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REVIEW

Potential contribution of microbiome in neurodegenerative diseases: Alzheimer's disease

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Alzheimer's Disease (AD) is described as a gradual decrease in cognition and memory frequently causing dementia in most cases. Human microbiome (HM) contribute to the regulation of multiple neuro-chemical and neuro-metabolic pathways. The pathological features of AD include amyloid beta peptide (Aβ) deposition, neuronal tangle formation and granulovacuolar degeneration. Aβ protein is a normal part of the innate immune system, the body's first-line defense against infection. However recent report shows that Aβ expression protects against fungal and bacterial infections in mouse, nematode, and cell culture models of AD. Recent reports suggest that these proteins are also expressed on bacterial and fungal cell surfaces and might contribute to immune response. In addition to commensal microbes, there are other pathogens like Chlamydophila pneumoniae, Toxoplasma gondii, Viroids, Hepatitis, Cytomegalovirus have been suspected to be involved in AD. Microbes are proposed to play an important role in the pathophysiology of neurodegenerative disease. Microbes are shown to produce relevant neurotransmitter, modulate immune response and translocate through blood or lymphatic system to brain from the site of infection. Here we elaborated on the emerging ideas showing the contribution of the gut microbiome to human neurological diseases with special emphasis on AD. The evidences described here may be helpful in designing further studies for taxonomic and functional profiling of microbiota in patients with AD which may open doors for advanced therapeutic inventions.

Keywords: Microbiome; Alzheimer's disease; BDNF; BMAA; Germ free mice

Abbreviations: AD, Alzheimer's Disease; Aβ, amyloid beta peptide; CNS, central nervous system; GIT, gastrointestinal tracts; ApoE4, epsilon 4 allele of apolipoprotein E; HM, human microbiome; GABA, γ-aminobutyric acid; NMDA, N-methyl-D-aspartate; LPS, lipopolysaccharide; TLR2, toll like receptor 2; NF-κB, nuclear factor-kappaB; PGN, peptidoglycan; CRP, C Reactive Protein; BMAA, β-N-methyl amino-L-alanine; PD, Parkinson-dementia; HSV-1, herpes simplex virus-1; NO, nitric oxide; ssRNA, single-stranded RNA; dsDNA, double-stranded DNA; SPs, senile plaques; AIDS, acquired immune deficiency syndrome; HCV, Hepatitis C virus; HCMV, human cytomegalovirus; ANS, autonomic nervous system.

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Introduction

Alzheimer's disease (AD) is characterized by a slowly progressive decline of cognition and memory and is the most frequent cause of dementia. The major factors for AD are unknown, however age is considered as a significant risk factor. About 5% of AD cases have a genetic or familial cause although the vast majority of all AD cases (~95%) are of sporadic origin [1-4]. Disrupted innate immune response, neuro-immune markers or inflammatory signaling processes are crucial in the degenerative process of AD [5-7]. There is currently no cure or adequate treatment for AD, and it remains unclear how it originates and propagates throughout the brain [1]. The pathological features in AD include amyloid beta

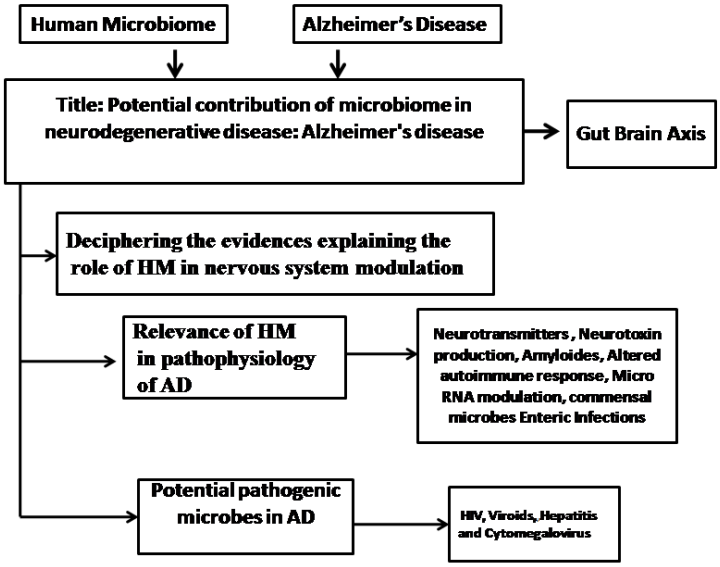

Figure 1. An overview describing the contents of the review.

peptide (Aβ) deposition, neuronal tangle formation and granulovacuolar degeneration and senile plaques [8]. Mutation in epsilon 4 allele of apolipoprotein E (ApoE4) are considered as risk factors [9]. Presenilin 1 and Presenilin 2 genes are implicated in early onset AD [10]. Polymorphisms in various inflammatory genes are also implicated as risk factors [11]. The intercellular spreading required for AD 'staging' and propagation is carried out by small molecular pathogenic factors and blood borne neurotoxic elements from the environment [12-14]. Aβ protein is a normal part of the innate immune system, the body's first-line defense against infection. Recent report also shows that Aβ expression protects against fungal and bacterial infections in mouse, nematode, and cell culture models of AD [14]. Evidences suggesting the involvement of innate immune system in the onset of AD supports a role for microbes that initiate innate immune responses [15, 16].

Human Microbiome

Accumulating evidence has drawn our increased awareness towards the relevance of human microbiome and the healthy and homeostatic human physiology. Various areas of the human body, including conjunctiva, respiratory tract, oral, and otic cavities, and majorly the gastrointestinal tracts (GIT) serves as ecosystems for microbial communities comprising the human microbiota [1]. The human gut harbors a dynamic and complex microbiome consisting of nearly 10^{14} micro-organisms spanning over 1000 distinct microbial species which outnumber human somatic cells[17-19].

