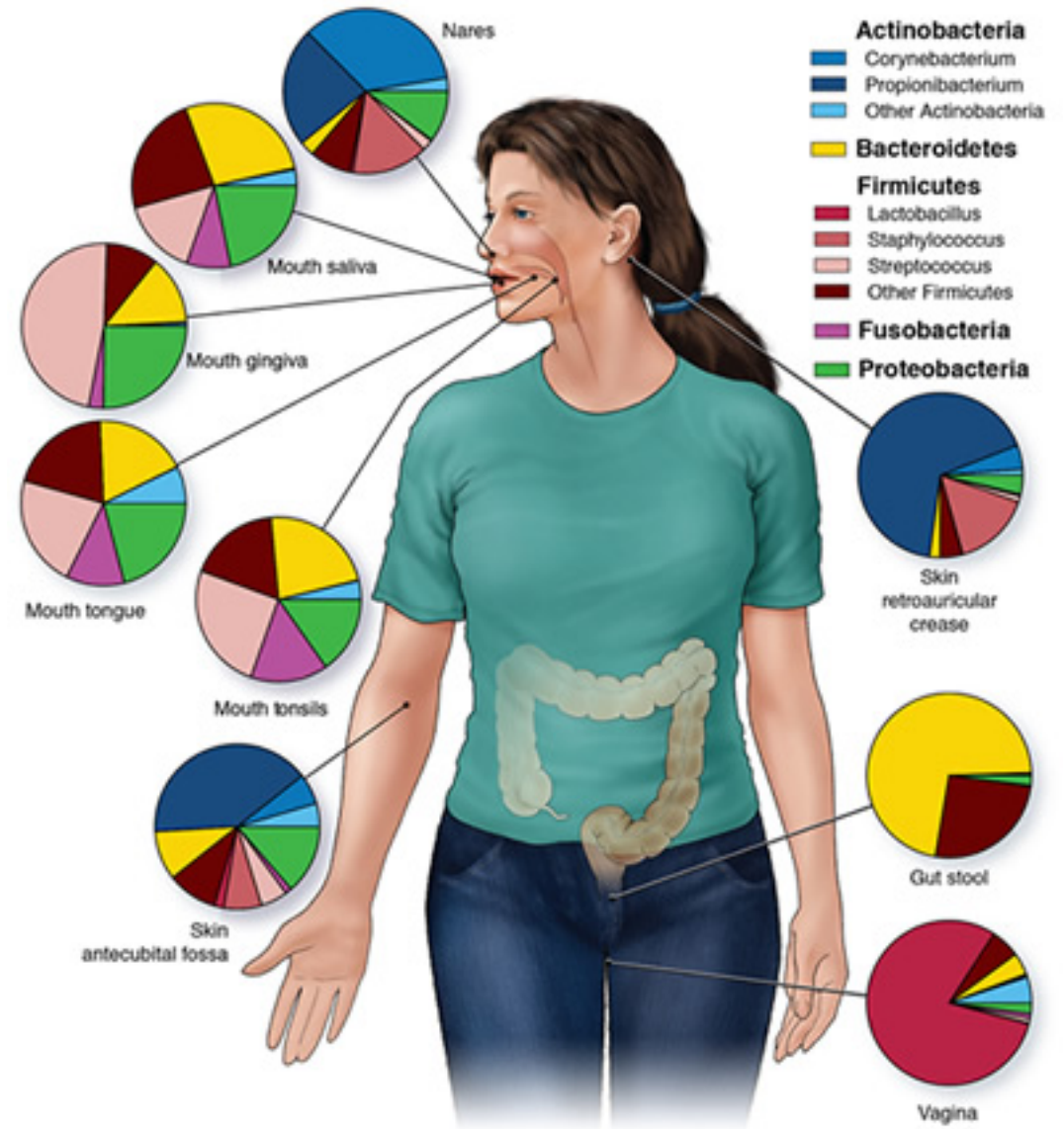
Reduced Scores

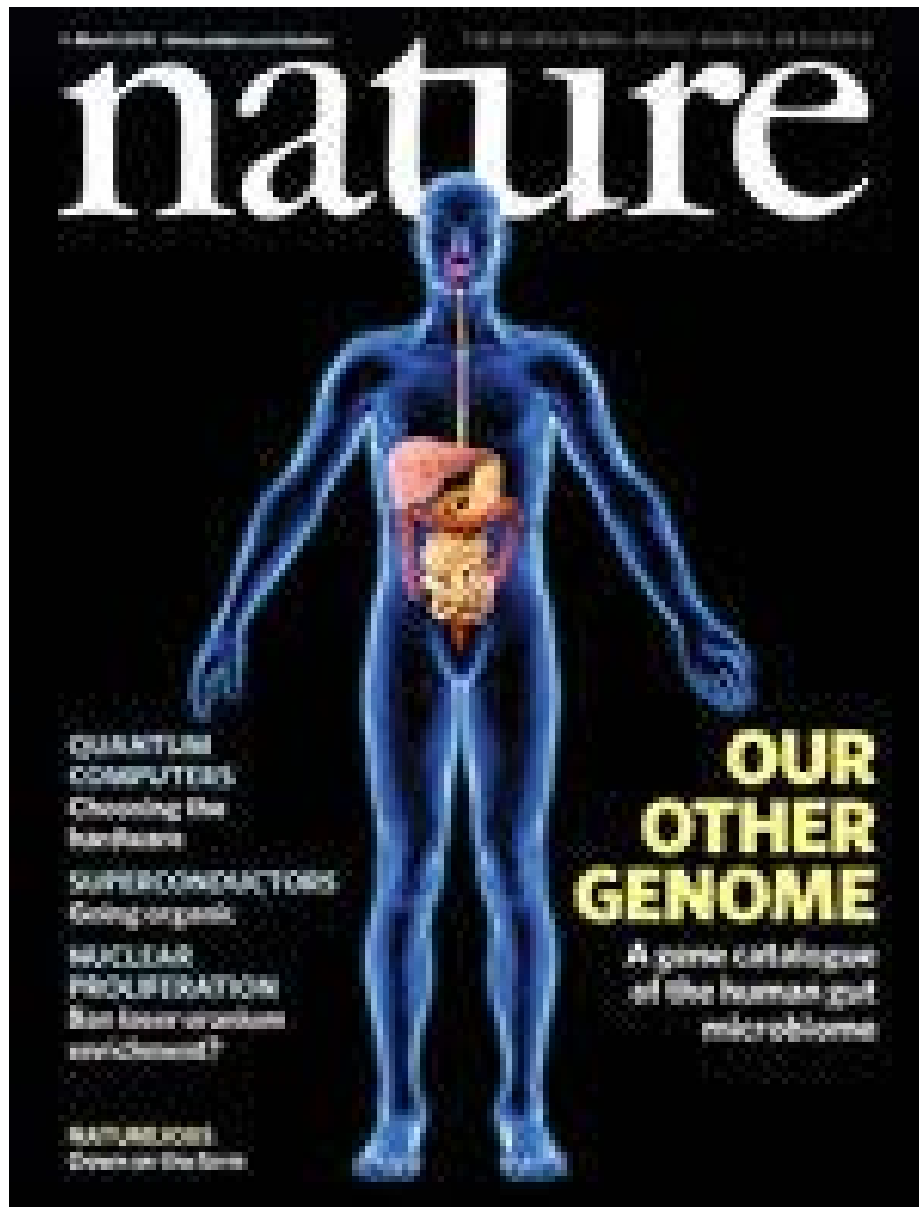
Reduced Scores



# What is the Microbiome?

The communities of microbes living in and on the various parts of your body make up your microbiome. They help you **digest** your food, offer **protection** against dangerous bacteria and viruses, and keep your **immune system** responsive to your environment and running smoothly.





$10^{14}$  Microbes in your microbiome

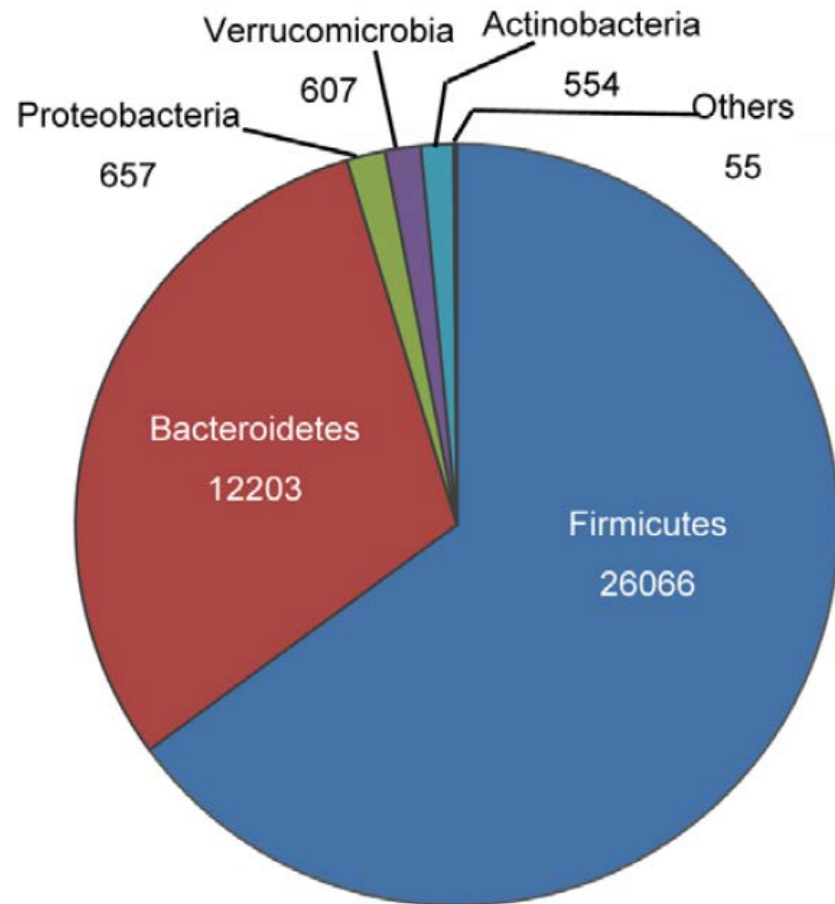
150x more genes than human genome

- The international MetaHIT (Metagenomics of the Human Intestinal Tract) project
- A gene catalogue of the human gut microbiome derived from 124 healthy, overweight and obese human adults, as well as inflammatory disease patients, from Denmark and Spain.
- Credit: Roger Harris /Science Photo Library.

