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Neurotoxic Heavy Metals in the Human Brain - IV. The Mercury - Alzheimer Connection

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Abstract

Mercury is one of the most widespread toxic environmental pollutants with multiple effects on organisms even at low concentrations. Exposure to it is associated with numerous central nervous system disorders that frequently trigger Alzheimer's disease. Alzheimer patients have higher concentrations of mercury in their blood and brain tissue. Many concerning elements involve the interactions in neuronal degeneration, apoptosis, autophagy, oxidative stress, mitochondrial malfunctions, gastrointestinal microflora, infertility, and alteration of gene expression. In this article, the sources of exposure to mercury will be visited and the corresponding toxicological effects described. The implications of mercury poisoning in Alzheimer's will be analyzed and the mechanisms of action of this metal in the brain will be presented. Further, the link between mercury exposure and Alzheimer's disease will be elucidated. In addition, our two interacting brains (brain under the skull and brain in the gut) and gut microbiota will be described as a modulator of mercury neurotoxicity. Still further, protective compounds against mercury-induced neurotoxicity will be presented. Lastly, two sidebars will respectively review the physicochemical properties of mercury and our two brains' etiologic modulations of neurodegenerative diseases.

Abbreviations

AD: Alzheimer's disease; Apo: Apolipoprotein; APP: Amyloid precursor protein; BBB: Blood-brain barrier; CNS: Central nervous system; ENS: Enteric Nervous System; FDA: (U.S.) Food & Drug Administration; GBA: Gut-brain axis; GI: Gastrointestinal; HPA: Hypothalamic-Pituitary-Adrenal Axis; JAMA: Journal of the American Medical Association; LPS: Liposaccharides; mRNA: messenger Ribonucleic acid; MS: Multiple sclerosis; NAC: N-acetyl cysteine; NDD:

Neurodegenerative diseases; NFT: Neurofibrillary tangles; OS: Oxidative stress; PCD: Programmed cell death; PD: Parkinson's disease; PNS: Peripheral Nervous System; PTSD: Post-traumatic stress disorder; ROS: Reactive oxygen species; SSRI: Selective Serotonin Reuptake Inhibitors; WHO: World Health Organization.

Chemical elements: Al: Ag: Silver; Al: Aluminum; Br: Bromine; C: Creatine; Cs: Cesium; EtHg: Ethylmercury; Ga: Gallium; Gd: Gold; GSH: GSH: Glutathione; H2S: Hydrogen sulfide; Hg: Mercury; HgCl: Mercury chloride; Hg0: Elemental mercury; HgS: Mercury sulfide; MeHg: Methylmercury; NO: Nitric oxide; Rb: Rubidium; Se: Selenium; SH: Sulfhydril.

Drugs cited: Selective serotonin inhibitors.

Diseases mentioned: Alzheimer's disease; Anorexia; Autism; Inflammatory bowel disease; Irritable bowel syndrome; Minamata disease; Multiple sclerosis; Osteoporosis; Parkinson's disease; Post-traumatic stress disorder.

Keywords: Environment-disease interactions; Ethylmercury; Inorganic mercury; Memory impairment; Mercury poisoning; Methylmercury; Neurodegenerative diseases; Neurotoxicity; Oxidative stress; Poisoning.

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Introduction

Mercury (Hg) is one of the most widespread toxic environmental pollutants with multiple effects on organisms even at low concentrations. The World Health Organization (WHO) deemed it to be one of the top ten chemicals or groups of chemicals of public health concern. Hg exposure was associated with numerous central nervous system (CNS) disorders that frequently trigger Alzheimer's disease (AD). Patients with AD have higher concentrations of Hg in their blood and brain tissue. Many concerning elements involve the interactions between Hg and AD in neuronal degeneration, apoptosis, autophagy, oxidative stress (OS), mitochondrial malfunctions, gastrointestinal (GI) microflora, infertility, and altering gene expression.

Exposure to Hg

One notable though tragic illustration of exposure to Hg is that of Minamata City, Japan – a city internationally known for the "Minamata disease", a neurological disorder caused by Methylmercury (MeHg) ingestion from contaminated food. That ecological catastrophe was a massive Hg poisoning caused by irresponsible industrial chemical disposal in the Minamata Gulf.

