Our Guts are ALIVE!

We Have More Bacteria Cells Than Human Cells in Our Bodies!

Just like soil or dirt, our “guts” (e.g., our digestive tracks, mostly our intestines) are home to **trillions of living microorganisms**, including bacteria, viruses, and fungi. In fact, it’s estimated we have **40 trillion bacteria cells in our bodies** (e.g., in our guts, mouths, skin, ears, noses, etc.) and **30 trillion human cells**, meaning we are technically more bacteria than we are our human selves (Sender et al., 2016)!

When We Feed Ourselves, We Also Feed Our Gut Bacteria

This microbial community (AKA our **gut microbiome)** eats the same food we eat, so when we feed ourselves, we are feeding our gut microbiome too! These gut microbes mostly like to eat **insoluble plant fibers** (the parts of plants – fruits, vegetables, nuts/seeds, legumes, whole grains – that the human parts of our bodies don’t really use) (Beane et al., 2021; Thomson et al., 2021; Wastyk et al., 2021).

Our Gut Bacteria Love to Eat Insoluble Fiber (Veggie Stems & Peels)

Our gut bacteria love to eat things like **broccoli stems, carrot peels, and asparagus stalks**. They also love to eat whole grains and legumes (**beans, lentils, oats, quinoa**), nuts and seeds (**almonds, flax seeds, and chia**). One of their favorites foods is a fiber called **fructans** that is found in **garlic, onions, leeks,** and **artichokes**. Luckily, these bacteria are small, so we don’t need to eat a lot of these foods to keep them fed and happy.

We call these foods **prebiotics** (the root word, “**biotic**” comes from the Greek work **"biōtikos,"** which means **"pertaining to life"** and the precursor “**pre**” means to precede or support. So the word “prebiotic” literally means “that which supports life [in our guts – and – in our bodies, in turn].”

Our Gut Bacteria Improve Our Health!

Our gut microbes earn their keep! They eat the parts of our food that we don’t use or need, and in turn they produce a lot of really good substances that help us live and thrive (and that we actually require to live and thrive)! We call these substances **postbiotics** or “metabolites.”

Our Gut Bacteria “Poop Out” Postbiotics that Improve Our Health!

You can think of postbiotics as **gut microbe “poop.”** However, unlike human poop, good gut microbe poop is really good for us! In fact, it is critical for our **digestion**, **immune function**, **body weight** and **physical health**, and our **mental health (Lipski, 2020)**! Let’s walk through some of these great benefits.

Our Gut Bacteria Are Critical for Our Digestion

“Good gut microbes” produce digestive enzymes like **amylase, protease, lipase, cellulase,** and **lactase** (“ase” is the part of the word we use to refer to an enzyme).

These enzymes help us break down and digest starches, proteins, fats, plant fibers, and lactose into simple sugars and amino acids that we can use for energy ([Oliphant & Allen-Vercoe, 2019](https://microbiomejournal.biomedcentral.com/articles/10.1186/s40168-019-0704-8)).

Our Gut Bacteria Are Critical for Immune Function

Our immune system is like our body’s **security and defense team**. It uses **barriers** (like our skin and brain and gut membranes), cells, and **antibodies** to protect our bodies (and our health and ourselves) from potentially harmful microbes (bacteria, fungi, viruses) and cells that can make us sick. About 70 – 80% of our body’s immune system resides in our guts (Lipski, 2020). Moreover, our gut microbes are responsible for producing important components of our immune system (Lipski, 2020). Before we get into these details of which pieces of our immune system our gut microbes help produce or support, let’s first provide a brief overview of our body’s immune system.

Immune Health 101: Barriers (Skin, Mucus, Membranes; Building Walls)

Our immune system’s first-line of immediate defense is/are our **body** **barriers** (skin, mucus linings, gut and brain membranes, and even our cell membranes). These act as **shields** to protect us (and our individual organs and cells) from germs or “**foreign bodies**.”

If we think of our bodies as high-security buildings, our barriers would be the building walls, doors, and locks.