*Nature 464 (2010) 59-67*

# Gut Bacteria Composition

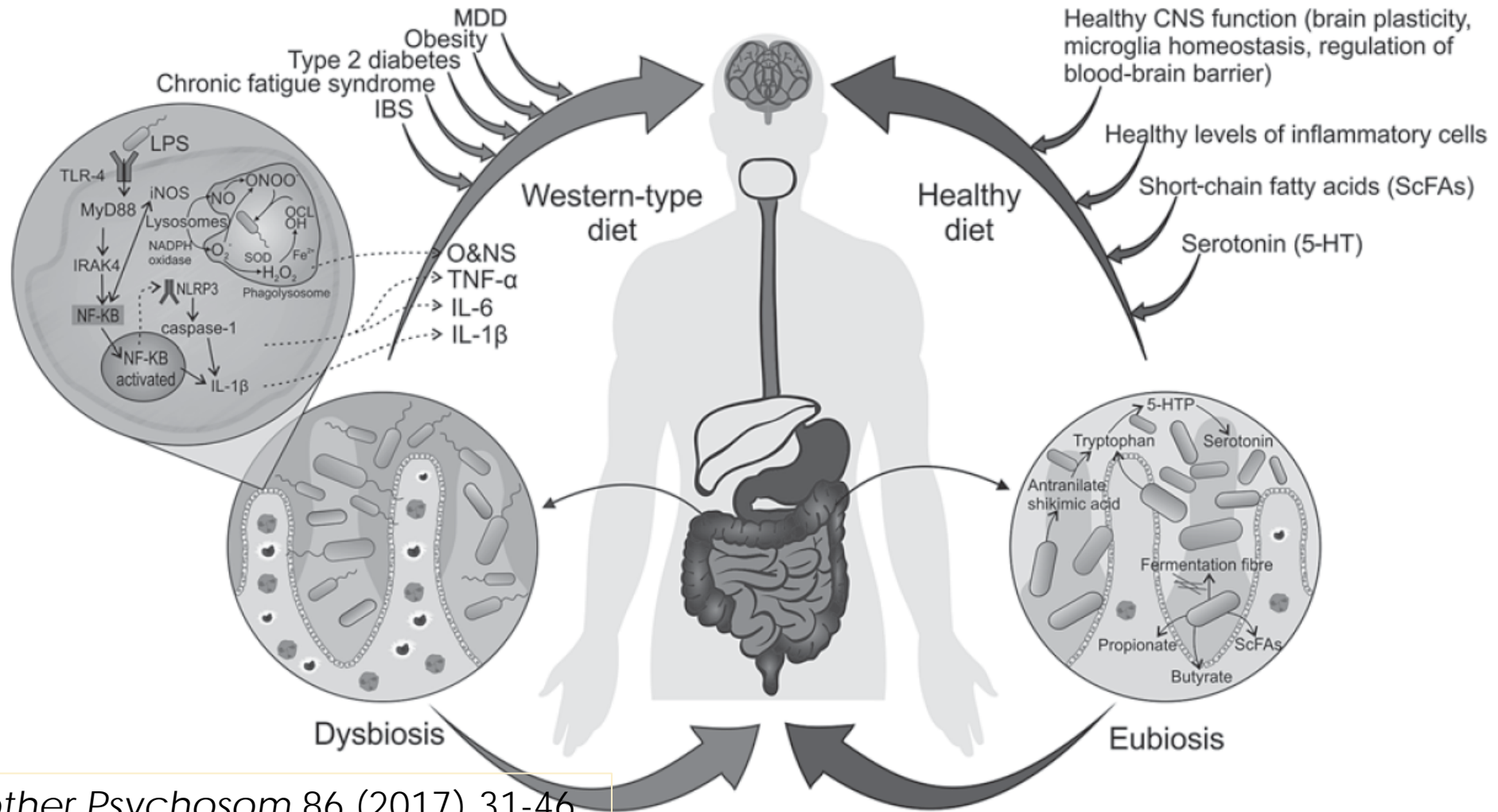
PLoS One 4 (2009) e6074



Phyla: Firmicutes and Bacteroidetes occupy 65% and 30% of the pie, respectively, while 11 additional phyla comprise the remaining 5%

- Culture-independent 16S rRNA sequence analysis
- The total number of genes is estimated to be ~ 9MM

# Microbiota-gut-brain axis



# Immunity: Where does it all begin?

*Proc. Natl. Acad. Sci. U.S.A.* 107 (2010) 11971–11975.

- Birth-canal bacteria are critical for gut health
- Vaginal delivery fosters the growth of commensal bacteria
  - Fecal microbiota resembles that of the maternal gastrointestinal tract and vagina
- Issues with Cesarean births
  - Delays breast feeding
  - Requires antibiotics
  - Babies delivered by C-section have less diverse flora, more *C. diff*
  - Fecal microbiota resembles that of the maternal skin



# Commensal vs. Pathogenic Bacteria

- The commensals - These microbes are (usually) more friendly to their host, using a microscopic region of the host's body as their habitat.
  - Both host and microbial agent benefit
- Commensals are also the first line of defense against pathogenic microbes.
- Pathogens – those that cause illness in the host organisms they invade.
- Pathogens flourish in the absence of commensals.
- Commensals become pathogenic when the immune system is weakened.

# Early Gut Microbiome

*Neuropsychopharm Rev* 42 (2017) 178-192

- Early colonization is critical for development of the immune system
- Full-term, vaginally delivered babies born to healthy mothers who are breast fed and non-antibiotic treated have an optimal development of the neonatal microbiota
- Formula-fed infants have high proportions of
  - Bacteroides
  - Clostridium
  - Enterobacteriaceae
- Infant formulas are now developed with ingredients (prebiotics) that foster the growth of beneficial bacteria
- Within 3 years of age the microbiota fully resemble that of an adult



# Evolution of gut microbiome

**TABLE 1** Gut Microbiota Composition Throughout the Life Span

Composition		References
Neonatal	Low diversity and a relative dominance of the phyla <i>Proteobacteria</i> and <i>Actinobacteria</i>	Eckburg et al (2005), Qin et al (2010)
Adult	Dominated by members of the <i>Bacteroidetes</i> and <i>Firmicutes</i> phyla	Turnbaugh et al (2006)
Old age	<i>Bacteroides</i> and <i>Firmicutes</i> are the dominant phyla Significant loss of diversity especially in frail elderly	Claesson et al (2011)

*Neuropsychopharmacology Reviews* 42 (2017) 178-192



# Nutritional needs for cognitive development in the young

*Frontiers in Human Neuroscience* 7 (2013) article 97

- Omega-3 fatty acids: Long Chain polyunsaturated fatty acids, DHA and EPA
- Vitamin B12 and folic acid
- Choline
- Minerals
  - Iron: Affects myelination of neurons and is a co-factor for enzymes involved in neurotransmitter synthesis,
  - Iodine: Needed for thyroid hormone function
  - Zinc: A structural component of many enzymes
  - Zinc, selenium and chromium are implicated in brain protection
- These deficiencies are most apparent in areas of extreme poverty
- The complexity of a Western diet should provide sufficient amounts of these nutrients

