ISSN: 2306-6091

International Journal of Pharmaceuticals and Health care Research (IJPHR)

IJPHR |Vol.13 | Issue 2 | Apr - Jun -2025

www.ijphr.com

DOI : https://doi.org/10.61096/ijphr.v13.iss2.2025.244-256

Review

Involvement of the gut-brain axis in neurological disorders

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Published on: 29 May 2025

Published by:
DrSriram Publications

Abstract

The prevalence of neurological disorders such as anxiety, depression, Parkinson's disease, and Alzheimer's disease is increasing worldwide. Although the exact mechanism is not clear various factors and mechanisms are involved in their pathogenesis. One of the major factors is the diet which contributes to disease occurrence by stimulation of the gut-brain axis. This crosstalk between the gut-brain axis is not only involved in regulating gastrointestinal homeostasis but also influences behavior, motivation, and cognitive function. Therefore, there is a significant need to explore this vast area, the gut-brain axis, and its association with neurological disorders. It is a well-known fact that commonly prescribed antibiotics are responsible for dysbiosis on the other hand food like probiotics are beneficial for maintaining the diversity of the microbiome. In this review, we have compiled the reports and evidence that link the gut-brain axis to different neurological disorders as it will help identify potential novel therapeutic drug targets. The effect of both western and healthy diets has been discussed which could be beneficial for encouraging people to opt for a healthy lifestyle.

Keywords: The blood-brain barrier, Gut-Brain axis, immune system, microbiota, neurological disorders

INTRODUCTION

It has been seen that disease prevalence has increased due to changes in gut microbiota with the rise in preference towards western diet and supplements [1,2]. This "crosstalk" is communication or linkage between the brain and digestive system and has become a hot topic with a link to various diseases. Communication between the gut-brain indicates the role of signals generated by the gut microbiota in influencing the brain's activity, as well as the involvement of brain signals in altering gut microbiota and gastro-intestinal permeability [3]. Gut and

brain communication is not only limited to the nervous system but there is equal involvement of hormones and the immune system [4]. Microorganisms in the gut help modulate the body's immune response [5]. As per the previous reports, various diseases are linked to the gut-brain axis such as depression/anxiety [6], Parkinson's disease [7], and Alzheimer's disease [8] (Figure 1). Talking about the prevalence of these diseases about 1-2 person per 1000 of the population is suffering from Parkinson's disease [9], worldwide there are 50 million cases of dementia out of which 60-70% cases are of Alzheimer disease [10], worldwide 1 in 160 children is affected with Autism spectrum disorder [11], around 322 million people are living with depression and 264 million with anxiety [12]. This huge population affected with different neurological disorders makes it more prominent to explore the unclear mechanisms involved in gut-brain interaction.

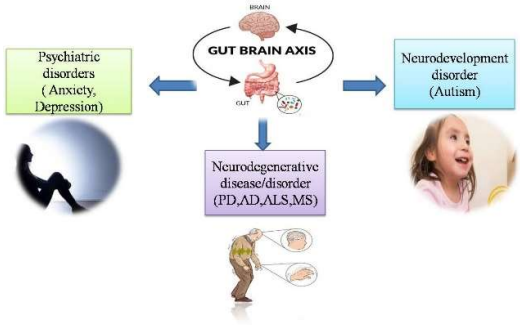

Figure 1- Various diseases associated with gut brain axis:-The gut-brain axis is responsible for the regulation of immune responses in both the intestines and the brain, with all aspects being heavily affected by the activity of intestinal microorganisms. It is no wonder then that dysregulation of gut microbiota may lead to various disturbances and diseases in the human body. This figure shows various Psychiatric disorders (anxiety and depression), neurodenerative disease (Parkinson's disease (PD), Alzheimer diease (AD). Amylotrophic lateral sclerosis (ALS), Multiple Sclerosis (MS)) as well as neurodevelopment disorder i.e Autism associated with disturbed gut brain axis.

This two-way communication amongst the central nervous system (CNS) and the enteric nervous system (ENS) is responsible for interconnecting emotional and cognitive areas of the brain with peripheral intestinal functions is called as gut-brain axis (GBA) [13],[14]. This bidirectional link includes the CNS, both brain and spinal cord, the autonomic nervous system (ANS), the hypothalamic-pituitary-adrenal (HPA) axis, and ENS [15–17] (Figure 2)

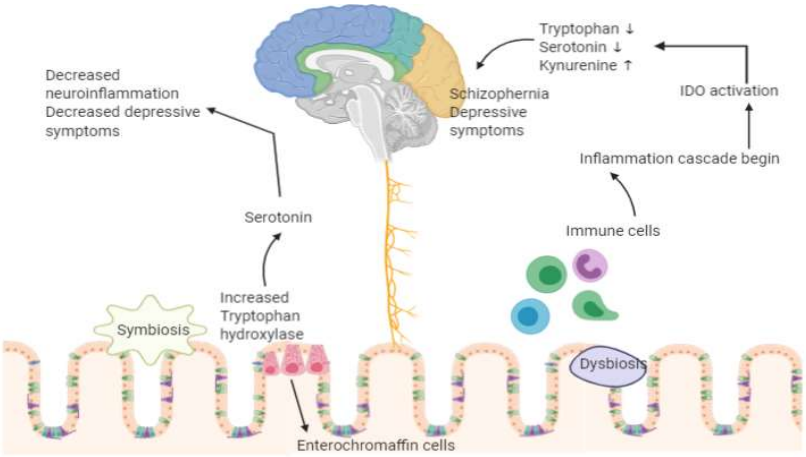

Figure 2- Involvement of central nervous system, enteric nervous system and immune system in crosstalk between gut and brain :-In cross talk between gut and brain various system are involved. When an individual is exposed to any bacterial endotoxin example lipopolysaccharide various changes occurs first is increase of immune response by microglial activation which cause increased level of pro-inflammatory cytokines which is further responsible for causing neuroinflammation and produce Parkinson' s disease (PD)symptoms, these inflammatory cytokines also disrupt integrity of Blood Brain Barrier. Also changes gut microbiota led to gut dysbiosis and stimulates ENS inflammation, increase deposition of synuclein fibrils in ENS. Another major system involved is CNS stimulation of gut microbiota stimulates vagus nerve and affects CNS and cause injury in substantia nigra

Communication between gut and brain is vice versa, the stress produced in the brain influences gut, and any disturbance in gut microbiota affects the brain [18]. There are various mechanisms responsible for the alteration of bacterial composition of the gastrointestinal (GI) tract through stress. It also causes alterations like changes in epithelial cell function, GI motility, and mucus secretion [19–21]. Stress causes the release of norepinephrine into the GI tract which further stimulates the growth of specific strains of bacteria[22–24]. Through both preclinical and clinical studies act as supportive evidence for the linkage between gut and brain [25]. This review will provide an insight into the mechanism involved in GBA and associated disorders, and factors playing role in gut-brain interaction.

