Brains and Bacteria

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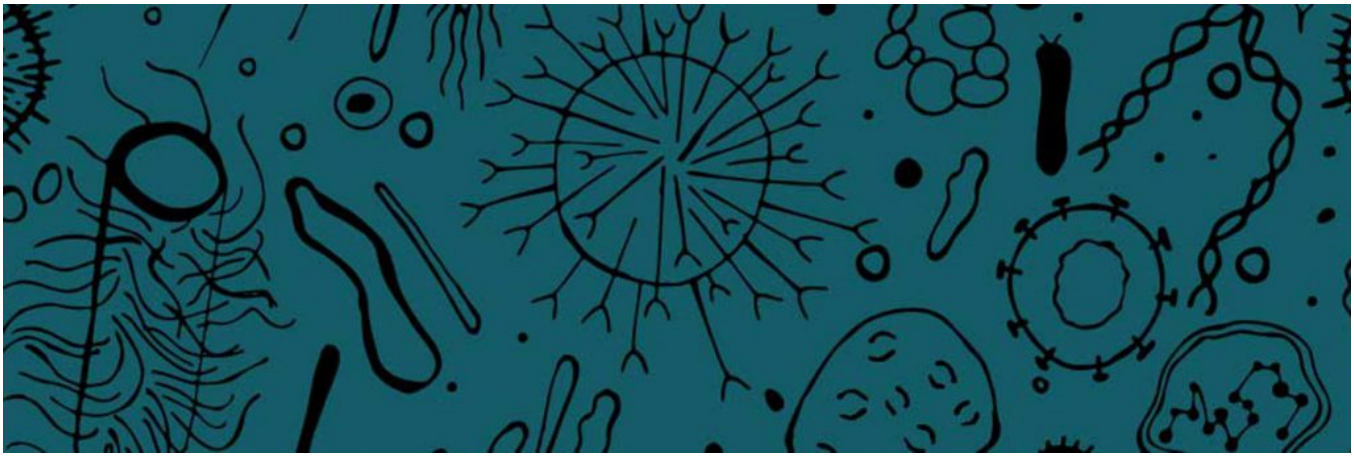

Sidebar: How Mitochondria Keep Our Brains and Minds Moving

It's tempting to tell yourself that you, or rather your brain, is the only driver behind the wheel when it comes to controlling your mind and body. According to emerging research on bacteria and our brains, however, we may actually have some pretty powerful passengers riding shotgun: the trillions of organisms that make up each of our microbiomes.

Microbiologists estimate that for every human gene in our bodies, there are hundreds, if not thousands, of microbial genes, and that there may be at least as many microbial cells in our bodies as human cells. Furthermore, while human DNA may only differ by about 0.1% from person to person, the DNA of our microbial partners can differ by roughly 50% between individuals.

From the bacteria that flourish on healthy human skin to microbiota that serve as a barrier to pathogens in adults and foster robust development in newborn children, microorganisms perform countless functions that make our lives possible. Of these, the 40,000 species of "human flora" in the gastrointestinal (GI) tract – which includes not just the stomach, but the mouth, esophagus, pancreas, liver, gallbladder, small intestine, and colon – may be among the most influential, write research associates Leigh Smith (University of California, Davis) and Emily Wissel (Emory University) in an article in *Perspectives on Psychological Science*.

Our brains and the bacteria in our guts have a bidirectional, often mutually beneficial relationship unique to each individual, the authors explain. There is a staggering amount of diversity both in the bacteria we carry and in how our bodies react to them.

“Different bacteria can have drastically different functions, and therefore significantly different effects on their host,” Wissel and Smith explain. “But differences in humans matter too. Our genes, health, and psychological states can all impact how our brains interpret the signals bacteria generate.”

In a study of 124 participants, for example, researchers found that drinking milk with probiotics (similar to the live bacteria found in yogurt) improved the mood of those who self-reported higher levels of negative affect on the Profile of Mood States (POMS). Probiotics had little effect, on the other hand, on those who reported a more positive outlook prior to the study.