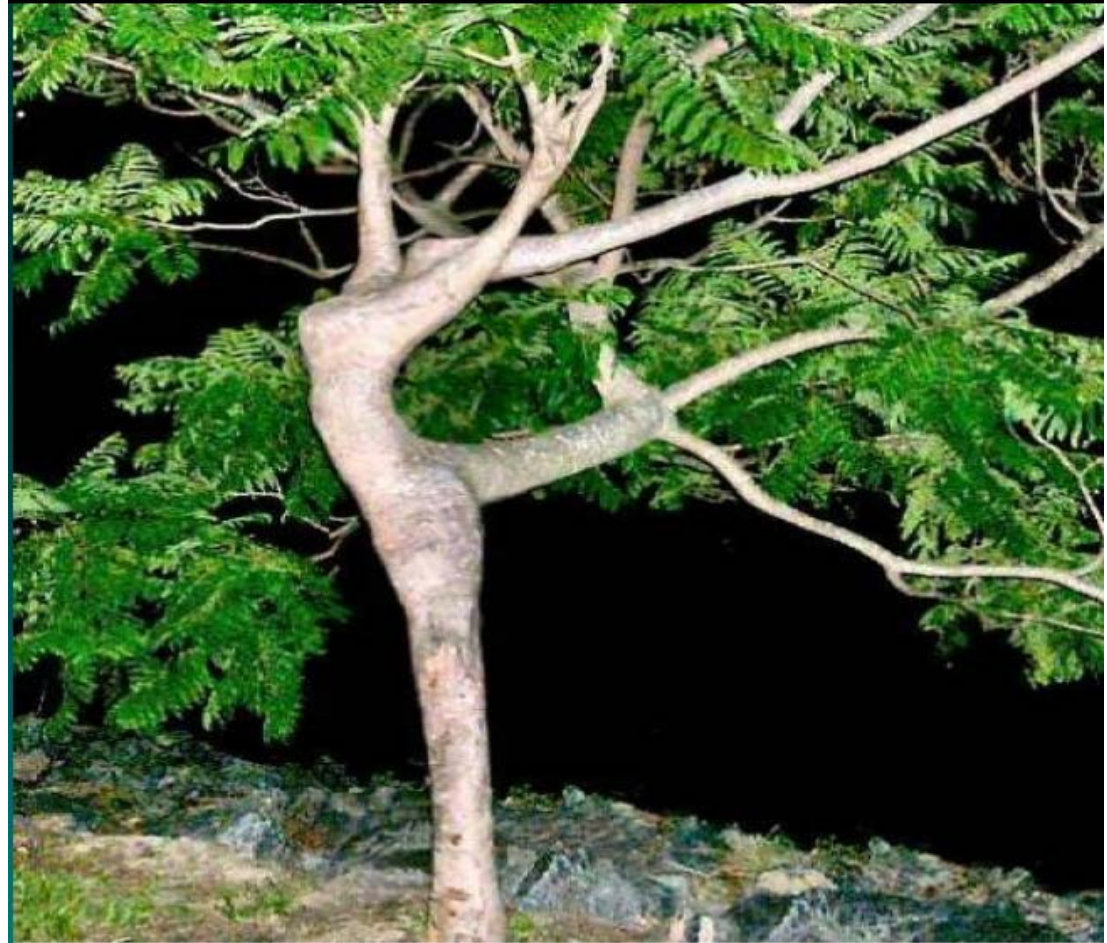
# Factors that affect early colonization and the immune system

- Antibiotic use
- Diet
- Mode of Delivery
- Environmental factors
- Maternal microbiome
- Preterm infants
  - Low acidity in the stomach, require more frequent feeding
  - More gut pathogens
  - Less microbial diversity



## Other impacts on diversity

- Antiseptics
- Antibiotics
  - People
  - Animals
- GMO foods
  - Pesticides, herbicides
- Excessive hygiene



# Microbial benefits to human health

Nutr Rev. 2012 August ; 70(Suppl 1): S2–S9

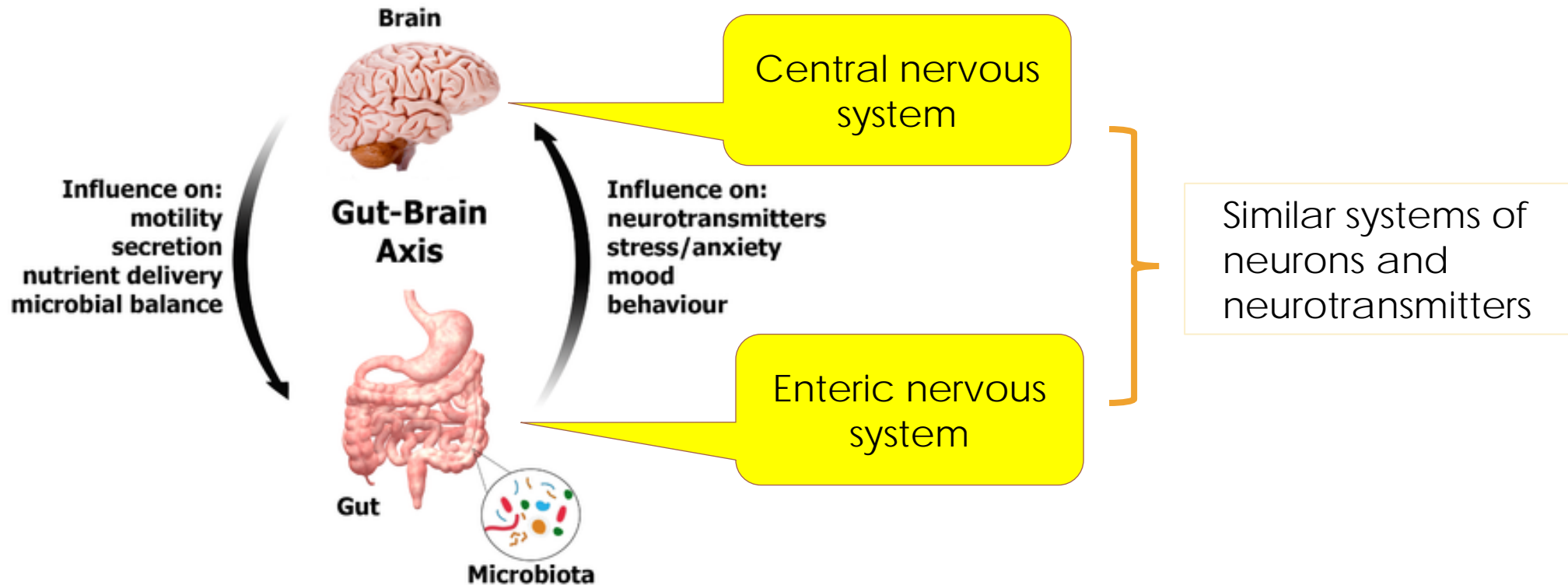
- Food digestion, nutrient metabolism and processing
- Detoxification of xenobiotics
- Regulation of human metabolism
  - Energy extraction from macronutrients
  - Cholesterol lowering
- Production of vitamins
  - B Vitamins
  - Vitamin K
- Anti-cancer
- Production of neurotransmitters: Serotonin, dopamine

# Microbial benefits to human health

Nutr Rev. 2012 August ; 70(Suppl 1): S2–S9

- Production of neurotransmitters, serotonin, dopamine, acetylcholine
- Development and terminal differentiation of host mucosa
- ‘Education’ and regulation of immune system target recognition and responses;
- Integrity of the barrier function of the skin and mucosal lining
- Prevention of colonization and invasion of the host by pathogens

# How are the gut and the brain connected? That “gut feeling”



<http://beyondaddiction.ca/2016/09/04/gut-brain-addiction/>  
*Medical Hypotheses* 93 (2016) 77-80

# Neurotransmitters and endocannabinoids

- Serotonin
  - Serotonin-90% made in the GI tract
  - Three-fold higher in conventional mice vs germ-free
  - *B. infantis* increases levels of tryptophan in plasma of rats and reduced depression in forced swim test
- Dopamine
  - Gastrointestinal dysfunction occurs in 80% of Parkinson's disease patients
    - Mov disord 30 (2015) 350-358
  - Gut dysbiosis is associated with Schizophrenia
    - Schizophren Res 2014
- Endocannabinoids (*Nat Rev Endocrin*, 12 [2016]133-143)
  - Receptor sites are widely distributed in the brain
  - Implicated in obesity, appetite stimulation
  - *Lactobacillus acidophilus* reduces abdominal pain in rodents

# Communication *via* Neuropeptides

Neuropsychopharmacology REVIEWS 42 (2017), 178–192

- Bacterial by-products that come in contact with the gut stimulate production of:
  - PYY: A peptide released from cells in the ileum and colon that acts to reduce appetite
  - Neuropeptide Y: a neurotransmitter in the brain that controls food intake, fat storage and other measures of well-being
  - Cholecystokinin: Facilitates digestion within the small intestine.