CNS component involved in GBA function

Immune cells

Although CNS is frequently considered an immune-privileged site, the functional lymphatic vasculature (in the dural meningeal membrane surrounding the brain) and the permeable brain–blood barrier could serve as a gateway for signals transmission, thereby suggesting a role of immune cells in CNS during challenges [26, 27]. Not only glial cells but other immune cells including macrophages, $CD8^+$ T cells, Treg cells, and $CD4^+$ T helper cell (Th) also potentially modulates innate and adaptive immune response [28–30]. Gut microbiota is already reported to increase activation of immune signaling pathways and antigen stimulation thus promoting different subsets of $CD4^+$ T cells e.g. *Bacteroides fragilis* enhance the development of Th1 cells via polysaccharide A-dependent pathway. Another example is *clostridium* which is responsible for facilitating Treg cell differentiation.

Microglia and astrocytes

From previous reports, it is a well-known fact that microglia plays important role in the protection of the brain from different pathological conditions, by regulating immune response activation, cytokine production, and phagocytosis [23,24]. Furthermore, microglia control synaptic transmission, neuronal circuit formation, and synaptic pruning, which contributes to the development of the brain and homeostasis. Erny D, et al, conducted a study that showed that microglia in germ-free mice (without microbiota) shows variation in their morphological characteristics, gene expression. In addition to the rise in the number of premature microglia in the brain cortex, they exhibited inhibition in their maturation state.

Similarly, astrocytes also play a major role in maintaining the integrity of the CNS which includes controlling blood perfusion in the cerebrum, maintaining the stability of the blood-brain barrier, and regulating neuron transmission. Overactivation of astrocytes led to increased production of immune-inflammatory substances which ultimately causes CNS dysfunction and neurological disorders. Gut flora-mediated metabolites also cause astrocytes activation by acting on aryl hydrocarbon receptors (AHR) preclinically in animal models.

Neurogenesis

Various environmental factors affect the generation of neurons during CNS development and host-microbiota also show changes in their composition during brain development. From past studies, it is evident that gut microbiota plays important role in directing as well as modulating neurogenesis in CNS. The importance of microbiota in neurogenesis in the hippocampus and its potential link with memory depletion is derived from studies conducted in germ-free (GF) mice. The proliferation of neurons at the dorsal hippocampus is greater in GF mice than in conventional mice. However, post-weaning exposure of GF mice to microbial clones did not influence neurogenesis, suggesting that neuronal growth is stimulated by microbiota at an early stage [30].

The blood-Brain barrier (BBB)

As already known that BBB act as a selective barrier for the passage of signals from the gut to the brain. Only those compound which is lipid-soluble, have low molecular weight, and no charge can cross BBB. Intestine also has such metabolic products possessing these attributes which allow their free passage through BBB thus alter brain physiology. The study conducted by Braniste V, et al., is proof that in absence of gut microorganisms in germ-free mice disruption of BBB occurs due to decreased expression of occluding and claudin 5 which are tight junction proteins in brain epithelial. In addition, reports also suggest that sterile fetuses have greater BBB permeability than adults.

Vagus nerve

The Vagus nerve is a principal component of the parasympathetic nervous system and plays a vital role in communication between gut microbiota and CNS. Past studies suggested that vagal nerve control and modulate the response of the brain towards different pathophysiological or environmental conditions due to an increase in the release of neurotransmitters. This inappropriate vagus nerve activation further impairs the digestive process and alters gastric motility. A study has also shown macrophages and pro-inflammatory cytokines level is alleviated by abdominal surgery due to electrical vagal stimulation.

Neurotransmitters involved in gut-brain interaction

Serotonin and catecholamines are major neurotransmitters regulating the gut-brain axis and changes in their level are involved in various diseases. It has become important to understand the role of neurotransmitters in numerous brain disorders like autism as autistic patients have gut abnormalities or disturbances.

Serotonin

Serotonin is a vital signaling regulator which modulates various physiological functions such as controlling body temperature and gastric secretion. Furthermore, serotonin dysfunctioning in the gastrointestinal system impairs brain function including mood, sleep, and behavior [18]. Serotonin also modulates immune reactions through 5-hydroxytryptamine (5-HT) receptors as they are present in lymphocytes, monocytes, macrophages, and dendritic cells [20].

Catecholamine

Catecholamines are monoamines consisting of a catechol group and an amine side chain. Norepinephrine (noradrenaline), epinephrine (adrenaline), and dopamine are the three main catecholamines; norepinephrine and epinephrine are also considered as the "fight or flight" peripheral catecholamines whereas dopamine act as centrally acting catecholamine. Through a study conducted by Freestone et al., it is evident that certain bacteria also produce or respond to catecholamines for example growth of *E. coli* O157:H7 (EHEC) increases during the existence of dopamine and norepinephrine. In addition, their motility, biofilm formation, and virulence also increase in the presence of norepinephrine. Bacteria including *E. coli, Proteus Vulgaris, Serratia marcescens, Bacillus subtilis*, and *Bacillus mycoides* are known to produce dopamine and norepinephrine. Diaz Heijtz et al., showed germ-free mice have increased dopamine, serotonin, and norepinephrine not only in the gut but in the brain also [22]. It is well known that bacteria can produce as well as consume γ-aminobutyric acid (GABA) and GABA shunt is a pathway involved in consumption [74]. Germ-free mice have decreased luminal and serum GABA levels but not much change is seen at the cerebral level which makes it obvious that microbiota is involved in influencing GABA levels. All these studies show how important it is to explore the molecular mechanism by which neurotransmitters modulate the gut-brain axis and influence various brain diseases.