Immune Health 101: Antibodies (TSA, Authorization Systems)

Our immune-system’s second-line of immediate defense is/are our **antibodies**, also known as **immunoglobulins (Ig)**. Antibodies (AKA immunoglobulins) are proteins produced by specialized immune cells called B cells. There are few different types of antibodies (Igs) that exist in the body, including IgG, IgA, IgM, IgE, and IgD (each with a specific resident location and role). Collectively, Igs act like tiny **detectives**, scanning, finding, marking, and neutralizing pathogenic invaders (called “**foreign bodies**”).

If we think of our bodies as high-security buildings, our antibodies would be like the identification systems that lets authorized personnel in and keep unauthorized personnel out by notifying security guards when unauthorized personnel enter the building.

Immune Health 101: White Blood Cells (Security Guards with Memory)

Our immune system’s next line of defense are our **white blood cells** (AKA WBCs or “**leukocytes**”). Our bodies have three main types of white blood cells: **T cells** (which are made in the thymus) and **B cells** (which are made in the bone marrow) and **Natural Killer cells (**NKs). Collectively, WBCs recognize antibody “tags” on harmful cells and surround/contain/detain them, and remove them from our systems, in the same way that security guards might locate, detain (if needed) and escort unauthorized personnel out of a high-security building.

White blood cells also **store memory information** about harmful cells that they identify, catch, and remove, to more easily detect them in the future. This is similar to the way security guard personnel might take a photograph of an unauthorized personnel they have to escort out, so they can better recognize the unauthorized individual in the event of future break-in or security breech attempts.

Immune Health 101: Inflammation (The S”ecurity Action” System that Locates, Detains, and Removes Pathogens)

When a **harmful substance** (e.g., a **pathogen**) gets into our bodies, white blood cells locate, surround, detain, and remove the pathogen from our bodies. In some cases, WBCs may also attack pathogens directly. This security process (e.g., surrounding, detaining, and attacking or removing pathogens) is done through a process called **inflammation.** This process involves a lot of white blood cells and often has a quality of “puffiness” to it. If you’ve ever had an allergic reaction, you might recall that your skin or eyes or nasal/sinus cavity became red, itchy, and ***puffy***. That ***puffiness*** is a result of your immune’s inflammatory processes at work – helping to protect you from a pathogen (in this case, one you’re allergic to).

Inflammation is a really important part of immune function. However, like any security or alarm system, it tends to be **good in the short-term** but **not so good if it stays active for long periods of time**. In the long-term, inflammation can lead to tissue breakdown, general fatigue, reduced function, negative mood states like depression and anxiety, and negative metabolic states like diabetes and weight gain. Chronic inflammation can also lead to a large variety of negative health conditions that can include autoimmune disorders (when the body starts to mislabel itself as “unauthorized personnel” and attack itself). **Because inflammation is critical for short-term health but harmful over long periods of time, good regulation of this system is critical for overall health function**.(We’ll address how the immune system regulates inflammatory processes below).

Our Gut Bacteria Can Strengthen Our Immune *Barriers*

Our gut microbes play a crucial role in immune function. They do this in a few specific ways. First, our gut microbes produce **postbiotic** compounds (e.g., “good gut microbe poop”) that help **strengthen and tightening our intestinal barriers**. This prevents harmful substances from getting into our intestines. It also prevents harmful substances from traveling from our intestines into our blood, bodies, and brains. For example, our gut microbes produce compounds that help produce the mucus that lines and protects our intestines. Gut microbes also produce **short chain fatty acids (SCFAs)** like **butyrate** that nourish gut cells, reduce inflammation, and help keep our gut barriers strong and healthy.

We might think of this support as that of a construction worker or janitor, who is constantly checking the bricks and mortar of our body building.

Our Gut Bacteria Produce Inflammation Regulators (“Cytokines”)

Our gut microbes also produce **anti-inflammatory cytokines** that help support our immune system health and **prevent our immune system and inflammation systems from going into overdrive** and staying on for too long or attacking our own bodies and cells.