The route of exposure to MeHg was through the consumption of contaminated fish and shellfish, the primary food sources of the local population. The disease symptoms include uncontrolled limb movements, impaired motor functions, impaired speech, and disturbed vision and hearing. In 2013, 128 countries signed the Minamata Convention to protect the environment and human health from anthropogenic emissions and releases of Hg and Hg compounds.

Exposure to Hg can occur from both natural and artificial sources. Natural Hg sources are volcanic activity, erosion, volatilization of the Hg present in the marine environment, forest fires, and biomass burning. Nowadays, Hg is considered one of the most toxic widespread environmental pollutants, having multiple effects on organisms even at low concentrations.

It can reach ecosystems through anthropogenic activities, including the burning of fossil fuels, Chlor-alkali industries, mining, and the use of coal and petroleum. Surprising, MeHg and Ethylmercury (EtHg) are still being used in various vaccines.

Sources of Hg exposure encompass:

• **Environmental pollution:** Sources include the burning of fossil fuels and various industrial activities.
• **Occupational exposure:** Certain professions, such as mining and some industrial fields, involve higher exposure risks.
• **Fish consumption:** MeHg accumulates in the food chain, particularly in large predatory fish. The (U.S.) Food & Drug Administration (FDA) provides advice about eating fish to manage Hg intake.
• **Dental amalgams:** These fillings contain about 50% Hg, which can release Hg vapor into the body.

Researchers have found proof of a correlation between AD and Hg exposure and shown that deceased patients who suffered from neurodegenerative diseases have higher levels of Hg in their nerve tissue than healthy people. Neurotoxic proprieties of MeHg can alter messenger ribonucleic acid (mRNA) expression, decrease mitochondrial function, increase reactive oxygen species (ROS) production, and induce apoptosis. Mitochondria is the primary site for ROS generation under neurotoxic proprieties of OS, ROS aggregation, and MeHg.

Toxicological effects of Hg exposure

Hg has toxic effects on the nervous, digestive and immune systems and in the lungs, kidneys, skin, and eyes. The route of entry can be cutaneous, digestive or by inhalation. In case of severe intoxication, it can lead to death. In mammals, Hg-induced pathogenesis of the nervous system, increases membrane permeability and neuronal protein production, leading to disruptions of metabolic functions and structures and causing loss of enzyme functions, difficulty of locomotion, reduced vision, general weakness, tremors, loss of consciousness, and ultimately death. However, the connection between increasing Hg exposure and neurodegenerative disorders is not yet fully known. In their comprehensive review, Paduraru *et al.* (2022) investigated Hg's availability and its toxicological effects, its poisoning implications in AD, the gut microbiota as a modulator of Hg neurotoxicity, and association with fertility potential. They concluded that"…Hg plays an indisputable vital part in neurotransmitter metabolism, progression of neuroinflammation, and AD evolution".

Several toxic effects of Hg ions provoke corrosive action, enzyme inhibition, and protein precipitation. Over 250 symptoms are associated with Hg exposure, complicating an accurate diagnosis. Medical diagnosis starts with a physical examination and patient history. In humans, laboratory analysis consists of blood, urine, hair analysis and, if necessary, a tissue biopsy.

Hg gets rapidly removed from the blood system, segregated and redistributed to different tissues and, in this state, a correlation between the concentration of Hg in the blood and gravity of Hg poisoning cannot be made. Once in the body, Hg immediately finds its way through the brain, ganglia, spinal cord, peripheral neurons and autonomic ganglia to which it attaches tightly. The CNS takes care of storing Hg. The transient and residual distribution of Hg in these systems can cause many symptoms in different organs. MeHg exposure creates an imbalance in redox reactions in the occipital cortex and the liver, and generates hepatic glycogen accumulation and neurodegeneration. Organic Hg can affect the cerebellum and lead to impairments such as acute psychosis and erethism, apoptosis, neuropsychological disorders, oxidative damage, neuroblastomas, and glioblastomas.

Hg poisoning implications in AD

AD mechanisms and pathways interactions

Hg, known as one of the most toxic heavy metals, is frequently believed to set in motion AD - an irreversible, progressive brain disorder, which affects

memory and cognitive function. AD is the most common cause of dementia among adults (for more information, see Fymat 2020-2025). In most people with AD, symptoms appear in the elderly. This process involves two proteins called β-amyloid (senile plaques) and tau (neurofibrillary tangles, NFT), which become toxic to the brain. It seems that abnormal tau aggregates, ultimately forming tangles inside neurons and β-amyloid, cluster into plaques, gently building up between neurons. As the level of amyloid reaches a tipping point, there is a rapid spread of tau throughout the brain. Abnormal deposits of proteins form amyloid plaques and tau tangles through the brain. Once healthy neurons stop working, they lose connections with other neurons and eventually die.