Neuropeptides involved in gut-brain interaction

Not only neurotransmitters but various neuropeptides are involved in bidirectional communication of gut and brain including substance P, somatostatin and corticotropin-releasing factor, calcitonin gene-related peptide, and neuropeptide Y (NPY). It is well known that a large amount of neuropeptides is produced by central as well as peripheral neurons besides endocrine cells in the gastrointestinal tract and other active endocrine organs. Gut microbiota has an interactive relationship with epithelial cells such as enteroendocrine L cells present in the distal ileum and colon; they release peptide tyrosine (PYY), peptide tyrosine on stimulation by certain nutrients and digestive products. Short-chain fatty acids (SCFAs) comprising acetate, butyrate, and propionate cause stimulation of L cells through activation of G protein-coupled receptors such as Gpr41 (also known as free fatty acid receptor 3 or FFAR3). Reolon GK et al., showed butyrate eliminate aging-related memory deficits in rat but its effect on anxiety and depression-like behavior is inconsistent. Contrary to other propionate is known to evoke autism spectrum disorder-related behavior in rats and mice. It has been seen that taking probiotics in human cause increased concentration of plasma Glucagon-like peptide-1 (GLP-1) and PYY and further decrease postprandial glucose level. This suggests that prebiotic supplementation has great therapeutic potential and a pharmaco-nutritional approach to treat intestinal dysbiosis.

Association of GBA with different neurological disorders

GBA in Depression and anxiety

The Gut-brain axis is associated with depression and anxiety as the alteration in the microbiome modulates serotonergic and GABAergic signaling systems in the CNS. Through previous studies link between microbiota and anxiety/depression is already reported using animal models. Serotonin is a major neurotransmitter involved in the regulation of mood. It plays a pivotal role in the gastrointestinal tract in various actions such as production, release, sensing, and signaling. An enormous amount of serotonin is produced in the gastrointestinal tract (GIT) by enterochromaffin cells present in the gut. Some bacteria produce distinct microbial metabolites which increase colonic and blood serotonin levels. Clinically reduced level of the serotonin precursor, tryptophan peripherally is linked with depression. Gut microbiota influences the availability of tryptophan at multiple development stages. Furthermore, the expression of toll-like receptor-4 (TLR-4) is significantly high in depressed patients, which could be related to bacterial translocation. The intestinal barrier plays important role in regulating the permeability of essential ions, nutrients, water and prevents entry of harmful substances in its lumens from entering into the bloodstream. Various specialized components, cell types, and intercellular tight junctions work together in regulating the movement of substances across the intestinal epithelium. Three major pathways including the trans-cellular pathway, the carrier-mediated pathway, and the paracellular pathway (passive

diffusion between the spaces through adjacent cells) are responsible for the transport of molecules across the intestinal barrier. The epithelial tight junction proteins (occludin, claudins, zonula occludens (ZOs), tricellulin, cingulin) seal the paracellular space between the cells and tightly restricts the transport of harmful molecules. Losing of these tight junctions leads to disruption of the intestinal barrier and promotes a leaky gut. In normal conditions, tight junction protein in epithelial cells of the gut keeps gram-negative bacteria separated from the lymphatic system and systemic circulation. However leaky gut may hinder this separation leading to overexpression of immune responses which may contribute to depression by activating TLR-4 due to translocation of lipopolysaccharide into the systemic circulation.

A study was conducted by M Lyte et al, "anxiogenic effect of subclinical bacterial infection in mice in the absence of overt immune activation" which shows that oral administration of *Campylobacter jejuni* in rats in subclinical doses led to anxiety-like behavior. Researchers by using an animal model of anxiety and depression through olfactory bulbectomy have given evidence showing that uplifted level of corticotrophin-releasing hormone (CRH), elevation in c-Fos activity, serotonin levels, and colon motility were correlated with an altered intestinal microbiome. This was due to the activation of the HPA axis [108]. A high-fat diet is also known to have an impact on anxiety and depression-like behaviors [22] (Figure 3). It was seen that administrating a high-fat diet to mice causes glutathione depletion in the blood which is an antioxidant. Another study has also linked reduced blood glutathione to anxious behavior [30].

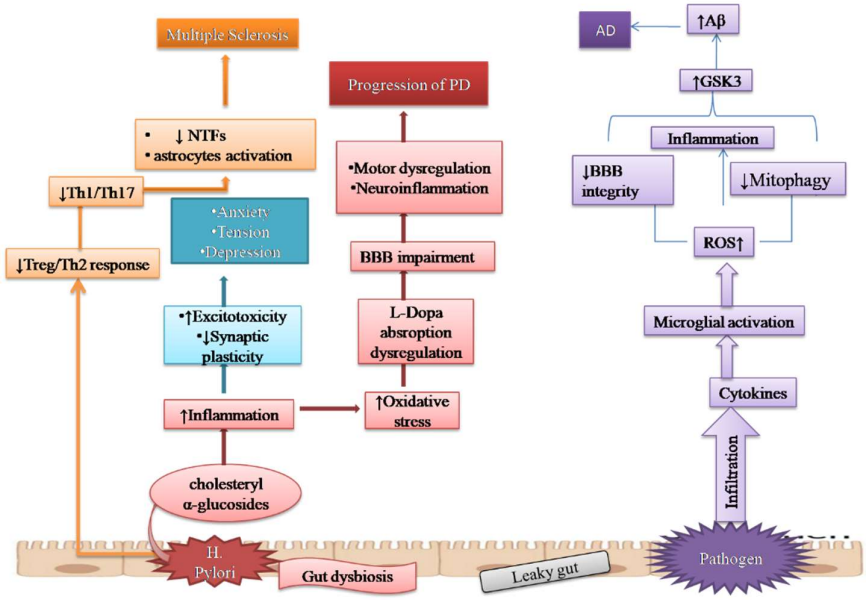

Figure 3- The association of gut brain axis with neurodegenerative disorders:- When gut comes in contact with pathogen infilteration of cytokines occurs leading to microglial activation this cause elevation of (reactive oxygen species) ROS, ROS then cause decreased integrity of Blood Brain Barrier , decreased mitophagy and increased inflammation this further led to increase Glycogen synthase kinase 3 (GSK3) in turn increase accumulation of Amyloid beta and increase disease progression of Alzheimer disease (AD). Also on H.pylori exposure cholesteryl α-glucosides present in it aggravates inflammation which further increase excitotoxicity and decreased synaptic plasticity and cause anxiety and depression, Also disruption of gut by H. Pylori increase oxidative stress further impairing blood brain barrier and L-Dopa absorption dysregulation and produce motor dysregulation , progression of PD. Another disease linked with gut is Multiple sclerosis (MS), gut dysbiosis and H. plyori decrease regulation of the T helper cell type 2 (Th2)/T regulatory cell (Treg) cell which further decrease neurotrophic factor (BDNF) and increase astrocytes activation which contribute to progression of MS.

