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Our Two Interacting Brains – Etiologic Modulations of Neurodegenerative and Gastroenteric Diseases

Alain L Fymat*

Professor, International Institute of Medicine & Science, California, U.S.A

***Corresponding Author:** Alain L Fymat, Professor, International Institute of Medicine & Science, California, U.S.A.

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Running Title: Our two interacting brains

Abstract

ABSTRACT – Humans live in a symbiotic relationship with the commensal indigenous microbial communities living within them, forming an integrated ecosystem. Our two brains (brain-in-the-skull, brain-in-the-gut) communicate bi-directionally through the gut-brain pathway (or axis). Dysbiotic states of the gut microbiome can be correlated with neurodegenerative disorders, contributing to or modulating their etiology(ies) but *not* being their root cause(s). Effects on neurodegenerative and gastroenteric diseases are shown. Examples include, in particular, Parkinson's and Alzheimer's disease, effects of certain antidepressant medications (selective serotonin reuptake inhibitors) meant to cause chemical changes in the mind showing gastrointestinal side effects, irritable bowel syndrome, osteoporosis (the bone-deteriorating disease in postmenopausal subjects), and developmental disorders (such as autism). In the same manner that connections between the brain and spinal cord lesions indicate multiple sclerosis, connections between the gut and enteric nervous system lesions may explain gastroenteric diseases. Cutting-edge research is currently investigating how the second brain also mediates the body's immune response.

Keywords: *Gastroenteric diseases; Immune system; Interacting brains; Neurodegenerative diseases; Pathogens*

Abbreviations: AD: Alzheimer's Disease; BBB: Blood-Brain Barrier; CNS: Central Nervous System; ENS: Enteric Nervous System; GBA: Gut-Brain Axis; HPA: Hypothalamic-Pituitary-Adrenal Axis; IBD: Inflammatory Bowel Disorder; IBS: Irritable Bowel Syndrome; MS; Multiple Sclerosis; NDD; Neurodegenerative Disease; PD: Parkinson's Disease; PNS: Peripheral Nervous System; SSRI: Selective Serotonin Reuptake Inhibitors.

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Introduction

Evolutionarily, since times immemorial, humans have lived and continue to live in a permanent symbiotic relationship with the commensal indigenous microbial communities living within them, forming an integrated ecosystem. Of particular interest is the gut microbiome, which affects the host's physiology in health and disease. Disruptions in its balanced composition (so-called "dysbiotic states") can be correlated with neurodegenerative disorders such as Alzheimer's (AD), Parkinson's (PD) and others, contributing to or

modulating their etiology(ies) but not being their cause(s). Connecting the two brains (the brain-in-the-skull and the brain-in the gut) is the gut-brain axis (GBA) along which bidirectional communication takes place. Mediators of this communication include neurons (vagal afferent, spinal sympathetic), immune pathways, the hypothalamic-pituitary-adrenal axis (HPA), and metabolic mechanisms.

Having traveled along the above communication pathways, bacteria, viruses, fungi, and other microbes are part of a growing list of pathogens found in the brains of patients with neurodegenerative diseases (NDDs). Microbes in the brain may indicate meningitis or encephalitis, two diseases that are active infections with inflammation. For diseases like PD, AD, and other NDDs that were not thought to be infectious, finding pathogens in the brain is both surprising and concerning. Table 1 of References [1, 2] provided an extensive (though perhaps still incomplete) listing of some of the various pathogens found in the brain [3]. Shown below is an extract from this Table limited to only those pathogens that possibly originated from the gut (our "second brain") and other pathogens of unclear origin that may have a similar origin and effect:

Pathogen	Origin/cause	Effects
H1N1 virus (HSV1, 2)	Moving indirectly into the brain as it cannot penetrate the blood-brain barrier (BBB)	• Encephalitis lethargica (a possible precursor of Alzheimer's disease) • May not cause Parkinson's disease (PD) directly but may delay it. It may prime the central nervous system and, with the addition of toxin(s), lead to PD. • May cause central nervous system (CNS) immune cells (the microglia) to flow into the *substantia nigra* and the hippocampus, causing inflammation and cell death in the area
H5N1 virus (a subset of H1N1)	Manifesting as digestive tissues, then moving indirectly into the brain by infecting neurons first in the gut, then, into the vagus nerve, and subsequently into the *substantia nigra*	• Parkinsonism (symptoms: brain inflammation, tremors, other motor malfunctions) • May degenerate into Parkinson's disease
Fungi *aspergilli*	Unclear	Brain infection as cysts
Protozoa *Toxoplasma gondii*		
Parasites *Taenia solium*, pork tapeworm		
Ehrlichia	Unclear	Infects white blood cells
Babesia (relative of the malaria parasite)	Unclear	Infects red blood cells
Bartonella	Unclear	Infects blood vessels

