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Review Article

The Role of Microbiome on Neurodegenerative Diseases

Palak Bafna*

Medical Biotechnology, Dr. DY. Patil University, India

***Corresponding Author:** Palak Bafna, Medical Biotechnology, Dr. DY. Patil University, India.

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Abstract

Neurodegenerative diseases (NDDs) are a heterogeneous group of neurological disorders adversely affecting the lives of millions of people worldwide and entail the progressive loss of neurons in the central nervous system (CNS) or peripheral nervous system (PNS). They present a unique challenge in the modern research landscape. Despite decades of research, our understanding of the underlying causes and mechanisms still needs to be improved, and very few effective treatments exist. Given the lack of progress, the research community's attention has recently shifted toward other mediators of neurological disease that may present future targets for therapeutic research. One such mediator is the gut microbiome, which communicates with the brain through the gut-brain axis and has been implicated in various neurological disorders.

The gut-brain axis, encompasses the bidirectional interaction between the gut and brain through neural, immune, endocrine, and metabolic channels.

Keywords: Neurodegenerative Diseases (NDDs); Central Nervous System (CNS); Peripheral Nervous System (PNS)

Alterations in the gut microbiome have been associated with numerous neurological and other diseases, and restoration of the dysbiotic gut has been shown to improve disease conditions. One method of restoring a dysbiotic gut is via fecal microbiota transplantation (FMT), recolonizing the "diseased" gut with a normal microbiome. This treatment involves the transfer of gut microbiota from a 'healthy' individual to one who has a "diseased" gut microbiome, typically with the goal of correcting dysbiosis in the recipient [2]. It is usually used to treat Clostridium difficile infection (CDI, for which it is remarkably effective, however, it is increasingly being used to treat other gastrointestinal diseases. In the past few years, it has also emerged as an intriguing option for treating neurological disease, resulting in a rapidly growing pool of literature.

Therefore, This review aims to summarize recent research on the relationship between gut microbiota and neurodegenerative diseases involving fecal microbiota transplantation for the study or treatment of neurodegenerative diseases like Alzheimer's and Parkinson's disease.

Gut-brain axis

Gut bacteria are thought to affect a multitude of metabolic, gastrointestinal, and neurological problems [3]. These microbes may also have an impact on brain chemistry and behavior because of the intricate information transfer through the gut-brain axis and the network of communication between the gut bacteria and the brain. The neuroendocrine and neuroimmune systems linked to stress and stress-related illnesses, as well as the sympathetic

and parasympathetic branches of the autonomic nervous system (ANS), are just a few examples of the mechanisms and channels by which the CNS and microorganisms interact and influence host behavior.

The following discussion will center on important neurobiological and communication pathways, such as those that cross cell walls, metabolites, neurotransmitters, and brain neurotrophic factors. These pathways taken together might provide insight into the function of the microbiome in complicated CNS disorders and homeostasis.

The vagus or tenth (X) cranial nerve, which transmits sensory data between the central and peripheral nervous systems, is a direct conduit from the gut to the brain [3]. The central nervous system and gut bacteria communicate via the primary afferent channels that pass through the vagus nerve, these findings suggest that one potential neurological mechanism behind these correlations is the activation of c-FOS in vagal sensory neurons and following vagotomies [2].

Increased neuronal c-FOS mRNA and c-FOS expression have been proposed as markers of recent brain activation. Interestingly, visceral sensory nuclei in particular autonomic and brain regions had higher levels of c-FOS in pathogenic animals with Campylobacter jejuni and Citrobacter rodentium infections than noninfected animals did [3]. The vagal nerve pathway is thought to be involved in the transfer of gut immunological signals to the central nervous system, according to investigations on vagotomy performed on rats infected with Salmonella typhimurium to simulate the situation of a real bacterial infection. After cutting the vagal nerve pathway, there were fewer immune cells and reduced c-FOS expression in those neurons [3]. To create behavioral problem-solving therapy strategies, it may be helpful to understand the role of the vagal afferent pathways in mediating communication between the brain and gut bacteria.