In a study conducted by Desbonnet L et al., plasma tryptophan levels were increased when rats were given *Bifidobacteria infantis* for 14 days. As per reports fructose malabsorption and lactose malabsorption are linked to early signs of depression, especially in female patients. Fructose malabsorption results in changing GI motility and microbiota profile. Thus reducing fructose from the diet can contribute to improvement in depression. Furthermore, in comparison to Specific pathogen-free rats (SPF), GF rats produce more fecal boli. Also, they have decreased intestinal motility due to have structural and functional differences in the digestive tract. According to Prutz and Belzung, 2003 reduced intestinal motility is contradictory to the increased defecation behavior of GF rats in open field tests and thus can be attributed to an anxiety-like response to stress.

It is already reported that probiotic supplementation is responsible for improved microbial regulation in anxiety or stress-induced neuroendocrine signaling. Specifically, the bacterial strain of *Lactobacillus* and *Bifidobacterium* exert anxiolytic effect by influencing the release of GABA, 5-HT, and SCFAs, and by suppressing HPA adrenergic reaction.

From past studies, it is evident that complete disconnection of abdominal vagal afferents in rats led to a decreased anxiety-like response in the behavioral test which is commonly used preclinically in the assessment of anxiety disorders in rodents.

GBA in Alzheimer Disease

Alzheimer's is a neurodegenerative disease progressing with short-term memory loss and further leads to difficulty in speech and environment responses. It affects different parts of the brain that controls thought, memory, and language. It can drastically affect a person's ability to carry out day to day routine. In Alzheimer's, there is an accumulation of amyloid-β protein followed by the growth of phosphorylated tau (pTau) proteins into neurofibrillary tangles (NFTs). Amyloid β plaques and NFTs both hinder normal neuronal cell function by interfering with proper synaptic signaling and cause damage to neurons, eliciting cognitive decline [130]. Advancement of NFTs starts from the medial temporal lobe to other associated regions and eventually hits the cortex, followed by severe cognitive dysfunction in Alzheimer's disease (AD) patients .

Amyloid is the common term used for any aggregated, insoluble, lipoprotein-rich deposit which exhibits β-pleated sheet structures oriented to the fibrillar axis. Several bacterial strains produce and secrete extracellular protein fibers which are responsible for creating and maintaining a biofilm and help offer safety against various environmental stresses as well as regulating adherence to biotic and abiotic surfaces. Both cerebral amyloid and bacterial amyloid have similar pathogen-associated molecular pattern (PAMPs) configuration and physicochemical features, despite the fact they don't have the similarity of amino acid sequences to human Amyloid-β (1-42). However same TLR_2/TLR_1 receptor system recognizes both bacterial as well as human amyloids and activates a cascade of the release of pro-inflammatory cytokines (IL-17 and IL-22). It needs to be highlighted that in a healthy condition also man is exposed to an enormous amount of lipopolysaccharides (LPS) and amyloid proteins which are incessantly produced by the human microbiome. This becomes even more dangerous to health in aging conditions when BBB and gastrointestinal mucosa undergo structural changes and increase permeability. Both amyloid proteins and LPS strongly activate TLRs and RAGE receptors for advanced glycation end-products, and their co-activation will intensify inflammatory signaling cascade being a key factor causing prolonged chronic inflammation in AD.

The overwhelming majority of the supportive evidence from animal models link gut microbes to AD. It is reported that bacteria present in gut microbiota produce a notable quantity of amyloids and LPS which in turn modulate signaling cascades and the increasing production of proinflammatory cytokines and initiate the progression of AD (Figure 3). The presence of bacterial amyloid proteins in the gut activates the immune system further priming the immune response to endogenous production of neuronal amyloid in the brain. A study reported that *E.coli* produces curli [144] which increases neuronal alpha-synuclein (α-syn) deposition in both the gut and brain and increases expression of TLR2, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) .

GBA in Parkinson disease

Parkinson's disease (PD) stands second among common neurodegenerative disorder, it is a multicentric disease which is manifested by the deposition and aggregation of alfa-synuclein (α-syn) in the substantia nigra which gradually cause degeneration of motor function as a result of depletion of dopamine-producing brain cells. From past reports, it is evident that GBA is associated with PD which suggest that pathological process starts from the gut and proceed to the brain [21]. Enteric dopaminergic neurons are allocated in an oral aboral gradient through the GI tract. The upper part of the GI tract consists of 14% - 20% of dopaminergic neurons and 1%-6% is distributed in the lower small intestine and large bowel. Gut microbiota up-regulate inflammation both locally and systemically due to LPS produced from bacteria in the gut which enhance the production of inflammatory cytokines. Bacterial overgrowth stimulates the innate immune system and produces CNS inflammation. Evidence from previous research suggests that α-syn pathology spread to the midbrain in two ways. One is through the nasal route via the olfactory bulb to the temporal lobe and another one starts from ENS and spread towards CNS .

Direct evidence was provided by Holmqvist et al. through a study conducted on rats showing retrograde transport of alpha-synuclein from the intestinal wall to the brains. The incidence rate of PD is higher in patients with type 2 Diabetes mellitus suggesting the interaction of gut-brain such as insulin dysregulation may underlie this condition . PD patients have an elevated number of bacterial metabolite indican (a marker of dysbiosis) showing the link between dysbiosis and neurodegeneration.nFrom reports, it is evident that leaky gut is more prominent in patients suffering from PD rather than healthy control. WA Banks et al., and WA Banks et al., conducted a study that shows that gut-derived LPS is responsible for disruption of BBB and led to neuroinflammation promoting injury in substantia nigra. Despite several research and studies, there is no cure for PD. The most commonly prescribed medication in PD is levodopa however its response also fluctuates due to GI

disturbances in PD patients. This shows the importance of GBA and the need to focus more on gut food-based therapies (Figure 4). Perez- Pardo et al., from his study showed how nutritional therapies containing both phospholipids precursors as well as cofactors for phospholipid along with probiotic fibers, are beneficial in combating motor and GI abnormalities in PD patient.

