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Mind Matters: Possible Links Between Gut–Microbiota with Psychiatric and Neurodegerative Disorders

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Abstract: *Numerous health conditions, including neuropsychiatric disorders like Attention Deficit/Hyperactivity Disorder (ADHD) and neurodegenerative diseases like Parkinson's Disease (PD), have been linked to the gut microbiome, a diverse community of microorganisms in the gastrointestinal tract. This review explores the gut-brain axis and how it affects the pathophysiology of Parkinson's disease and ADHD. According to recent studies, the gut microbiota can affect various disorders by influencing immune system interactions, neurotransmitter regulation, and inflammatory responses. Changes in the makeup of the gut microbiota have been connected to behavioral symptoms in ADHD, suggesting a possible relationship between neurodevelopmental processes and gut health. It is believed that gut dysbiosis plays a role in Parkinson's disease progression, with particular microbial patterns perhaps causing neuroinflammation and neuronal degeneration. This review summarizes the available data, investigates gut microbiome-targeting therapy approaches, and emphasizes the need for more study to fully understand the complex gut-brain connections and create microbiome-based treatments for PD, depression, anxiety, and ADHD.*

Key words: Gut microbiome, Attention Deficit/Hyperactivity Disorder, depression, anxiety, Parkinson's Disease

INTRODUCTION

There are 1014 bacterial species in the human gastrointestinal system (Savage, 1977). The human microbiota is thought to be the second genome of humans and carries a variety of genomes (Grice and Segre, 2012). The gut is home to more bacteria than the body's somatic cells. The term "commensal microbiota" refers to all of these bacteria. Normal physiology depends on the symbiotic relationship that these bacteria establish during the first few postnatal days. According to Nicholson *et al*. (2005), this lifetime relationship is crucial for food absorption and metabolism as well as host pathogen defense. Immunologists have been aware of this system and its importance to the development of the mucosal and systemic immune systems for a long time (Backhed *et al*. 2005, Cebra, 1999). The central nervous system (CNS) and behavior are influenced by gut bacteria, according to new research (Sudo *et al*., 2004).

Through their interactions with the host in metabolic, immunological, neurological, and endocrine pathways, gut microbiota significantly influences both health and disease. Known for its critical roles in host health, the gut microbiota behaves as an endocrine organ that affects systems outside of the gastrointestinal tract. Hormones produced by this "virtual organ" affect distant organs, such as the brain. The gut microbiota produces neurotransmitters like GABA, dopamine, and serotonin, surpassing the biochemical complexity of conventional endocrine organs due to its diverse microbial composition. Notwithstanding the difficulties in cultivating gut bacteria, improvements in research techniques have clarified their function in insulin resistance, behavior, metabolism, and hunger (Pires *et al.* 2024).

Numerous research on the gut microbiome-the collective genome of bacteria that live in the gastrointestinal tract-and illnesses have been published in recent decades. The field as a whole lacks systematic and quantitative study, despite narrative assessments of the gut microbiota and specific disorders. In order to give a comprehensive understanding and suggest future research directions, an effort has been made to summarize the current state of the gut microbiome and mental health research and offer insights on its advancements and features. The brain-gut axis is regulated in both directions by the gut microbiota, which is vital to health. By producing and altering a variety of metabolic, immunological, and neurochemical variables in the gut that eventually affect the central nervous system, microorganisms have an impact on the brain (Enry *et al*., Clarke *et al*., 2013; 2015, Morais *et al*., 2020). Consequently, the makeup of the gut microbiota is likewise influenced by brain activity (Kuwahara *et al.*, 2020, Mohajeri *et al.*, 2018). In addition to producing neuroactive substances including neurotransmitters, amino acids, and microbial metabolites like short-chain fatty acids, the gut microbiota also affects the integrity of the gut barrier(Morais *et al.*, 2020, Dalile *et al.*, 2019). These metabolites have the ability to influence local neuronal cells and afferent pathways that send signals straight to the brain, interact with the host immune system, and act on the central nervous system by controlling gene expression, epigenetics, and neuroplasticity (Dalile *et al*., 2019). Gut microbiota imbalance may play a role in the pathophysiology of neurodevelopmental disorders and mental health outcomes, as evidenced by the dynamic, two-way communication between the gut microbiota and the central nervous system that affects brain function, cognition, and behavior. The microbiota outside the gut contributes significantly to the development of two-way communication between the gut and the brain (Carabotti *et al.*, 2015). Numerous pathogenic illnesses, including neurological disorders like Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD), depression, anxiety, and autism, are linked to imbalances in the normal gut microbiota (Grasset and Burcelin, 2019). This study examines the relationship between gut microbiota and a number of mental health conditions, including PD, ADHD, depression, schizophrenia, and Alzheimer's disease. Research on the relationship between gut microbiota and illness has been booming, and this trend is predicted to continue. All things considered, there are many opportunities and challenges in this field of study.

