

*"Beneficial Gut Bacteria" by the National Human Genome Research Institute. Flickr.*

# How the Bacteria in Your Gut May Calm the Butterflies in Your Stomach

By Hailey Naiper

This weekend I attended a wedding. On the morning of the ceremony I ate breakfast with the bride and some of her family members. She was so nervous that all she could stomach was a piece of toast and a few nibbles of bacon. To help calm her down, we decided to go around the table listing other stressful things she'd done that went well. She'd performed in multiple musical theater productions, she'd made presentations to critical audiences of powerful people, she'd taken many difficult tests, she was even once dragged across a lake by a runaway capsized sailboat. Comforted by the reminder that she had succeeded before, she finished her breakfast. A few hours later she walked down the aisle, and she looked beautiful, despite her fears that she'd trip and fall over or appear disheveled.

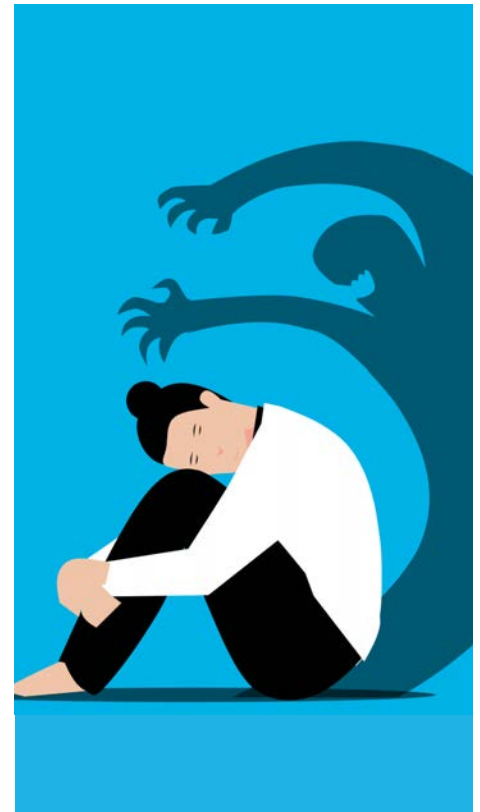
Whether or not you've gone through the nerve-racking process of planning a wedding, you've probably experienced a similarly stressful event in your life. Perhaps you were in the spelling bee as a child, or you climbed up a tall tree to rescue a cat. Maybe you've had to complete a project on a tight deadline or you've experienced meeting a significant other's family. Recently, we've all been experiencing sustained levels of high stress, apart from these isolated stressful incidents. In the past two years, stress has become increasingly present in day-to-day life, be it from the COVID-19 pandemic, increased racially-targeted violence, economic hardship, or growing political partisanship. Last year, the American Psychological Association deemed stress in America a "national mental health crisis". In a survey conducted in August 2020, 67% of adult respondents said they had experienced increased stress during the course of the pandemic (1). Increased

stress seems to be impacting younger generations more. From 2018 to 2020, Gen Z adults (born between 1995 and 2001) have consistently reported higher average levels of stress than the average stress levels reported by adults as a whole (1). This concerning fact indicates a possible upward trend in stress overall as we move into the future, suggesting that stress is a health concern that will necessitate increasing attention in coming years. Furthermore, long term stress, such as that Gen Z adults appear to be facing, can result in more severe mental health issues such as depression and anxiety, which can negatively affect them for the rest of their lives. Indeed, Gen Z adults also report higher rates of stress than the general adult population. This worrying trend means that stress and anxiety will likely become a more significant problem among the general population, and this doesn't show signs of slowing.

## Anxiety vs. Stress: What's the Difference?

Although they are related, stress and anxiety are two distinct phenomena. While stress is your body's response to a present threat, anxiety is a response to a threat that isn't actually there. For example: if you see a tiger in the woods, your heart rate will increase and you will experience the "fight or flight" response associated with stress. Prolonged stress oftentimes leads to anxiety, particularly after the threat ceases to be an active danger. If you've been in a jungle filled with tigers for many years, you may still have anxiety about tiger attacks if you move to New York City.

