



Microbes and the mind: Implications of diet for managing mood and behavior disorders

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Microbes and the mind??

Emerging relationship between gut health and brain health, emotion, and behavior

Key factor in this relationships: our trillions of microbes can influence mood and behavior

Who are the microbes, and what are they doing?

How can microbes in our guts influence our minds?

What can we do to get, and keep, a healthy microbe population?



Who are the microbes?

Trillions of “commensal” individuals

- Bacteria: gram positive and gram negative
- Fungi/ yeast= “mycobiome”
- Viruses

We each have a unique population of microbes (like fingerprints?) but unlike fingerprints, can change. Based on environment, family, pets, and diet

“Old Friends” idea: some species associated with fermented foods have been with us for thousands of years



What are the microbes doing?

Microbes live throughout our GI tract from mouth to anus, but most live in the colon

Most are our friends. They synthesize vitamins (e.g. biotin, folate, vitamin K), ferment things we can't digest. They collaborate with and can "program" our gut immune system

Some provide BUTYRATE- critical energy source for gut epithelial cells

Produce hormones, neurotransmitters and nutrients than can influence our immune and nervous systems (as well as other bacteria). This is a key communication pathway between "us" and "them".

They influence immune system and brain development, including "developmental programming" of stress responses. Animals born without gut microbes have learning and behavior deficits that are reversed with exposure to microbes.

***For microbe
populations,
balance is
key!***

**Imbalance in microbe populations is called *dysbiosis*
(SIBO is a type of severe dysbiosis)**

Dysbiosis is usually a consequence of low *microbial diversity* (super important!)

**Dysbiosis is associated with many disease conditions,
including metabolic disease, mood disorders, and
neurological conditions**

**Main causes of dysbiosis are heavy antibiotic use
and poor diet**

Stress effects on gut microbes

Stress hormones from us can affect our gut microbes

Norepinephrine (neurotransmitter of sympathetic nervous system) causes some bacteria to grow faster. This can result in overgrowth and dysbiosis

Norepinephrine can also make some bacteria virulent. "Pathobionts" are microbes that are commensal (and might even be beneficial) but under conditions that cause them to overgrow (such as poor diet or stress) they cause disease. An example is *Helicobacter pylori* and GI ulcers.

What happens in the gut does not stay in the gut

GI disorders often also associated with problems in other tissues (e.g. brain, lung, skin, joints)

One important link is the gut immune system (70% of all immune cells are in the gut)

Immune dysregulation is common in schizophrenia, bipolar disorder, autism

Some microbes (gram positive) seem to help keep the gut immune system in a "tolerant" state

Some microbes (gram negative) can trigger gut immune cells to become pro-inflammatory

Microbes may also be "programming" other immune cells (such as T cells) that cycle through the gut

“Leaky Gut” is a thing

Lining of gut (epithelium) has a tough job: absorbing all the nutrients we need while keeping toxins and other pathogens out