A **cytokine** is a protein that helps immune cells communicate and regulate immune responses. There are two main types of cytokines that “good gut microbes” produce (that help support our immune systems and function): **interleukins** (**ILs**) and **growth factors (GFs)**.

Immune Health 101: Interleukins (“Generals” that Communicate & Coordinate Immune & Inflammation Attacks)

The first type of cytokine that “good gut bacteria” produce are **interleukins**,a family of **white blood cells** that **signal and communicate with each other** to support our immune function and health. “Good gut microbes” produce **interleukins** like **IL-10, IL-22, and IL-35** that can communicate with other immune cells to turn immune “attack” programs (like **inflammation**) on or off. If “inflammation” is like the body going to battle, interleukins are like the generals that talk and signal to each other and their soldiers to coordinate when to “fight/attack,” “retreat,” “stay alert but wait,” or “rest for a bit while they keep watch.” Specifically, IL-10, IL-22, and IL-35 are known for their ability to **reduce excessive immune responses**, preventing chronic inflammation (or, chronic body battle states) and **help maintain the integrity of barriers like the gut lining**.

Immune Health 101: Growth Factors (Regulate Cell Growth & Immunity)

The second type of cytokine that “good gut bacteria” produce are **growth factors** like **Transforming Growth Factor-Beta (TGF-B).** TGF-B is a cytokine that plays a role in regulating cell growth, differentiation, immune suppression, and tissue repair. They are involved in **immune strength/tolerance** and in a variety of important health conditions that include:

* **Autoimmune conditions** like **lupus** and **rheumatoid arthritis**.
* **Fibrosis.**
* **Inflammatory bowel disease**, including **Chron’s Disease** and **Colitis**.
* **Neurodegenerative diseases** like **Alzheimer’s Disease.**

<https://copilot.microsoft.com/shares/igEMe5cA6eVR3MNibkGoG>

1. fermented foods (pickles and anything pickled, apple cider vinegar),
2. Mood states vary with different gut microbes and probiotic strains. The influence can be positive or negative.
3. Specific foods contain different gut microbes and probiotic strains.
4. Some food products are helpful for different mood states. (CALL TO ACTION)
5. There are VERY simple “hacks” like apple cider vinegar (with the ”mother”), anything pickled, etc (EASY NUDGE CALL TO ACTION)

In Warm & Gratitude,

Brenna


**Brenna Bray, PhD**

Founder, Director, CEO, & Principal Investigator
[NourishED Research Foundation | www.nourishedrfi.org](http://www.nourishedrfi.org/)
[Research Staff | National University of Natural Medicine](https://nunm.edu/profile/bbray)

[Adjunct Associate Professor | Naropa University](https://www.naropa.edu/)

[Director of U.S. Marketing & Research | ANNi Project](https://ann-i.com/)

+1 206.819.9647 | brenna@nourishedrfi.org

<https://www.linkedin.com/in/brenna-bray-39891914/>

[60-min Booking Here](https://calendly.com/brennabray/60-min-meeting-with-dr-bray).







**From:** howardrose1@icloud.com <howardrose1@icloud.com>
**Date:** Monday, May 5, 2025 at 1:49 PM
**To:** Brenna Bray <brenna@nourishedrfi.org>
**Cc:** Apley Mitch <mitchapley@gmail.com>
**Subject:** Re: Grateful Meeting Follow-Up!

Brenna,

That was amazing! Thank you for sharing all that. Very helpful and I’m learning so much.

Since you have provided so much good science and we have a great compelling story, I’m excited to use this as a test case for us to efficiently get ourselves to a story as efficiently as possible so I don’t need to do a PhD in each subject area. ;-). I want to do this in bite sized chunks so I can make sure we are on the right track. I’ve boiled down the gist of what you shared and used a bit of AI to summarize.

**KEY POINTS from your notes:**

- Mood states vary with different gut microbes and probiotic strains. The influence can be positive or negative.