Research on the gut-brain axis is still in its infancy, but collaborations between psychological scientists and microbiologists can uncover the affective, cognitive, and personality-related factors that moderate these differences, add Smith and Wissel, who study social psychology and human microbiome metagenomics, respectively.

Fecal matter transplants, which entails the transfer of microbiota from one person to another via stool, are fertile ground for such findings. While there are currently strict medical guidelines that donors must meet for their stool to qualify for transplantation, the exclusion criteria almost never include measures of mental health. “Understanding the humans behind the microbes,” Wissel and Smith write, “could allow researchers to more precisely measure what types of mental and biological traits are being transferred along with the donor’s stool.”

“Gut-brain axis research should begin systematically connecting the genomic data of the microbes back to the psychological data of the host,” Wissel and Smith argue. “Accounting for, rather than ignoring, this diversity is an essential next step for microbiome research.”

A Bacterial Balancing Act

Our relationship with microbes begins mostly at birth, said Jane A. Foster, an associate professor of psychiatry and behavioral neurosciences at McMaster University in Hamilton, Ontario Canada.

Although a relatively small number of microorganisms occupy the uterus and placenta, infants receive a kick start to the colonization and maturation of their gut microbiome from the symbiotic bacteria they encounter as they pass through the vaginal canal, Foster explained. Babies born by Cesarean section would have different bacteria following birth and may take longer to develop a diverse range of microbiota, but breastfeeding can also help transfer some of these beneficial bacteria from the mother.

In a foundational 2004 study by internal medicine researchers at Kyushu University in Japan, germ-free (GF) mice showed more extreme stress responses than did mice with normal microbiomes. GF mice had substantially higher levels of stress hormones, such as corticosterone, in their blood after being restrained in a small tube, but exhibited the same hormone levels as germ-carrying mice when exposed to the anesthetic properties of ether.

Drawing from this work, Foster and colleagues conducted a series of follow-up studies. In a study of 24 rodents, Foster observed GF and typical mice in isolation chambers and elevated mazes before collecting blood and brain tissue samples. They found that bacteria in the gut (or lack thereof) influenced the animals’ behavior, reducing the level of anxiety-like behavior and showing increased exploration.

“The gut-brain axis is all encompassing and actually is designed to put us back to balance,” Foster said at the 2015 Province of Ontario Neurodevelopmental Disorders Family Research Day, where parents of children with conditions such as autism spectrum disorder (which is often accompanied by gastrointestinal issues) gathered to identify avenues for future research.

These findings have also been extended to humans. For example, researchers at the Oppenheimer Center for Neurobiology of Stress and Resilience, led by Mind Body Research Program Director Kirsten Tillisch, have used functional magnetic resonance imaging (fMRI) to investigate the relationship between microbes in the gut and emotional processing in the brain.

In one pilot study, 40 female healthy participants submitted fecal samples for bacterial profiling before undergoing a set of three MRI scans during which they viewed positive, negative, and neutral mood-inducing images. The seven participants with a greater proportion of *Prevotella* genus bacteria in their systems exhibited decreased activity in the hippocampus while viewing negative images, and reported more negative affect afterward, than did participants with a greater number of *Bacteroides* genus bacteria. The fMRI scans also detected differences in the density of participants’ white and gray matter, with the high-*Prevotella* group demonstrating lower hippocampal volume and greater white matter with more coordinated activation, or connectivity, between areas of the brain associated with depression.

While further research is needed to expand on this proof-of-concept study, it’s possible that these patterns of microbial clustering could represent vulnerability factors for psychiatric conditions such as posttraumatic stress disorder and borderline personality disorder as well, the authors wrote.

As part of the Kyushu University study, researchers were able to reduce the exaggerated stress response in the GF mice to baseline levels by reintroducing microbes into their systems at 6 weeks of age, but they found no such effects when the microbes were introduced after the mice had fully matured. Studies from Foster’s lab showed that although “conventionalized” adult mice exposed to microorganisms developed complete microbiomes, it wasn’t enough to alter there GF-related reduced anxiety-like behaviors.

