Gut-Brain Axis

Cool Brain Nerds
Neil Beluso, Marine Delgrange, Seo-Jin Yang (Joy), Alexis Pierce, Mengqun Lyu (Monica), Lauren Ring
Introduction

Neil Beluso
“Gut feeling”  “Trust your gut”  “Gut-wrenching”
What is the gut?

Gastrointestinal tract: a food-processing tract starting at the mouth and ending at the anus

IMAGE SOURCE: https://patient.info/health/dyspepsia-indigestion/features/the-digestive-system
What is the gut?

**Mouth** - salivary enzymes begin to break down food

**Esophagus** - lubricates foods & carries it down towards the stomach

**Stomach** - chemicals digest food, lining absorbs some foods/liquids, stores food until rest of tract is ready

**Small intestine** - absorbs nutrients into bloodstream

**Large intestine** - contains bacteria for the final stages of digestion; absorbs water and remaining nutrients from chyme

**Rectum** - allows excretion of feces through the anus
What is in the gut?

Gut microbiota: microbe population living in one’s intestine; tens of trillions of microorganisms (bacteria, archaea, yeasts, Helminth parasites, viruses, protozoa)

- There exists 1000-2000 different bacteria species
  - Contains more than 3 million genes (150x more than human genome)
  - ~150-170 species predominate in a host
  - ⅓ of microbiota is common to most people, ⅔ of microbiota is host-specific
- Can weigh 1-2 kilograms (roughly same as human brain)

Main function of gut microbiota = digestive health
- Help digest certain foods that stomach & small intestine cannot digest
- Help with production of certain vitamins (B, K)
- Provides barrier effect to support immune system against other microorganisms
Development of gut microbiota begins at birth

- Babies are considered to be born sterile - gut microbiota is "acquired" from the mother (exposure to vaginal microbiota through birth canal), environment of delivery, surrounding air, etc.
- Composition of intestinal flora directly dependent on infant’s feeding
  - Breastmilk contributes Bifidobacteria, differently from infant flora
- Microbiota diversity is stable & similar to adults by age 3
Major microbiota

Two major phylotypes: **Bacteriodes** and **Firmicutes**
- Other phyla found in low abundance: Proteobacteria, Actinobacteria, Fusobacteria, Verrucomicrobia
- Main difference: Gram-positive versus Gram-negative (cell wall differences)
- Bacteriodes/Firmicutes ratio implicated in development of diseases

**Bifidobacteria & Lactobacillus**: “friendly” bacteria that helps body digest food more properly
- Often incorporated in foods as **probiotics**, supplements that help microbiota balance, diversity & integrity
  - Contrasts to **antibiotics**, which can help destroy disease-causing bacteria but also creates imbalance
- **Prebiotics**: “food” to help bacteria improve functioning, growth, activity
Factors that influence gut microbiota

- Host genetics
- Health status
- Lifestyle
- Mode of delivery at birth
- Antibiotic use

Some influences explored here: communication with brain & other systems, age, dietary patterns, neuropsychiatric disorders, stress
The gut-brain axis: a bidirectional communication

Marine Delgrange
The enteroendocrine cells (EECs) in the gut
The enteroendocrine cells (EECs) in the gut

EECs are mainly involved in (but not only):

- Digestion and absorption of nutrients
- Defense responses of the gut

They represent 1% of the total gut epithelial cells

Open type: apical prolongation, microvilli facing lumen => directly activated by luminal content

Closed type: close to basal membrane, lack microvilli => indirectly activated through humoral or neural pathways
Enteroendocrine cells: the largest endocrine organ in the body

<table>
<thead>
<tr>
<th>Neuropeptide</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrin</td>
<td>Gastric acid secretion</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>Inhibits gastric acid secretion</td>
</tr>
<tr>
<td>5-HT</td>
<td>Intestinal motility</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Increase in appetite and food intake</td>
</tr>
<tr>
<td>Leptin</td>
<td>Decrease in appetite</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Regulates postprandial glucose levels, promotes satiety, release of insulin</td>
</tr>
<tr>
<td>PYY</td>
<td>Inhibits food intake + ileal brake</td>
</tr>
<tr>
<td>GLP-2</td>
<td>Intestinal lipid absorption, mucosal defense</td>
</tr>
<tr>
<td>CCK</td>
<td>Activates intestinal feedback through vagal pathway. Controls inhibition of gastric emptying and acid secretion</td>
</tr>
</tbody>
</table>
Sternini et al (2008), *Enteroendocrine cells: a site of “taste” in gastrointestinal chemosensing*