# Communication *via* Neuropeptides

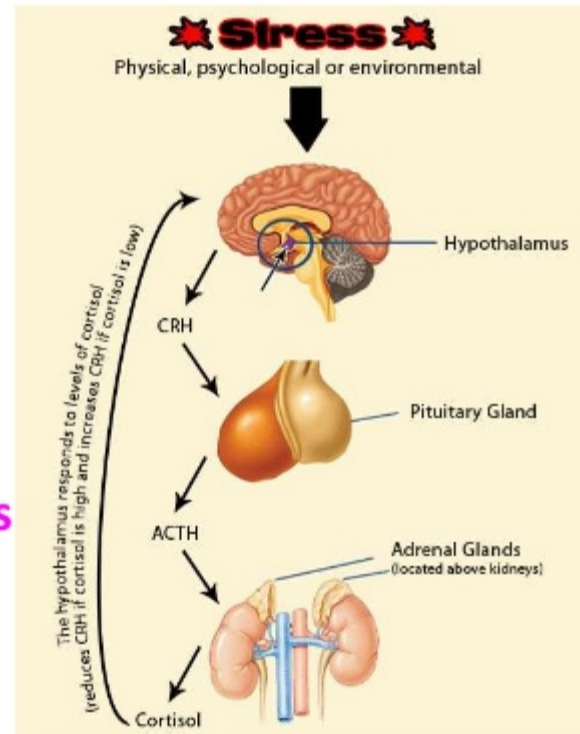
Neuropsychopharmacology REVIEWS 42 (2017), 178–192

- Bacterial by-products that come in contact with the gut stimulate production of:
  - GLP-1: an incretin that increases insulin and decreases glucagon from the pancreas
  - Substance P: Participates in vasodilation, pain, mood, inflammation, emesis, cell growth and proliferation
  - Oxytocin: Plays a role in social bonding, sexual reproduction in both sexes, and during and after childbirth

# Microbiota and the HPA axis

## HPA axis

- **Hypothalamus** triggers the release of
- CRH (Corticotrophin releasing hormone) which activates the
- **Pituitary Gland** which releases the hormone
- ACTH (Adrenocorticotrophic hormone) which is carried by the blood to the
- **Adrenal gland** which releases stress hormones
- Cortisol/ Adrenalin and Noradrenalin
- Hormones that enable the body to deal with stress

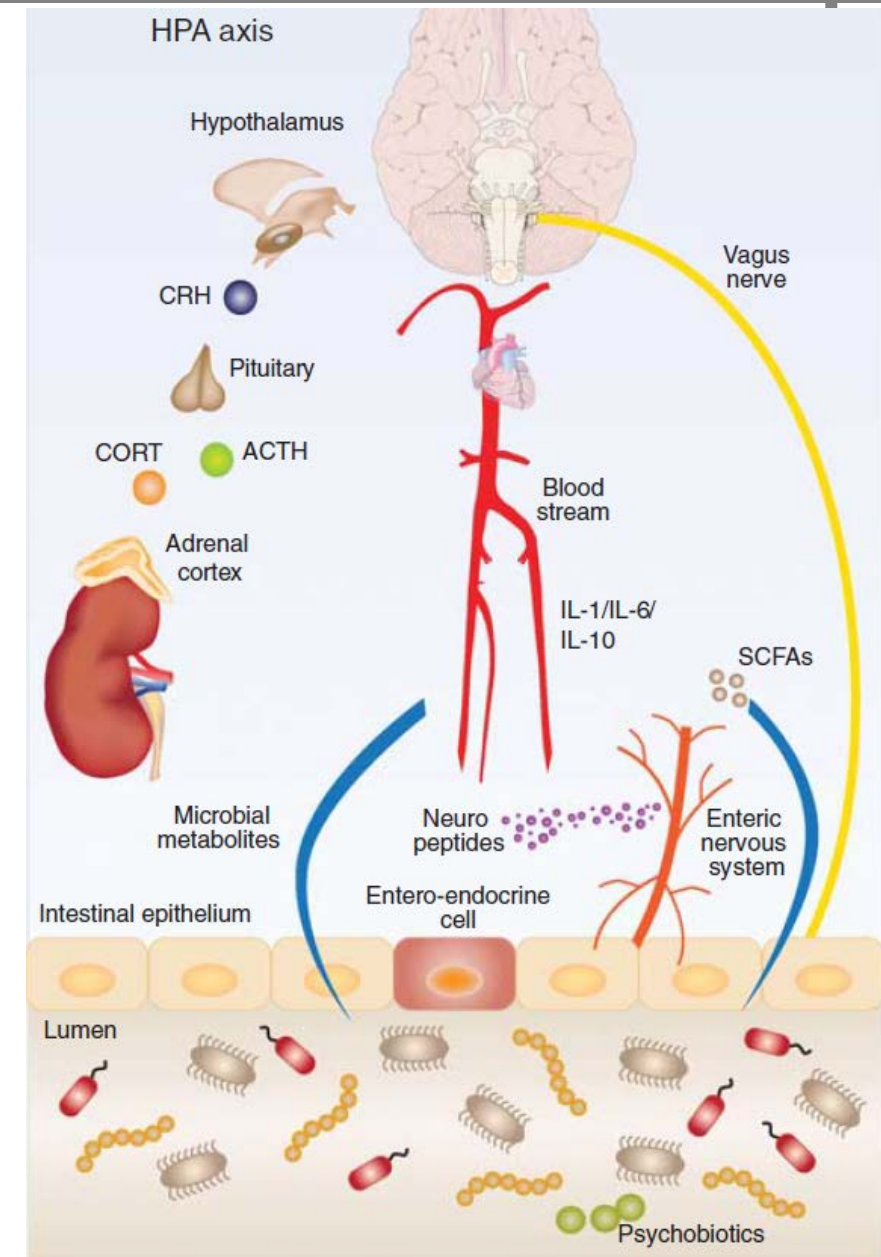


Colonization with commensal bacteria must occur in early life to ensure normal development of the HPA axis

# Microbiota and Stress Response

- Neurotransmitters produce in the gut
  - Serotonin (>90%)
  - Dopamine (50%)
  - Acetylcholine
- Gut microbes and socialization
  - Microbiota-free mice display reduced socialization, increased social cognition deficits and repetitive grooming
  - These behaviors were reversed by bacterial transplantation

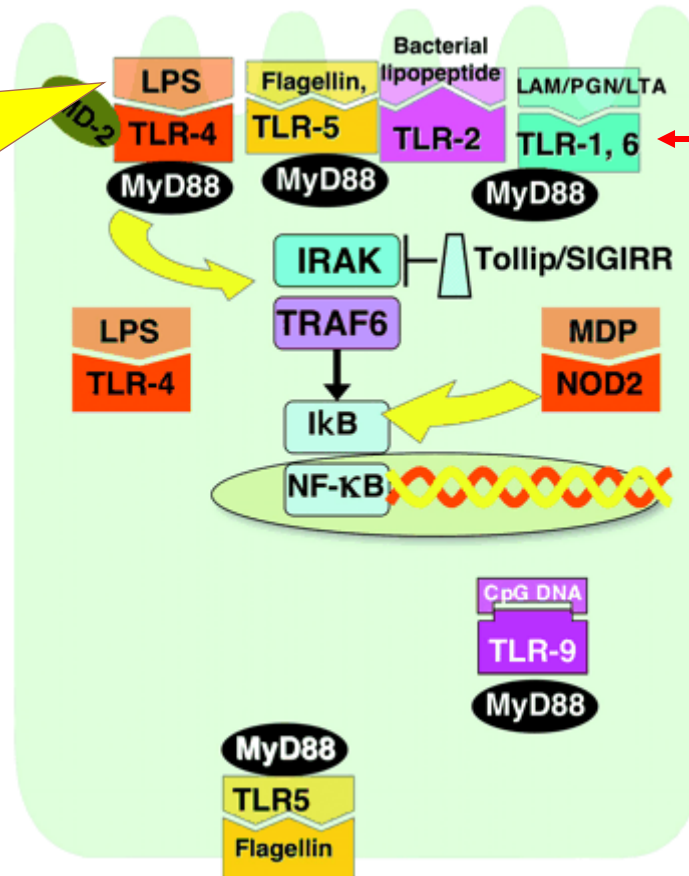
*Medical Hypotheses* 93 (2016) 77-80



# Communication with host through Toll-Like Receptors

## Defense against pathogens

Lipopolysaccharide (LPS) is a component of gram negative bacterial cell walls



- Pattern Recognition Receptor
- Allow bacteria to communicate with their host
- Present on cells of the innate immune system

TLR activation leads to proinflammatory cytokine release

# Many infectious states correlate with depression

*Psychother Psychosom* 86 (2017) 31-46

- Irritable Bowel Syndrome
  - 30% of IBS sufferers present with depression
  - Microbiota composition is distinctly different compared to healthy controls
  - Microbiota profile in IBS is similar to that seen in Major Depressive Disorder (MDD)
    - 2:1 ratio of Firmicutes to Bacteroidetes
    - Increase in *Dorea sp*, *Runinococcus sp.*, and *Clostridium spp.*
    - Decrease of *Bifidobacterium sp.* and *Faecalibacterium sp.*
    - Higher peripheral levels of LPS
    - Probiotic administration reduces pro-inflammatory cytokines and T-cell function and preserves the integrity of the gut mucosa

Many infectious states correlate with depression  
*Psychother Psychosom* 86 (2017) 31-46

- Chronic Fatigue Syndrome
  - Persistent fatigue worsened by physical and mental exertion
  - Higher peripheral levels of IL-1, IL-6 and TNF- $\alpha$
  - Mitochondrial dysfunction
  - Increased oxidative and nitrosative stress
    - Characterized by over production of reactive oxygen and nitrogen species
      - Damage DNA, lipids and proteins
  - Microbiota changes mirror that seen in depression
  - Diminished antioxidant levels

Many infectious states correlate with depression  
*Psychother Psychosom* 86 (2017) 31-46

- Obesity and Type 2 Diabetes
  - Metabolic Mood Syndrome
    - Characterized by changes in mood and metabolism following chronic stress
    - Cognitive dysfunction
    - Increase levels of IL-6, TNF- $\alpha$  and IL-1 $\beta$
    - Elevated c-Reactive Protein, plasminogen activator inhibitor, serum amyloid A
    - Immune cell profiles mirror that seen in depression
    - Infiltration of abdominal adipose tissue with macrophages
    - Elevated markers of oxidative stress
    - Reduced levels of vitamins E and C
    - Elevated peripheral levels of LPS