- Specific foods contain different gut microbes and probiotic strains.

- Some food products are helpful for different mood states. (CALL TO ACTION)

- There are VERY simple “hacks” like apple cider vinegar (with the ”mother”), anything pickled, etc (EASY NUDGE CALL TO ACTION)

I also put your papers into Zotero and used Aria to search and summarize what to me seems like the essential question: **How do gut pathways affect positive and negative mood states?**

Gut pathways significantly influence both positive and negative mood states through various mechanisms involving the microbiota-gut-brain axis. Key points from the provided documents include:

1. **Production of Neurotransmitters**: Gut microbes, such as Bifidobacteria and Lactobacilli, can produce neurotransmitters like serotonin and GABA, which are crucial for mood regulation. These neurotransmitters primarily act locally in the gut but also have the potential to influence brain chemistry and behavior (Item ID: 20290).

2.  **Psychobiotics**: Certain psychobiotics, when ingested in adequate amounts, can positively affect mental health. These psychobiotics can modulate neuroimmune regulation and control axes such as the hypothalamic-pituitary-adrenal axis, influencing mood and cognitive functions (Item ID: 20294).

3.**Impact on CNS Function**: Probiotics have shown potential in impacting  central nervous system  functions, which in turn affects mood states. While some studies show no significant effect on mood compared to placebo, others indicate slight improvements in conditions like depression when probiotics are used (Item ID: 20293).

4. **Neurogenesis and Behavior**: Changes in gut microbiota, such as those induced by antibiotics, can affect hippocampal neurogenesis and memory retention, which are linked to mood and cognitive functions. The restoration of normal gut flora and interventions like exercise or probiotic supplementation can mitigate these effects, mediated in part by immune cells like Ly6Chi monocytes (Item ID: 20291).

5. b: The microbiota-gut-brain axis is being explored for its therapeutic potential in treating psychiatric disorders such as depression, anxiety, and schizophrenia through the modulation of gut microbiota (Item ID: 20292).

Once we have the framework of the science, the next step is to frame out a story. Then we can fill in the details as we go.

LMK how we’re doing. Have we missed big points?

On May 5, 2025, at 9:07 AM, Brenna Bray <brenna@nourishedrfi.org> wrote:

Greetings Howard & Mitch!

You both beat me to the punch on follow-up emails!

It was and is a true joy to be able to be included your work. First and foremost: thank you!

Second, as I mentioned previously, I’m a bit slow on the response this week and last (my students’ semesters ends this week, which includes MS thesis paper reviews and presentations, and my mom’s been visiting this weekend to provide a guest lecture to my students). Apologies for my delayed replies!

I’m drafting a few follow-up emails to send.

THIS email provides a few overview sources on the gut-brain axis, the gut-immune-brain axis, and the impacts of gut microbes on inflammation, brain health, mood and psychological/psychiatric and behavioral states in turn. I’ve also included my excel doc of gut microbe strains, probiotics, and certain food products and supplements associated with “good bacterial health” and positive psychological, psychiatric, and behavioral states in turn.

**The excel doc attached** is one I created in ~2015 based on Cryan & Dynan’s 2012 review of the gut-brain axis and gut impacts on brain and behavioral health. There are several pages in the doc:

* One shows mood states associated with different gut microbes and probiotic strains.
* One shows the same in reverse (gut microbes and probiotic strains associated with different mood states.
* One shows food products that contain different gut microbes and probiotic strains.
* One shows the reverse (gut microbes and probiotic strains that can be found in different food products.
* The first page shows food products that can be helpful in the context of different mood states.
* NOTE: I created this based on a list of food products I regularly used at the time (and still do). The list is not exclusive. Moreover, it does not include several VERY simple “hacks” like apple cider vinegar (with the ”mother”), anything pickled, etc.

I also attached **6 pdfs documents (excessive, I know)** on the gut brain barrier that might be helpful. NOTE: I’d suggest JUST simply opening these, scrolling down to the figures, and see the notes I’ve provided here. Scan the abstracts, figure legends, etc. if you want (but not required).