Rogers and associates (2016) investigate the complex relationships between mental health and gut microbiome. It explores how dysbiosis, or disturbances in the gut microbiome, can affect behavior, cognition, and brain development, possibly leading to mental disorders. The study indicated that alterations in gut microbiota can result in depressive-like behaviors and other mental disorders, highlighting the two-way connection between the gut and brain axis.

According to Neufeld (2009), psychiatric disorders are influenced by the gut-brain axis, a two-way communication link between the central nervous system and the gastrointestinal tract. They draw attention to new data showing that gut flora can influence mood, anxiety, and cognitive abilities.

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Depression Anxiety and Stress-connection with gut microbiome.

Research has shown that gut bacteria play a crucial role in controlling stress reactions by interacting with the body's circadian rhythms. The gut-brain axis is a communication channel that works both ways. Through the vagus nerve, the gut receives messages from the brain and responds by communicating with the brain. Through hormones, neurotransmitters, and cytokines, the gut microbiota affects the brain. Neurotransmitters are chemicals that help brain cells (neurons) communicate with one another. There are neurons in the gut as well. Serotonin, which is crucial for mood, is one of the neurotransmitters whose levels are influenced by the gut microbiota. Ninety-five percent of the body's serotonin is made in the gut by neurons that are found in the GI tract, and by immune cells and so-called enterochromaffin cells in the gut. Nerve terminals in the digestive tract that connect to the central nervous system can be activated by gut serotonin (www.psychologytoday.com).

Hormones are also produced in the gut and have the ability to affect the brain. Gut hormone levels, including those of the mood-influencing hormone ghrelin, can be influenced by the gut microbiota. An key contributing element to anxiety is inflammation. Leaky gut syndrome, in which the intestinal barrier becomes porous, can result from dysbiosis, an imbalance in the gut microbiome. LPS (lipopolysaccharide), a molecule derived from the outer membrane of gram-negative bacteria, and peptidoglycan, a substance derived from the bacterial cell wall, are examples of bacteria and bacterial metabolites that can enter the bloodstream. The immune system reacts, causing persistent inflammation that impacts the brain as well. Crucially, anxiety can result from this inflammation. Anxiety and intestinal dysbiosis can also result from prolonged stress. The hypothalamic-pituitary-adrenal axis, or HPA, is triggered by stress and causes cortisol levels to rise. Leaky gut syndrome is brought on by that hormone, which increases the permeability of the intestinal lining. After the stressor is eliminated, cortisol levels return to normal. Nonetheless, cortisol levels stay elevated with prolonged stress. Dysregulation of the HPA axis results from prolonged stimulation. Additionally, pro-inflammatory cytokines caused by stress cause inflammation.

This study, which was published in Cell Metabolism, highlights the complex connection between the gut microbiota and the body's primary stress response mechanism, the hypothalamic-pituitary-adrenal (HPA) axis. According to the study, the loss of gut bacteria causes the HPA-axis to become hyperactive at certain times of the day. This, in combination with changes to the brain's stress and circadian response areas, causes changes in stress responsiveness throughout the day.The study also identifies some gut bacteria as important regulators of this circadian-regulated stress mechanism, such as a strain of Lactobacillus (Limosilactobacillus reuteri). A potential strain that links the normal diurnal oscillations of the microbiota with altered stress response is L. reuteri, which controls glucocorticoid secretion (stress hormones).