G-protein coupled receptors act as sensors:
- T1R2&T1R3: sweetness
- T1R1&T1R3: amino acids
- T2R: bitter taste

Hypothesis: the secretory function of EECs works through taste sensing, leading to an increase in intracellular calcium concentration and exocytosis of secretory vesicles
Enteroendocrine cells: communication pathways

Hormones secreted by EECs can:

- Enter the circulation and act as classic hormones on distant targets
- Act locally on neighboring cells (paracrine function)
- Act on neuronal pathways:
  - Enteric (intrinsic) neurons
  - Extrinsic neurons -> direct EEC-neurons connections via basal cytoplasmic processes (neuropods) or peptide release

Sternini et al (2008), *Enteroendocrine cells: a site of “taste” in gastrointestinal chemosensing*
Enteroendocrine cells: communication pathways
How enteroendocrine cells communicate with the brain

Dysfunction of this brain-gut communication can cause diseases such as irritable bowel syndrome.

Food aversion, nausea and vomiting are associated with vagal and NTS activation.

Ex. rotavirus inducing 5-HT secretion.

Neuronal pathways: CCK, GLP-1 and PYY

CCK

- Plays a role in satiety and inhibits gastric emptying
- *Whited et al* (2006): CCK receptor knockout in mice leads to a decrease in activation of *vagal pathways* compared to WT mice.
- Co-administration with leptin enhances the effects of CCK
- Role in glucose homeostasis: CCK1 receptors activate PKA pathway in NMDA receptor, which mediate *neuronal transmission in NTS*, an area regulating glucose homeostasis

PYY

- Mainly produced in ileum and colon in response to lipids
- Acts on *Y2 receptors (hypothalamus)* to decrease appetite (anorexigenic)

*Latorre et al* (2016), *Enteroendocrine cells: a review of their role in brain-gut communication*
Neuronal pathways: CCK, GLP-1 and PYY

GLP-1

- Released in small intestine in response to especially carbohydrates and fats
- Main effect: blood glucose homeostasis -> induces insulin secretion and reduces appetite
- Has receptors in the gut, pancreatic beta cells, kidney AND vagus nerve, NTS, hypothalamus
- Questions remain on its effects on hypothalamus and brain stem because of its short half-life

SUMMARY

- Hormones released by EECs activate vagal afferent pathways
- Direct cell-to-sensory nerves -> complexity of bidirectional communication
- Potential therapeutic target ex. GLP-1R agonist used to treat T2D because helps in insulin secretion. Also GLP-1 and PYY secretion in reduction of food intake ex. for patients undergoing gastric bypass surgery -> treat obesity too.
Short Chain Fatty Acids (SCFAs): how microbiota helps maintaining homeostasis in the gut

What are SCFAs?

- Products of the fermentation of non-digestible carbohydrates by the colonic microbiota
- Saturated aliphatic organic acids of 1-6 carbons
- Composed of acetate, propionate and butyrate at more than 95%
- Bind to both FFA receptors (2&3) found on immune cells and GPR41 on EECs

Morrison et al (2016), Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism
Short Chain Fatty Acids (SCFAs): how microbiota helps maintaining homeostasis in the gut

1. **Maintain the gut integrity**
   - Maintain of colonic epithelium (especially butyrate)
   - Regulation of tight junction proteins (TJPs) ->
     decrease LPS translocation, activation of macrophages and production of proinflammatory cytokines

2. **Contribute to glucose homeostasis**
   - Propionate: gluconeogenic, via AMPK pathway. Also induces GLP-1 release by EECs
   - Plasma acetate inversely related to plasma insulin levels

Morrison et al (2016), *Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism*
Short Chain Fatty Acids (SCFAs): how microbiota helps maintaining homeostasis in the gut

3. Regulate lipid metabolism

- Acetate reduces adipocyte lipolysis, thus reducing free fatty acid flux to the liver, and stimulates leptin secretion in adipocytes
- Further studies needed on role of SCFAs in obesity

4. Appetite regulation

- SCFAs can directly modulate neurons of the autonomic and somatic nervous systems
- Short-term appetite regulation through PYY and GLP-1 secretion by binding to G-protein receptors on EECs

Morrison et al (2016), *Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism*
Short Chain Fatty Acids (SCFAs): how microbiota helps maintaining homeostasis in the gut

