

Exploring the Connections Between the Microbiome and the Brain

A conversation with Ioannis Gampierakis

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Inflammation is the body's ancestral response to threat, its first line of defense against injury and foreign pathogens. But as modern threats evolve, science is discovering how inflammation simmers under the surface, not only in leading killers such as heart disease and cancer, but also in psychological symptoms like depression and anxiety.

In this conversation, Harvard neurobiologist Ioannis Gampierakis discusses his research on the impact of inflammatory stress on depression and anxiety – a paradigm-shift understanding of the role of the gut, the microbiome, systemic inflammation, the immune system, and adult neurogenesis, and how they all contribute to brain function.

Keywords: inflammation, neurogenesis, gut-brain axis, microbiome, HPA axis, oxytocin endorphins

■ **Antigone:** *Can you tell us about your scientific background?*

Ioannis: I'm a neurobiologist. I studied systems biology and neuroscience. I am currently a post-doctoral fellow at Harvard University in the Department of Stem Cell and Regenerative Biology. I completed my master's in molecular neuroscience at the University of Athens, Department of Medicine, and my Ph.D. at the University of Crete in Greece.

My Ph.D. project focused on inflammatory stress and adult neurogenesis. I investigated the effects of intestinal inflammation on adult neurogenesis and innate immune response in the brain. Adult neurogenesis is a process where new neurons are born in specific areas in the adult brain, and I focused my research on how systemic factors regulate neurogenesis.

Adult hippocampal neurogenesis is a novel field in neuroscience that focuses on the region of the hippocampus, which is implicated in learning and memory. I was interested in how systemic factors in the blood regulate adult hippocampal neurogenesis, and how this affects behavior. During my Ph.D. studies, I formulated the idea that systemic peripheral inflammation somehow affects adult hippocampal neurogenesis, and therefore brain cognition and behavior.

It is well known from the literature that inflammatory disease, autoimmune disease, and diseases of the gut, such as Crohn's disease and ulcerative colitis, exert a negative impact on brain function. Interestingly, many clinical studies have shown that patients with irritable bowel syndrome (IBS), Crohn's disease, and ulcerative colitis also develop psychiatric disorders. It seems that gut inflamma-

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tion has debilitating effects on brain function. This field is vastly unexplored, and our goal is to study the cellular and molecular mechanisms implicated in this process.

I have been particularly interested in the gut-brain axis, a bidirectional communication network where the brain and gut communicate through three main pathways.

— **Antigone:** *In our field, we are not well versed in this subject, so I have some basic questions to ask you before we move forward.*

Aline: *We are still struggling to bring the field of psychology out of the dichotomy of having spilt off the mind from the body.*

Antigone: *Body psychotherapy and somatic psychology are the only psychological approaches that understand that the connection between the body’s systems and organs are responsible for our well-being on all levels. The gut is an organ that is not well understood. So, before we go on, it’s important to understand what the gut does, and how it affects the brain.*

We should mention that the gut is innervated by its own enteric nervous system, and also by extrinsic neurons that originate in the spinal cord and brainstem. From within the gut, the nervous system plays a significant role, not only for gut function in general, but also for integrating signals between the periphery, the gut, and the brain. There is bidirectional communication between them.

For neuroscientists who study the gut, this system includes one more variable: the microbiome, which is why we also refer to it as gut-brain-microbiota axis. The microbiome plays a significant role in communication between the gut and the brain. We found that the microbiome – and this is interesting for the behavior of the human brain – secretes many factors, including serotonin and GABA, and several other neurotransmitters that affect the gut’s nervous system as well as the brain’s. The various factors secreted by these microbes af-

fect the gut’s nervous system, and then, through the vagus nerve and circulation, these factors can reach the brain and affect its function.

Some interesting clinical studies – and there are only a few because this field is largely unexplored – show that when patients with major depression are supplemented with probiotics, they experience improvement in depressive symptomatology after four weeks. These studies suggest that the microbiome and the levels of various microbes could affect behavior. We don’t know exactly how this happens on a cellular and molecular level, but we are actively trying to find the mechanisms by which manipulating the intestinal microbiome could affect the nervous system – not only in the gut, but also in the brain.