Interactions with and between these pathways are thought to be involved in neuronal degeneration, such as inflammation, malfunctioning mitochondrial mechanisms, apoptosis, autophagy and OS:

• **Apoptosis or programmed cell death (PCD):** Apoptosis is a process by which cells trigger their self-destruction in response to a particular signal; its defective development of apoptosis leads to a series of pathological conditions by intensification or reduction. Excessive apoptosis can contribute to neurodegenerative diseases (NDD) like multiple sclerosis (MS), Parkinson's disease (PD) or AD.

• **Autophagy:** Autophagy plays a decisive role in the pathological genesis of NDDs. It indicates the cellular recycling mechanism where cytoplasmic constituents get sent to lysosomes for discarding, thus supporting homeostasis at the cellular level by safeguarding cells from useless cellular residues. There are three significant varieties of autophagy: macroautophagy, microautophagy and chaperone-mediated autophagy. Persistent dysfunction of the autophagic system leads to a build-up of unprocessed degraded components and failure to process them, weakening the autophagosome surface and generating toxicity, a process noticed in AD. Analysis of brain tissue sections from human subjects with neurological decline displays the accumulation of autophagic vacuoles. Further test results revealed that AD patients have elevated autophagosome numbers in their brains.

• **Oxidative stress (OS):** OS is the process of a quantitative imbalance in the production of reactive oxygen species (ROS) and antioxidants, leading to cell damage, protein oxidation or the appearance of various diseases, such as AD or PD. ROS attack proteins, oxidizing their base structure and side groups. Experimental models suggest that OS plays a crucial role in the toxicodynamic of heavy metals, including Hg. Both in vivo and in vitro models show that Hg exposure can cause OS in the biological system with the generation of ROS, glutathione (GSH) depletion, and decreased sulfhydryl (SH) protein group. Some studies show that OS can cause apoptosis through the mitochondria-dependent and mitochondria-independent pathways.

Poisoning implications

The CNS is the main target of MeHg toxicity, reflecting its efficient transport in the brain. The brain is composed primarily of easily oxidizable lipids and a high O2 consumption rate. With no substantial antioxidant defenses, it is vulnerable to oxidative damage. A higher level of oxidation in the brain has been observed in aging, which is the most consistent risk factor for AD. Further, exposure to Hg in low concentrations induces OS, cellular cytotoxicity and an increase in β-amyloid, and is associated with NDDs such as AD in adults.

The degenerated AD brain absorbs or accumulates more easily Hg. While 3%-5% of cases likely have a genetic origin, environmental factors represent one of the fundamental promoting causes of the onset and progression of AD. Countries with a flourishing industry and energy production have the highest number

of cases of dementia due to increasing Hg emission. China has the highest number of patients with dementia (19.9% of cases) followed by the United States (8.9% of cases), India (8.7% of cases), with an estimated 57 million people living with dementia worldwide as of 2021 - a number projected to nearly triple to around 139–153 million by 2050. An increase in the number of cases of patients with dementia is anticipated in industrialized countries and double or even triple it by 2050.

Numerous studies highlight the role of Hg as an extensive factor in the pathological effects of AD. Patients with AD have a higher Hg level of Hg blood concentration in cerebral tissue; the level may be twice as high as that of depressed patients and patients without psychiatric disorders. Chronic exposure to Hg can get misdiagnosed as AD because of the symptoms that include personality changes and memory loss in aged people. Nonetheless, meta-studies sustain a potential connection linking Hg and AD.

Mechanisms of Hg action in the brain

Studies have indicated that Aβ accumulation in the brain is a hallmark of AD pathology. Hg exposure disrupts γ-secretase activity and leads to an increase in Aβ levels and OS through free radical production, which mediates Aβ toxicity. In the brain and in vitro, the activity of the kinase creatine (C) protein is reduced by Hg in a concentration-dependent manner. Hg levels may be responsible for the α-secretase activity by protein kinase reduction, leading to increased Aβ formation due to activation of the α-secretase pathways by kinase C protein.