5. Regulate the immune system and the inflammatory response

- Butyrate inhibits nuclear factor NF-κB in macrophages and histone deacetylation (HDAC)
- Propionate and butyrate regulate T cell production through inhibition of HDAC
- Whether SCFAs act as a signal to induce tolerance or directly reduce inflammatory responses remains to be fully elucidated

Morrison et al (2016), Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism
Influence of Age

Seo-Jin Yang (Joy)
Terms

- **Anaerobic** = relating to, involving, or requiring an absence of free oxygen.
- **Gram Positive** = bacteria that give a positive result in the Gram Stain Test. Bacteria take up the crystal violet stain used in the test because of the thick peptidoglycan layer in the bacterial cell wall that retains the stain after it is washed away in the decolorization stage of the test.
- **Gram Negative** = bacteria do not retain the crystal violet stain used in the staining method.
- **Gram Stain** = a method of staining used to distinguish and classify bacterial species into two large groups. It differentiates bacteria by chemical and physical properties of their cell walls by detecting peptidoglycan.
Influence of Age: Birth to Weaning Period

- Gut microbiota changes across the life-span
- One of the key players → diet
- Impact of diet varies across different stages in life
- Composition of gut microbiota during early stages of life has significant effect on structuring the person’s physiology and immune system

*Weaning* = gradual replacement of breastfeeding with other foods and ways of nurturing
Influence of Age: Breast Milk & Formula Diet

- What infants encounter first as source of nutrient/food
- Optimal diet for infants
- Abundant in various important bacteria species:
  - Prebiotics, nucleotides, immunoglobulins, cytokines, SCFAs
- Breast milk abundant in **oligosaccharides**
  - Balance of bacteria in the bowel, calcium absorption, immunity, inflammation
  - Growth of probiotic bacteria
  - Recent research: influencing mood, food choices, hunger/satiety, weight
- Abundance of **bifidobacteria**
- Breast milk fed infants -- fewer bacterial species associated with pathogenesis compared to formula-fed infants
- Formula-fed infants have more diverse microbiota
Influence of Age: Postweaning

- Breast milk/formula diet → solid diet
  - Increase in firmicutes to bacteroidetes (F/B) ratio in the gut
  - Decrease in bifidobacteria
  - Overall increase in different functional genes (observed in adult microbiota)
- Diet in earlier stages of life is critical for growth and microbiota construction

*Firmicutes : Bacteroidetes (F/B) Ratio* = correlated with obesity and other diseases (lower the better)
Malawian Infants

- Breast milk of mothers in Malawi lack sialylated HMO
- Study showed that Malawian infants fed on this breast milk for 6 months displayed severely stunted growth
- Similar result in germ-free (GF) mice colonized with these infants’ microbiota
- The condition improved when supplied with sialylated bovine milk oligosaccharide (S-BMO)

*Commensal* = living in a relationship in which one organism derives food or other benefits from another organism without hurting or helping it

*Human Milk Oligosaccharides (HMO)* = found in and unique to human breast milk; function as a prebiotic helping to establish commensal bacteria. Also function as anti-adhesives that help prevent attachment of microbial pathogens to mucosal surfaces

*Mucosa* = membrane that lines various cavities in the body and covers the surface of internal organs

*Sialylated HMO* = promote growth of animals colonized with infant microbiota

*Stunted Growth* = typically have short heights and low body masses for the age group
Blanton LV, Charbonneau MR, Salih T, et al.

- Malnourished children microbiota → GF mice
  - Growth impairment, altered bone morphology and dysregulated brain metabolism

- Adult microbiota (includes ruminococcus gnavus and clostridium symbiosum) → GF mice
  - Effects lightened

- But the study also suggests that there is a limit to how much deficits in microbiota during early stages of life can affect microbiota construction as the individual ages

*Clostridium* = spore-forming gram-positive bacterium that is found in many environmental sources as well as in intestines

*Ruminococcus Gnavus* = anaerobic, gram-positive gut microbes (gastrointestinal microbiota)

*Symbiosis* = any type of a close and long-term biological interaction between two different biological organisms
Influence of Age: Adult to Elderly

- Age-related factors play an important role:
  - Nutritional behavior
  - Digestion system
  - Teeth condition
  - Intestinal (bowel) transit time
  - Stress
  - Lifestyle

- Elderly people demonstrate a decline in microbiota (diversity, composition)
  - With age, there is a decrease in bifidobacteria, bacteroides
  - Increase in ruminococcus, clostridium, enterobacteria and lactobacilli