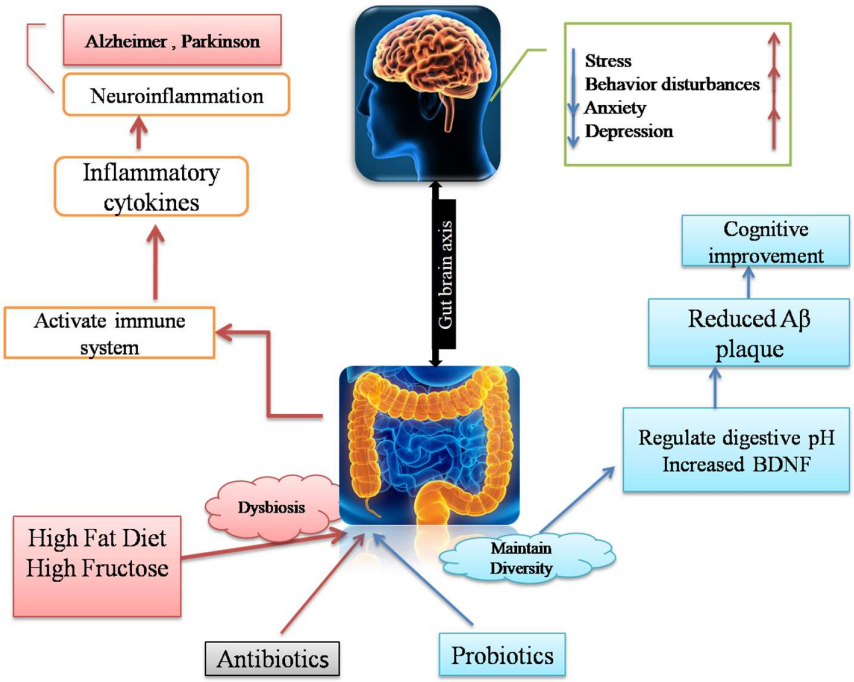

Figure 4- Dietary interventions on stimulating GBA in AD, PD:- This figure shows how high fructose and high fat diet cause dysbiosis and aggravates neurological disorders where as healthy diet with probiotics maintain microbiota diversity and reduced anxiety /stress by increasing brain derived neurotrophic factor (BDNF).

GBA in Amyotrophic lateral sclerosis (ALS)

It is a motor neurodegenerative disease affecting the brain and spinal cord neurons and usually leads to death. Reports have also suggested that ALS is a multisystem disorder that affects the GI tract. Leaky gut promote the transfer of toxin from intestinal lumen to blood Nübling et al., 2014; Toepfer, 2000; Toepfer et al., 1999, 1997]. An increase in circulating LPS activates innate immune responses and leads to the progression of the pathogenesis of ALS . It is also shown that a decrease in tight junction protein (spinal cord) and abnormality in tissue barrier, blood –spinal cord barrier, and BBB is responsible for ALS. With this knowledge, it is relevant to link Gut-brain in ALS, as disrupted barriers stimulate motor neuron sensitivity to a toxin released from the gut. Another possible mechanism is neuroinflammation caused by activation of microglia and reactive astrocytosis which is involved in the genesis of ALS. Bacterial strains (*Clostridium botulinum and Clostridium tetani*) affect the motor system selectively by producing neurotoxins.

Bacterial endotoxin (LPS) is not only limited to the pathogenesis of AD or PD but also plays a major role in ALS by disrupting the intestinal barrier and promoting passage of toxin from the intestinal lumen into blood, further activating immune response. Longsteth et al., also showed ALS patients have disturbed tissue barriers and reduced tight junction protein in the lumbar spinal cords [178]. Another study was done by Zhang Yong – Guo et. al., has shown that intestinal microbiota attenuates the advancement of ALS by using an animal model (G93A transgenic mice) which mimics human ALS conditions. A natural bacterial product 2% butyrate was orally administered in mice, in the drinking water as a treatment to alleviate the symptoms of ALS. Results showed the restoration of intestinal microbial homeostasis, improvement of gut integrity, and prolongation of the life span of the ALS mice model in comparison to control mice. Another study by Zhong Zhao et. al. showed the beneficial effect of the ketogenic diet in ALS

GBA in Autism spectrum disorder

Autism spectrum disorder (ASD) can be described as a sequence of neurodevelopmental disorders, marked by both social and cognitive functions deficits The exact mechanism and etiology of ASD are not clear

but the disturbance in the microbiota-gut-brain axis is known to be an emerging factor in the development of autistic behaviors. When a small number of autistic patients were compared with controls, on basis of culture and molecular-based analyses it was found that autistic patients have a greater prevalence of *clostridial* species. It is clinically proven that GI disturbance and changes in gut microbiota composition occur along with cerebral disorder in ASD patients.

SCFAs (short-chain fatty acids) are known to be a key driving force in the microbiota–GBA that can penetrate the BBB and have the ability to modulate brain activity directly. From a study conducted by Wang et al., it is evident that autistic children have elevated levels of total SCFAs in their stool samples along with increased ammonia concentration. Gut permeability is interconnected in influencing the microbiome directly and indirectly in causing CNS disorders. Mainly GI abnormalities that are found in autistic children are malabsorption, maldigestion, microbial overgrowth (fungal, bacterial, and viral), and disrupted intestinal permeability. Autistic children face difficulty in eating habits due to specific food selectivity [193–195] and poor digestion as well as inflammatory conditions in the gut. They also have poor vitamin-producing microbiota in the intestines which consequently causes low nutritional status.

It is a well-known fact that probiotic is beneficial in curbing GI disturbances such irritable bowel syndrome or inflammatory bowel disease and infectious diarrhea. But it is not just limited to GI disorders. Hsaio et.al. has highlighted the importance of probiotics in ameliorating autism-related behavioral abnormalities as well as GI disturbances. In this research, oral treatment of *Bacteroides fragilis* was given to the maternal immune activation (MIA) mouse model that is a well-known model for ASD. Thus it will not be wrong to say that microbiome-related factors are also contributing to the increased prevalence of ASD. It has been speculated that various diet regimens are proved to be beneficial in ASD patients by regulating the gut microbiome in addition to its effects on the brain. According to another report, ASD groups with GI symptoms have increased Firmicute to Bacteroides ratio in comparison to the non- ASD group [20]. Few studies also suggest that there is an imbalance in levels of mammalian- microbial cometabolites like dimethylamine, hippurate, and phenylacetylglutamine in the ASD group.