Table 1: *Possible gut pathogens in the brain*

Source: Reference [1]

But, how do the above-listed organisms, and others, get into the brain since it is protected by the blood-brain barrier (BBB)? They do so when the barrier is disrupted and looses some of its impermeability. Other avenues for reaching directly the brain are (a) the intra-nasal and sinus access, (b) the mouth (through the lingual nerve, which runs down the jawline and into the tongue), (c) the eye (through the olfactory bulbs), and, importantly here, (4) the gut (through the vagus nerve, which travels through the neck and thorax to the stomach), all of which connect to the brain by replicating and spreading.

On The Pathogen-Brain Connection and Neurodegenerative Diseases

The pathogen-brain connection has been reported since before the mid-19th century and continues to this day. To summarize, in 2003, Heiko Braak [4] proposed that PD starts in the gut, then, moves into the brain in a process that may take place over 25-30 years over the life of the infected individual. In 2008, in ducks infected by the H5N1 virus, Smeyne et al. [5] wondered whether a connection existed between the viral infection and the extensive neurodegeneration they observed (namely, the devastation of the *substantia nigra*, often damaged in Parkinson patients, and the obliteration of all neurons).

In people infected with H5N1, the symptoms are inflammation of the brain that leads to tremors and other motor malfunctions, which is Parkinsonism, involving only a subset of the disease's symptoms. In sum, the virus induced inflammation and death into those parts of the brain that degenerate in PD. Rejoining the Braak hypothesis, Smeyne also suggested a possible pathway for the virus to spread from the body into the brain by infecting neurons first in the gut, then into the vagus nerve, and subsequently into the *substantia nigra*. Still further, he remarked that in rodents, which have a much shorter lifetime than humans, the same travel from the gut to the brain may take only a few weeks as opposed to decades in humans. Even if they cannot reach the brain, the viruses can still play a role in neurodegeneration by triggering severe inflammation.

In 2009, in mice, Smeyne also observed that H5N1 not only is not blocked by the BBB from entering the brain but it can easily infiltrate nerve cells in the brain and kill them, especially targeting the dopamine-producing neurons in the *substantia nigra*. Further, while H1N1 could not penetrate the BBB, it still caused central nervous system (CNS) immune cells (the microglia) to flow into the *substantia nigra* and the hippocampus, causing inflammation and cell death in the area. Interestingly, we have here two different flus, two different mechanisms, but the same effect! Inflammation and death are induced in that part of the brain that degenerates in PD.

It must be noted that Smeyne's experiments are not the only ones to suggest that viral infections can contribute to NDDs, and the connection is not limited to influenza. As shown in Table 1 [1, 2], several different viruses, including measles and herpes can give rise to symptoms of multiple sclerosis (MS) in rodents [6]. Also, levels of herpes virus are higher in the brains of people who died from AD than in those without the disease. Further, some HIV patients develop dementia that appears to be associated with the infection. Later, in 2017, after administering the toxin MPTP, a byproduct of a bad batch of synthetic heroin that led users to develop PD, Smeyne et al. observed that the treated mice developed signs of PD and lost 25% more neurons in the *substantia nigra* than uninfected mice treated with the toxin. He, then, concluded that whereas the H1N1 viral infection alone may not cause PD, it primed the nervous system to be sensitive to other things that would.

Notwithstanding these several instances of the link between viruses and NDDs, particularly along the GBA, Fymat concluded [7-11] that they remain correlations or contributions but *not* causes of the diseases. He further posited that these diseases are but the manifestation of a runaway autoimmune disease.

On The Enteric Nervous System-Brain Connection and Gastroenterologic Diseases

The enteric nervous system (ENS) consists of sheaths of neurons embedded in the walls of our alimentary canal. It likely evolved to perform digestion and excretion "on-site," rather than remotely from our brain. Filled with important neurotransmitters (it uses more than 30 neurotransmitters, just like the brain), it handles much more than mere digestion. About 90% of the fibers in the primary visceral nerve (the vagus) carry information from the gut to the brain and not the other way around.