*Bacteroides* = gram-negative, obligate anaerobic bacteria
*Enterobacteriaceae* = include pathogens. Several strains of these bacteria are pathogenic and cause opportunistic infections in immunocompromised hosts
*Lactobacillus* = gram-positive, facultative anaerobic. Major part of the lactic acid bacteria group (convert sugars to lactic acid)
*Obligate anaerobes* = microorganisms killed by normal atmospheric concentrations of oxygen
Diet Changes the Gut Microbiota

● Change in diet → change in gut microbiota
  ○ Even if you change your diet for a day
  ○ Example: plant-based diet → animal-based diet

● The type of diet also has an impact on gut microbiota composition

● For example, high fat or protein diet reduces bifidobacteria and butyrate-producing bacteria
  ○ Adding fermentable fibers/probiotics to the diet restores the reduced levels of these bacteria

● Studies are suggesting that diet is playing a critical role in contributing to the increased rate of chronic illnesses (e.g., inflammatory bowel disease, obesity, diabetes, allergies, depression), and even neuropsychiatric disorders

*Butyrate* = major metabolite in colonic lumen arising from bacterial fermentation of dietary fiber; has been shown to be a critical mediator of the colonic inflammatory response.

*Probiotics* = live bacteria and yeasts that have health benefits such as reducing gastrointestinal discomfort, improving immune health, and relieving constipation.
Western vs. Mediterranean Diet

- **Western Diet**
  - Rich in fats, salt and sugar

- **Mediterranean Diet**
  - Mainly consume: cereals, legumes, nuts, vegetables, fruits
  - Moderately consume: fish, poultry
  - Infrequently consume: meat
Western Diet

- Rich in fats, salt and sugar
- Linked with obesity and chronic illnesses
- Consumption of this diet demonstrated similar Firmicutes to Bacteroides ratio to the ones in individuals with obesity
- Researchers supplied mice (colonized with human microbiota) with high-fat diet for one day
  - Noticed a big alteration in gut microbiota
  - Significant increase in Firmicutes and decrease in Bacteroides
  - Bacteria associated with obesity present in individuals that consume Western Diet
Mediterranean Diet

- Considered “healthy” diet
- Observed in individuals that consume this diet:
  - Reduced mortality rate
  - Lower chance of getting chronic illnesses (e.g., cancer, neurodegenerative and autoimmune diseases)
  - Improve Crohn’s disease patients’ health
  - Increase in SCFAs
    - SCFAs levels correlated with high intake of fruits, vegetables, legumes and cereals
  - Reduction in trimethylamine oxide

*Crohn’s Disease = inflammatory bowel disease; causes inflammation in the digestive tract
*Trimethylamine Oxide = common metabolite in animals and humans. High levels are associated with an increased risk of major adverse cardiovascular events
Summary:

- **Non-Western Diet**
  - Increase in bifidobacteria, bacteroides, prevotella and SCFA level
  - Decrease in firmicutes
  - Improved mood disorders

- **Western Diet**
  - Decrease in bifidobacteria, bacteroides, prevotella, and SCFA level
  - Increase in firmicutes
  - Increased anxiety
  - Induced depression

*Prevotella* = may cause infections, but can also co-exist harmlessly in the host. Increased level may simply be an indication of a fiber-rich diet.
Mediterranean Diet as Therapeutic Intervention?

- Possible treatment for neuropsychiatric conditions?
- Consumption of Mediterranean diet shown to ameliorate clinical depression and reduce antidepressant medication usage (in young adults)
- Mediterranean diet is rich in vitamin B
- Vitamin B associated with neurotransmitters synthesis
  - 5-HT, NE, DA
  - These neurotransmitters are linked with major depression
Mediterranean Diet and Oxidative Stress

- **Oxidative Stress** = imbalance between production of free radicals and the ability of the body to counteract (detoxify) their harmful effects
  - Damage to lipids, protein, DNA, cell and organ
  - Critical factor contributing to psychiatric disorders

- Mediterranean diet consists of red wine, olive oil and fruits
  - Have antioxidant properties
  - Rich in polyphenols
    - Protective role against cancer and other inflammatory diseases
    - Research shows that polyphenols modulate pathways involved in cognitive processes and synaptic plasticity
      - This mediates neuroprotective effect
    - Increase BDNF expression
      - In neuropsychiatric conditions like depression and schizophrenia, BDNF levels are altered

*BDNF* = protein that helps support the survival of existing neurons and encourage the growth of new neurons and synapses

*Polyphenols* = antioxidant; fight oxidative stress and aging-related diseases (e.g., heart disease, high blood pressure, cholesterol)
Carbohydrates

- Highly efficient energy
- Resistant carbohydrates
  - Indigestible
  - Ex. Cellulose and hemicellulose (found in plants)
  - Degradation of cellulose is mediated by Bacteroides and Ruminococcus and results in the production of SCFAs
    - Mediterranean diet: high Bacteroides
    - Western diet: reduced Bacteroides
  - Mouse study (6 weeks resistant starch): Proteobacteria increased by 36%
Carbohydrates cont.