Gut-brain axis in Schizophrenia

Another multi-dimensional neurological disorder that is liked with gut microbiota is schizophrenia (SCZ). Almost 1 % of the total population is affected by SCZ. According to a study life period of schizophrenia patients is 15 years shorter than healthy individuals, possible reasons are suicide attempts as well as a defect in the cardiovascular system due to metabolic syndrome. Schizophrenia patients can experience symptoms like auditory hallucinations along with delusions either in late or early adulthood.

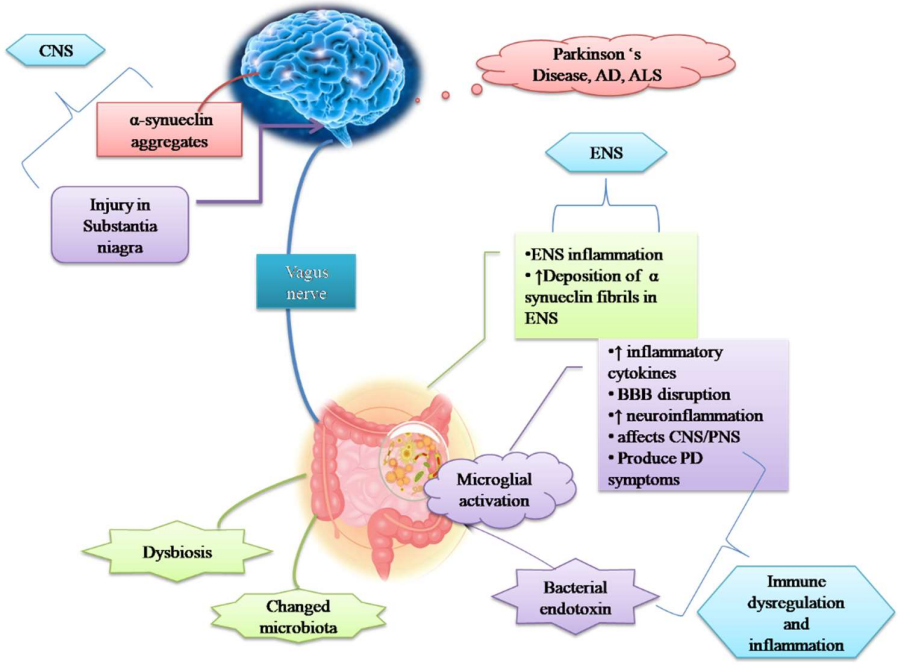

Figure 5- Involvement of gut in Schizophrenia:- Gut microbiota plays vital role in producing one of the major symptoms of schizophrenia that is depression. This figure depicts how symbiosis and dysbiosis effect brain functioning. Dysbiosis (imbalance in gut micro flora) lead to activation of immune system by disrupting intestinal permeability, and cause increased expression of inflammatory markers which further activate IDO (indoleamine

2,3-dioxygenase) pathway. IDO on activation increases the tryptophan metabolism and cause decreased production of serotonin. As a result of which ration Kynurenine/ tryptophan is elevated and clinically increase in this ratio is linked to depressive symptoms in schizophrenia patient.

Though various studies have been done to find the link between gut microbiota and SCZ (Figure 5) there is no animal model which could enclose all the complication associated with SCZ making it more difficult to find an exact mechanism through with gut microbiota dysfunction lead to SCZ. Desbonnet L et. al, through a study on mice, showed that microbiota modulation influences social and cognitive behavior, similar attributes are known to be affected in SCZ. Furthermore, human studies have also linked alteration in the gut microbiota with SCZ and also indicate the role of immune responses with SCZ. Severance EG et. al, showed the link between leaky gut with SCZ. A major finding from their research was that level of inflammatory marker CD14 was significantly higher in SCZ patients in comparison to controls. Yang Shen et. al., through a cross-sectional study, analyzed diversity of gut microbiota and auxillary diagnosis as biomarker in SCZ patients. They found that 99 % of the total bacteria in the intestinal tract of normal people contain mainly four types of bacteria including *Bacteroidetes, Proteobacteria, Firmicutes, and Actinobacteria*. Whereas SCZ patients have a higher count of *Proteobacteria* than the normal control. Tanya T. Nguyen et. al., - also conducted a similar study to compare the composition of gut microbiota in SCZ patients versus healthy persons. Their major finding is that *Proteobacteria and clostridium* count is lower in SCZ patients than normal control which is opposite to that study conducted by Yang Shen et.al.,.

Peng Zheng et. al., - conducted a study on how gut microbiota of SCZ patients alters glutamate-glutamine GABA cycle and studied various behavior changes related to SCZ in mice. Through this, they highlight that mice incorporated with the microbiome of SCZ patients showed SCZ like behavior changes and altered gut microbiota composition whereas mice with healthy control microbiomes show no such changes. Also their metabolomic profiles of fecal, serum, and hippocampal differ from mice receiving a sample of healthy control microbiota. Combining all this study suggest that glutamate circuit is affected in SCZ rodent models which means SCZ patients have decreased hippocampal glutamate. Gut-brain interaction is linked to SCZ through various mechanisms one such mechanism is the indoleamine 2,3-dioxygenase (IDO) pathway. When bacterial endotoxin LPS enters the bloodstream it disrupts gut permeability and causes leaky gut which increases expression of pro-inflammatory markers IL-6, IL-10, TNF-α and thus activates tryptophan/kynurenine pathway/IDO pathway. On IDO activation tryptophan degradation fasten as a result of which the kynurenine to tryptophan ratio increases and these factors are known to be implicated in the pathogenesis of SCZ.

GBA in Multiple sclerosis

Multiple sclerosis **(**MS) is an autoimmune neurodegenerative disease manifested by demyelination, disruption of the integrity of BBB followed by degeneration of neurons, and age group ranging from 20-40 is mostly affected by MS. Worldwide around 2.5 million people are suffering from MS. Apart from other symptoms like fatigue, cognitive deficits, depression, bowel dysfunction is also seen in MS patients linking MS to gut.