There is mounting evidence linking gut microbiota to extra-gastrointestinal and gastrointestinal disorders. Anxiety and depression, two mental diseases that are common in today's society, have been connected to gut inflammation and dysbiosis (Clapp *et al*., 2017). For instance, anecdotal accounts of antibiotic-related psychiatric side effects, even in people without a history of premorbid psychiatric disorders, have been around for a while (Sternbach and State, 1997). In an effort to improve therapeutic outcomes, efforts have also been made to alter the gut microbiota's composition. For instance, in the early 20th century, probiotic medicines containing Lactobacillus strains were widely advertised as a way to cure psychiatric problems or enhance mental health (Bested *et al*. 2013). Research on mice has demonstrated that modifying the gut's microbial makeup can result in behavioral changes, which suggests that the microbiome may be therapeutically manipulated.

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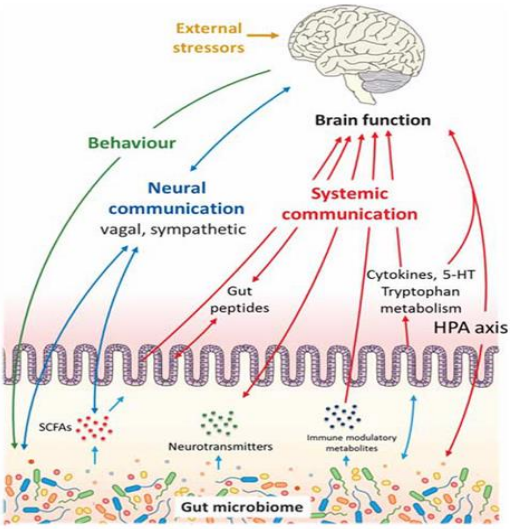
Improving gut microbiome health to reduce anxiety

Techniques to enhance the health of the gut microbiota, which could help lower anxiety Consuming nutritious foods like whole grains, fruits, and vegetables benefits the gut flora. Fiber that cannot be broken down in the stomach and travels to the intestines is what GI tract bacteria eat. Good bacteria transform this so-called prebiotic fiber into compounds called short-chain fatty acids. Short-chain fatty acids alter the amounts of neurotransmitters like glutamate and GABA in the hypothalamus of the brain. A healthy microbiome is improved by consuming less alcohol and avoiding processed foods, added sweets, and antibiotics. Using stress-reduction techniques such as yoga, meditation, deep breathing, and exercise. Practicing good quality sleep, Consumption of probiotics to improve gut microbiome health(www.psychologytoday.com).

Attention Deficit/ Hyper activity Disorder (ADHD) and Gut microbiome

The most common neurodevelopmental problem today is attention deficit hyperactivity disorder (ADHD). Its origin remains unknown after years of investigation, and diagnosis and therapy remain difficult. Changes in the makeup of the gut microbiota have also been connected to several factors that have been linked to the risk of developing ADHD and/or to various manifestations of the disorder, indicating a connection between the microbiota and the disorder (Cenit *et al*. 2017).



According to research from Henry Ford Health, a child's gut microbiota may have an impact on their risk of developing ADHD, one of the most prevalent neuropsychiatric conditions. Researchers analyzed stool samples for various bacteria in children born between 2003 and 2007 to women who received prenatal care at Henry Ford Health between the ages of one month and six months. When the kids were ten years old, they were returned. Researchers discovered that six-month-old infants with a greater variety of bacteria in their gut were more likely to acquire ADHD at the age of ten than infants with a less diverse gut. The neurodevelopmental illness known as attention-deficit/hyperactivity disorder (ADHD) is typified by a recurring pattern of impulsivity, hyperactivity, and inattentional symptoms that cause dysfunction in two or more facets of a person's life (Faraone *et al*., 2015; Franke *et al*., 2018). ADHD has a significant socioeconomic impact and is linked to declines in the social, familial, academic, and/or professional functioning of those who are affected (Thapar and Cooper, 2016). Approximately 5.3% of children have ADHD, and 50–70% of them will continue to exhibit symptoms as adults (Polanczyk *et al*., 2007). The average heritability is 74%, indicating a complex and multiple etiology(Faraone and Larsson, 2019). According to Aarts *et al*. (2017), people with ADHD had a nominally higher Bifidobacterium, which was linked to a markedly higher projected production of the dopamine precursor phenylalanine. In a similar vein, Jiang *et al.* (2018) found that treatment-naïve children with ADHD had lower levels of Dialister, Lachnoclostridium, Sutterella, and Faecalibacterium compared to healthy controls. They also found a negative correlation between the abundance of the last taxonomic group and parental reports of ADHD symptoms.