According to the Anxiety and Depression Association of



America, anxiety affects about 40 million adults in America alone each year. That's 18.1% of the adult US population (2). Anxiety can develop as a result of many interacting factors including genetics, life events, and brain chemistry.

In the body, anxiety and stress are most closely linked to the hypothalamic-pituitary-adrenal axis, or the HPA axis. The HPA axis is a communication system between the hypothalamus (a region of the brain that is involved in integrating body information and producing broad responses), the pituitary gland (a small structure that kind of looks like a pea sitting on the bottom of the brain, which is involved in hormone secretion), and the adrenal glands (small organs located on top of the kidneys that also produce hormones) (3). The HPA-axis is in charge of assessing threats and producing hormones like cortisol, the primary stress hormone, which speeds up your heart rate and prepares that "fight or flight" response (3, 4).

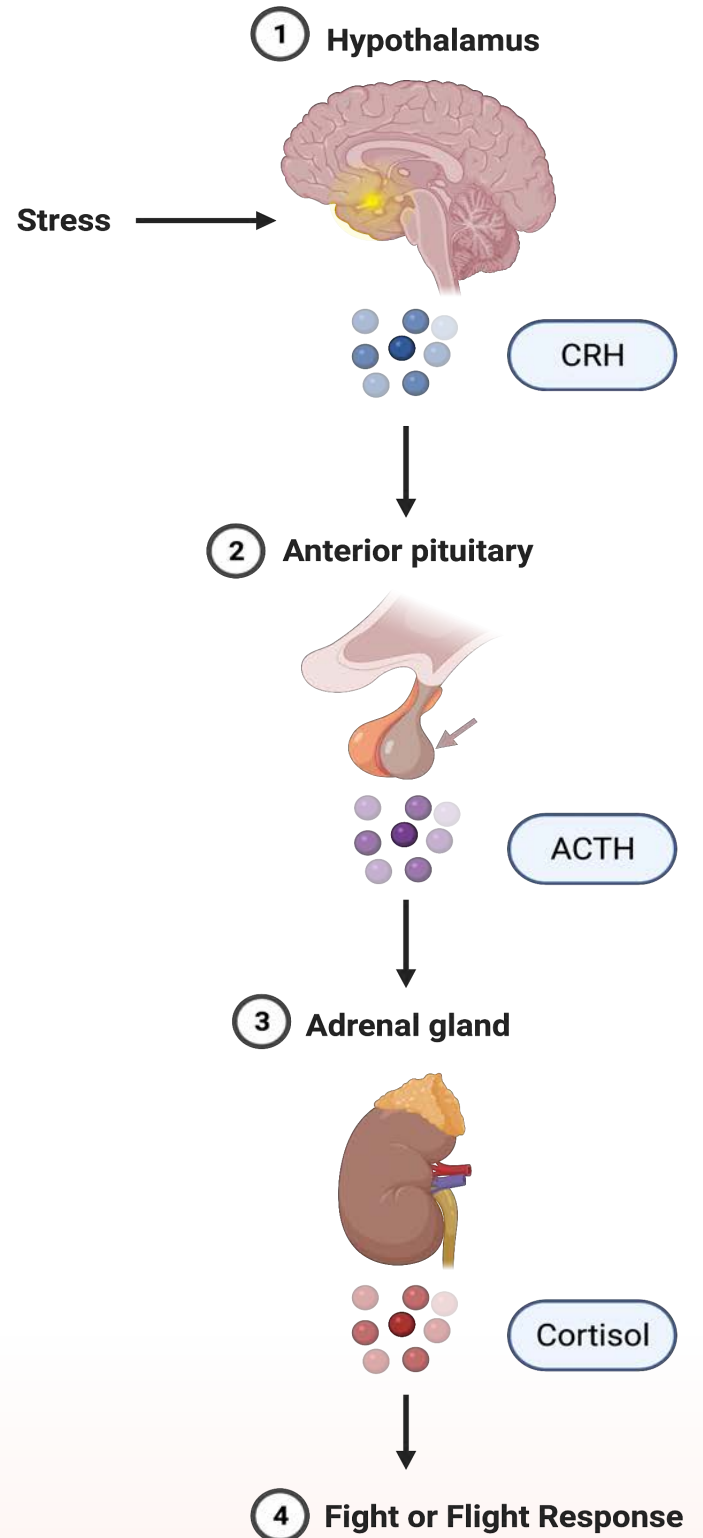
## Stress Specifics

A system called the HPA axis controls the stress response, also known as the fight or flight response. When you experience a stressful situation, a part of your brain called the hypothalamus secretes a hormone called CRH. CRH causes a gland in your brain, the anterior pituitary gland, to secrete another hormone called ACTH. ACTH then travels through your blood and prompts the adrenal gland to secrete cortisol, which produces the effects we associate with stress.

## The Gut-Brain Axis and the Gut Microbiota

Long term, or chronic, stress signaling from the HPA-axis can have many negative effects throughout your body, including increased risk of heart disease, memory impairments, depression, and gastrointestinal distress... yes, you read that right, stress in your brain can affect your gut (3, 4, 5)! Recent studies have shown that the brain and gut communicate with each other via a pathway known as the gut-brain axis (6–8). Chronic stress signaling from your brain can lead to imbalances in the bacteria in your gut, as well as increased inflammation and dysfunction of gut tissues, which can promote gastrointestinal diseases like irritable bowel syndrome (5).