An additional pathological feature of AD is the presence of NFTs and their elements, consisting mainly of hyperphosphorylated tau. The phosphorylation state of the tau protein can be significantly affected by Aβ and OS. OS can cause cell death via both pathways, mitochondria-dependent and mitochondria-independent, primarily by accumulated, produced and impaired functionality in the mitochondria.

Hg reaches the motor cortex and accumulates in deposits, increasing nitric oxide (NO) generation, promoting lipid peroxidation and disrupting membrane lipids. These facts lead to an apoptosis process that kills glia and neurons. Therefore, Hg toxicity can (i) cause OS, (ii) increase amyloid beta precursor protein (APP) expression on neuron and amyloidogenic pathways, (iii) suppress kinase C, and (iv) stimulate tau hyperphosphorylation.

Link between Hg exposure and Alzheimer's disease

Along with other heavy metals (see Articles 1-3 in this series), Hg is an instrumental cofactor for AD. Various tests have confirmed its role in neurotransmitter metabolism in addition to the progression of neuroinflammation, although other factors may also lead to the development of AD in distinct disease forms. Clinical trials have also linked high Hg concentrations in nervous tissue and blood of patients with AD. These several findings and others justify further investigation to understand Hg's underlying neurotoxicological mechanisms.

While the link between Hg exposure and AD remains controversial, research suggests that Hg may be a contributing risk factor or cofactor in the disease's development and progression. Studies show that Hg exposure can induce many of the pathological changes observed in AD at a cellular and molecular level, though direct causation in humans remains unproven.

The key evidence and research findings include:

• **Pathological mimicry:** In vitro and animal studies demonstrate that Hg exposure can replicate key hallmarks of AD pathology, including the increased formation of amyloid beta-protein (plaques),

hyperphosphorylation of tau-protein (neurofibrillary tangles, NFTs), and the generation of oxidative stress (OS).

• **Hg levels in patients:** Some autopsy studies have found higher Hg concentrations in the brain tissues of deceased AD patients compared to controls. However, other studies have reported inconsistent or no significant differences in Hg levels in the blood, urine, or brain tissue.

• **Neurological effects:** Memory loss, cognitive decline, and personality changes are symptoms of both Hg toxicity and AD, which can lead to potential misdiagnosis. Occupational exposure studies have found significant memory deficits and other cognitive impairments in workers exposed to Hg.

• **Mechanisms of toxicity:** Hg's high affinity for sulfhydryl groups in proteins and its interaction with selenium (Se) can disrupt vital enzyme functions, antioxidant defenses such as glutathione (GSH), and mitochondrial function, all of which are implicated in AD pathology.

• **Genetic susceptibility:** Genetic factors, such as the apolipoprotein E4 (ApoE4) allele, which increases AD risk, may also reduce the body's ability to bind and detoxify Hg, potentially increasing vulnerability to its toxic effects.

• **Seafood consumption:** One large cross-sectional study published in the Journal of the American Medical Association (JAMA) found that while moderate seafood consumption (a primary source of MeHg exposure) was associated with higher brain Hg levels, it was also correlated with less AD neuropathology (possibly due to the protective effects of omega-3 fatty acids or Se found in fish). This suggests the relationship is complex.

• **Detoxification:** Individual case reports have documented significant cognitive improvement in patients diagnosed with AD following Hg detoxification protocols and diet changes (e.g., eliminating high fish Hg consumption), though larger clinical trials are needed to confirm these findings.

Our two interacting brains and gut microbiota as a modulator of Hg neurotoxicity

Commensal enteric microorganisms ensure the host's eubiosis and prevent impairment of the intestinal barrier. Their dysfunction causes a leaky gut marked by elevated circulating lipopolysaccharides (LPS) that cross the blood-brain barrier (BBB). Consequently, the brain returns signals through which the immune system is activated and subsequently triggers a pro-inflammatory cascade of cytokines.

MeHg provokes pronounced alterations in the metabolism of various model organisms because it binds covalently to the cysteine residues and inhibits the growth of Lactobacillus. Studies carried out in vitro and in vivo led to intriguing findings. Those in vitro revealed that incubation of MeHg with experimental models or human stool results in the production of Hg0. In vivo protocols affirmed the significance of bacterial demethylation. This process plays a fundamental role in the successful removal of Hg.

Etiologic modulations of neurodegenerative diseases

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 (GBA). 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 PD and AD, effects of certain antidepressant medications (selective serotonin reuptake inhibitors, SSRI) meant to cause chemical changes in the mind showing gastrointestinal side effects, irritable bowel syndrome (IBS), osteoporosis (a 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 MS, 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. (For further details, refer to Sidebar 2.)