— **Antigone:** *Before I interrupted you, you were talking about three levels of communication between the gut and the brain.*

There are three main pathways of communication. The first one is called systemic or humoral, and functions through the secreted factors (e.g. neurotransmitters) produced by the microbiome in the gut. The second is the immune pathway. There are studies showing that immune cells from the gut can translocate to the brain. The majority of the body’s immune system is located in the gut, and the immune system is somehow trained by the microbiome and the gut nervous system. The third communication pathway is the neuronal pathway, through the vagus nerve.

— **Antigone:** *I’m impressed by the fact that the immune system begins in our gut.*

Aline: *The connection between the immune system, gut, and brain seems so important.*

It is. The immune cells express receptors for neurotransmitters; immune cells communicate with neurons. There is an intense neuroimmune interaction. For example, immune cells can “read” the levels of dopamine and serotonin secreted by neurons. Neurons and immune cells communicate not

only in the gut, but also in the brain. Immune cells can affect neuronal function through secreted factors that can be “sensed” by both populations. That is really interesting, because it has been shown that in depression, for example, there is increased peripheral inflammation, and an increased percentage of immune cells are present in the brain. So, there are interactions of the adaptive and innate immune systems with the neuronal system.

— **Antigone:** *I did not think there was such a strong connection between the immune and nervous systems.*

In the central nervous system, there are innate immune cells inside the brain, which are called microglia. There are also other glia populations called astrocytes. All these cells communicate with neurons, so there is constant communication between immune and neural cells. We discovered this about 10 to 20 years ago. Now, with genetic and transcriptomic studies, we know that immune cells not only function as protectors against pathogens, viruses, etc., but also play an elegant role in how immune cells communicate with the nervous system.

— **Aline:** *I've always thought that the body is intelligent. I don't know if intelligence is the right word, but the sophistication of internal communication is astonishing. As you talk, I see that the collaborative community that is our body is awesome.*

That's true. It is amazing, but unfortunately we don't know much about it! We have to study, for example, how the immune system communicates with neurons, with microbes, and so much more. So yes, it's really fascinating!

— **Aline:** *You are describing such an intimate internal connection! The fact that the psychological field has split the psychological and biological – the cognitive and the body – is absurd. There can be no separation, yet we have gone through decades of theorizing as if there were no psychological/biological connection.*

There is a connection. If your immune system, your gut microbiome, works in balance and is functional, then it affects your behavior: it affects your mind, it affects how you think, it affects your psychology. Experimentally and clinically speaking, it is true – all the systems are interconnected, and should function properly.

— **Antigone:** *Okay, we have inflammatory stress. Can this inflammatory stress begin psychologically? So far, we have talked about how the gut affects the brain. But if, psychologically speaking, we have a stressful situation, how does this affect the gut?*

This is a really interesting question. Stress can activate a sequence of events in the brain. I don't know if you are familiar with the HPA axis (hypothalamic-pituitary-adrenal axis) – the stress axis response. When psychological or other stressors activate the HPA axis, the adrenals produce cortisol. Cortisol affects how immune cells operate and function. Subsequently, cortisol reaches the brain through the circulation, and affects neuronal function. We know that this stress system also affects the levels of neurotransmitters, including serotonin and dopamine. It decreases the levels of serotonin, and affects the microbiome in our gut.

Studies show that patients with anxiety disorder, depression, and PTSD have altered microbiomes. For example, the population of “good” bacteria is decreased, while the population of “bad” bacteria, such as *Escherichia coli* and *Protobacteria*, is increased. So, stress itself affects not only the levels of gut bacteria, but also the function of the immune system. They are all interconnected. Inflammation in the periphery can affect brain function, but daily stress can also affect how the body functions, as well as the levels of cortisol and neurotransmitters.

— **Antigone:** *Are there any studies about oxytocin and endorphins?*

That's also interesting! The gut microbiome affects the levels of oxytocin and endorphins in the brain.

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In patients with anxiety, oxytocin and endorphin levels are decreased, which could affect the microbiome and the population of several species of microbes. We don't know the mechanism, but we know that the levels of various neuropeptides are decreased. When patients with anxiety disorder are supplemented with probiotics, it appears to ameliorate their anxiety symptoms. Moreover, probiotic supplementation seems to increase oxytocin levels in mice. Overall, if you intervene in the gut microbiome, you can possibly affect the production of oxytocin, serotonin, dopamine, and other neurotransmitters.