Gut-brain communication is a two way street though, so your gut is also able to signal to your brain (9). Many hormones and neurotransmitters that are used in your body are produced in your gut. Tryptophan, for example, is an essential amino acid that we use to make proteins and neurotransmitters. Our bodies, however, are unable to produce tryptophan, so we can only get it from foods that we eat. Eggs, cheese, and nuts, for example, are all foods that contain high levels of tryptophan (7). After we consume these foods, they are broken down by enzymes in our stomachs and filtered into the small intestine. Many microorganisms reside within the small intestine, making up what is known as the gut microbiota. The microbiota aids in the digestion of proteins like those in eggs, cheese, and nuts, producing tryptophan.



HPA Axis. Original image by Hailey Naiper.  
Created in BioRender

## The Gut-Brain Axis and the Gut Microbiota

Gut-produced tryptophan is then either shuttled into the bloodstream or used to make other molecules, such as melatonin and serotonin. Serotonin is an important neurotransmitter involved in mood, sleep, and eating. Low levels of serotonin are closely connected to anxiety, and drugs that increase the amount of available serotonin in the brain, such as selective serotonin reuptake inhibitors (SSRIs), are frequently used to treat anxiety (7). Cells and bacteria within the gut make up to 95% of your body's serotonin, but since serotonin is unable to cross the blood-brain barrier, the brain has to produce its own supply using tryptophan transported in the blood (9). The brain is therefore dependent on gut supplies of tryptophan which it needs to generate serotonin. If you were to stop eating tryptophan-containing foods, for example, your brain would no longer be able to produce any serotonin, which would certainly be very harmful to your mental health.

## The Relaxing Journey of Dietary Fiber

Let's follow another nutrient to get a better understanding of how the gut can influence stress in the brain specifically. We'll begin the journey with a snack: hummus with carrots and whole grain pita bread. Each of these foods contains dietary fiber, which is another important nutrient we can only get from the things we eat. Dietary