1. **Cryan & Dinan 2012**
	1. **Tim Dinan & John Cryan are — IMO — really the grandfather pioneers of this field.**
	2. This article is 2012 but still relevant and a nice primer/intro.
	3. **Fig 1**shows different pathways that enable the gut and the brain to communicate (see description provided in # 3 below).
	4. **Fig 2**shows a visual depiction of the animal research used to arrive at our current understanding of the gut brain axis. **Fig 3**depicts how gut microbes impact the gut-brain axis and psychology and psychiatry in turn.
2. **Dinan & Cryan 2017**
	1. **Tim Dinan & John Cryan are — IMO — really the grandfather pioneers of this field.**
	2. **Figure 1**shows routes of communication between gut microbes and the brain.
	3. **Figure 2**shows a model of IBS (e.g., how the brain can influence gut health) but if you follow it in reverse, it can also show a model of gut-induced neuroinflammation and depression (e.g., how gut health can influence brain health and function).
3. **Mohle et al., 2016 (Graphical Abstract)**
	1. The graphical abstract in Mohle et al., 2016 provides a nice higher-level depiction of how the gut and the brain communicate with- and influence one another.
	2. For example, **negative gut factors**(e.g., high processed food consumption or diet, antibiotics (in most cases), physical restraint or restraining movement (e.g., working a sedentary 9-5 job, traveling in a car, especially in traffic, etc.), chronic or prolonged stress exposure (which can include family stress, relationship stress, nutrition stress//poor nutrition//high processed diet) can (and do) alter gut microbe health (supporting thrivency of “bad gut microbes” and killing “good gut microbes”). This can result in higher population of gut microbe secretion of proinflammatory cytokines that - in the brain - can cause neuroinflammation, which is strongly associated with negative impacts on brain cell health (e.g., killing brain cells, preventing neurogenesis (new brain cell birth)), and negative mood states and behaviors (e.g., depression, anxiety, cognitive rigidity, OCD, rumination, disinhibition, poor emotion regulation, poor self-regulation, impulsivity and compulsivity, ADD/ADHD, drug-seeking, craving, and associated behaviors of isolation, hyperactivity or hypoactivity, lethargy, disordered eating, changes in sleep and movement, etc.).
	3. On the other hand, **positive gut factors** (like whole-food consumption and diet, certain probiotics, fecal transplants, voluntary exercise, most serotonergic antidepressants, psychedelics, meditation, hypnosis, and many other mind-body interventions) can (and do!) support “good gut microbe” health. This can result in greater gut microbe production of serotonin precursors (like tryptophan), anti-inflammatory cytokines, short-chain fatty acids (SCFAs), and brain-derived neurotrophic factor (BDNF), which is like fish food for your brain cells, stimulating new brain cell birth (neurogenesis), growth, and integration into neural systems that enable new cognitive and behavioral patterns to emerge. These microbe metabolites (e.g., tryptophan, anti-inflammatory cytokines, SCFAs, BDNF) can cross the gut- and blood-brain barriers and travel into the brain where they can reduce neuroinflammation and enhance neurogenesis and neuroplasticity/synaptogenesis (formation of new connections between brain cells). Inflammation and brain cell death are both strongly associated with negative mood and behavioral states (anxiety, depression, social isolation, suicidality, schizophrenia, drug-seeking and craving, ADD and ADHD, and eating disorders), and gut-induced tryptophan, anti-inflammatory cytokines, SCFAs ,and BDNF can reverse these processes (reverse neuroinflammation and stimulate neurogenesis, synaptogenesis, etc.), reversing negative mood states and behaviors in turn (e.g., reversing depression, anxiety, suicidality, schizophrenia, drug-seeking, craving, attention and hyperactivity issues, etc.).
4. **Morkl et al., 2020 (Figure 1 & Table 2)**
	1. Morkl et al., 2020 focuses specifically on the ability of probiotics to influence depression, anxiety, and other psychiatric states (an emerging field termed “psychobiotics”). The point of sharing this is simply to show there is an abundance of empirical investigation though the field is still ongoing.