Various animal and human studies have made it evident that modulation of the gut microbiome can influence immune responses by increasing the expression of inflammatory markers. One of the major components of bacterial cell wall Peptidoglycan (PGN) is also a connecting link between gut microbiota and MS. Both toll-like and nucleotide-binding oligomerization domain-like receptors (NOD-like) receptors recognize PGN and initiate inflammatory cascade by activating mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (17). Hoogen et al. -, highlighted the importance of diet in modulating the microbiome which further influences immune disorders. Probiotics are responsible for maintaining gut symbiosis. Studies Salehipour Z et. al, - and Tankou SK et. al, - also showed that probiotic consumption plays a vital role in improving MS. The science involved in probiotics being beneficial in MS is that it will increase microbiota diversity, increase mucus release. which further prevents deterioration of tight junction proteins and prevent leaky gut by the reduction in the production of LPS. All these changes ultimately decrease the expression of inflammatory biomarkers and suppress the over-activated immune system. Furthermore, serotonin is another link that connects the gut and MS. Gut dysbiosis causes indoleamine 2,3-dioxygenase (IDO) activation and in turn lead to depletion of tryptophan, clinically depressive patients have low tryptophan level and depression is a major symptom in MS patients. From the comparative analysis of microbial composition done between healthy controls and MS patients, it is evident they have altered composition. *Bacteroides* species are reduced in MS patients whereas there is an increase in *Methano brevibacter* and *Akkermansia muciniphila* species. From the above studies it becomes obvious that bacterial translocation is increased in MS patients and GBA can become a good therapeutic target.

GBA in Stroke

Stroke is cerebrovascular disease and the second most leading cause of various disabilities across the globe. Stroke can occur as a result of various abnormalities including high oxidative as well as nitrative stress, apoptosis, and neuroinflammation. Obstruction and rupturing of the blood vessel in the brain leads to stroke, ischemic and hemorrhagic stroke respectively. Both clinical and preclinical data make it evident that altered

intestinal microbiota is linked to acute ischemic stroke. Alteration in the gut includes enhanced gut permeability and disturbed gut motility, dysbiosis in the gut followed by necrosis of intestinal epithelium. In addition, it is seen that in stroke patients, systemic inflammation and changes of post-stroke infection are associated with LPS binding protein (LBP) indicating disturbed intestinal barrier. Stanley D et. al., - determined that microbiota diversity reduction and excessive growth of *bacteroidetes* are major factors of dysbiosis post-stroke in mice. Stroke patients having GI complications increase severity by increasing death rates and destruction of neurological functioning.

Studies including Singh V et. al., Winek K et. al, Boehme AK et. al, and Ritzel RM et. al., reported that gut dysbiosis occurs after aged animals suffer stroke. Gut microbiota is known to synthesize neurotransmitters like GABA, noradrenaline, and dopamine and also plays a vital role in modulating immune responses. Ischemic brain injury becomes more severe when activated gut T- cells migrate to the site of injury after stroke condition and further increase expression of pro-inflammatory cytokines at injury site. Gut dysbiosis also creates an imbalance of T-cells such as Th1. Th2, Th17, and Treg cells and are held responsible for initiating autoimmune diseases. Th1 cells via increasing secretion of inflammatory markers (IL-2, IL-12, TNF-α, interferon-gamma IFN-γ) stimulates immune responses and are thought to be involved in the progression or pathogenesis of stroke (Figure 6). This increased production of inflammatory markers contributes to neuroinflammation followed by the breakdown of BBB and promotes ischemic stroke. It is reported that dietary intervention can be beneficial in combating stroke outcomes like short-chain fatty acids SCFAs administration inhibits post-stroke leaky gut by improving tight junction proteins of intestinal epithelium. Other studies also showed that SCFA supplementation improves mucus production after stroke and promotes intestinal differentiation and growth.

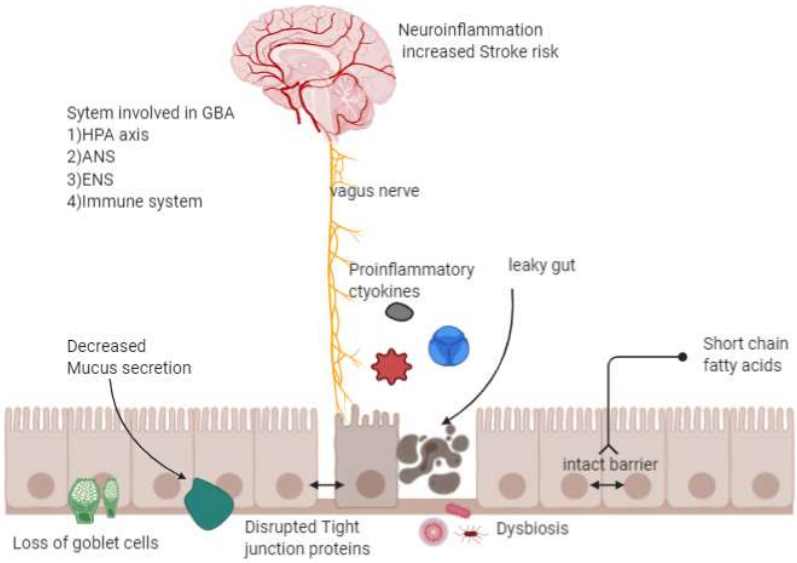

Figure 6- Alteration in gut that leads to stroke:- Various alteration like loss of goblet cells, decreased mucus production, dysbiosis, and disrupted tight junction proteins cause destruction of intestinal permeability. As a result, leaky gut is responsible for over expression proinflammatory markers followed by neuroinflammation and increased stroke risk. Whereas diet containing short chain fatty acids can be prevent leaky gut by maintaining integrity of intestinal barrier.

GBA in Epilepsy

Another common neurological disorder is epilepsy. Worldwide more than 50 million people are suffering from epilepsy which accounts for 0.5% of the total disease burden. It is a pathological condition in which there is a spontaneous generation of seizures followed by plenty of neurological, cognitive, and psychological disturbances. Ever after contributing decades in research of epilepsy, the exact etiology of epilepsy is still not clear. Studies including Lindefeldt et al., Peng et al., and Xie et al., showed differences in fecal microbiota composition of epileptic patients from those of healthy individuals. Various factors contributing to epileptic seizures are antibiotics, disturbed gut, and infections. Antibiotics are known to alter the gut microbiome and promote seizures directly and indirectly. It is also reported that the risk of epileptic seizure increases in case a single patient is prescribed large numbers of antibiotics. Zhang et al., also reported that cephalosporin intake elevates the risk of seizures in hemodialysis patients. In addition, reports also suggest that carbapenem significantly increases the seizure risk during randomized controlled human trials. Another study linked imipenem

with enhanced epileptogenesis. During comparative analysis of healthy and epileptic patients, it was seen that level of inflammatory biomarkers was higher in the peripheral blood sample of the diseased group as compared to normal controls indicating the involvement of the immune system in epileptogenesis (Figure 7).