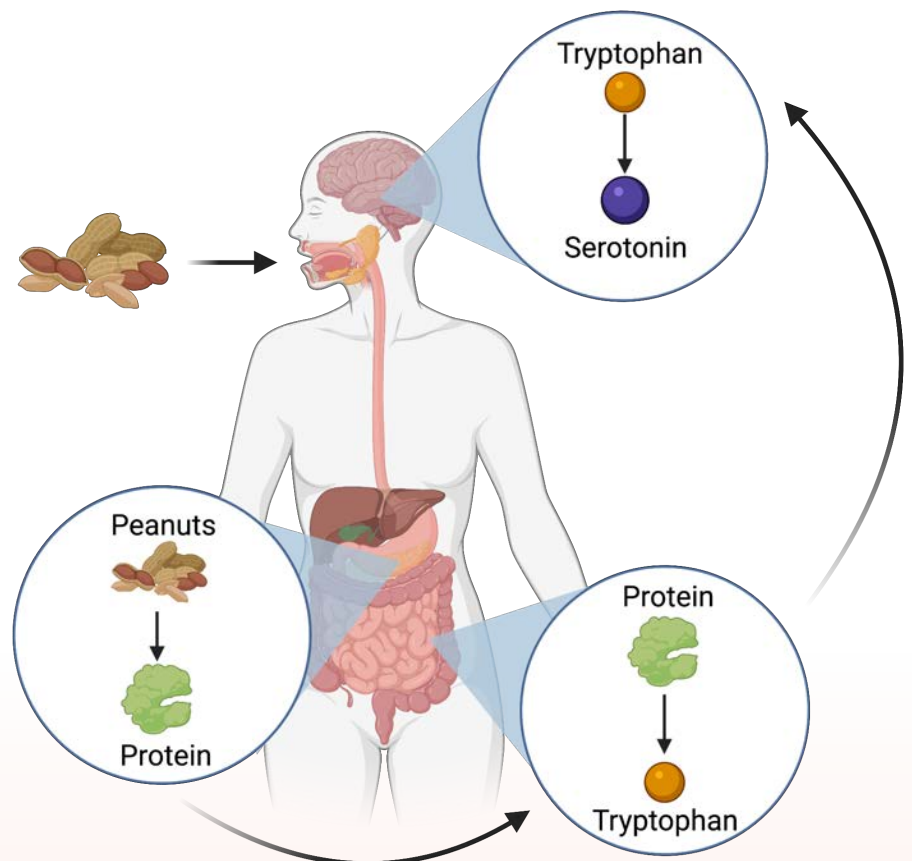
fiber is plant material that can't be digested by human stomach enzymes. You may have heard that fiber is important for regulating bowel movements, that's because it increases the size and weight of stool, but also softens stool so it's able to move smoothly through the large intestine. Dietary fiber is important for more than just poop though! It also lowers blood sugar and cholesterol, and helps prevent/combat stroke, heart disease, diabetes, and obesity (11).

Since dietary fiber can't be digested in the stomach, it continues along through the small intestine with the other non-digestible foods and some waste products. The next stop of the journey is the large intestine. Like the small intes-

tine, the large intestine is home to many different types of bacteria that feed on the pieces of food we're unable to digest.

Some of these bacteria break down dietary fiber, producing short chain fatty acids, which are relatively small molecules with many very important functions. Although we still don't understand everything they do, studies have shown that short chain fatty acids decrease inflammation, mediate brain development, and have the potential to alleviate the symptoms of many illnesses, from depression to Alzheimer's to Parkinson's disease (8, 12, 13).

From the gut, many short chain fatty acids diffuse into the bloodstream where they have



### From Peanuts to Serotonin

After you eat peanuts, the protein is extracted by enzymes in your stomach. This protein is then converted to tryptophan by bacteria in your small intestine. The tryptophan travels to your brain, where enzymes make it into serotonin.



broad effects on many organs throughout the body (8). In the nervous system, short chain fatty acids have been shown to decrease stress signaling in the HPA axis (14). These discoveries are still very new, and it's unclear how SCFAs are able to lower stress signaling. The authors of one study suggested that short chain fatty acids might activate receptors in the nervous system that send signals to decrease HPA axis activity (14). Recent studies have also demonstrated that increasing short chain fatty acids levels (which can be accomplished by eating more dietary fiber-rich foods) can decrease levels of the stress-related hormone, corticosterone (14). They can also reduce some of the other effects of chronic stress, including heart disease (16).

## Depression in the Gut

Depression is a mental health disorder that may result from a combination of gut bacteria imbalances, short chain fatty acid deficits, and prior experiences with chronic stress. Depression is characterized by feelings of hopelessness and lack of motivation. You likely know someone who suffers from depression. About 21.0 million people experienced a major depressive episode in 2020, as reported by a survey of the US population conducted by the National Institute of Mental Health in 2020 (15).