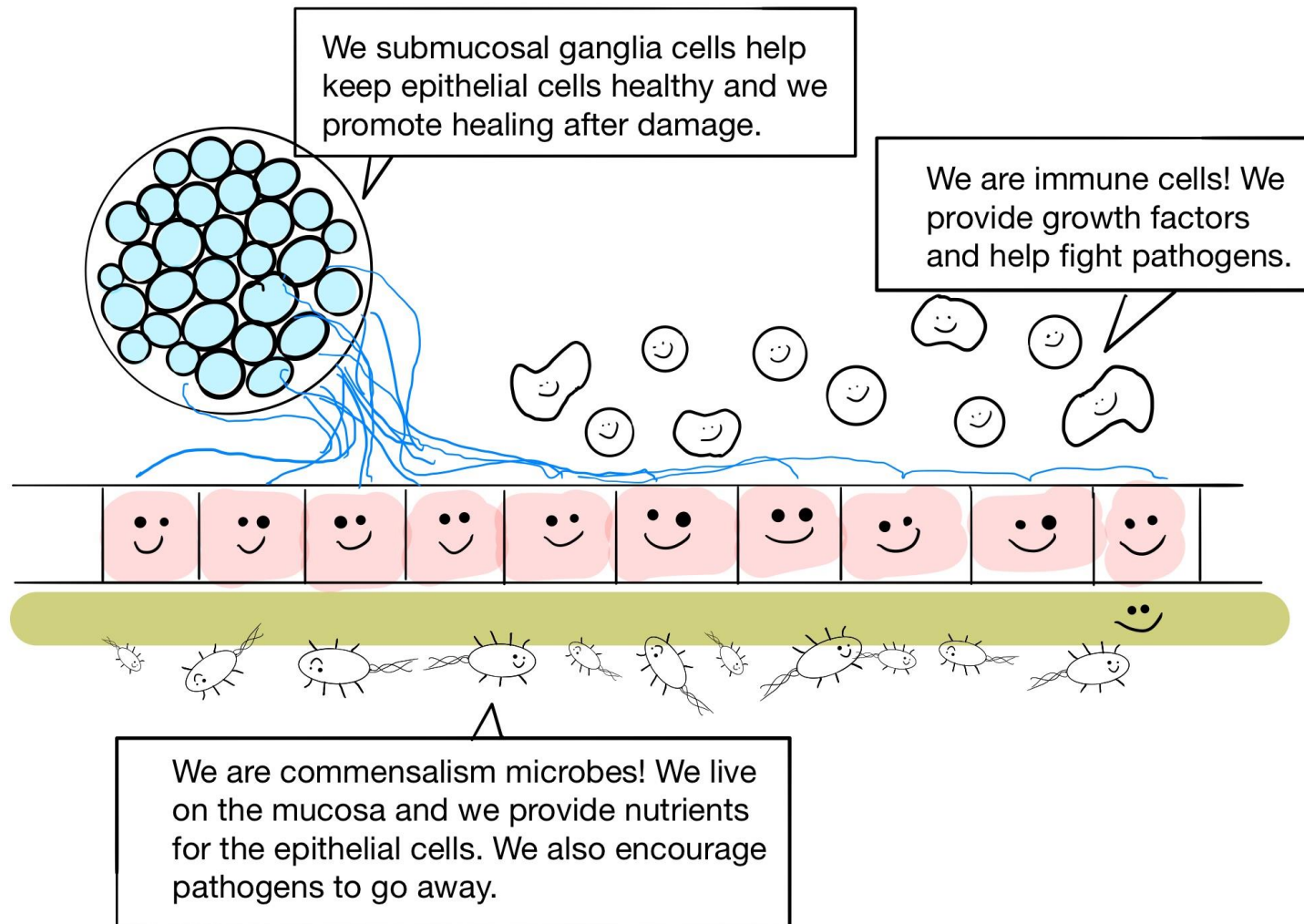
The Gut Barrier is a functional collaboration between the epithelial cells, neurons, immune cells, and microbes