Many infectious states correlate with depression  
*Biol Psychiatry* 74 (2013) 720-726

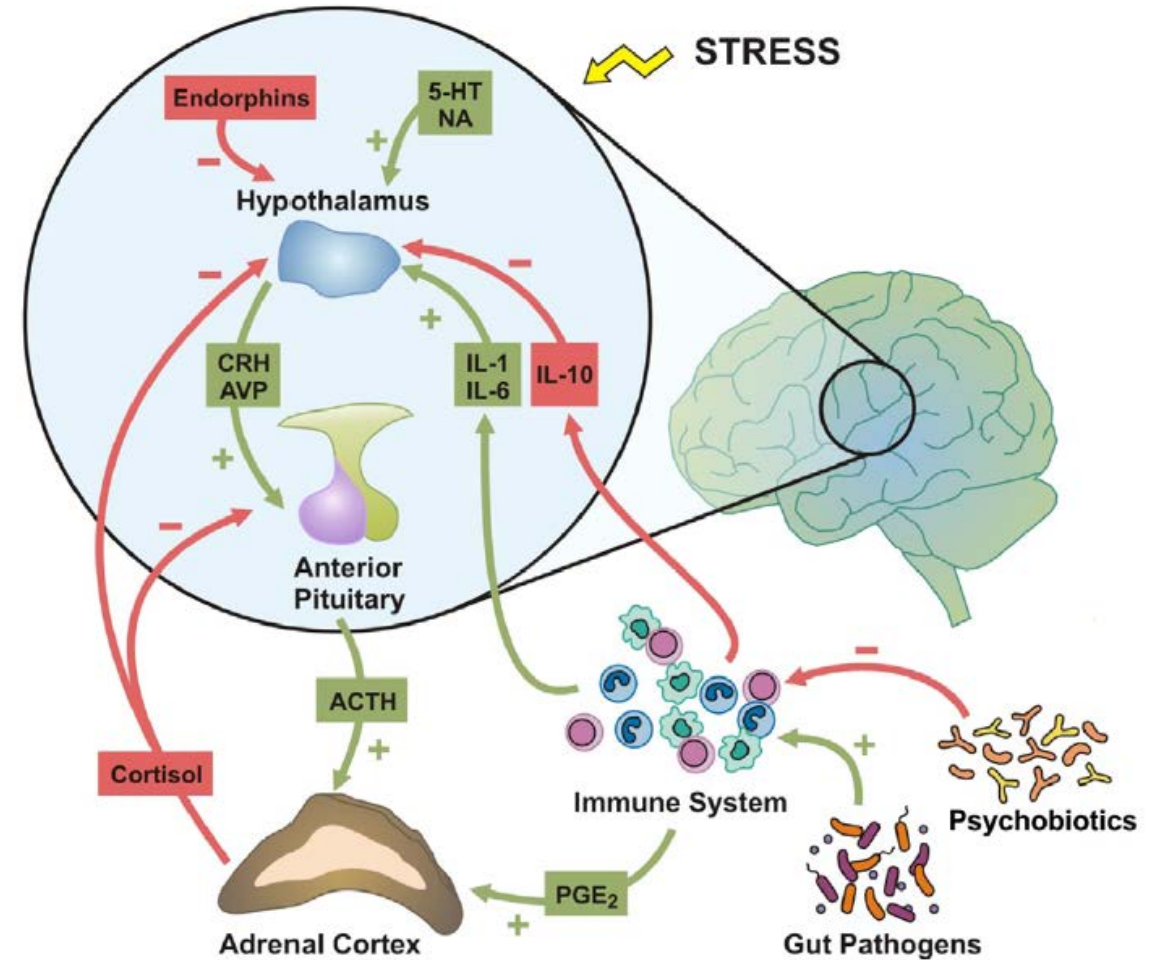
- Syphilis
  - Chronic infection leads to dementia
- Lyme disease: Infection with the *Borrelia burgdorferi* spirochete
  - Poor memory and concentration
  - Depression
- Subclinical doses of *Camphylobacter Jejuni* induces anxiety-like behavior in mice



# Psychosocial stress is a dominant factor in major depression

- Stress leads to activation of the HPA axis
- Altered gut barrier function with LPS secretion into the bloodstream
- Increases inflammatory cytokines
- Psychobiotic organisms upregulate IL-10, an anti-inflammatory cytokine

• *Biol Psychiatry* 74 (2013) 720-726



# Sequela to Major Depressive Disorder (MDD)

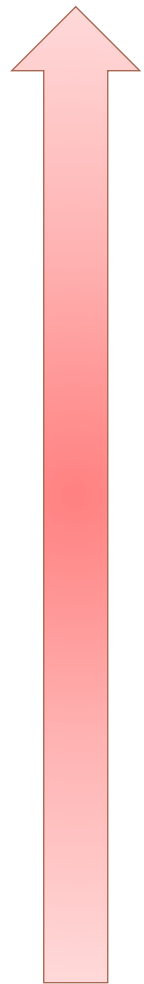
*Psychother Psychosom* 86 (2017) 31-46

1. Disruption of tight junctions of the gut epithelia
2. LPS secretion from gram negative bacteria
3. Stimulation of TLR4
4. Stimulates release of inflammatory cytokines, TNF $\alpha$ , IL-6, IL1 $\beta$
5. Inducible NO synthase, NADPH oxidase
6. Microglia activation
7. Disruption of Blood Brain Barrier

# Probiotics, brain development, behavior and mood

- Reduced cortisol levels in healthy volunteers following consumption of probiotic containing milk
- *Alistipes* overrepresented in depression and chronic fatigue
  - Administration of *L. casei* Shirota decreased anxiety in Chronic Fatigue
  - Prebiotic galactooligosaccharide reduces anxiety in IBS
- *Elevation of Clostridium in Autism Spectrum Disorder (ASD)*
- *Improved behavior and communication in ASD subjects treated with antibiotics and probiotics*
- *Underrepresentation of Bacteroidetes in depression*

# Treatment of depression

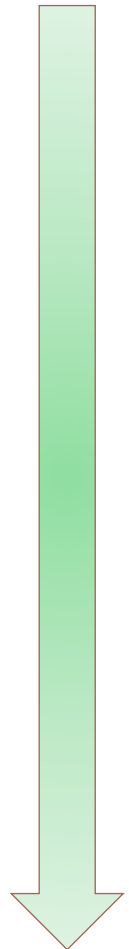


## Increased depression

- Cytokines
- cRP
- LPS
- Pathogenic bacteria (Faecalibacterium spp )

## Reduced depression

- Antidepressants reduce inflammation
- Antibiotic treatment
- Probiotic treatment (also reduces pain and inflammation)



# Summary of studies with Psychobiotics

## Preclinical data

*Biol Psychiatry* 74 (2013) 720-726

- Germ-free studies
  - Decreased behavioral but increased endocrine response to stress
  - Altered serotonergic development, Brain-derived neurotrophic factor (BDNF), and glutamate expression
  - Partial reversal by *B. Infantis* or fecal ingestion

# Learnings from Germ-Free (GF) mice

- GF mice have no commensal bacteria, undeveloped immune system
- GF studies prove that gut microbiota mediate neuronal function of ENS neurons (*Neurogastroenterol Motil* 25 [2013]4–1)
  - Increased HPA response when kept microbiota-free from birth
    - HPA activity reversed with microbiota transplant
  - Reduced brain-derived neurotrophic factor (BDNF)
  - Reduced expression of the NMDA receptor subunit 2a in the cortex and hippocampus

## Learnings from Germ-Free (GF) mice

- Altered neuropeptide production (*ISME J.* 7 (2013) 743-55)
  - Increased spontaneous motor activity
  - Altered exploratory behavior
  - plasma serotonin levels of conventional mice are almost three-fold higher than GF mice
- *Lactobacillus rhamnosus* (JB-1)
  - *Reduced anxiety*

# Summary of studies with Psychobiotics

## Preclinical data

*Biol Psychiatry* 74 (2013) 720-726

- Maternal Separation
  - Long term HPA changes
  - Long term changes to the microbiome
  - *B. Infantis* normalizes behavior
  - *Contradictory findings for psychobiotic effects on corticosterone*
- Restraint Stress and Social Stress
  - Altered microbiota and increased proinflammatory cytokines
- Acute Stressors (Elevated Plus Maze)
  - *L. Rhamnosus* is anxiolytic and acts via the vagus nerve to produce changes in GABAA and GABAB expression



# Summary of studies with Psychobiotics

## Human Studies

*Biol Psychiatry* 74 (2013) 720-726

- Irritable Bowel Syndrome
  - *B. Infantis* is effective and alters plasma pro-inflammatory to anti-inflammatory cytokine ratio
- Chronic Fatigue Syndrome
  - Decreased anxiety in those given *L. Casei* relative to placebo
- Healthy Volunteer Studies
  - *L. Helveticus* together with *B. Longum* decreases psychological distress relative to placebo and decreased urinary free cortisol output.