A prominent physiological feature of depression is a higher level of full-body inflammation than non-depressed individuals. Some scientists speculate that this inflammation may at least in part, be driven by the gut. Imbalances in gut bacteria in depression tend to favor inflammatory pathways. At the same time, gut dysregulation can lead to a 'leaky' gut wall, where the cells that line your intestines become less tightly

regulated, letting some molecules that would normally remain in the gut sneak into the body. Cytokines are immune system molecules that tend to increase inflammation. The combination of increased inflammatory signaling and increased gut 'leakiness' means that cytokines can infiltrate the rest of the body, increasing general levels of inflammation, particularly in the brain (8, 13).

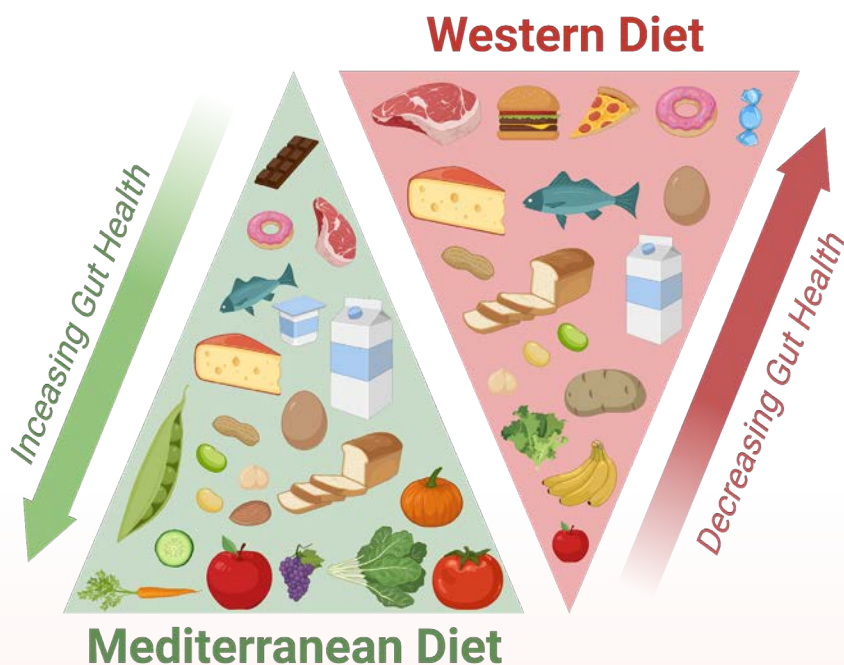
A high-fiber diet offers a possible treatment in this situation as well. Short chain fatty acids are known to be beneficial for targeting some of the effects of depression on the brain, again in ways we don't yet fully understand. They also seem to decrease the 'leakiness' of the gut, keeping cytokines and other gut-molecules from reaching other parts of the body (8, 13). Short chain fatty acids may even act to decrease the production of cytokines, limiting inflam-

mation at the source (8, 13).

## The American Health Crisis

Maintaining a healthy level of fiber in your diet is possibly an important tool for combating stress, anxiety, and depression, but adults in America still fail to consume even half of the recommended amount of dietary fiber per day. Adult women should eat about 25 grams of dietary fiber per day, while adult men should eat 38 grams (15). To put that into perspective, you'd be getting about 36 grams of dietary fiber if you ate whole grain toast with peanut butter for breakfast, veggie chili for lunch, a granola bar for a snack, and a burrito bowl with spinach and brown rice for dinner.

When we think of eating healthy, we tend to associate it with physical strength and well-



### The Mediterranean Diet vs. the Western Diet

*The Mediterranean diet is primarily made up of fruits, vegetables, and whole grains, with small amounts of meat and other animal products. The Western diet is composed primarily of high-fat and high-sugar foods as well as animal products, with little focus on fruits and vegetables.*

being. Similarly, when we think of sugary, high fat foods, we link them to negative impacts of cholesterol and diabetes. While it's true that these are also impacts of poor dietary health, it's becoming clear that the modern western diet is detrimental to our brains as well as our hearts, bridging the gap between mental and physical health.