- Fibers
  - Not easily digested
  - Critical for the maintenance of a healthy microbiota
    - Low-fiber diet in mice: irreversible, transgenerational loss of microbiota diversity
  - High fiber diet
    - Enriches Bifidobacterium in the intestine
    - Reduces BMI and obesity-induced inflammation
    - Regulates circulatory estrogen
  - Galacto-oligosaccharides (GOS)
    - Used as an infant prebiotic
    - When used to supplement formula, increases Bifidobacteria and Lactobacilli levels to level of breastfed infants
    - Increases Bifidobacteria and Bacteroides in the elderly, with anti-inflammatory effects
    - 3 week application resulted in decreased salivary cortisol levels & altered behavior
  - Fructo-oligosaccharide
    - Bifidogenic dietary fiber
Carbohydrates cont. cont.

- **Inulins**
  - Plant storage polysaccharides
  - Prebiotics
  - Fermented by Bifidobacteria
  - Supplementation to Western diet increases Bifidobacteria and Lactobacilli
  - Usage with GOS during pregnancy protects against food allergies

- **Beta-glucans**
  - Polysaccharides present in seeds and cereals
  - Reported to reduce hyperglycemia, hyperlipidemia, and hypertension
  - Antioxidant
  - Trigger immune response (potential for cancer research)
Proteins

- Increase in protein in diet
  - Increase in Bacteroides
    - This is because B is associated with proteolysis of the protein to amino acid
  - Increase in other gut bacteria associated with protein fermentation (ex. Atopodium)
  - Increase in bile-tolerant microbiota
  - Reduction of firmicutes
  - Increase in Bilophila wadsworthia
    - Associated with colitis in mice
Bile Acids

- Synthesized in hepatocytes
- Critical for the emulsification and solubilization of fats
- Intestinal microbiota and bile acids have a bidirectional relationship
  - Microbiota transform primary bile acids into more usable deconjugated and secondary bile acids
  - Bile acids induce an antimicrobial effect to regulate intestinal microbiota expression
- Fecal Microbiota Transplantation
  - Restores intestinal microbiota/bile acid composition in patients with C. difficile infection
  - Primary bile stimulates C. difficile while secondary bile inhibits it
  - Restore microbiota facilitates acid conversion
Polyunsaturated Fatty Acids (PUFAs)

- Found mainly in fish and some plant oils
- Omega 3
  - Neuroprotective effects
  - Restoration of energy metabolism
  - Regulation of neurotransmitter levels
  - Maintenance of membrane structure and composition
- Protective to microbial composition
  - Early-life Omega 3 exposure
    - Prevents gut microbiota alterations, metabolic disorder, and chronic inflammation
  - Long-term Omega 3 exposure
    - Increases Bifidobacteria and Lactobacilli
Vitamins

- Intestinal microbiota synthesize vitamins B12, B6, B5, B3, D, and K
- Dietary vitamins are absorbed in the small intestine
- Microbial-produced vitamins are absorbed in the colon
- Vitamin deficiency
  - Affects appropriate immune responses through microbiota interactions
  - Vitamin A deficiency: loss of T-helper 12 cells and Clostridiaceae bacteria (associated with TH17)
  - Supplementation of vitamin D3: increase in CD8+ T cells (“T-killer” cells)
Vitamins cont.

- **Biotin**
  - Cannot be produced by mammalian cells, so the body relies on the gut microbiota for its supply
  - Required for biotinylation
    - Epigenetic process that involves attaching biotin to histone proteins
      - Important for gene regression, DNA repair, and chromatin structure

- **Folate**
  - Also produced by intestinal bacteria
  - Availability affects efficiency of DNA replication, repair, and methylation
  - Deficiency is associated with treatment resistant depression
Polyphenols

- Compounds characterized by hydroxylated phenyl moieties (functional groups of a molecule)
- Found in things like red wine, chocolate, and green tea
- The majority of polyphenols are fermented by microbiota in the large intestine
Polyphenols cont.