This suggests there may be a critical period in the development of the hypothalamic-pituitary-adrenal axis and the central nervous system (CNS) during which microbes can influence behavioral traits that become resistant to change in adulthood, Foster and colleagues wrote in *Communicative and Integrative Biology*.

Defending Against Disease Threat

Not all of the microorganisms that exert influence over our brains through the stomach and other organs are helpful to us, of course. One of the most extreme examples of this, according to Mats Lekander, a professor of health psychology at Stockholm University and the Karolinska Institute in Stockholm, Sweden, is a genus of fungi known for turning ants into “zombies”.

When an ant is infected with *Ophiocordyceps*, the zombie fungus releases a series of compounds tailor made to hijack the ant’s CNS. This allows the fungal colony to chemically manipulate the ant into climbing and latching onto surrounding vegetation before killing its host, at which point hyphae – branches of fungi – grow from the shell of the ant’s body to disperse new spores and repeat the cycle.

The fungus is only able to exert this behavioral control, however, when the species of *Ophiocordyceps* and the species of ant coevolved together – if the fungus doesn't "recognize" an ant's biology, it releases a different set of compounds that simply kill the ant.

The microorganisms that typically infect human hosts may not have such dramatic aims, but the struggle to secure the survival of our genes has resulted in the evolution of a range of immune defense strategies, Lekander continued. The immune system not only collects information about foreign invaders; it also signals the brain to carry out defensive behaviors in response to microbial threats.

Using fMRI, Lekander and colleagues investigated how white blood cells with receptors that act as the "eyes of the immune system" interact with bacteria and then the brain. Half of the 48 participants were injected with lipopolysaccharides (toxins from bacteria cell walls), while the control group received a placebo. Several hours later, volunteers who received these "endotoxins" reported back pain and general discomfort, among other symptoms. According to the fMRI scans, they also exhibited greater connectivity between the left anterior insula and the left midcingulate cortex, regions associated with negative emotion, pain processing, and self-reflection.

This suggests that the "interoceptive cortex" may be involved not only in processing pain, but in an increased sense of focus on the body when sick, Lekander continued. This may in turn support the energy-preserving behaviors necessary to recover from an infection.

Talking Back to Your Immune System

Communication between the immune system and the brain is made possible by cell signaling proteins called cytokines, said Robert Dantzer, a professor of symptoms research at the University of Texas MD Anderson Cancer Center. The cytokines produced by white blood cells flush out microbial invaders by causing inflammation throughout the body and, when detected by the CNS, trigger a set of behavioral and metabolic responses familiar to anyone who's felt anxiety, low mood, decreased appetite, sleepiness, and fatigue.

"A will free of all bodily contingencies is just an illusion — the illusion of temporarily healthy creatures," said Dantzer.

While these effects may seem to do little more than bring you down, they're designed to preserve the energy needed to fight microbial infections. Much like hunger drives us to eat, fear drives us to fight or run away, and curiosity drives us to explore, sickness is a motivational state that drives us to care for our sick bodies, Dantzer explained.

Illness competes with these other motivational states as well. In a study of mother mice, Dantzer and colleagues found that sick mice ate and drank less than their healthy counterparts, and laid on their sides rather than engaging in the upright, crouched nursing posture best suited to feeding their pups. When researchers took the pups away from their mothers and placed them throughout the cage, however, the mother mice overcame their fatigue to retrieve their young just as those in the control group did.

This suggests that overcoming bacterial threats takes precedence as a motivational state only until another motivation, such as maternal drive, becomes paramount to survival. If sickness is a motivation

like fear, which can result in disorders such as anxiety and PTSD, Dantzer added, then it makes sense that there would be sickness disorders. Fatigue and depression, which have been linked to the inflammation response caused by cytokines, are two such possibilities.

Just because the immune system is often giving orders to the brain doesn't mean the CNS doesn't have its say when it comes to sickness, though. Research published in *Psychological Science* suggests that just as activating the immune system can make us more sensitive to signs of disease and ill health in others, witnessing symptoms of sickness can trigger our immune systems to ramp up, as well.