Over the past century, food in the United States had experienced a precipitous decline in fiber content while simultaneously becoming exceedingly sugary. At least partly due to this dramatic decrease in general nutritional value, America has seen increases in obesity, diabetes, and heart disease, coupled with a hidden depression, stress and anxiety epidemic. It has taken the onset of multiple traumatic stressors including social isolation during pandemic lockdowns, a polarizing presidential election, and increased racially and politically motivated violence, for the impacts of our poor health practices to be realized. The American Psychological Association is missing the full picture when they refer to America's "mental health crisis". Separating mental health into its own bucket (as something that is not treatable in the same ways one might combat high blood pressure) is simplistic and dangerously impacts the ways we assign blame when discussing mental health, as well as the tools that we use to fix it.

As our cultural understanding of mental health stands currently, the blame for mental health disorders is placed on the person experiencing them, instead of the culture that has worked to foster poor mental health practices. Shifting our consideration of mental health towards the way we view physical health will give people experiencing mental health difficulties agency for treatment, while

simultaneously shifting the burden of responsibility off of them. That said, it's important to remember that, just as some physical diseases are genetic and therefore cannot always be cured with simple methods like changing diet, mental health illness is often complicated and driven by more nuanced factors than diet and exercise alone, although both are contributors to overall health.

## The Mediterranean Diet Fix

With this caveat in mind, the Mediterranean diet may present a solution to the health crisis brought on by the Western diet. In order to follow the Mediterranean diet, consider adding these tips to your meal planning:

Eat Frequently: fruits, vegetables, legumes, whole grains, nuts, and seafood

Eat in Moderation: poultry, eggs, and dairy products

Eat Rarely: red meat, candy, soda, processed foods, and added sugars

Focusing on consumption of fruits, vegetables, and legumes as opposed to red meat and processed sugar, the Mediterranean diet provides a framework for increased dietary fiber intake relative to the Western diet. The constant availability and relatively low cost of vegetables and beans furthermore makes the Mediterranean diet easy to integrate into your lifestyle. High in fiber and nutrients that support gut microbiome health, the Mediterranean diet therefore also supports brain health. It is furthermore low in refined sugars and saturated fats, decreasing risk of diabetes and heart disease. Example meals include:

### *Chickpea pasta with sweet potatoes, cauliflower, olive oil, and garlic*

*Preheat the oven to 425 degrees Fahrenheit. Cube the sweet potatoes and cut or break the cauliflower into small pieces. Toss the veggies with olive oil and roast until tender. Meanwhile, cook the pasta according to the directions on the package. Mince the garlic while the pasta and sweet potatoes are cooking, then combine with a few tablespoons of olive oil and salt. When the pasta and veggies are finished cooking, toss the veggies with the pasta and add the garlic/olive oil mixture. Finally, add salt and pepper to taste. Serve hot.*



*"Pasta with Chickpeas" by Pug Grill. Flickr.*



## Caprese sandwich on whole wheat bread

Cover one side of one slice of whole wheat bread with a thin spread of pesto or pesto mayonnaise. Layer sliced tomato, arugula, mozzarella cheese on top of the bread and close with another slice of whole wheat bread. Grill on the stove or panini press. Serve hot.



*"Caprese sandwich" by Dana McMahan. 2009. Flickr*



*"Planked Alaskan salmon and asparagus" by WordRidden. 2010. Flickr.*

## Salmon with brown rice and asparagus

Cook rice according to package directions. Pre-heat the oven to 450 degrees Fahrenheit. Season the salmon with salt and pepper. Roast until cooked, approximately 12-15 minutes. Coat the bottom of a frying pan and warm it on the stove. Prep the asparagus by snapping the ends off. Toss in salt, pepper, rosemary, and olive oil. Saute until soft. Serve hot.

All recipes developed by Hailey Napier.

Making simple changes, like incorporating more plant-based foods in your diet can potentially have positive effects on your health, even if you don't make a full conversion to a Mediterranean diet or similar meal planning structure. Changing just a small part of your diet has the potential to dramatically improve the balance of bacteria in your gut, resulting in broad health impacts, including increased serotonin production and decreased stress signaling. These alterations can do more than just make you feel happy, they can also help you to maintain regular sleep patterns, strong memory, low cholesterol, low blood pressure, and can lower your chances of developing obesity or diabetes. All of these factors likely work together to lower your

body's overall stress, and improve your general quality of life.