- **Beneficial effects**
  - Inflammation reduction, neuroprotection, antioxidant, cardiovascular diseases, cerebral ischemia, and metabolic disorders, learning and memory, neurotransmitter level modulation
    - Ex. Resveratrol (found in red wine and grapes) increases monoamine neurotransmission, increases hippocampal BDNF levels, and has antidepressant effects
  - Microbiota may be responsible for these effects
    - Some polyphenols enhance gut microbiota diversity, others inhibit certain populations
      - Ex. Resveratrol increases Bifidobacteria and Lactobacilli, while cocoa decreases Bacteroides, Clostridium, and Staphylococcus
Role of Diet and Microbiota in Neuropsychiatric Disorders

Alexis Pierce
Overview

- Diets and Their Role in Cognition
- Autism Spectrum Disorder and Related Microbiota
- Diet and Its Role in Autism
- Treatment of ADHD Symptoms Using Diet
- Link Between Dysregulation of Microbiota and Depression
- Diet Differences and Their Impact on Depression
- Impact of Microbiota on Anxiety-Like Behaviors
- Means of Improving Anxiety
Diets and Their Role in Cognition

- Why Is This Important?
- Can we design diets to ensure brain health?
- Cognitive impairment as a result of diets that contain high amounts of saturated fat
- Cognitive benefits as a result of diets that contain high amounts of PUFA (Polyunsaturated Fatty Acids)
- Pathology in common neuropsychiatric disorders (Autism, Depression, and Anxiety) may actually be the result of microbiota dysregulation
- Improve Diet = Improve Dysregulation = Improve Behavior
Autism Spectrum Disorder (ASD) and Related Microbiota

● What is ASD?:
  ○ Neurodevelopmental disorder that affects communication and behavior
  ○ Strong genetic component
  ○ Often co-occurs with gastrointestinal issues

● Related Microbiota:
  ○ Autistic children showed altered levels of: Bacteroidetes and Firmicutes phyla
    ■ Abundance of Clostridium phyla
    ■ Altered Commensals: Bifidobacterium, Lactobacillus, Prevotella, and Ruminococcus genus
  ○ Severely Autistic: Increase in microbiota diversity
    ■ Uncharacteristically high amounts of Bacteroidetes
    ■ Hugely different in Actinobacteria and Proteobacteria phyla
Diet and Its Role in Autism

● Changes in food patterns and nutritional intake may result in autistic behaviors
● Children with ASD showed a dramatic elevation in the amount of cyanobacteria/chloroplast phyla in their feces (Possibly as a result of a diet rich in chia seeds)
● Removal of gluten and casein foods improves symptoms
● Naltrexone relieves symptoms of ASD
● Diet associated with proinflammatory response in ASD
● Children with ASD show elevated levels of IL-6 and TNF
● However, luteolin normalizes levels of IL-6 by preventing its release (Potential treatment for ASD social issues)
Treatment of ADHD Symptoms Using Diet

- What is ADHD (Attention Deficit Hyperactive Disorder)?
  - Presents 1st in children
  - Symptoms like hyperactivity, impulsivity, and inappropriate attention
- Diet used as a nonpharmacological treatment for ADHD symptoms
- Significant reduction in ADHD symptoms through supplementation with free fatty acids
- Children that have ADHD typically develop hypersensitivities to foods
- Diet restriction as a potential treatment for ADHD?
- More studies needed
Link Between Dysregulation of Microbiota and Depression

- **What is Depression?**
  - Stress-related mood disorder
  - Characterized by disruption of HPA axis and immune system

- **Gut microbiota plays major role**
  - Depression: Increased alpha diversity of gut microbiota, as well as significantly decreased numbers of *Bifidobacterium* and *Lactobacillus*, compared to control
  - Major Depression: High levels of Firmicutes, Actinobacteria, and Bacteroidetes
    - Significant increases in genus: *Eggerthella*, *Holdemania*, *Gelria*, *Turicibacter*, *Paraprevotella*, and *Anaerofilum*
    - Decreases in genus: *Prevotella* and *Dialister*

- Microbiota from major depressive patients transferred to rats → Transferred behavior and physiological phenotypes to rats
Diet Difference and Their Impact on Depression

- **Positive Effects:**
  - Mediterranean diet decreases onset of depression

- **Negative Effects:**
  - Western diet increases risk for depression
  - Shift towards Western Diet is problematic
    - Altered fatty acid concentration → Increase in saturated fatty acids → Reduction in intake of omega 3 fatty acid
    - Depletion of omega-3 PUFA → Major depression, depressed mood, or postpartum depression
    - Omega-3 diet can help to protect against depression