	2. Figure 1 provides a higher-level figure depicting how the enteric nervous system (e.g., the microbes in our gut) can impact the central nervous system, and induce psychiatric states of depression, anxiety, and schizophrenia in turn).
5. **Le Morvan de Sequeira et al., 2022 provides a meta-analysis of the impact of probiotics on psychiatric states.**
	1. By recollection — when I was more engaged in this field this fall, this is one of the most current meta-analyses we have on the efficacy of psychobitoics.
	2. Forrest Plots are used to depict efficacy of probiotics in the context of depression, anxiety, perceived stress, and a variety of other states.
	3. When reading forest plots: look for the large diamond at the bottom of the graph. If the diamond is crossing the midline, this suggests the data is (a) not yet conclusive or (b) shows not significant change. If the diamond is NOT crossing the midline, this suggests that based on current data, the intervention (probiotics) DOES have a significant impact on the outcome (e.g., depression, anxiety, etc).
6. **Bermudez-Humaran et al., 2019. (Figures 1, 2, 4, 6)**
	1. This is probably more detail than you want or need but… in case not…
	2. You don’t need to read anything more than the abstract (if anything), but the figures here can be helpful. There are three primary systems in the body that are “activated” in response to stress: (1) the sympatho-adrenal medullar (SAM) axis responsible for immediate adrenaline/epinephrine stress responses; (2) the hypothalamic-pituitary-adrenal (HPA) axis responsible for short- and long-term cortisol stress responses; and (3) inflammatory reflexes responsible for pro- and anti-inflammatory cytokine responses to stress. Importantly, each of these three systems have downstream effects in both the body and the brain. For example, steroid hormones like cortisol and inflammatory cytokines can cross cell- and organ membranes, so although they are secreted from the adrenal glands which sit atop the kidneys, they can (and do!) diffuse into the gut (by crossing the gut membrane) and the brain (by crossing the blood brain barrier), where they have short (nongenomic) and long-term (genomic) impacts on gut and brain neurotransmission and function. In the brain, cortisol and proinflammatory cytokines generally induce hippocampal cell death, amygdala hyperactivity, etc. that translate to states of anxiety, depression, cognitive rigidity, OCD, ADD/ADHD, etc.
	3. Figure 1 shows a depiction of how the SAM-a, HPA-a, and inflammatory reflexes regulate the neuroimmune axis. Figure 2 provides a complex depiction of the Gut-Brain Axis, showing that the HPA-induced cortisol and inflammatory cytokines can diffuse into the gut to alter gut microbe function. Certain gut microbes are responsible for metabolizing inflammatory cytokines, short-chain fatty acids (SCFAs), and neurotransmitter precursors like tryptophan (a serotonin precursor), which can then diffuse from the gut up into the circulation and into the brain, where they can influence neural function and activity and mood in turn (as referenced in #1 above). Figure 3 shows the serotonin system (depicting its role in the brain and the body). Figure 5 shows the impacts of chronic stress on gut microbes, causing greater production of proinflammatory cytokines that can induce depression and anxiety states in the brain.

I look forward to continued collaborations as time moves forward.

In Warm & Gratitude,

Brenna

**Brenna Bray, PhD**

Founder, Director, CEO, & Principal Investigator
[NourishED Research Foundation | www.nourishedrfi.org](http://www.nourishedrfi.org/)
[Research Staff | National University of Natural Medicine](https://nunm.edu/profile/bbray)

[Adjunct Associate Professor | Naropa University](https://www.naropa.edu/)

[Director of U.S. Marketing & Research | ANNi Project](https://ann-i.com/)

+1 206.819.9647 | brenna@nourishedrfi.org

<https://www.linkedin.com/in/brenna-bray-39891914/>

[60-min Booking Here](https://calendly.com/brennabray/60-min-meeting-with-dr-bray).

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