Alzheimer's disease (AD)

Alzheimer's disease (AD) is the most common neurodegenerative condition, accounting for 60-70% of dementia worldwide [4]. Clinically, Alzheimer's disease presents as progressive impairment in memory and cognition, resulting in a steady reduction in mental, behavioral, and functional activities, as well as a significant drop in patients' quality of daily life. Aducanumab was the sole drug FDA-approved in 2021 [5] out of more than 20,000 compounds tested over the course of several decades as a possible treatment for AD. Lack of knowledge of the precise mechanisms underlying AD development and progression is one of the key causes of the difficulties in treating AD [6].

A-amyloid (A) from the periphery, especially that found in the gut, may help to create A-plaques in the brain, and gut flora may also play a role. Appears to exert an impact on Alzheimer's disease (AD) via the gut-brain axis, although detailed mechanisms are not clearly defined [7].

Aside from the source of Aβ, the gut-brain axis has received ample attention recently along with the discovery that the gut microbiota (GM), trillions of bacteria, fungi, and viruses found in the gastrointestinal (GI) tract, play a pivotal role in the human diseases, including AD [8].

Particularly, recent clinical studies observed alterations in the composition of GM in AD patients compared with healthy controls [9-11], strongly supporting the involvement of GM in AD pathogenesis. Furthermore, colonization of germ-free mutant APP/presenilin 1 (APP/PS1) transgenic mice with GM derived from conventionally-raised APP/PS1 transgenic mice drastically increased the cerebral Aβ pathology compared to wild type (WT) and germ-free transgenic mice [12] signifying that GM may play a causative or contributory role in AD onset and progression. However, the precise regulatory mechanism of GM in AD pathogenesis remains to be characterized.

A recent small study ($n < 120$) explored the links between microbiota profile and brain volume in people with and without obesity [19]. These findings conjointly emphasize the possible effects of the gut microbiome on cognitive function and brain structure, which might be further linked to the occurrence and development of dementia [20]. Nevertheless, direct evidence from large human cohorts is still lacking, leaving a research gap in this field.

Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting 3-5% of the population over

65 [13]. It is characterized by the gradual loss of dopaminergic cells in substantia nigra pars compacta combined with the aggregation of α-synuclein (αSyn) into Lewy bodies [13]. PD is predominantly associated with motor symptoms such as tremors or postural instability, but it also presents with several non-motor symptoms, such as sleep disturbances, psychiatric conditions, and sensory symptoms [14]. PD is also associated with significant alterations in the gut microbiome [15] and gastrointestinal dysfunction [16], with constipation, specifically considered one of the earliest markers of prodromal PD [17].

Many treatments exist, including exercise therapy, dopamine replacement and other pharmacologic treatment, and deep brain stimulation. However, effectiveness varies, with the most effective treatment in the early stages of PD, levodopa (L-dopa), being associated with adverse side effects such as dyskinesias and lack of impulse control. Hence, there is a need for additional treatment options that allow for symptom relief without significant adverse side effects. Given the link between gut symptoms and PD, adjustment of the gut microbiome using FMT may be one such treatment. The current research is outlined below and summarized in table.

Neuropsychiatric disorders

Neuropsychiatric disorders consist of cognitive, mental, and behavioral disorders, such as schizophrenia, depression, anxiety, stress and bipolar disorders, autism, eating disorders, and epilepsy [23]. In the last decades, the incidence of these conditions increased dramatically, reaching a percentage close to 40% of affected people worldwide [23]. These patients have impaired health and ability to conduct a healthy life, learn and work, which implies enormous health and economic effort from society. The etiology of these conditions includes genetic predisposition, injuries, infections, and environmental factors, such as the microbiota.

Depression

Patients suffering from major depressive disorder (MDD) had increased fecal α-diversity (increased levels of Enterobacteriaceae and Alistipes but reduced levels of Faecalibacterium) compared to drug responders MDD patients and healthy controls according to the study done by Jiang H, Ling Z, Zhang Y, Mao H, Ma Z, Yin Y., *et al*. and published in the paper "Altered fecal microbiota composition in patients with the major depressive disorder" [24]. The authors, therefore, reported a negative correlation between Faecalibacterium and the severity of depressive symptoms [24]. An additional study suggested that the administration of probiotics (Lactobacillus acidophilus, Lactobacillus casei, and Bifidobacterium bifidum) to MDD patients significantly reduced depressive symptoms compared to placebo [25]. From a large microbiome study on a Flemish population cohort, some bacteria have been associated with high quality of life, such as butyrate-producing Faecalibacterium, Coprococcus bacteria, and others with low quality of life and signs of depression, such as Bacteroides enterotype 2 [26]. From fecal metagenomic data, the bacterial capacity to synthesize 3,4-dihydroxyphenylacetic acid, a dopamine metabolite, correlates positively with mental quality of life and suggests a potential role of microbes to produce different neuroactive molecules during depression than during healthy conditions [26].