The second brain contains some 100 million neurons, more than in either the spinal cord or the peripheral nervous system (PNS). This multitude of neurons enables us to "feel" the inner world of our gut and its contents. Much of this neural firepower comes to bear in the elaborate daily grind of digestion: breaking down food, absorbing nutrients, and expelling waste, requiring chemical processing, mechanical mixing, and rhythmic muscle contractions to move everything on down the line.

In connection with our brain, our second brain determines our mental state and plays key roles in certain diseases throughout the body. However, despite its far-reaching influence, the second brain is not the seat of any conscious thoughts or decision-making process. Equipped with its reflexes and senses, it can control gut behavior independently of the brain. It also informs our state-of-mind in other more obscure ways in that a big part of our emotions is probably influenced by the nerves in our gut, for example, "butterflies" in the stomach signal our physiological stress response, gastrointestinal (GI) turmoil can sour one's moods, etc.

Everyday emotional well-being may rely on messages from the brain below to the brain above. For example, electrical stimulation of the vagus nerve—a useful treatment for depression—may mimic these signals and other depression treatments that target the mind can unintentionally impact the gut. Another example is provided by our body's serotonin ~95% of which is found in the bowels. Because antidepressant medications called selective serotonin reuptake inhibitors (SSRIs) increase serotonin levels, it is little wonder that medications meant to cause chemical changes in the mind often provoke GI issues as a side effect. Irritable bowel syndrome (IBS), which arises in part from too much serotonin in our entrails, could perhaps be regarded as a "mental illness" of the second brain.

Serotonin seeping from the second brain might also play a role in counteracting several other diseases including osteoporosis (the bone-deteriorating disease in postmenopausal women) and autism (the developmental disorder often first noticed in early childhood, explaining why so many kids with autism also have GI motor abnormalities). In the same way that connections between the brain and spinal cord lesions indicate multiple sclerosis (MS), it is conjectured that connections between diseases and lesions in the gut's nervous system may be found [12, 13].

Further, since at least 70% of our immune system is aimed at the gut to expel and kill foreign invaders, the second brain may be mediating the body's immune response.

How Do Our Two Brains Communicate?

The brain in our skull - a part of our central nervous system (CNS) - and the one in our gut – a part of the intrinsic or enteric nervous system (ENS) - are in constant communication. How do they do it? Until recently, we thought the two systems communicated solely via enteroendocrine cells scattered throughout the gut's lining. When stimulated, these cells release hormones that either enter the bloodstream or activate nearby nerves to stimulate appetite. The sensory signal from a nutrient is transformed into an electrical signal that alters behavior. Endowed with microvilli (or tiny protrusions exposed to the gut) but also a foot-like extension (called a "neuropod"), enteroendocrine cells have similar physical attributes to neurons and might be wired to them. Some make physical contact with the ENS, forming synapses with nerves. Beyond the gut, the linings of our body's organs (lungs, prostate, and vagina) all possess sensor cells similar to enteroendocrine cells. The brain perceives signals from these organs and affects our reactions to them.

Charting the GBA communication pathway could someday lead us to new treatments for non-NDDs including autism, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), obesity, and even disorders once thought to be solely psychological such as anorexia, chronic stress, and post-traumatic stress disorder (PTSD).

Conclusion

Our two brains (brain above, brain below) communicate bi-directionally through the gut-brain pathway (or axis). Dysbiotic states of the gut microbiome can be correlated with neurodegenerative disorders, contributing to or modulating their etiology(ies) but not being their root cause(s). Effects on neurodegenerative and gastroenteric diseases have been shown. Examples include Parkinson's and Alzheimer's disease, effects of certain antidepressant medications (selective serotonin reuptake inhibitors) meant to cause chemical changes in the mind showing gastrointestinal side effects, irritable bowel syndrome, osteoporosis (the bone-deteriorating disease in postmenopausal subjects), and developmental disorders (such as autism). In the same manner that connections between the brain and spinal cord lesions indicate multiple sclerosis, connections between the gut and enteric nervous system lesions may explain gastroenteric diseases. Cutting-edge research is currently investigating how the second brain also mediates the body's immune response.

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