- **Probiotics helped to reduce depression-related behaviors**
  - *Lactobacillus* phyla used to repress depressive behaviors

- **Other strains that are beneficial for mood disorders:** *Bifidobacterium*
  - Potential antidepressant-like behavior (animals)

- **Diet is potentially the cause and cure**
Impact of Microbiota on Anxiety-Like Behaviors

● What Is Anxiety?:
  ○ Includes: generalized anxiety disorder, phobias, panic disorder, post-traumatic stress disorders (PTSD), and obsessive-compulsive disorder (OCD)
  ○ Activation of HPA axis from external stressors that result in endocrine, immune, and system disturbances

● Animal studies reveal role of gut microbiota
  ○ Gastrointestinal inflammation associated with behaviors related to anxiety
  ○ Increased anxiety-related behaviors in elevated maze:
    ■ Two days after infection: Campylobacter jejuni
    ■ 8 hours after infection: Citrobacter rodentium; C. jejuni
  ○ Increased anxiety related behaviors: Infected by Trichuris muris (Associated with Gastrointestinal inflammation) → B. longum helped get rid of behaviors

● Phenotype similar to anxiety as a result of GI inflammation or microbiota absence
Means of Improving Anxiety

- Altering diet can help to improve anxiety
- Type of anxiety disorder strongly correlated to peripheral BDNF protein levels
- Omega 3 PUFAs (Polyunsaturated Fatty Acids)
  - Mostly in fish or plant oils
  - Controls BDNF levels
  - Produces anti-inflammatory response

→ Potential treatment for anxiety disorders
Stress and Microbiome

Mengqun Lyu (Monica)
Microbiota influence Stress-related Behaviors

- Antibiotic treatment during adolescence mice altered microbiota composition and diversity (Desbonnet et al., 2015)
  - Reduction in anxiety-like behavior
  - Accompanied by cognitive deficits.

- **Germ-Free (GF)** mice: surgically delivered and raised in sterile isolators
  - Reduced anxiety-like behavior in the light-dark box test and in the elevated plus maze (Luczynski et al., 2016)
  - Increased anxiety-like behavior (Crumeyrolle-Arias et al., 2014)
Microbiota and the Brain

- Required for normal brain development (Diaz Heijtz et al., 2011)
  - Lack of microbiota affects multiple stress–related NT systems across multiple brain regions.
    - Altered gene expression associated with plasticity and metabolic pathways including steroid hormone metabolism.
- Crucial role in brain function
  - GF mice have exaggerated HPA (Hypothalamic-Pituitary-Adrenal) axis response
  - Gene expression within hippocampus is different in GF mice.
    - Hippocampus exerts strong control over the HPA
Microbiota and the Brain

● Crucial role in brain function
  ○ Affects the structure and function of the amygdala
    ■ Emotional learning
    ■ Social behavior
    ■ Monitor the behavioral and physiological responses to stressful stimuli.
      ● Anxiety / fear
  ■ Associated with
    ● Autism Spectrum Disorder
    ● Anxiety Disorder
  ■ GF mice
    ● Increase amygdala volume
    ● Altered gene expression
Major Depressive Disorder (MDD)

- “Leaky gut” Hypothesis
  - Stress ➡ compromised epithelial barrier of the GI tract ➡ increased intestinal permeability and translocation of gram-negative bacteria across the mucosal lining to access immune cells and the ENS (Endocrine Nervous System) ➡ Increased production of Inflammatory Mediators ➡ Mood Disorders

- Failed to identify differences in microbial diversity within faecal samples obtained from MDD patients and control (Naseribafrouei et al., 2014).
- Increased diversity of several types of microbiota in faecal sample (Jiang et al., 2015)
Major Depressive Disorder (MDD)

- Maternal separation: early life stress that provokes adult depressive and anxiety-like phenotype.
  - Rhesus monkey: decreased faecal Lactobacillus 3 days post-separation (Bailey and Coe, 1999)
  - Rodents: disrupts microbiota and promotes colonic hypersensitivity (O’Mahony et al., 2009, 2011)

- Olfactory bulbectomy in rodents induced physiological and behavioral symptoms similar to MDD
  - Affects gut transit and the composition of the microbiota
Treatment?

- Probiotic supplement
  - Microbial regulation over stress and anxiety
    - Anxiolytic influence of Lacobacillus and Bifidobacterum
    - Positive neurological changes
      - Increased BDNF - Brain-Derived Neurotrophic Factor
      - Altered expression of PFC and hippocampal GABA receptors
      - Increased circulating glutathione
      - Reduction in inflammatory markers.