Schizophrenia

Patients affected by schizophrenia have also an altered and less rich gut microbiota composition with 77 differently expressed operational taxonomy units (OTUs) compared to healthy individuals [27]. The fecal samples derived from these patients were transplanted into GF rodents and could transfer schizophrenic-associated behaviors, such as locomotor hyperactivity and decreased anxiety- and depressive-like behaviors, in the recipients [27]. The mice that received fecal samples from schizophrenic patients showed several differentially regulated metabolic pathways in the feces, serum, and hippocampus [27]. In particular, glutamine and GABA were elevated in the hippocampus [27]. Glutamate was decreased in the stool and hippocampus of these mice, compared to mice transplanted with healthy patient feces [27].

Autism

Regarding human autism spectrum disorder (ASD), studies showing the importance of the microbiota in the pathogenesis are few and mostly inconsistent, with some exceptions concerning the differences observed for bacteria, such as Prevotella, Firmicutes, Clostridiales, like Clostridium perfringens, and Bifidobacterium species [28], between the ASD patients and the controls. Colonizing

GF mice with fecal microbiota from patients affected by ASD was sufficient to promote ASD-like behaviors in the animals [29]. This approach seemed to be due to a deficit in the production of two bacterial metabolites, 5-amino valeric acid (5-AV) and taurine, both weak GABAA agonists, in ASD individuals compared to controls [29]. Maternal immune activation (MIA) is a situation in which the maternal immune system gets activated by infections or infections-like stimuli, like LPS, and it features ASD in the offspring. In MIA animal models, scientists highlighted the importance of specific commensal bacteria in ASD protection. Interestingly, offspring coming from MIA dams showed intestinal microbial dysbiosis with 67 different OTUs compared to the control group, dysregulation of the intestinal barrier integrity with increased permeability, as reported already in children affected by ASD [30], and alteration in their metabolomic profile [31]. The pure administration of two bacterial strains as probiotic treatment, such as Bacteroides fragilis (and Bacteroides thetaiotaomicron but not Enterococcus faecalis), could improve the gut dysbiosis, intestinal barrier integrity, the metabolic profile of the animals, and the communicative, repetitive, anxiety-like, and sensorimotor behaviors in the MIA model [31]. Concerning the metabolites that could be induced by the intestinal bacteria under certain pathological conditions, in the MIA model, 4-ethyl phenyl sulfate (4EPS), indole pyruvate, serotonin, glycolate, imidazole propionate, and N-acetyl serine were enormously increased in the serum of MIA offspring and entirely restored by the single B. fragilis treatment [31]. Remarkably, the injection of only 4EPS metabolite in the naïve healthy animals was sufficient to induce anxiety-like behaviors similar to the ones showed by the MIA offspring [31].

Immune system regulation

The communication between the CNS, the intestine, and the microbiota happens through the so-called Gut-Brain Axis (GBA), a complex bidirectional communication network between the intestine and the CNS [23]. This axis involves different pathways such as the autonomic and enteric nervous system, the endocrine system, the hypothalamic-pituitary-adrenal axis (HPA), the immune system, and the microbiota and its metabolites [32]. Several neurotransmitters [33] and metabolites such as essential vitamins, secondary bile acids, amino acids, and short-chain fatty acids (SCFAs) [34], modulate many immune system pathways [23] that in turn influence behavior, memory, learning, locomotion, and neurodegenerative disorders [35]. Among those pathways, researchers showed that the inflammasome plays a role in depressive- and anxiety-like behaviors, and locomotor activity. A potential role of dysbiosis has been suggested as the cause of these mood and behavioral defects [23], however, the exact mechanism behind these phenomena still needs to be understood.

Despite growing evidence, a significant gap of knowledge still exists in understanding the exact mechanisms involved in the communication between the gut and brain during health and disease. In this review, we provide an overview of the current state of research about the effect of microbiota on the GBA in homeostasis and disease states, with a particular interest in the different bacterial metabolites involved.