As life returns to a version of normal, it's important to remember that the effects of the COVID-19 pandemic on the collective mental health of our world will continue to impact us going forward. The chronic stress we have all experienced over the past two years has changed us in ways that will continue to affect our mental and physical health for the rest of our lives. In coming years we may see higher rates of depression and anxiety, and we need to pay attention to these mental health difficulties. We have learned to be particularly cautious about spreading disease to others, we sanitize our hands and take days off work if we get sick with the flu, and it's important to remember to be

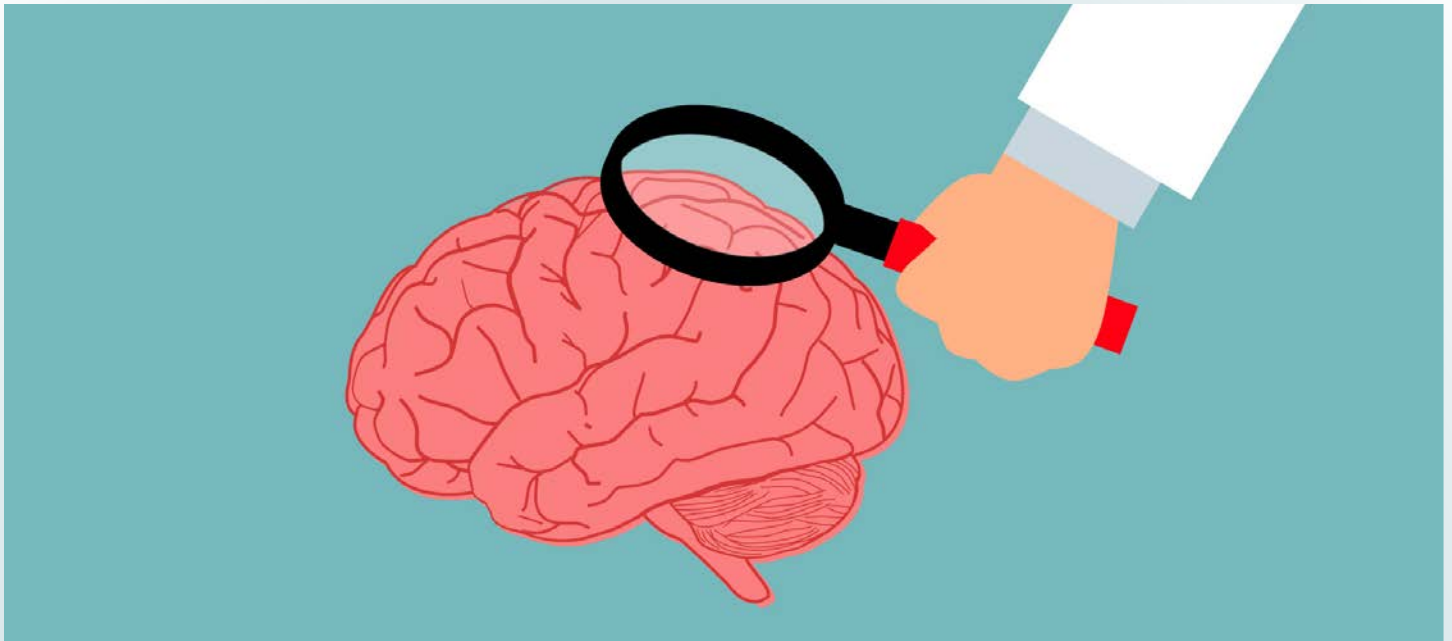
kind and understanding of mental health in the same way, both towards others and ourselves. Many people have developed tools to maintain mental health during the pandemic. Some of these include regular outdoor exercise, new hobbies, therapy, meditation, or cooking healthy meals. It's important to continue integrating these tools after we return to a more normal life in order to continue caring for ourselves in the aftermath of a chronically stressful event.