# Short Chain Fatty Acids (SCFA)

- Short chain, water soluble fatty acids, readily absorbed
- Produced in the human gut as the end products of anaerobic bacterial fermentation of carbohydrates
- Acetate - Used by skeletal and cardiac muscle, and adipocytes
- Butyrate - Metabolized in the gut epithelium to make ketone bodies
- Propionate - Poorly understood but appears to involve transport to the liver

# Short Chain Fatty Acids (SCFA)

- Possible function
  - Prevention of DNA and cell damage
  - Participate in immune and inflammatory responses
  - Antidepressant effects (sodium butyrate)
  - Epigenetic regulation (HDAC inhibition)
  - GPCR signaling (GPR43)

# Ketone bodies and cognition

- Ketones are thought to provide brain cells (neurons and astrocytes) with an energy source that is more efficient than glucose
- Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI)
- Studies that show ketones (beta-hydroxybutyrate) alleviate symptoms of AD
  - *Neurobiol Aging*. 3 (2004) 311-314.
  - *Alzheimers Dement*. 11 (2015) 99-103.
- Ketogenic diets improve behaviors associated with autism spectrum
  - PLoS ONE 8 (2013) e65021
- Ketogenic diets reduce seizures in epilepsy
  - *Lancet Neurology* 17 (2018) 84-93

# Gut Microbiota and Autism

*Dig Dis Sci* 57 (2012) 1987-1989

- Dysfunctions in:
  - Social interaction
  - Communication skills
  - Repetitive behaviors
- Underlying cause:
  - Genetic
  - Environmental
    - Pre- or post-natal exposure to chemicals or drugs
    - Stress
    - Maternal infection
    - Dietary factors that may preclude nutrient absorption

# Autism Spectrum Disorder (ASD)

Dig Dis Sci (2012) 57:1987–1989

- Germ-free mice have reduced sociability, social cognition deficits and increased repetitive grooming (Mol Psychiatry 19 (2014) 146-148
  - Sociability deficits and repetitive behaviors were reversed by bacterial transplantation
- Repetitive dietary behaviors
- Strong preferences for starches, snack and processed foods
- *Clostridium* is elevated in ASD
- Higher fecal bacteria fermentation product and ammonia conc. in ASD vs non-ASD
- Intervention with antibiotics and probiotics improves behavior and communication in ASD

# The Gut Microbiome: A New Frontier in Autism Research

Curr Psychiatry Rep . 15 (2013) 337

- Food selectivity
- Preference for processed foods
- High consumption of fats
- Refusing fibrous foods that rely on gut microbiota for processing in order to avoid pain associated with difficulties with digestion
  - Reduced growth of commensal bacteria
  - Increased growth of less beneficial bacteria

# Utilization of probiotics and prebiotics

- **Probiotics** clearly have the potential to drive CNS function
- Can microbiota profile change permanently?
  - Is the Microbiome as fixed as your DNA?
  - Can lifestyle be used to drive the growth of commensal bacteria?
- **Prebiotic** foods and functional foods
  - A functional food is a food or food component that provides a health benefit beyond basic nutrition
  - Altering the composition and/or activity of the gastrointestinal microbiota would certainly be considered a health benefit.



# Prebiotics

- Nondigestible carbohydrate fiber that selectively stimulate the growth and/or activity of one or more bacterial species in the colon beneficially affecting the host
  - GOS-galactooligosaccharide
  - FOS-fructooligosaccharide
  - Fermentable oligo-di- and mono-saccharides
  - Inulin (A FODMAP)
  - Resistant starch

# Prebiotics

- Protect against pathogens
- Increase levels of commensal bacteria in the intestine
- Reduce awakening cortisol in healthy volunteers
- Bone-health-promoting potential (J. Nutr. 137 [2007] 838S–846S)
- More Clinical trials needed to document efficacy

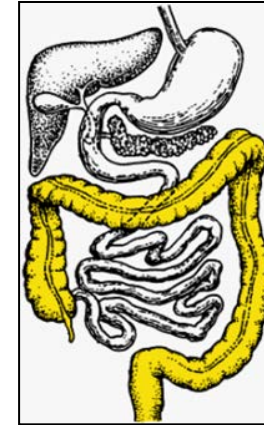
# Fermentable Fibers Shift Microbiota Composition (Examples from clinical studies)

- Bifidogenic effects
  - Inulin
  - Fructooligosaccharides
    - FOS and scFOS
  - Galactooligosaccharides
  - Resistant Starch
- Specific effects
  - Inulin
    - *F. prausnitzii*
  - GOS
    - *F. prausnitzii*
  - *Resistant Starch-Type 2*
    - *Ruminococcus bromii*
    - *Eubacterium rectale*

Rhonda Witwer  
Witwer Works, LLC

# What is Resistant Starch?

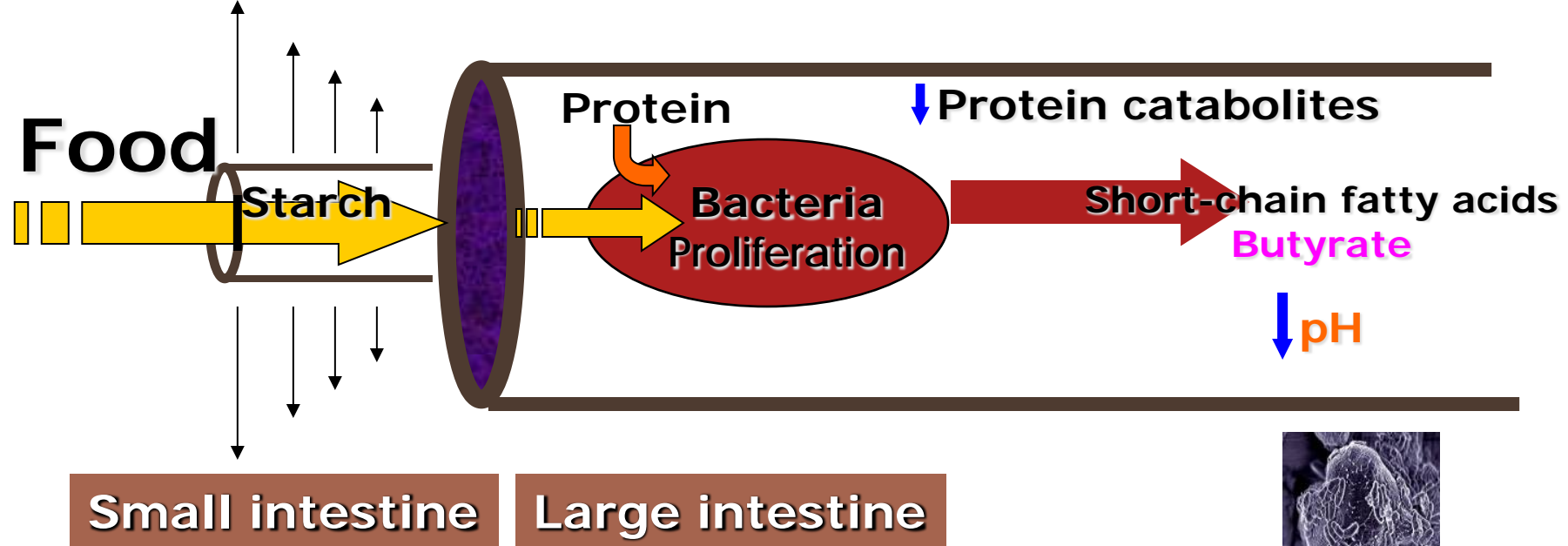
- Starch that resists digestion in the small intestine
  - Reaches the large intestine
  - Natural resistant starch is fermentable fiber
- Found in whole grains, beans, bananas and cooked & cooled starchy foods
  - Americans consume ~4.9 grams of resistant starch/day\*



Eriko Sugita / Reuters  
("Japan Goes Bananas for a New Diet"  
October 17, 2008 TIME Magazine,  
WORLD edition)