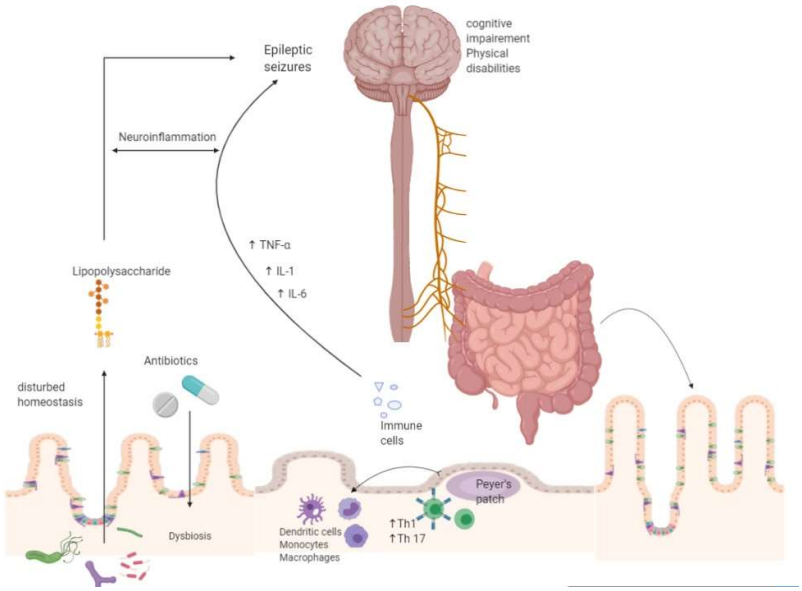

Figure 7- Gut microbiota and its link with epilepsy:- This figure depicts antibiotics and bacterial endotoxin lipopolysaccharide cause dysbiosis due to which Th1 and Th17 cells along with monocytes come out of Peyer's patch and immune system activation occur leading to neuroinflammation. Lipopolysaccharide on the other hand also activate toll- like receptor and cause release of inflammatory markers and thus lead to neuroinflammation which is known cause of epileptic seizures

It is evident from reports that the amount of *Bacteroides* is high in a healthy individual in comparison to epileptic patients. *Bacteroides* are known to metabolize high-fat diets and thus maintain expression of IL-6 and IL-17 in dendritic cells (DCs), thus make it more relatable to the generation of seizure . Other bacteria genus including *Blautia, Erysipelato clostridium, Streptococcus*. *Bifidobacterium* is also helpful in recovery from epilepsy. Resistance towards anti-epileptic drugs is also linked to composition gut microbiota, *Bifidobacteria and lactobacilli* are known to be effective in epilepsy in normalizing gut microbiota composition thus reducing drug-resistant epilepsy and serves to be an efficient target for epileptic therapy.

From all the above-mentioned studies it is clear that communication between gut and brain is emerging as an exciting area for research in health and disease. It is reasonable to conclude that a decrease in healthy bacterial count in the GI tract will lead to deterioration of intestinal membrane, activating the immune system, and further lead to progression of the disease. Diet is playing a major role in some neurological diseases, western diets cause dysbiosis whereas probiotics maintain the diversity of microbiota. Studies have proved that the western diet provokes inflammation due to low contents of plant-derived nutrients (fiber and phytochemicals) and high-fat content. Acellular nutrients present in the western diet can alter the composition of gut microbiota. Clett Erridge through his studies reported that highly processed foods like cheeses, ice cream, chocolate contain PAMPs which induce the release of inflammatory cytokines. It is reported that the western diet could cause permanent loss of bacteria essential for proper microbiome functioning. Furthermore, it could lead to metabolic changes that transferred to later generations. Western diet is rich in additives, saturated fat, sugar, and salt content thus alter intestinal integrity due to dysbiosis.

In contrast, probiotics and fermented foods (kefir, yogurt) are proved to be beneficial for gut microbiota. Probiotics have the potential to reduce the level of pro-inflammatory cytokines. Swiatecka D. et.al. demonstrated that including vegetal proteins (pea) proteins in the diet causes increased concentration of Bifidobacterium and Lactobacillus. In addition, omega-3, polyphenols, and micronutrients also have positive effects on gut microbiota. This emphasizes the role of a healthy and balanced diet. Exploring this vast area of GBA will prove to be an effective drug target to produce safe and effective drugs.

CONCLUSION AND FUTURE PROSPECTIVE

Summarizing this article, secretory products produced from the gut microbiome are very powerful activators of the proinflammatory complement system and innate –immunity. These in turn are proved to have great potential to aggravate pro-inflammatory cytokines and altered immunogenicity in the brain. A series of provocative studies have also strengthened the concept of the gut-brain axis. The microbiome modulates major aspects of the CNS, immunity, and behavior linked with health as well as disease conditions, though the mechanism involved and role of the microbiome in brain disorders are still not fully explored. Though GBA is not the only cause of neurological disorders but several other causes along with disturbed gut microbiota are responsible for the pathogenesis of various disorders. Suggesting GBA could be a promising target to reduce CNS disorders. Targeting the microbiota-gut-brain axis to improve brain and behavior will be a research hotspot in neuroscience, psychology, and psychiatry. Various neurotransmitters and neuropeptides are involved in this bi-directional communication but the molecular mechanism behind them is not fully explored thus it becomes more important to bring light upon this vast area i.e GBA. Not only medicaments but a healthy nutritional diet or simple probiotic supplementation is proved to be beneficial in suppressing behavioral changes. Probiotics act as adjuvant therapy in various brain diseases which makes this interaction more important. Further, as the use of probiotics is growing exponentially, there is a need to determine the long-term safety of such therapeutic intervention also. Through this review, we have covered the importance of GBA concerning different neurological disorders. Apart from past studies highlighting only GBA association with neurological disease, here we also reviewed components of GBA and the role of both western and healthy diets in modulating different neurological conditions. Taken together, studies included in this review showed gut microbiota can alter mood and cognitive function. In the future, a well-designed study is needed to explore the molecular mechanism of GBA-associated neurological disease to find better therapeutic interventions.

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