Protective compounds against Hg-induced neurotoxicity

Presently, knowledge about available treatments and products that can protect or mitigate the effects in Hg-exposed individuals is insufficient, although we understand that Hg exposure can affect brain development and function.

Lately, several studies have established that natural products with antioxidant and free radical scavenging properties can ameliorate or protect against the brain effects induced by diverse forms of Hg (Table 1).

Chemically synthesized or natural compound	Hg Type	Experimental Model	Results	Reference
***Celosia argentea* and vitamin E**	$HgCl_2$	Rats	Protected against the Hg-induced gross, oxidative, cerebral and cerebellar damage	[161]
Launaea taraxacifolia	$HgCl_2$	Rats	Mitigated the Hg-induced behavioural changes and alteration of the microanatomy of cerebral cortex, hippocampus and cerebellum	[162]
***Citrullus lanatus* seed extract and Vitamin E**	$HgCl_2$	Rats	Protected against the Hg-induced degeneration of frontal cerebral cortical neurons	[163]
Curcumin	$HgCl_2$	Rats	Detoxification and antioxidant effects	[164]
	$HgCl_2$	Rats	Ameliorated the behavioral and biochemical alterations in the offspring	[165]
Diallyl sulphide (DAS)	$HgCl_2$	Rats	Counteracted the oxidative damage and increased the anti-inflammatory response against the Hg-induced neurotoxicity	[166]
Dendropanax morbifera Léveille	Dimethylmercury-$(CH_3)_2Hg$	Rats	Reduced the Hg levels in hippocampal homogenates and increased the activities of antioxidant enzymes	[167]
Bacopa monniera	MeHg (CH_3Hg)	Rats	Protected against the Hg-induced OS	[168]
Grape Seed Proanthocyanidin Extracts	CH_3Hg	Rats	Counteracted the oxidative damage	[169]
Vitamin K	CH_3Hg	Primary cultured neurons from the cerebella of rat pups	Protected the neurons against Hg cytotoxicity	[170]
Sodium selenite (Na_2SeO_3)	CH_3Hg	Rats	Modulated the autophagic and apoptotic milieu of the cells via inhibiting the ROS-mediated apoptosis	[171]
NAC	CH_3Hg	Rats	Reduced the Hg-induced toxicity in the developing rat hippocampus	[172]

Table 1: Chemically synthesized and natural compounds used to minimize Hg neurotoxicity

Several Hg toxicity experiments investigated whether curcumin is a biologically active compound. Curcumin has a prophylactic effect on Hg-induced OS parameters, such as lipid peroxidation and GSH levels, as well as the activities of superoxide dismutase (SOD) – a group of antioxidant enzymes.

Some studies found that selenium (Se) supplementation reduced Hg-induced neurotoxicity by inhibiting the mitochondrial apoptotic pathway. On the other hand, co-administration of N-Acetylcysteine (NAC) can attenuate the Hg toxicity in the perinatal brain by preventing the reduction in DNA synthesis and the marked increase in caspase-3 immunoreactivity.

Conclusions and take-aways

- Mercury (Hg) is one of the most widespread toxic environmental pollutants with multiple effects on organisms even at low concentrations. Alzheimer patients have higher Hg concentrations in their blood and brain tissue.
- Many concerning elements involve the interactions between Hg and Alzheimer′s disease (AD) in neuronal degeneration, apoptosis, autophagy, oxidative stress, mitochondrial malfunctions, gastrointestinal microflora, infertility, and altering gene expression.
- Exposure to Hg can occur from both natural and artificial sources and can reach ecosystems through anthropogenic activities.
- Current evidence points to Hg as a probable cofactor in the development of AD, exacerbating the disease process through various mechanisms like oxidative stress and protein aggregation. While a definitive causal link for the general population remains a subject of ongoing research, many experts advocate for the reduction of Hg exposure as a sensible public health measure.
- Sources of Hg exposure encompass environmental pollution, occupational exposure, fish consumption, and dental amalgams.
- Hg has toxic effects on the nervous, digestive and immune systems and the lungs, kidneys, skin, and eyes. The route of entry can be cutaneous, digestive or by inhalation. In case of severe intoxication, it can lead to death.
- Several toxic effects of Hg ions provoke corrosive action, enzyme inhibition and protein precipitation. Over 250 symptoms are associated with Hg exposure, complicating an accurate diagnosis.
- Hg gets rapidly removed from the blood system and, once in the body, it immediately finds its way through the brain, ganglia, spinal cord, peripheral neurons and autonomic ganglia to which it attaches tightly.
- Interactions with and between these pathways are thought to be involved in neuronal degeneration, such as inflammation, malfunctioning mitochondrial mechanisms, apoptosis, autophagy, and oxidative stress.
- Hg reaches the motor cortex and accumulates in deposits, increasing nitric oxide generation, promoting lipid peroxidation and disrupting membrane lipids, leading to an apoptosis process that kills glia and neurons. Therefore, Hg toxicity can cause oxidative stress, increase amyloid beta precursor protein expression on neuron and amyloidogenic pathways, suppress kinase C and stimulate tau hyperphosphorylation.
- The key links between Hg exposure and AD include pathological mimicry, Hg levels in patients, neurological effects, mechanisms of toxicity, genetic susceptibility, seafood consumption studies, and case studies of Hg detoxification.
- Protective compounds (both chemically