Role of bacterial molecules and metabolites in development and health

The influence of the intestinal microbiota in neurodevelopment was known since the early 2000s. Early experiments using germ-free (GF) or specific pathogen-free (SPF) mice treated with antibiotics, to reduce the microbial diversity within the intestine, showed that several neurological problems occur in mice with reduced or lack of proper mature gut microbiota [36]. In detail, compared to colonized mice, GF mice showed exaggerated hypothalamic-pituitary-adrenal (HPA) restrain stress reaction (10), impaired social behaviors (12, 15, 82), reduced anxiety-like behavior [36], and increased motor and rearing activity (80, 84). Consistently, certain altered brain developments and behaviors observed in GF mice could be resolved/improved when newborn animals were reconstituted with a diverse and intact flora [37]. Antibiotic treatment results in reduced expression of the tight-junction forming proteins, occludin, and claudin-5, in the brain, increased BBB permeability, reduced anxiety-like behaviors, and elevated exploratory behavior and home-cage activity (35). The altered behavioral phenotype was associated with the dysregulation of genes and metabolites known to be involved in motor control and anxiety-like behavior pathways, like adrenaline, dopamine, 5-hydroxytryptophan (5-HT), postsynaptic density protein 95 (PSD-95), and synaptophysin [38].

Lately, it is becoming more evident that microbes can produce neuroactive molecules that directly contribute to the communication between the gut and the brain. Neurotransmitters, such as acetylcholine, GABA, and serotonin, produced by bacteria belonging to Lactobacillus, Bifidobacteria, Enterococcus, and Streptococcus species, can influence brain cell physiology directly and indirectly [23]. Strikingly, 90% of serotonin required for mood, behavior, sleep, and several other functions within the CNS and gastrointestinal (GI) tract is produced in the gut [39]. The binding of serotonin to 5-HT receptors on microglia induces the release of cytokine-carrying exosomes, providing another mechanism for gut-induced modulation of neuroinflammation [39]. Another microbial metabolite that influences microglia activity is tryptophan, a serotonin precursor [39]. Bacterial metabolites derived from dietary tryptophan could control CNS inflammation through an aryl hydrocarbon receptor (Ahr)-mediated mechanism acting on microglial activation and the transcriptional program of astrocytes [39]. The importance of tryptophan metabolism in maintaining CNS homeostasis was already known a few years earlier, since male GF animals have significantly higher levels of 5-hydroxytryptamine and 5-hydroxy indole acetic acid in the hippocampus and the serum, compared with conventionally colonized control animals [23].

These findings suggest that systemic circulation could be the route through which the microbiota influences CNS serotonergic neurotransmission. Interestingly, colonizing GF animals post-weaning was sufficient to restore the levels of tryptophan in the periphery and to reduce anxiety in GF animals, but was insufficient to reverse the CNS neurochemical consequences present in adult GF animals [23]. This approach highlighted once more the importance of intact and diverse microbiota from birth on. More recently, it has also been reported that the metabolism of tryptophan by activated microglia produces the neurotoxin quinolinic acid, an N-methyl-D-aspartate agonist, implicated in several neurological conditions, including Huntington's disease and depression [23]. Recolonizing GF mice with particular bacteria belonging to the Clostridia family, such as Clostridium tyrobutyricum, known to colonize the intestinal mucus layer, regulates immune and gut barrier homeostasis through the production of anti-inflammatory metabolites (e.g. butyrate), induces elevation of occludin and claudin-5 levels in brains of GF mice and restores their BBB integrity to the level of SPF mice [23]. Furthermore, probiotic supplementations, such as Lactobacillus rhamnosus (JB-1), in already colonized mice, reduced anxiety- and depression-like behavior in steady-state conditions [23]. In 2019, Artis D.'s group showed that SPF mice treated with a cocktail of broad-spectrum antibiotics, GF mice, GF mice recolonized after weaning age with a simple microbiota or a complex microbiota, have defects in fear extinction learning, compared to SPF mice or GF mice colonized with SPF flora at the time of birth [23].