— **Antigone:** *You are saying that there is a second level of control that is not in our brain, but in our gut. We say, “a gut feeling.” In Greek, we have this expression, “I swallowed my feelings.” It’s interesting that an intervention that goes to the gut changes our entire mood, emotion, and cognition.*

Aline: *I’m thinking of patients who have a kind of intractable anxiety, who are on antidepressants and a cocktail of medications that have no effect on their level of anxiety. You are opening a new approach to treatment that could be much more successful.*

Yes, that’s true. And there are other interesting data regarding how the gut affects the subconscious mind. For example, we know that when certain cells in the gut sense sugar, they send a signal to the brainstem. These brain regions are implicated in “subconscious” thinking, and they affect behavior on a subconscious level. So, the gut plays a significant role in sensing signals from the surrounding environment, and then signaling back to brain regions such as the amygdala and the brainstem, which are implicated in the regulation of fear and emotions. It seems that this aspect of gut function is not “connected” with the conscious parts of the brain, such as the prefrontal cortex. Therefore, the gut might play a significant role in regulating

the “subconscious” mind and thinking, which is really interesting.

— **Antigone:** *I would like to ask about aging. Is there a cutoff point when the effects of stress are not reversible? How can we help the gut in order to help our brain? Because I suppose that your work extends to degenerative disease as well.*

The question is how exactly to help the gut, how to make the gut healthy. There are many interventions, but they are still experimental. This field is in its infancy. We know that prebiotics, probiotics, and exercise play a significant role in maintaining a healthy gut. Exercise plays a significant role in communication between the gut and brain because it increases the level of a well-known trophic factor called brain-derived neurotrophic factor (BDNF), which affects the function of neurons, increases neurogenesis, and positively affects learning, memory, and cognition. Interventions like prebiotics, probiotics, and exercise can play a significant role. Antidepressants and other mood regulators also have a significant impact; however, they are not as effective. It seems that if you combine probiotics, prebiotics, antidepressants, and exercise, you can reach maximum regulation of not only the microbiome, but also of the levels of several neurotransmitters, such as serotonin, that play a significant role in depressive and anxiety disorders.

It is an interesting question, but this field is vastly unexplored. We are trying to explore it at a cellular and molecular level. We now have the technology to study these questions in mice, and given that there are developments and advances in the field of brain imaging, in the next few years we will be able to have some answers.

— **Antigone:** *Do the microbiome and all these connections affect aging?*

In my lab at the Department of Stem Cell and Regenerative Biology at Harvard University, we try to find ways to rejuvenate the aging brain. There are a few studies on how aging affects the gut-brain

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axis. With aging, we see a deterioration in immune system function. There is a term in the field of aging for this process: it is called *inflammaging*. As we age, inflammation increases, and increased inflammation affects behavior. It can accelerate neurodegeneration, like Alzheimer’s or Parkinson’s disease. Some neurodegenerative diseases seem to begin in the gut. For example, studies show that proteins that accumulate in the brain and cause Parkinson’s start in the gut, and propagate through the vagus nerve into the brainstem. From there, they spread through the brain, causing toxic effects on neurons.

In older human populations, the microbiome is tremendously affected. Why? One possible reason is that the Western world overuses antibiotics, which could alter the gut microbiome and subsequently affect the aging process by depleting populations of useful gut bacteria. For example, mice that lack a microbiome (germ-free mice) seem to age faster. The lack of microbiome affects their immune system, adult neurogenesis, and neuronal function.

What can we do to reverse the negative effects of aging? We can take care of our diet and exercise. We know that exercise plays a significant role in reducing the probability of developing Alzheimer’s and Parkinson’s disease. We were really surprised when we found that the best “medicine” for the degenerative brain is exercise. As I mentioned, exercise induces the secretion of a significant neurotrophic factor that can regulate the gut microbiome. I strongly believe that in the next few years, studies will show that specific treatment with prebiotics, probiotics in combination with exercise, and other drugs could prevent the development and progression of neurodegeneration in humans.

■ **Antigone:** *Well Ioannis, I am speechless!*

Aline: *It is sinking in that we have given the brain in our heads so much power. You are telling us*

that the enteric nervous system, or the brain in the gut, is just as powerful. It regulates our body functions, how our consciousness develops, and how we respond to problems, challenges, and anxieties. This is all regulated from the gut, and not from the brain in our heads.