*If you or a loved one are experiencing stress, anxiety, or depression, seek professional help. The National Suicide Prevention Hotline is 800-273-8255 if you find yourself in immediate distress.*



*"Brain for everybody" by Ars Electronica. 2013. Flickr.*





## References

1. American Psychological Association, "Stress in America™ 2020: A National Mental Health Crisis" (2020), (available at <https://www.apa.org/news/press/releases/stress/2020/sia-mental-health-crisis.pdf>).
2. Anxiety and Depression, Facts & Statistics. Anxiety Depress. Assoc. Am. ADAA (2020), (available at <https://adaa.org/understanding-anxiety/facts-statistics>).
3. J. P. Herman, J. M. McKlveen, S. Ghosal, B. Kopp, A. Wulsin, R. Makinson, J. Scheimann, B. Myers, Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. *Compr. Physiol.* 6, 603–621 (2016).
4. R. Fraser, M. C. Ingram, N. H. Anderson, C. Morrison, E. Davies, J. M. C. Connell, Cortisol Effects on Body Mass, Blood Pressure, and Cholesterol in the General Population. *Hypertension.* 33, 1364–1368 (1999).
5. G. Zheng, G. Victor Fon, W. Meixner, A. Creekmore, Y. Zong, M. K. Dame, J. Colacino, P. H. Dedhia, S. Hong, J. W. Wiley, Chronic stress and intestinal barrier dysfunction: Glucocorticoid receptor and transcription repressor HES1 regulate tight junction protein Claudin-1 promoter. *Sci. Rep.* 7, 4502 (2017).
6. M. Naveed, Q.-G. Zhou, C. Xu, A. Taleb, F. Meng, B. Ahmed, Y. Zhang, K. Fukunaga, F. Han, Gut-brain axis: A matter of concern in neuropsychiatric disorders...! *Prog. Neuropsychopharmacol. Biol. Psychiatry.* 104, 110051 (2021).
7. S. M. O'Mahony, G. Clarke, Y. E. Borre, T. G. Dinan, J. F. Cryan, Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. *Behav. Brain Res.* 277, 32–48 (2015).
8. Y. P. Silva, A. Bernardi, R. L. Frozza, The Role of Short-Chain Fatty Acids From Gut Microbiota in Gut-Brain Communication. *Front. Endocrinol.* 11, 25 (2020).
9. J. Appleton, The Gut-Brain Axis: Influence of Microbiota on Mood and Mental Health. *Integr. Med. Clin. J.* 17, 28–32 (2018).
10. C. S. Reigstad, C. E. Salmonsén, J. F. R. Iii, J. H. Szurszewski, D. R. Linden, J. L. Sonnenburg, G. Farrugia, P. C. Kashyap, Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. *FASEB J.* 29, 1395–1403 (2015).
11. J. W. Anderson, P. Baird, R. H. Davis Jr, S. Ferreri, M. Knudtson, A. Koraym, V. Waters, C. L. Williams, Health benefits of dietary fiber. *Nutr. Rev.* 67, 188–205 (2009).
12. Y. Hou, X. Li, C. Liu, M. Zhang, X. Zhang, S. Ge, L. Zhao, Neuroprotective effects of short-chain fatty acids in MPTP induced mice model of Parkinson's disease. *Exp. Gerontol.* 150, 111376 (2021).
13. S. Sivaprakasam, P. D. Prasad, N. Singh, Benefits of Short-chain fatty acids and their receptors in inflammation and carcinogenesis. *Pharmacol. Ther.* 164, 144–151 (2016).
14. M. van de Wouw, M. Boehme, J. M. Lyte, N. Wiley, C. Strain, O. O'Sullivan, G. Clarke, C. Stanton, T. G. Dinan, J. F. Cryan, Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain-gut axis alterations. *J. Physiol.* 596, 4923–4944 (2018).
15. Major Depression. *Natl. Inst. Ment. Health NIMH* (2021), (available at <https://www.nimh.nih.gov/health/statistics/major-depression>).
16. How to add more fiber to your diet. (n.d.). Mayo Clinic. Retrieved March 18, 2022, from <https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/fiber/art-20043983>.