Fear extinction learning is a reaction that happens after experiencing an environmental danger and has been implicated in multiple neuropsychiatric disorders, including anxiety disorders like post-traumatic stress disorder [39]. The reasons for this altered behavioral response in the absence of a diverse and intact microbiota were reconducted to alterations in pathways involved in synapse formation and calcium signaling at the level of mainly neuronal and microglial cells [39]. The researchers showed that the microbiota-mediated changes in synapse formation and fear extinction behavior were not the results of the hypothalamic-pituitary-adrenal axis but of the reduced level of potential neuroactive metabolites (phenyl sulfate, pyrocatechol sulfate, 3-(3-sulfooxyphenyl)propanoic acid, and indoxyl sulfate) in the cerebrospinal fluid, serum and in fecal samples of GF mice compared to SPF mice [39]. However, the types of cells (host or bacterial) producing these metabolites are still undiscovered.

From an immunological and metabolomic point of view, GF, SPF mice treated with antibiotics, or gnotobiotic mice with limited microbiome diversity (colonized with ASF for example) showed impaired microglia maturation and immune response upon bacterial stimuli, compared to SPF mice (94). Moreover, the treatment of mice with *E. coli*, isolated from colitic mice, caused colitis and brain memory impairment [39]. In contrast, the treatment with *L. johnsonii* restored a healthy gut microbiota composition and attenuated both colitis and *E. coli*-induced memory impairment [23]. In addition, bacterial fermentation of indigestible dietary fibers produces among the SCFAs, butyrate, propionate, and acetate in the colon [38]. SCFAs maintain gut health by promoting intestinal barrier integrity, and mucus production, and supporting a tolerogenic response over inflammation [37]. However, their activity is not restricted only to the intestine. A small fraction reaches the systemic circulation and can cross the

tightly regulated BBB using their own transporters located on brain vascular epithelial cells [36]. SCFAs are, in fact, detectable in low amounts in the human brain under physiological conditions [23]. Additionally, they also affect the BBB itself; the colonization of adult GF mice with a complex microbiota or only with SCFAs-producing bacterial strains restores the integrity of the BBB. Remarkably, treating GF mice with the oral application of a mixture of the three major SCFAs acetate, propionate, and butyrate, was also sufficient to restore the normal maturation process of the microglia [23]. Moreover, SCFAs can modulate neurotransmitters, like glutamate, glutamine, GABA, and neurotrophic factors [23]. Propionate and butyrate can influence the cell signaling system via modification of the intracellular potassium levels [23], and they regulate the expression levels of tryptophan 5-hydroxylase 1, involved in the synthesis of serotonin, and tyrosine hydroxylase, which is involved in thebiosynthesis of dopamine, adrenaline, and noradrenaline [23].

Methodology and technique

A study, conducted by the team from Guangzhou Nutrition and Health Study (GNHS) analyzed the relationship between the gut microbiome and age-related cognitive impairment in three independent populations. The discovery cohort consisted of 1430 participants from the GNHS, with gut microbiome and cognitive assessment data available, of whom 272 individuals provided fecal samples twice before cognitive assessment [21]. The team selected 208 individuals with baseline microbiome data for brain magnetic resonance imaging during the follow-up visit. They used fecal 16S rRNA and shotgun metagenomic sequencing, targeted serum metabolomics, and cytokine measurements to carry out the GNHS. The validation analyses were conducted in an Alzheimer's disease case-control study (replication study 1, n = 90) and another community-based cohort (replication study 2, n = 1300) with the cross-sectional dataset.

Cognitive assessment was carried out using the Mini-Mental State Examination (MMSE) [22], which measures five domains, namely orientation, registration, attention and calculation, delayed recall, and language, with a higher score indicating better cognitive performance. The participants were classified according to a validated standard into corresponding degrees of cognitive impairment known as the staging model: 'normal' (score 30); 'questionable' (score 26-29); 'mild' (score 21-25); moderate' (score 11-20); and 'severe' (score 0-10).

In addition, fecal microbiota DNA extraction, 16S rRNA gene sequencing, and shotgun metagenomic sequencing were carried out. Genera or species that were present in less than 10% of the samples or had an average relative abundance of less than 0.01% in each dataset were excluded from further analyses.