These findings were in line with a previous study by Wan *et al.* (2020) found that ADHD patients have greater levels of Odoribacter and Enterococcus and a lower relative abundance of Faecalibacterium (Wan, 2020). Additionally, Prehn-Kristensen noted that ADHD participants have higher Neisseria and lower Prevotella and Parabacteroides, among other microbial taxa with differential abundance (Prehn-Kristensen, 2018). When Wang *et al.* (2020) examined the fecal microbiota composition of children with ADHD who were not taking medication and healthy controls, they discovered that the control group had an enrichment of Lactobacillus and a Fusobacterium genus as a marker for ADHD. Lastly, a recent study by Szopinska-Tokov *et al*. (2020) found a correlation between ADHD inattention symptoms and the relative abundance of the Ruminococcaceae _UCG_004 genus. However, all of these earlier studies had small sample sizes (ranging from 14 to 51 ADHD patients), mostly examined the disorder's childhood/adolescent form, and revealed no overlap or inconsistency in their findings.

Furthermore, mice colonized by microbiota from subjects with ADHD showed altered microbial composition as well as behavioral and brain abnormalities compared to mice transplanted with the microbiota from individuals without ADHD (Tengeler, 2020). Clinical evidence also suggests that probiotic intervention in early life may improve later outcomes and reduce the risk of neuropsychiatric disorders (Partty, 2015).

These findings provide more evidence that the composition of the gut microbiota may affect behavior and brain function and contribute to the condition (Tengeler, 2020, De Theije, 2014; Sharon, 2019; Hsiao, 2013). The infusion of distinct microorganisms may be clinically beneficial in situations when the absence of specific bacterial species is associated with altered brain function. For instance, Bifidobacterium infantis therapy normalizes the immunological response, reverses behavioral abnormalities, and restores basal noradrenaline concentrations in the brainstem of rats who were denied mother contact at a young age (Desbonnet *et al*. 2010). However, exposure to B. longum normalizes anxiety-like behavior in a mouse model of gastrointestinal inflammation and infection (Bercik *et al*. 2010; Bercik, 2011). Probiotic therapies also reduce the effects of psychosocial stress in rats (Zareie et al. 2006; Ait-Belgnaoui, 2012). In healthy women, a probiotic cocktail changes the activity of brain areas that regulate the central processing of emotion and sensation. These effects are not restricted to rodent models (Tillisch, 2013). In general, these probiotic effects seem to influence behavioral changes by either modulating cytokine production (Desbonnet, 2008) or stimulating the vagus nerve (Bravo *et al*. 2012; Perez-Burgos *et al*. 2013 and Bercik *et al*. 2010).

Parkinson's disease

Over 6 million individuals worldwide suffer with Parkinson's disease (PD), which has doubled in prevalence in just ten years and is still rising quickly as the world's population ages (Collaborators, 2018). Progressive, incapacitating movement problems, gastrointestinal and autonomic dysfunction, sleep disturbances, and cognitive impairment are all consequences of Parkinson's disease (PD), a progressive degenerative disease that affects the brain, peripheral nervous system, and gastrointestinal tract. As of right now, there is no known way to prevent the disease, cure it, or reduce its progression.

In Parkinson's disease (PD), the gut microbiota has a significant effect on brain function (Bercik *et al*. 2011; Davari *et al*. 2013; Hsiao *et al*. 2013; Bruce-Keller *et al*. 2015). PD primarily affects dopaminergic neurons in the brain, resulting in decreased dopamine levels and motor impairments, including tremor, rigidity, balance issues, and loss of spontaneous movement (akinesia) (Shulman *et al*. 2011). The intracellular

accumulation of aggregated α-synuclein, which results in neuroinflammation and neuronal cell death, has long been thought to be its pathogenic characteristic (Keshavarzian et al, 2020). According to Bercik et al. (2011), Davari et al. (2013), Hsiao et al. (2013), and Bruce-Keller et al. (2015), the gut microbiota significantly affects brain function. When compared to neurologically healthy people, those with Parkinson's disease exhibit an imbalance in their gut microbiota, exhibiting variations in 30% of bacterial species, genera, and pathways (www.uab.edu).