“Permeability” of the gut barrier is tightly regulated

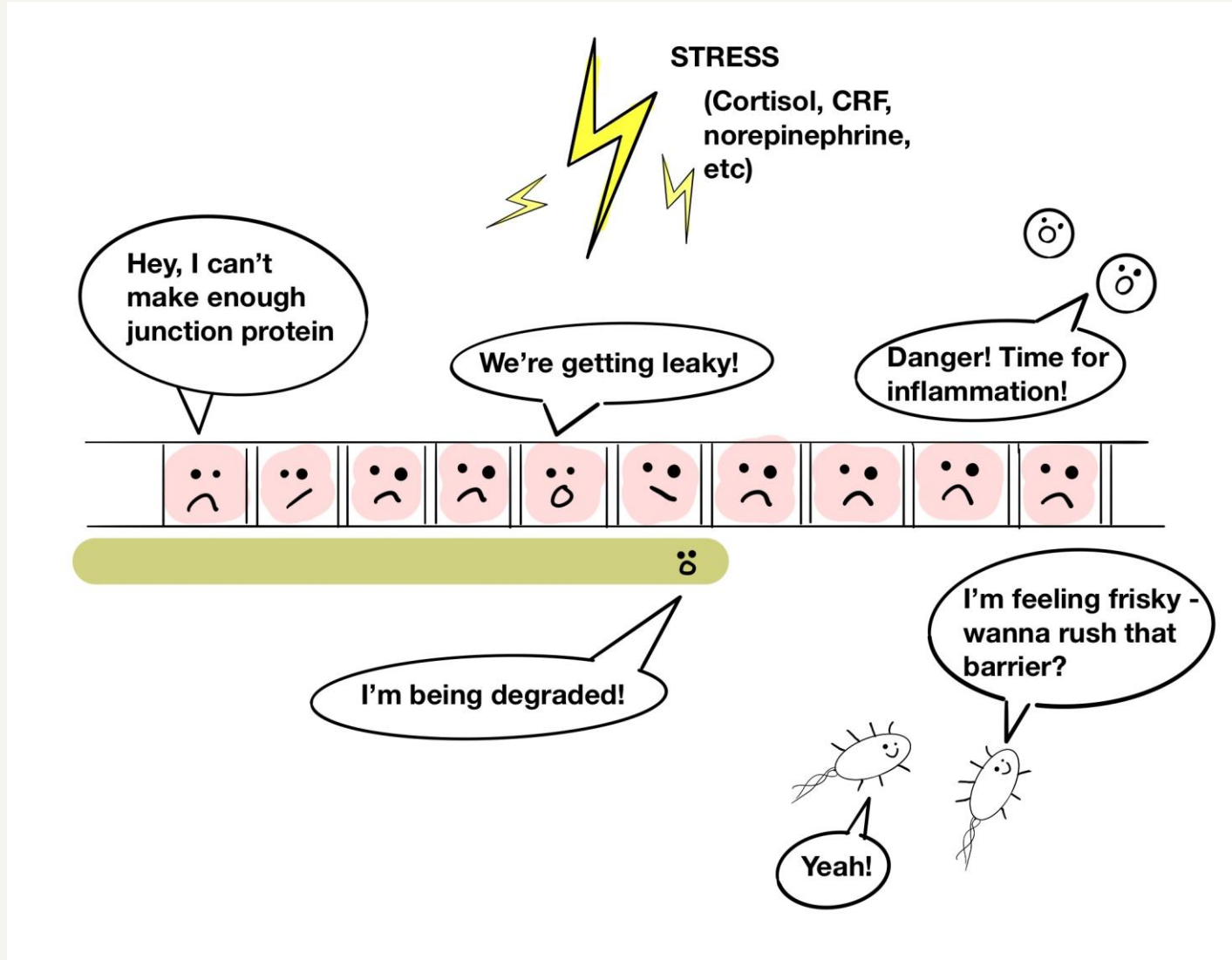
Stress, dysbiosis, and inflammation can cause the barrier to become “leaky”

Stress can cause bacteria to become more aggressive

The gut barrier



Gut barrier disruption



Consequences of a leaky gut

**Mood disorders: depression, anxiety,
worsening PTSD**

Fatigue

Cognitive “fuzziness”

Sleep problems

Metabolic disease

**Inflammation, including systemic
inflammation**

**These are all part of the “sickness
syndrome”**

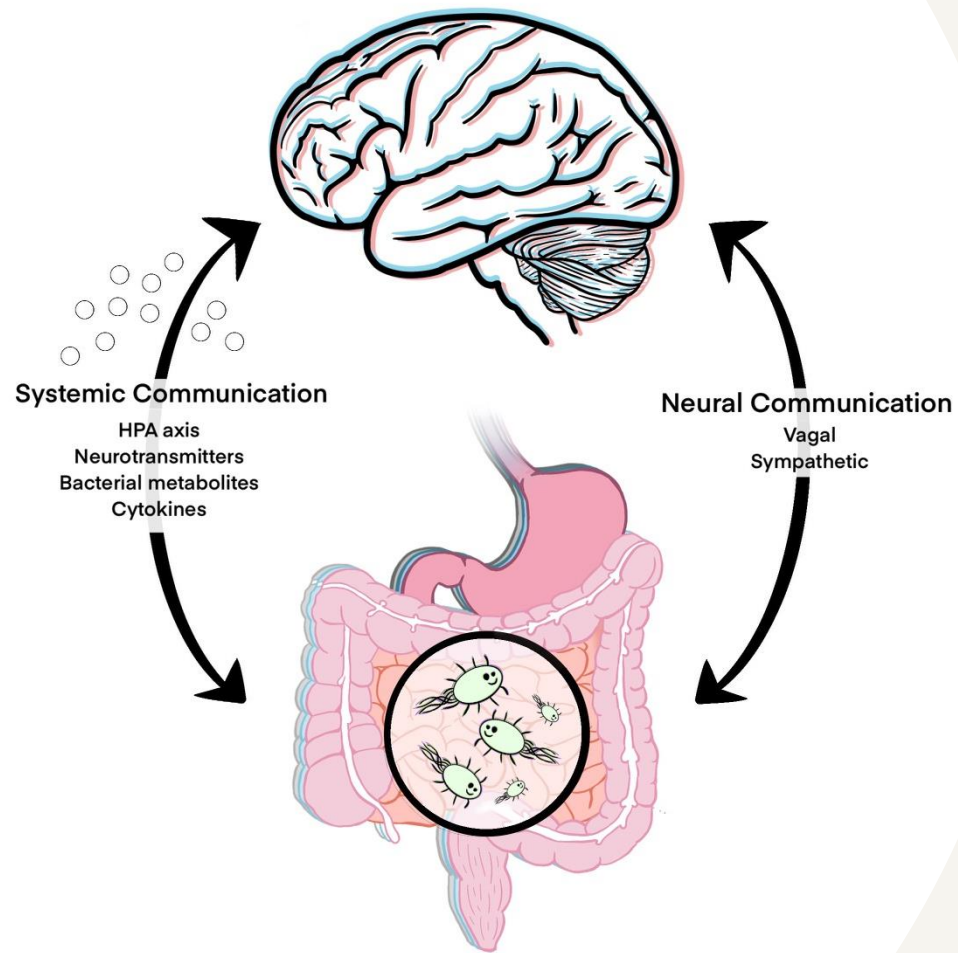
How do microbes influence the brain?