\* Murphy M. et. al., Journal of the American Dietetic Association, Jan 2008

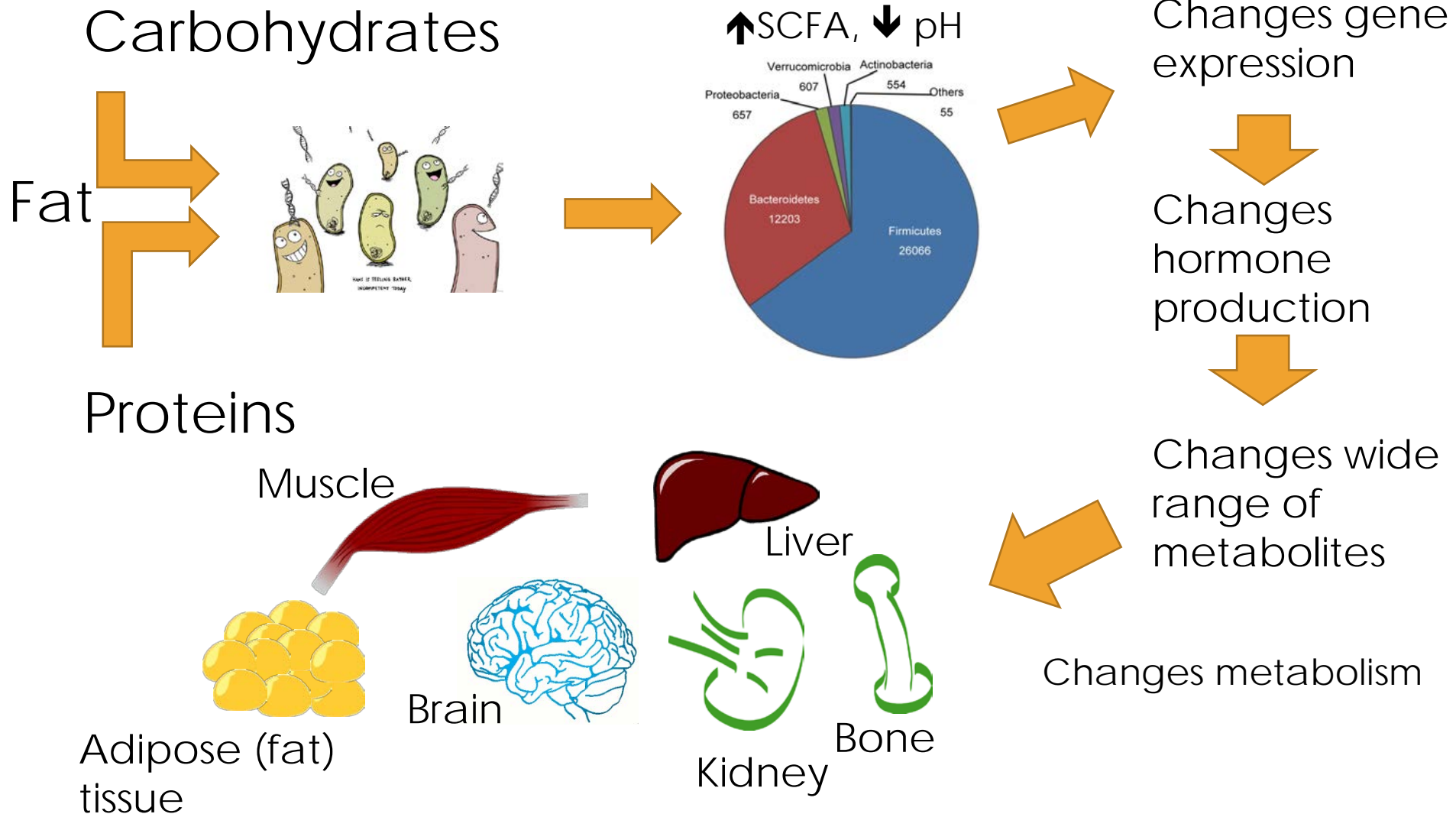
# Cascade of Effects



- Prebiotic fibers change multiple variables:
  - Starch (glucose chains) in varying degrees of breakdown
  - Microbial composition
  - SCFAs, pH
  - Thousands of other metabolites

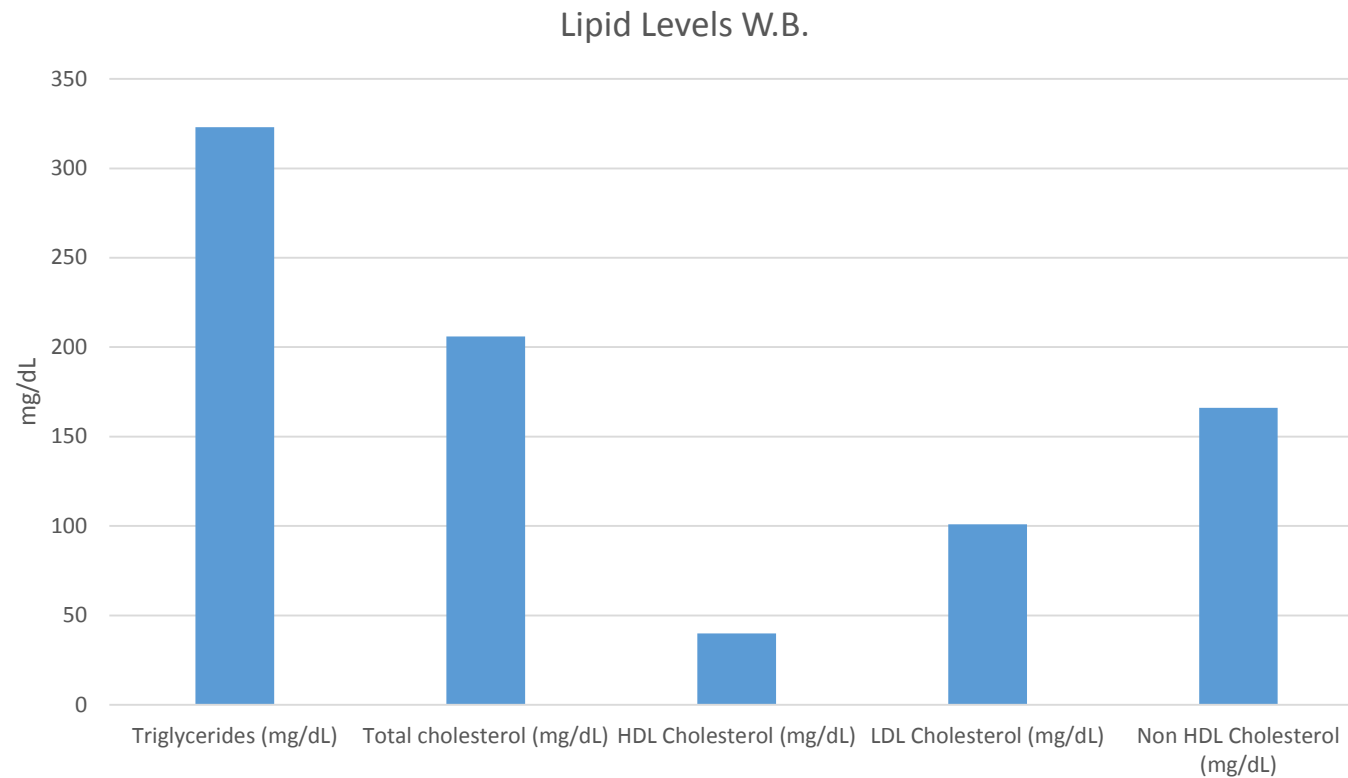
*Bifidobacteria* attached to Hi-maize starch granule

# Fermentation Generates a Cascade of Health Effects



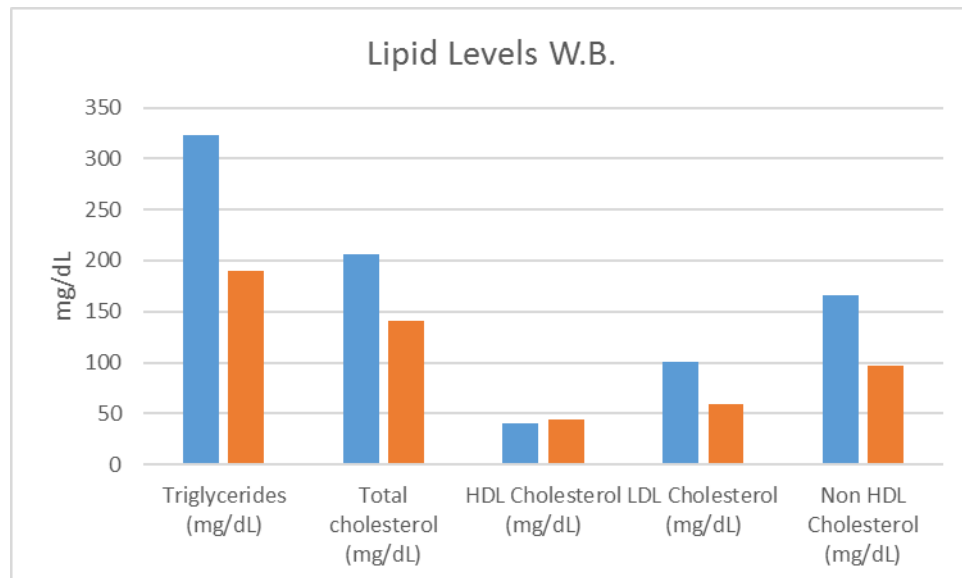
# Prebiotics and Autism

- 14-year old non-verbal autistic male, healthy weight



# Treatment plan

- 14-year old non-verbal autistic male
- Fructo-oligosaccharide protein shake daily
- Removed artificial ingredients and processed foods
- Mediterranean diet



## Observational results

- Improved behavior
- Improved cognitive function
- Improved bowel control-no diapers, first time ever!