Short chain fatty acids (SCFAs), an indicator of Parkinson's disease pathology, can penetrate the brain and have neuroprotective effects via increasing nerve growth factors, according to hypotheses published by the American Parkinson's Disease Association (APDA). PD patients' fecal samples contain fewer SCFAs than those of healthy controls, which may be a factor in the neuroprotection deficit that PD is fueled by. Gherin, a neuropeptide that increases appetite, is less abundant in those with Parkinson's disease. PD is further exacerbated by pro-inflammatory chemicals that can reach the brain, such as interferon-gamma and TNF-alpha. Neurotoxins may be able to penetrate the gut because the PD microbiota makes compounds more able to pass through the intestinal wall.

There seem to be some changes in the gut microbiomes of people with Parkinson's disease (PD) and those of people without the disease, according to a number of studies. Although the results of the studies vary, there are some commonalities among them. Certain bacterial groups, such as Lactobacillaceae and Verrucomicrobiaceae, are more prevalent in Parkinson's gut bacteria, while the Prevotellaceae family is less prevalent (APDA, 2021).

Intestinal infections can be diagnosed using two tests: One frequent bacterium that can lead to ulcers and gastritis is Helicobacter pylori. Increased motor fluctuations in Parkinson's disease have been associated with Helicobacter pylori intestinal infection. 2. The breath test for glucose hydrogen detects Abdominal pain, bloating, persistent diarrhea, and weight loss are all symptoms of small intestinal bacterial overgrowth (SIBO), a disorder where the number of bacteria in the small intestine is 100–1,000 times higher than usual. SIBO is also connected to worsening motor fluctuations in Parkinson's disease.

Recent studies have shown a link between the gut and the brain in Parkinson's disease (PD), with the gut microbiota perhaps contributing to the start of the disease. According to one study, mice with an intact microbiome had higher levels of alpha-synuclein accumulation (also referred to as Lewy bodies, the pathologic hallmark of Parkinson's disease) in their brains than mice raised in a germ-free environment with no bacteria in their guts in a mouse model of the disease that overexpressed alpha-synuclein. This lends credence to the idea that a certain gut microbiota enhances aberrant alpha-synuclein accumulation in the brain.

The balance of bacterial populations in the human gut shifts with age, leading to an increase in hazardous bacteria and a decrease in good bacteria. Such dysbiosis, whether brought on by aging or a bad diet, can result in a decrease in the body's ability to produce vital nutrients and an increase in toxins that cause inflammation, including neurodegeneration and neuroinflammation (Nobel et al. 2017 and Obrenovich, 2018). When PD patients' gut microbiomes are compared to those of healthy controls, they show a decrease in bacteria that are thought to produce short-chain fatty acids (SCFAs), like Butyricoccus (Lubomski et al., 2022, and Huang et al., 2023) and Coprococcus (Chen et al. 2021, Keshavarzian et al. 2015, and O'Donovan et al. 2020), as well as an increase in bacteria that may cause inflammation, like the genera Akkermansia

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(Keshavarzian *et al.* 2015, Barichella *et al.* 2019, Heintz-Buschart *et al.* 2018, Hill-Burns, *et al.* 2017, and Unger, *et al.* 2016).

The gut microbiota (Wallen et al. 2020) and the gastrointestinal tract (Traveagli et al. 2020, Horsager et al. 2020) are linked to Parkinson's disease (PD). The enteric nervous system (ENS) and parasympathetic nerves are two of the first and most commonly impacted tissues by alpha-synuclein pathology during Parkinson's disease (PD). As a result, gastrointestinal dysfunction—especially constipation—is a significant non-motor symptom of Parkinson's disease (PD) and frequently occurs years before motor symptoms appear. According to recent studies, intestinal bacteria communicate with the central nervous system and autonomic nervous system through a variety of channels, such as the vagal nerve and ENS. The degree of postural instability and walking difficulty was positively correlated with the relative concentration of Enterobacteriaceae.