By making neurotransmitters such as GABA, dopamine, serotonin, acetyl choline etc. that can interact with nerves such as the vagus

By making short chain fatty acids, such as butyrate and acetate which can circulate and enter the brain (anti-inflammatory/influence epigenetic modifications)

By programming immune cells that can influence brain functions

By regulating inflammation



**Brain and gut
communication
pathways are
bidirectional**

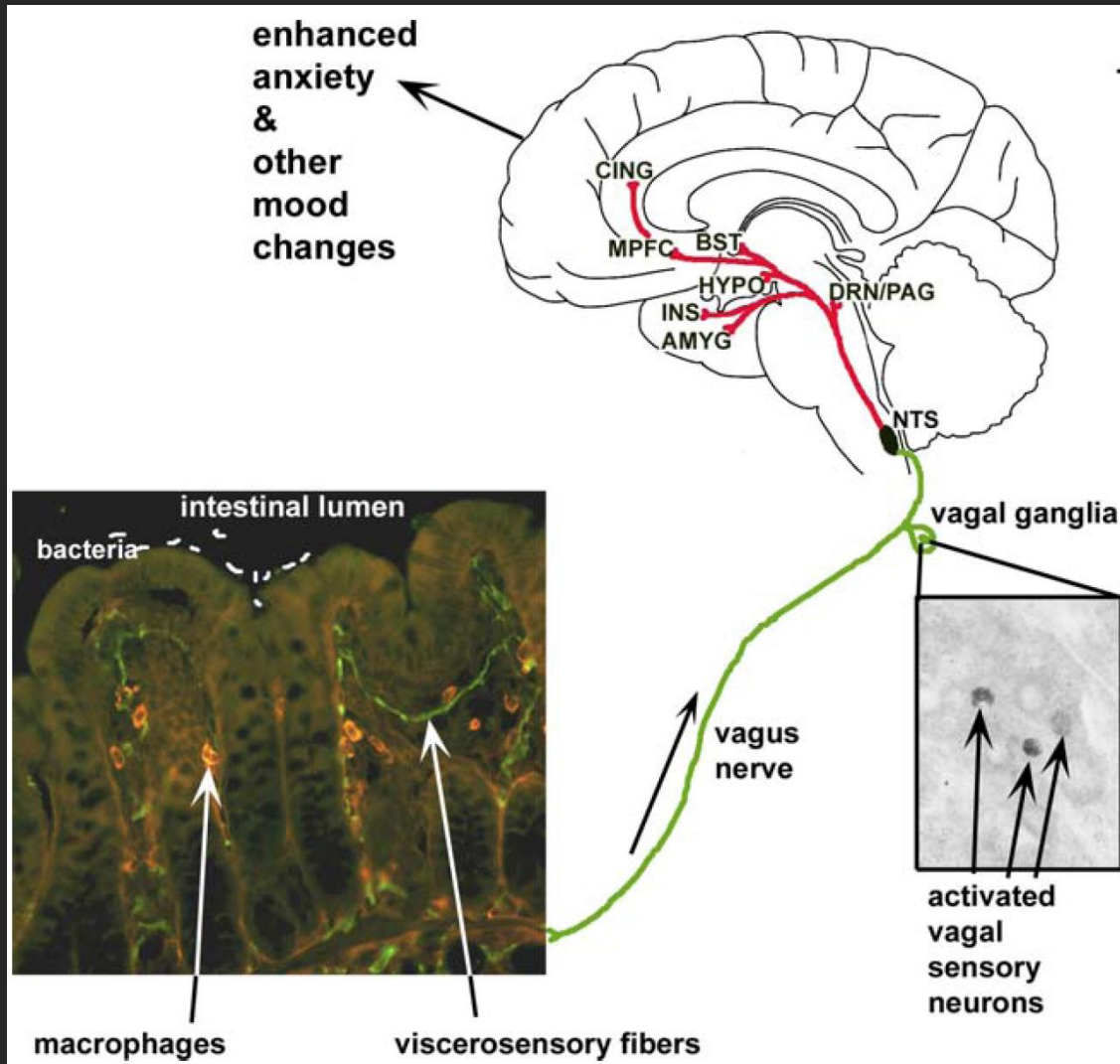
Key pathway: the Vagus Nerve

Gut microbes influence vagus nerve activity