In the 2010 study, APS Fellow Mark Schaller and colleagues at the University of British Columbia showed 28 participants both neutral images and slides of either people brandishing guns or displaying symptoms such as pox, skin lesions, and sneezing. Blood samples drawn before and after each slideshow were then exposed to a bacterial stimulus. Results revealed a 23% increase in production of the cytokine interleukin-6 after viewing the disease images, whereas there was no meaningful increase in the general threat condition.

These results suggest that visual signals of other people's disease can cause the immune system to respond more aggressively to microbes. Stress hormones such as cortisol and norepinephrine, which have been found to interact with the immune system, offer one potential medium for these messages. However this communication is carried out, these findings offer some much-needed assurance that while microbes may be at the wheel when it comes to some things, our brains can still get their hands on the gear shift every now and then.

Foster, Lekander, and Dantzer will further discuss the role of microorganisms in our cognitive and physiological health at "Our Minds Are Not Our Own: The Role of Guts and Germs," an Integrative Science Symposium at the upcoming International Convention of Psychological Science in Paris, March 7-9, 2019.

Leigh Smith, Emily Wissel, Jane A. Foster, Mats Lekander, and Robert Dantzer contributed to this article.

References

Benton, D., Williams, C., & Brown, A. (2007). Impact of consuming a milk drink containing a probiotic on mood and cognition. *European Journal of Clinical Nutrition, 61*, 355–361. https://doi.org/10.1038/sj.ejcn.1602546

Dantzer, R., Heijnen, C. J., Kavelaars, A., Laye, S., & Capuron, L. (2014). The neuroimmune basis of fatigue. *Trends in Neurosciences, 37*(1), 39-46. doi:10.1016/j.tins.2013.10.003

de Bekker, C. et al. (2014) Species-specific ant brain manipulation by a specialized fungal parasite. *BMC Evol. Biol.* 14, 166.

Lekander, M. et al. (2016). Intrinsic functional connectivity of insular cortex and symptoms of sickness during acute experimental inflammation. *Brain, Behavior, and Immunity, 56,* 34-41. doi:10.1016/j.bbi.2015.12.018

Neufeld, K. M., Kang, N., Bienenstock, J., & Foster, J. A. (2010). Reduced anxiety-like behavior and central neurochemical change in germ-free mice. *Neurogastroenterology & Motility, 23*(3). doi:10.1111/j.1365-2982.2010.01620.x

Neufeld, K. M., Kang, N., Bienenstock, J., & Foster, J. A. (2011). Effects of intestinal microbiota on anxiety-like behavior. *Communicative & Integrative Biology, 4*(4), 492-494. doi:10.4161/cib.15702

Mueller, N. T., Bakacs, E., Combellick, J., Grigoryan, Z., & Dominguez-Bello, M. G. (2015). The infant microbiome development: Mom matters. *Trends in Molecular Medicine, 21*(2), 109-117. doi:10.1016/j.molmed.2014.12.002

Schaller, M., Miller, G. E., Gervais, W. M., Yager, S., & Chen, E. (2010). Mere visual perception of other people's disease symptoms facilitates a more aggressive immune response. *Psychological Science, 21*(5), 649-652. doi:10.1177/0956797610368064

Smith, L. K., & Wissel, E. F. (2019). Microbes and the mind: How bacteria shape affect, neurological processes, cognition, social relationships, development, and pathology. *Perspectives on Psychological Science, 14,* 397-418. doi:10.1177/1745691618809379

Sudo, N. et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J Physiol.* 2004;558(Pt 1):263–275. doi: 10.1113/jphysiol.2004.063388.

Tillisch, K. et al (2017). Brain structure and response to emotional stimuli as related to gut microbial profiles in healthy women. *Psychosomatic Medicine, 79*(8), 905-913. doi:10.1097/psy.0000000000000493

How Mitochondria Keep Our Brains and Minds Moving

If you know a single fact about mitochondria, it's probably this: "The mitochondria are the powerhouse of the cell."