According to these results, the gut microbiota is changed in Parkinson's disease and is linked to motor phenotype (Scheperjans *et al*., 2015). In addition to contributing to the interindividual heterogeneity of clinical characteristics, gut microbiota may be an environmental modulator of the development of Parkinson's disease. Animal models of Parkinson's disease (PD) have shown behavioral and pathophysiological characteristics linked to changes in the composition of the gut microbiota (Livia H. Morais, 2025). Wallen *et al*. (2021) discovered dysbiosis of the gut microbiome in Parkinson's disease by a meta-analysis. Three microbial clusters with altered abundances were discovered, one of which contained opportunistic pathogens. Additionally, they discovered that the host genotype at the alpha-synuclein locus influences the excess of opportunistic infections in the PD gut, and that the variations in question alter the production of alpha-synuclein.

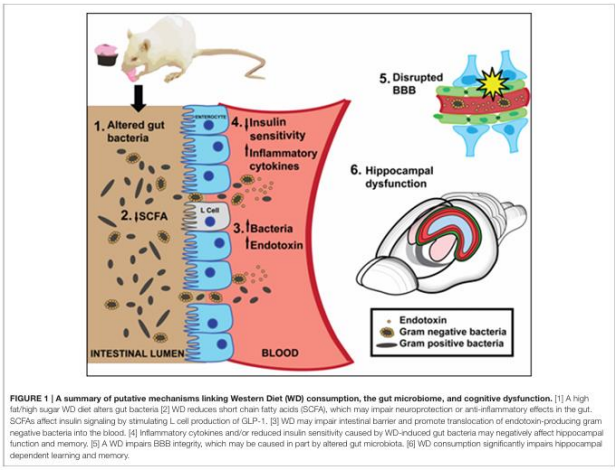

FIGURE 1 | A summary of putative mechanisms linking Western Diet (WD) consumption, the gut microbiome, and cognitive dysfunction. [1] A high fat/high sugar WD diet alters gut bacteria [2] WD reduces short chain fatty acids (SCFA), which may impair neuroprotection or anti-inflammatory effects in the gut. SCFAs affect insulin signaling by stimulating L cell production of GLP-1. [3] WD may impair intestinal barrier and promote translocation of endotoxin-producing gram negative bacteria into the blood. [4] Inflammatory cytokines and/or reduced insulin sensitivity caused by WD-induced gut bacteria may negatively affect hippocampal function and memory. [5] A WD impairs BBB integrity, which may be caused in part by altered gut microbiota. [6] WD consumption significantly impairs hippocampal dependent learning and memory.

Noble *et al*. (2017) investigate the evidence that the gut microbiota influences cognitive function through the gut-brain axis and that the proportions of commensal bacteria in the gastrointestinal tract are significantly altered by factors related to the western diet. Hippocampal neuronal abnormalities and related memory deficiencies are linked to diet-induced changes in gut microbiota that affect peripheral insulin sensitivity. In certain instances, taking particular probiotics or prebiotics can stop or even reverse some of the negative effects of eating a western diet on neuropsychological outcomes. This suggests that focusing on the microbiome could be an effective way to fight cognitive impairment linked to diet and metabolism. The potential for microbiota-targeted treatments to enhance mental health outcomes is highlighted by this study.

A sophisticated network of communication between the central nervous system and the gastrointestinal tract is known as the gut-brain axis. Numerous pathways, including neurological, endocrine, immunological, and metabolic processes, are involved in this two-way communication (Vasilev *et al*., 2024).

Research on the gut-brain axis has promise for creating microbiome-based treatments for a range of mental and neurological conditions. It could be feasible to enhance mental health and cognitive performance by modifying the gut microbiota through probiotics, dietary changes, and other methods. Probiotics and dietary changes are two examples of microbiome-based interventions that are being investigated as possible treatments for ADHD. The Mediterranean diet, which is high in nutrients that reduce inflammation, has also demonstrated potential in lowering anxiety and sadness. The ketogenic diet has demonstrated potential in reducing the neuroinflammatory symptoms of Alzheimer's disease and moderate cognitive impairment, whereas high-fiber diets support a healthy gut flora and can reduce anxiety symptoms. To completely comprehend the mechanisms underlying these interactions and to create efficient treatments, more research is required.

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