Dysbiosis activates the vagal sensory nerves and induces anxiety symptoms (preclinical)

Probiotics improve mood symptoms (preclinical) via the vagus

**Vagus is a major pathway for
*Interoception***



Vagal interoceptive pathway activated by gut microbes

Interoception, the brain “default network”, and the self

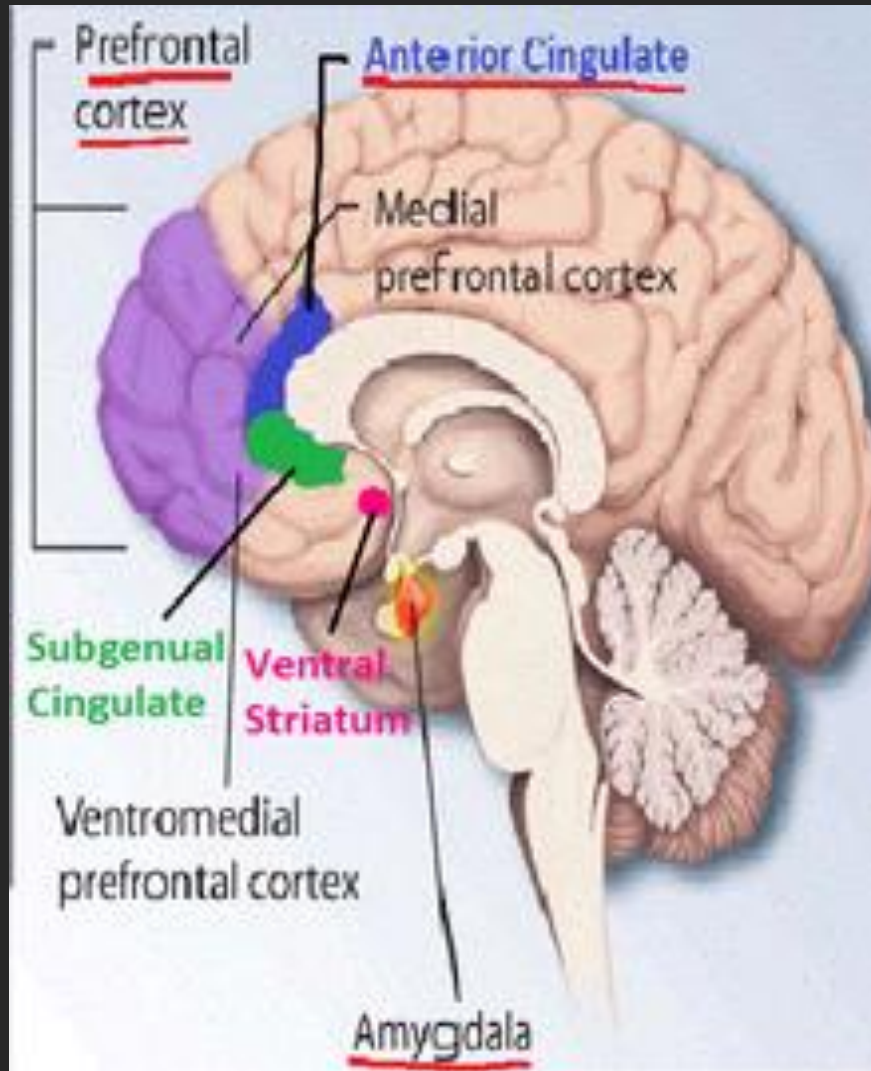
Interoceptive (sense of the condition of the body) information drives many brain regions, including “midline” regions associated with motivation, emotion, and memory