Antigone: *In Greece, we have an expression: νοῦς ὑγιής ἐν σώματι ὑγιεῖ (a healthy mind in a healthy body); this means that the brain is healthy when the body is healthy. So, what the ancient Greeks believed is true!*

Aline: *I have a question about neurogenesis. In my readings, I’ve come across texts that say we don’t produce new neurons, but rather we develop better connectivity between neurons. But I hear you talking about neurogenesis.*

This has been my field of research for eight years. Adult neurogenesis is the process of the production of functional newborn neurons in the adult brain. And it’s true; they do exist, but in specific niches in the brain.

There are two niches. The first is in the region of the hippocampus. The second is in the subventricular zone of the lateral ventricles. Adult hippocampal neurogenesis is an evolutionarily conserved mechanism in which new neurons are produced, migrate, and functionally integrate in the region of the hippocampus. These newborn neurons play a significant role in learning and memory, and, more specifically, in functions such as pattern separation and cognitive flexibility. Cognitive flexibility is implicated in reverse learning, and pattern separation is how you distinguish, for example, your car in a parking lot. These are cognitive functions that play a significant role in learning and memory. If learning is affected, then it seems that memory and memory storage are also affected. If memory storage is affected, this might play a role in the development of anxiety disorders, PTSD, and other related mood disorders.

So, yes, there is adult neurogenesis, and it is part of the process called neuroplasticity, which has to do with connectivity among mature neurons. The adult neurogenesis process in humans and rodents was discovered in 2000. There are several discrepancies among research groups about the existence of neurogenesis in the adult human brain. However, seminal studies have shown the presence of neural stem cells in the human brain.

When you manipulate adult neurogenesis, either physically or pharmacologically, the mice develop learning and cognitive deficits. For example, antidepressants and exercise are known to increase adult neurogenesis and improve cognitive function. In contrast, stress decreases neurogenesis. In mice, treatment with antidepressants and probiotics, as well as exercise on a running wheel, increases adult neurogenesis and improves memory and learning.

When you increase neurogenesis, you can affect the brain's ability to learn. You somehow rewire the brain, its connectivity, and the secretion of neurotrophic factors. Exercise has unbelievable effects on brain function. It increases the secretion of neurotrophic factors and the production of newborn neurons. I believe exercise has such tremendous effects on the brain because humans evolved to walk long distances.

— **Aline:** *Essentially, our work as therapists is to help people transition out of rigid patterns into new adaptive learning so that they can grow.*

Antigone: *We are now talking about networks of neurons. When we have information, or memory, we have a network, not just a focal point. What you are saying is very important: when we try to change our learning patterns, you are telling us that we create new neuronal networks.*

It is a dynamic process. Neurons somehow like to create networks, have “mates,” and connect together. The axons and dendrites of neurons dynamically change when they are exposed to new queues, new environments, and new learning pro-

cesses. There is constant dynamic change between our neural networks. It is a complicated process, but well-described in neuroscience textbooks. The gut microbiome, systemic inflammation, and the immune system could also contribute to these dynamic network processes.

In the next few years, I believe that the field of systems biology will play a key role in finding answers to questions about how the human body operates. This is why I am interested in these network connections among different parts of our body – the immune system, gut nervous system, microbiome, and brain.

— **Aline:** *What occurs to me now is that as body-centered psychologists, we need to be in close communication with your field so that we can develop treatments that use the developments in neurobiology, and build on what you are discovering. There is an important association needed between our two fields.*

I agree with you that psychologists, neuroscientists, and biologists should collaborate to find effective treatments, because our fields are not separate from one another. Biology utilizes scientific knowledge from various scientific fields, such as physics, chemistry, and bioengineering, to better understand the complicated human body. We cannot separate its parts. The body is not a car! The human body is conscious, and that is why I believe there should be active collaboration among scientific fields.

— **Antigone:** *Ioannis, thank you so much for being with us.*

We had a great discussion. I can provide scientific literature that may be helpful. There are interesting reviews of clinical studies that discuss the effects of probiotic and prebiotic treatments in patients with depression and anxiety.

— **Antigone:** *Again, we appreciate your time. I'm sure our readers will have a host of questions about this information.*



Medical Advice Disclaimer

This interview does not provide medical advice. The information included in the above interview is for informational purposes only. No material in this interview is intended to be a substitute for professional medical advice, diagnosis, or treatment. Always seek the advice of your physician or other qualified healthcare providers with any questions you may have regarding a medical condition or treatment before undertaking a new health regimen, and never disregard professional medical advice or delay in seeking it because of something you have read in this interview.



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