- Limitations:
  - Mostly animal studies and healthy human volunteer
  - Results from animal study failed to translate to humans
Irritable Bowel Syndrome (IBS)

- Most common functional gastrointestinal disorder
  - Abdominal visceral pain
  - Altered bowel habits
  - Strongly comorbid with anxiety and depression
- Early life stress as a key risk factor for IBS
  - Along with chronic stress later in life are thought to related to visceral pain responses and associated co-morbidities
Irritable Bowel Syndrome (IBS)

- Animal study showed antibiotic-induced dysbiosis influence the wiring of pain pathways early in life, and visceral hypersensitivity can persist even after microbial normalization later in life (O’Mahony et al., 2014).
Future Directions & Conclusions

Neil Beluso
Psychobiotics

- Certain strains of Bifidobacteria, Lactobacillus, or Bacteroides can have positive effects on cognitive processes & emotional learning
  - Limitation: only recently applied to humans, healthy volunteers only
- *Bifidobacterium longum 1714*: anti-stress & pro-cognitive effects found in anxious mouse strain
  - In healthy male volunteers placed in a cold pressor test, cortisol output & subjective anxiety was attenuated
- *Lactobacillus rhamnosus*: strongest preclinical profile for psychological benefits, but no discernible effect when tested in similar battery
  - More research needed!
  - Large-scale clinical trials and more focus on stress-related disorders
Microbiota and obesity-related T2DM

- Obese people with insulin resistance found to have altered gut microbiota (elevated Firmicutes/Bacteroidetes ratio)
  - This can modulate intestinal permeability & increase metabolic endotoxin secretion (leads to chronic low-level inflammation, insulin resistance and onset of T2DM)
  - Inflammation in T2DM accelerated by accumulation of gut-derived inflammatory molecules (LPS, peptidoglycans, flagellin)

- Probiotic strains can help modulate blood glucose homeostasis
  - Some down-regulate inflammatory cytokines (IFN-gamma & IL-2 or IL-1B), some enhance anti-inflammatory IL-10 production (diabetic animal studies)
  - *Lactobacillus reuteri* GMNL-263 was found to suppress serum glucose, insulin, leptin, glycated hemoglobin, GLP-1 levels
Microbiota and obesity-related T2DM

● Additional links between microbiota levels and T2DM-related complications: diabetic retinopathy, kidney toxicity, kidney stone formation, atherosclerosis, cystic fibrosis, and diabetic foot ulcers

● Anti-T2D drug regimens have been developed to modulate microbiota composition
  ○ Berberine (from Chinese herb *Coptis chinensis*)
  ○ Ginsing
  ○ Polyphenols (from diet)
Research here at UCSD!
American Gut Project

“Largest microbiome study ever to be published”

For $99, budding citizen-scientists receive a kit containing swabs, which they are instructed to dab on a used piece of toilet paper and mail to the Knight lab at UC San Diego.

Emerging trends found:

- Number of plant types in one’s diet correlates to diversity of microorganisms in their microbiome population
- People who took antibiotics = less diverse microbiota than those who didn’t
  - Ate more than 30 plants/week = fewer antibiotic resistance genes
  - Theorized that people who eat less plants eat more antibiotic-treated animals or processed foods antibiotic preservatives
- People with mental disorders have more microbiota in common

Future: collect samples internationally & draw comparisons
In conclusion

The gut microbiome is crucially implicated in your health!

● Helpful to take probiotic supplements to support microbiota diversity (especially after taking antibiotics)
● Pathology of many glycemic, neuropsychiatric, and stress-related disorders have bases in microbiota imbalance or dysregulation
  ○ Future research: elucidate correlations between specific bacteria levels and these health complications
  ○ Why are animal findings not translating to human clinical trials?
● Healthier diet options (e.g. Mediterranean diet) across ages can benefit gut health
Resources

https://drsarahbrewer.com/supplements/oligosaccharides-benefits

Latorre et al (2016), Enteroendocrine cells: a review of their role in brain-gut communication

Sternini et al (2008), Enteroendocrine cells: a site of “taste” in gastrointestinal chemosensing

Morrison et al (2016), Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism


American Gut Project:
http://ucsdnews.ucsd.edu/feature/whats-in-your-gut?utm_source=This+Week+Subscriber+List&utm_campaign=5f6f64bc15-THIS_WEEK_2018_5_17&utm_medium=email&utm_term=0_db568fca07-5f6f64bc15-92438665