The energy produced by these ancient bacterial invaders turned organelles is essential for powering everything we do, and that includes using our brains to learn, think, and feel. In a review published in *Perspectives on Psychological Science*, scientists explore how these evolutionary tagalongs contribute to outcomes related to both mental health and mental illness.

"Given the multiple first-rate jobs that mitochondria do in the nervous system, it is hardly accidental that their malfunctioning has been associated with virtually every mental or neurological affliction on earth," wrote researchers Peter Kramer and Paola Bressan of the Università di Padova in Italy. This includes everything from Alzheimer's and Parkinson's disease, anxiety, and depression to conditions like autism and Down syndrome, the pair wrote.

Mitochondria generate energy within our body's cells in the forms of adenosine triphosphate (ATP) and heat by consuming glucose from the food we eat and oxygen from the air we breathe. Throughout this process, they also create waste products like carbon dioxide, water, and free radicals, corrosive chemicals that can degrade our cells as well as the mitochondria themselves.

Our mitochondria have a number of methods for dealing with this damage, but these measures offer only temporary relief. A certain amount of mitochondrial dysfunction over time is inevitable, Kramer and Bressan wrote, and the brain, which uses up to 25% of the body's energy, is one of the most vulnerable targets.

In the case of degenerative conditions such as Alzheimer's and Parkinson's disease, the decrease in blood flow associated with aging has been shown to limit the amount of glucose and oxygen available to the brain's mitochondria for energy production. This energy deficit can cause neurons to degenerate, disrupting activity in more energy-demanding regions of the brain associated with memory (e.g., the hippocampus in Alzheimer's) and motor planning (e.g., the substantia nigra pars compacta in Parkinson's.)

Furthermore, findings from several studies of rats have suggested that the lower concentrations of ATP in the nucleus accumbens caused by mitochondrial malfunctioning may contribute to the symptoms of depression and anxiety, expressed as "submissive" behavior in animal models. The causal nature of this connection, Kramer and Bressan wrote, was established by exposing equally anxious rats to drugs that either inhibited or enhanced mitochondrial energy production. Those whose mitochondria had been inhibited were likelier to submit to their companions, whereas rats whose mitochondria had been stimulated exhibited less anxious behavior.

"Considering all of the above, it should come as no surprise that mental disorders are apt to hinge together," Kramer and Bressan wrote. "For example, schizophrenia patients are often depressed, autism patients are often anxious, Down syndrome patients tend to develop premature dementia, and current depression predicts dementia later on."

Although the exact mechanisms through which mitochondria may contribute to such a range of disorders is still poorly understood, the authors wrote, studies suggest that the path to mitochondrial health is a familiar one: Exercise, getting enough sleep, eating a nutrient rich diet, and engaging in stress-reducing activities like yoga and meditation can all have a positive influence.

In one study, rats who swam for 10 to 30 minutes a day for 20 weeks were found to have fewer mutations in their mitochondrial DNA than those who did not. Some research suggests that eating a ketogenic diet high in fat and low in carbohydrates and sugar may improve energy production.

"From the point of view of our mitochondria, proper food is whatever contains the materials they need for their job: vitamins, minerals, enzymes, antioxidants and so on," Kramer and Bressan wrote.

It's best to get these nutrients from unprocessed natural foods like fruits, vegetables, fish, and meats, rather than supplements, they added. Antioxidant supplements in particular can upset the balance of free radicals in the body, interfering with mitochondria's ability to monitor their own health.

Kramer and Bressan said they intended to further explore how these once-invasive bacteria team up either with or against us to influence our health and behavior.

“Our hope is that future research will explore whether psychotherapy or psychiatric treatment might be assisted, and sometimes perhaps even replaced, by interventions that target the selfish entities that cohabit with us,” they said.

Reference

Kramer, P., Bressan, P. (2017). Our (mother’s) mitochondria and our mind. *Perspectives on Psychological Science*. doi: 10.1177/1745691617718356