“Default mode network” is the collection of brain regions active when we aren’t doing anything (“being” rather than “doing”)- mostly along midline

Studies indicate these regions support our “sense of self”

These areas get information from interoceptive pathways- sense of self constructed (in part) from signals from gut

How the mind/body-brain/gut are interconnected and interact



**Medial prefrontal cortex:
Interface of self,
emotions, and autonomic
control**

Microbes and Mood: Anxiety

**Anxiety is a persistent, noxious feeling that
"something is not right"**

**Anxiety is closely associated with problems in the gut,
including dysbiosis**

**Pre-clinical studies studies show that dysbiosis induces
and anxiety-like behavior in mice**

**Many people are at risk for dysbiosis-induced anxiety:
heavy/frequent antibiotic use (e.g. military service
members, other government employees posted to
malaria-prone countries), poor diet especially "Western
Diet"**

**This "bottom-up" drive on anxiety may be hard to
correctly attribute**

Microbes and Mood: Depression

Depression is closely associated with inflammation- it is a key component of the “sickness syndrome” of mood symptoms, fatigue, anhedonia, cognitive “fuzziness” and sleep disturbances

Gut dysbiosis is associated with elevated inflammation and gut barrier disruption

Gut barrier dysfunction (aka “leaky gut”) associated with mood symptoms especially depression

Dysbiosis is reported to be common in depression, and some studies report probiotics can improve mood. However, most work is pre-clinical

Microbes and Substance Use Disorders

This is a developing story- relationships are still hypothetical

Substance use disorders often co-morbid with mood disorders and chronic pain

Microbe-driven interoceptive signals influence brain pathways that mediate motivation and reward

Drugs of abuse influence microbes, in part via diet

Some treatment approaches (antibiotics and butyrate) targeted to brain for SUD also influence microbes

Can we change our microbes?

If messed-up microbes contribute to mood and behavior disorders, can fixing them improve symptoms?

Antibiotics and probiotics: some evidence that in some circumstances can help

Overall populations patterns seem more key than specific individual species

Fecal Microbiota Transplant (yes that's what it is!): improve symptoms of depression and anxiety in patients with IBS or MDD. Relief was not usually long-lasting, however. Possibly because may not have changed diet to support new microbe populations

Changing diet: biggest "bang for the buck"; dramatic change in microbe populations seen within days after switching to veg diet, after gastric bypass; poor diets are linked to mood symptoms

What is a "poor diet" for Microbes?

"Western Diet" of refined and carbohydrates (sugar, white flour, white rice) white potatoes, processed low fiber foods, processed meats, commercially fried foods but few fresh fruits or vegetables

Western Diet foods don't provide adequate nutrition

Western Diet does not support a diverse microbial population and predisposes for dysbiosis

Western Diet is associated with mood disorders and chronic pain- bidirectional interaction and feed-forward loop

What is a "good diet" for Microbes?

All food is "pre-biotic"- so the more diverse the foods in the diet are the more diverse the microbial populations

Diets that include fiber, such as whole intact grains, nuts, mushrooms, beans, fresh fruit and vegetables support microbes that maintain the gut barrier and modulate gut immune function and inflammation

Fermented foods, such as plain yogurt, kefir, kimchi, kombucha contain "probiotic" Old Friends microbes that can help improve mood and GI symptoms

Bottom line is that diet pattern are more important than specific foods

Clinical trials support diet interventions for mood disorders

The “SMILES” trial: replaced high-energy Western Diet foods with whole/intact grains, fruits, vegetables and fiber for 12 weeks.

Depressive symptoms improved, and some (1/3) participants no longer met diagnostic criteria by end of trial

Other studies report similar results

Trials of “microbe-modulating” diets for anxiety show promising results but still need more studies

The Way Forward

The discovery of microbe- brain interactions has revolutionized the way we think about mind-body interactions, nutrition and food, and mental health

There is still much work to be done

Healthy microbe populations are only one reason to eat a nutritious, diverse diet but it can be hard to get people to change their eating habits

People with mood and behavior disorders face many barriers, including emotional, financial, and even neurological issues