synthesized and natural) used to minimize Hg neurotoxicity have been charted.

- Our two brains (brain-under-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 have been shown in Parkinson's and Alzheimer's diseases.

Sidebar 1 - Physicochemical properties of Hg

Hg is classified as elemental mercury (Hg0), inorganic mercury (Hg2+), and organic mercury. It is used commercially in thermometers and, more recently, in dental fillings. Hg2+ occurs naturally in the environment in the form of salts, skin-lightening cosmetic creams, homeopathic medicines, and batteries. Organic mercury is divided into MeHg and EtHg. EtHg has been used as a fungicide, an antimicrobial, and as a preservative called thimerosal used in vaccines. MeHg is common in the environment, is highly water soluble, and accumulates at higher concentrations in the aquatic food web.

A portion of Hg0 is released from amalgams by hot liquids and chewing is unavoidably inhaled and diffused across the alveolar membranes into the lungs and may cross the BBB. Once in the brain, it transforms into its oxidized form. MeHg, mostly obtained from foods, converts into an ionized form when transported to the brain via the bloodstream.

Hg reacts immediately with intracellular molecules or structures and interferes with normal cellular function. Its high affinity for the sulfhydryl groups within antioxidants results in a decreased ability of these molecules to relieve the body of its oxidative stress.

Due to its mechanism of action, Hg intoxication has been shown to cause a large range of symptoms that include excessive irritability to stimulation, short-term memory loss, difficulty with concentration, depression, anxiety, insomnia, disrupted sleep, and peripheral nerve function. The degree of the symptoms of Hg exposure may be proportional to the level of Hg poisoning. It is known that patients exposed to higher levels of Hg in their workplace experience memory loss and decreased concentration and attention. In groups with acute exposure to Hg, individuals concurrently exhibited cognitive deficits and emotional difficulties. However, chronic low levels also have significant effects on cognitive function, memory, attention, and motor skills. Peripheral neuropathy in those with long-term Hg exposure may last even after the exposure is terminated.

Although Hg intoxication has been shown to affect cognitive dysfunction, the association between Hg and AD development is still unclear although it may play a role as a cofactor in the development of AD.

Sidebar 2 – Our two interacting brains and their etiologic modulations of neurodegenerative

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 NDDs such as AD, PD and other diseases, contributing to or modulating their etiology(ies) but not being their root 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 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 2 below provides an extensive (though perhaps still incomplete) listing of some of the various pathogens found in the brain. It has been 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

Source: Fymat (2019)

Table 2: Possible gut pathogens in the brain

But how do the above-listed organisms, and others, get into the brain since it is protected by the BBB? They do so when the barrier is disrupted and loses 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 jaw line 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, particularly in the case of PD through the devastation of the substantia nigra 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. 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. In sum, the virus induced inflammation and death into those parts of the brain that degenerate in PD. A possible pathway for the virus to spread from the body into the brain is by infecting neurons first in the gut, then into the vagus nerve, and subsequently into the substantia nigra.

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 the alimentary canal. It likely evolved to perform digestion and excretion "on-site," rather than remotely from the 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.

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 the skull - a part of the CNS - and the one in the gut – a part of the 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 like 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).

In sum: 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 in PD and AD, 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 MS, connections between the gut and the ENS 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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