Targeted serum metabolomics was used to measure the concentrations of 199 serum metabolites among 820 participants. Inflammatory cytokines were measured, and the bioinformatic analysis of gut microbiota was detailed [21].(Figure 1)

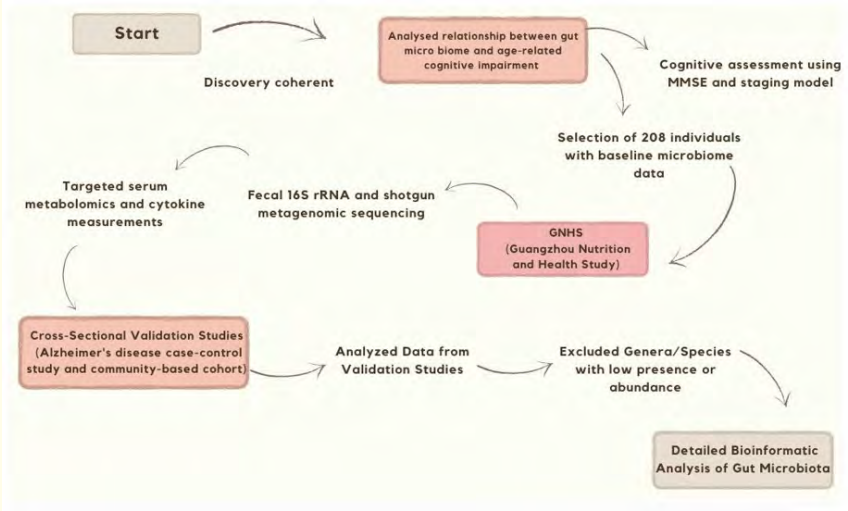

Figure 1: Simplified representation of the study's key steps and does not include all the specific details mentioned in the text.

Conclusions and Future Perspectives

The influence of intestinal inflammation on the nervous system is a crucial area of research that bridges the connection between these two organs, providing a deeper understanding of the synergistic communication within the gut-brain axis (GBA). This review has highlighted the role of certain bacterial species in shaping the host GBA under healthy and disease conditions. It has focused on elucidating the mechanisms by which bacteria produce molecules that can influence the immune and nervous functions of the host.

To achieve a comprehensive understanding of the molecular pathways involved in the pathogenesis of various disease conditions, a combination of clinical studies and animal experiments is necessary. This integrated approach would enable the examination of the mechanisms behind specific immunological or neurological effects observed in the presence or absence of particular bacterial species in specific pathogenic conditions. Specifically, future research should aim to uncover the involvement of individual bacterial molecules (products or metabolites) in disease progression or protection.

It is vital to investigate the precise mechanisms underlying the pro- and anti-inflammatory responses induced by microbes. Understanding the actions of specific bacterial molecules and metabolites at the CNS level and their mode of reaching the CNS is essential. Additionally, it is crucial to determine the specific cells on which these molecules act, the signaling pathways they activate or suppress, the affected organs, and whether they impact both the enteric and central nervous systems. Furthermore, the reciprocal relationship between host immune or nervous system alterations and the functions of the microbiota, mediated by inflammatory mediators and defensive molecules, should be explored.

The inflammasome, as a signaling pathway activated in the presence of certain bacteria and bacterial molecules, has been implicated in various neurological and intestinal homeostatic and inflammatory conditions. In some cases, it is involved in the pathogenesis of neurodegenerative diseases, such as experimental autoimmune encephalomyelitis (EAE), triggered by bacterial exposure. However, it remains unclear whether intestinal microbial alterations associated with neurological diseases are upstream or downstream of immunological (such as inflammasome) and neurological dysfunctions. Understanding the specific microbial conditions in which these mechanisms are activated and how they function is essential for designing more efficient therapies aimed at modulating the microbiota or host immune responses to ameliorate or cure specific neurological pathologies.

In summary, the exciting and important discoveries summarized in this review suggest that bacteria, including both pathogens and commensals, have the capacity to stimulate the host intestinal tissue and signal to the brain, influencing various aspects of host behavior and neurological disease pathogenesis. With the available tools and instruments to identify individual bacteria and their products, it is now possible to track their movement in various host tissues, determine their target cells, and elucidate the pathways they activate. This mechanistic approach is crucial for a better understanding of how the intestine influences the nervous system. Ultimately, this knowledge will lead to the development of better interventions and more efficient, personalized therapeutic strategies for patients affected by the neurological disorders discussed in this review.

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