- Microbes in the gut contribute to blood lipid levels  
*Circ Res.* 117 (2015) 817-824



# Foods for specific health use (FOSU), Japan

- G-Amino butyric acid, GABA
  - Anxiety and depression
  - Movement
  - Blood pressure
  - Pain perception
- GABA is produced by Lactobacilli
- Fermented foods containing GABA
  - Fermented dairy, yogurt, Kefir
  - Soybean
  - Kimchi
  - Juices

Aust. J Dairy Tech 64 (2009) 41-49

# Bioactive Fatty Acids

- Examples
  - alpha-linolenic acid (ALA)
  - arachidonic acid (AA)
  - eicosapentaenoic acid (EPA)
  - docosahexaenoic acid (DHA)
  - gamma-linolenic acid (GLA)
  - stearidonic acid (STA)
  - conjugated linoleic acid (CLA)
- Sources
  - Milk
  - Tissue fat from ruminant
  - Plant seed oils
  - Marine algae
- What are they?  
Conjugated polyunsaturated fatty acids
- Health benefits
  - Antiatherosclerotic
  - Antiobesogenic
  - Anticarcinogenic
- Produced by
  - *Lactobacillus*
  - *Propionibacterium*
  - *Bifidobacterium*
  - *Roseburia spp*

# The Gut Makeover Diet: An observational study

## PLOSone June 14, 2017

- Weeks 1-2
  - Three main meals, no snacks
  - 12h nighttime fast
  - Seven cups plant-based foods (20-30 varieties per week)
  - Eat protein with each meal (animal and vegetable)
  - Cook with EVOO and coconut oil
- Weeks 3-4
  - Add butter and ghee
  - Include probiotic foods and prebiotic vegetables
  - Include bone broth
- Exclude
  - Refined sugars
  - Grains
  - Legumes
  - Alcohol
  - Caffeine

Designed to  
improve the  
health and  
diversity of the  
microbiome

# Gut Makeover Observations

- Reduced weight (Primary objective)
- Improved digestion, lower frequency and severity of nausea, vomiting, diarrhea, constipation, bloating, gas, heartburn and stomach pain
- Improved well-being (Not an objective)
  - Reduction in mood swings
  - Reduced anxiety
  - Reduced irritability
  - Reduced depression
- Improved cognitive function

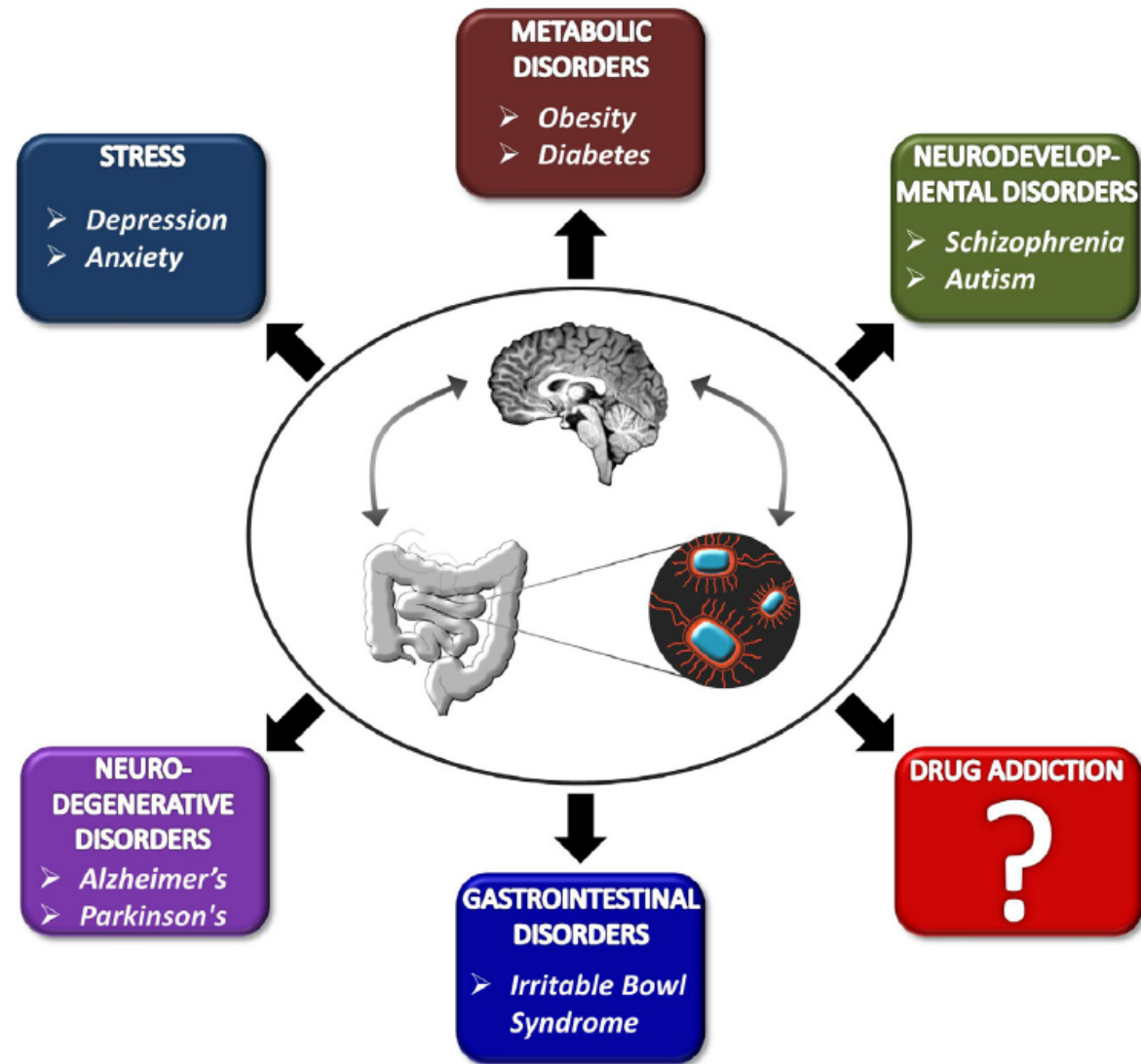


Fig. 1. Known disorders of the gut–brain axis. Microbiota in the gut play important roles in maintaining homeostasis, and their dysfunction has been linked to various psychiatric and nonpsychiatric disorders. Note that, to date, no studies have examined the gut–brain axis in drug addiction. Figure adapted from Burokas et al. [13].

## Leaky Gut and drug addiction *Medical Hypotheses* 93 (2016) 77-80

- Stress alters the gut barrier function
- LPS penetrates blood stream and stimulates TLR4
- TLRs stimulation precedes cytokine release

# Leaky Gut and drug addiction

*Medical Hypotheses* 93 (2016) 77-80

- Contributions to drug addiction
  - Dysregulated HPA increases stress
  - Depression is often comorbid with addiction
    - Over 90% of serotonin is synthesized in the gut
  - 50% of dopamine is made in the gut
    - Drugs that affect central dopamine-reward pathways
  - MRI studies show that individuals administered probiotics have reduced brain response to emotional stimuli (*Gastroenterology* 144 [2013]1394-13401)
    - Could this also impact brain response to drug cues?

# Drug addiction and brain-derived neurotrophic factor (BDNF)

- BDNF is a regulator of stimulant drugs of abuse such as cocaine and morphine.
  - *Science* 338 (2012) 124-128
- *BDNF is decreased in brains and serum from patients with anxiety, behavioral defects, schizophrenia, and AD*
- *Reduced BDNF expression in the hippocampus and cortex of germ-free mice*
  - *Associated with increased anxiety and progressive cognitive dysfunction*
  - *Altered expression of BDNF has been documented only in male GF mice*



# Breaking the cycle of addiction

## 5R GI Restoration Program

1. Remove
2. Replace
3. Re-innoculate
4. Regenerate
5. Retain

# The 5R GI Restoration Program

## 1. Remove

- Food intolerances
  - Elimination food plan
  - Supplement with low-allergy-potential medical food
- *Saccharomyces boulardii*

Removing the underlying issue of the imbalance is the first step in addressing the core issue of gastrointestinal complaints.

# The 5R GI Restoration Program

## 2. Replace

- Hydrochloric acid
- Digestive enzymes
- Lipotropic factors

Replacing and augmenting vital digestive chemistry allows the patient to improve digestion/absorption—the primary role of the gastrointestinal tract.

# The 5R GI Restoration Program

## 3. Re-innoculate

- Beneficial bacteria
  - *Lactobacilli*
  - *Bifidobacterium*

Reinoculating with probiotics supports a healthy and balanced population of intestinal bacteria.

# The 5R GI Restoration Program

## 4. Regenerate

- Glutamine, licorice, aloe
- Fiber/prebiotic
- Arabinogalactins, plantain fruit
- Turmeric, quercetin, rosemary, ginger
- Low-allergy-potential rice protein
- EPA/DHA

Regenerating utilizes specific macro- and micronutrients to nourish the cells of the colonic mucosa and support gastrointestinal integrity.

# The 5R GI Restoration Program

## 5. Retain

- Diet
  - Fiber, probiotics
- Stress reduction
  - Identi-T™
- Movement

Retain patients' lifestyle for lasting relief of gastrointestinal complaints. Determining the triggers or lifestyle habits that may have lead to the core issue.

# Outcomes of 5R Program

- 70-yr old female
  - Osteoarthritis, needs double hip replacement
  - Hip #1- Pain killers following surgery produced severe and profound withdrawal
  - Patient suffers from leaky gut
  - 5R gut restoration
    - Probiotics
    - Medical foods with prebiotic fibers
    - Vitamin D
    - Zinlori to rebuild mucosal lining
    - Glutagenics to heal the gut
  - Hip #2, Surgery 4 months after gut restoration
    - Tolerant to pain killers

## Limitations to exploit gut-brain axis relationship to improve cognitive health

- Cell culture
- Big data
- Metabolomics
- Biomarker identification
- Translation from preclinical to clinical
- Compliance for disease prevention