GIT is dominated by anaerobic *Firmicutes* (~51%) and *Bacteroidetes* (~48%). The remaining 1% consist of the *Proteobacteria*, *Verrucomicrobia*, *Fusobacteria*, *Cyanobacteria*, *Actinobacteria*, and *Spirochetes* other than few species of fungi, protozoa and viruses [20]. The microorganisms comprising the 1% of the microbiome are also considered relevant, as in the case of dysbiosis [17,21,22]. The relationship established between the intestinal microbiota and its human host provides mutual benefits. During homeostasis, the microbiota benefits from the nutrient-rich, warm, environment of the gut. In exchange, humans benefit from a highly adaptive metabolic engine [18]. The host and microbial communities consist mainly of a defined "core microbiome", despite having inter-individual differences at the phylotype level[23]. This core microbiome maintains a delicate balance that confers health benefits[24].

Varying combinations and strains of bacterial species amongst human populations might contribute to "*human-biochemical*" or "*genetic-individuality*" and resistance to disease[25]. Interestingly, HM participation in human physiology may explain the genome-complexity [19, 26, 27] (Figure 1).

HM in neurological disease

Role of HM in neurological disease is highlighted by studies on germ free mice, displaying abnormal behavior and brain chemistry. Some of the common gastrointestinal conditions, such as irritable bowel syndrome, involving dysbiosis of the intestinal microbiota, frequently coexist with psychiatric disorders [28].

Neufeld *et al*. showed that in the absence of a conventional microbiota, female germ free mice show reduced anxiety behavior. They also reported simultaneous upregulated expression of brain derived neurotrophic factor (BDNF) mRNA in the dentate gyrus of the hippocampus [29]. BDNF is essential in the maintenance and survival of neurons is known to affect neuronal development, differentiation, synapto-genesis, and the synaptic plasticity that are important for neuronal circuit formation and cognition. BDNF was found to

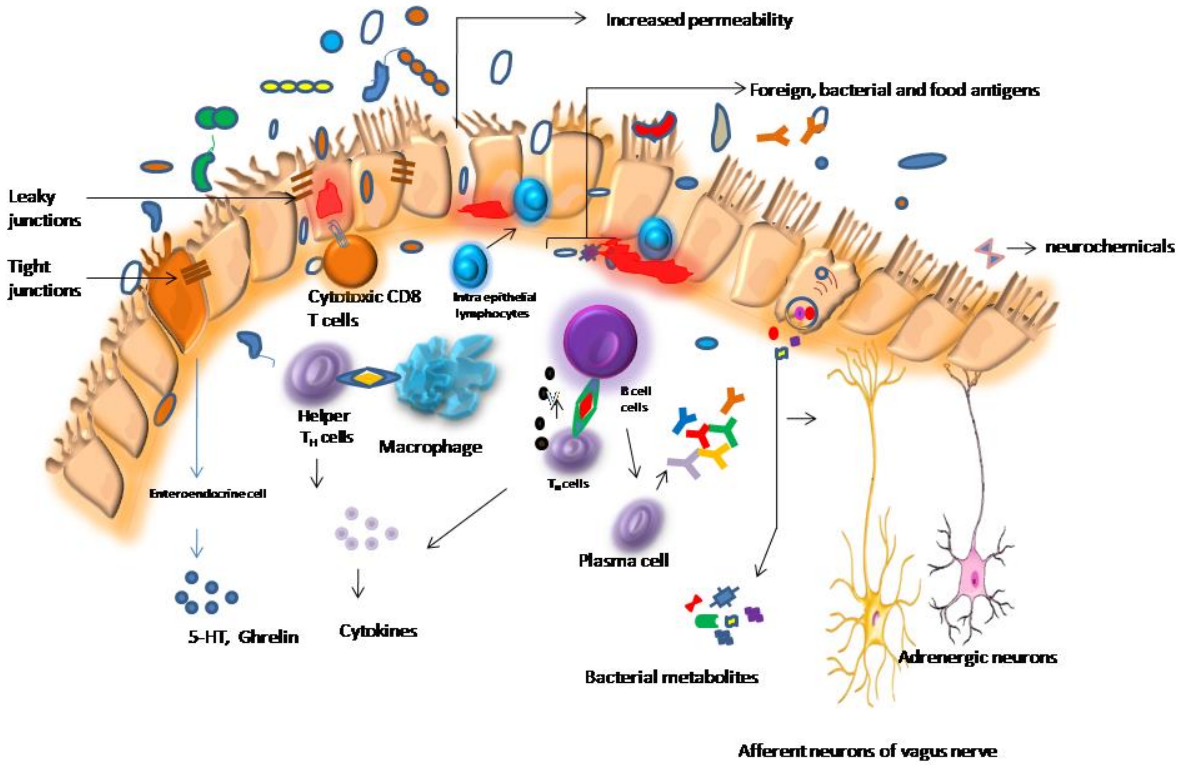

Figure 2. Implication of gut microbiota in nervous system and tis communicative factors.

be reduced in the hippocampus and cortex of "germ free" mice, and this was associated with increased anxiety behavior and progressive cognitive dysfunction [26, 30]. BDNF also has been found to be decreased in brain and serum from patients with anxiety, behavioral defects, schizophrenia, and AD [31,32]. Mice deficient in BDNF showed altered development of GIT innervations including the vagus nerve [33,34].

In experimental infection models known to lead to significant alterations in the microbiota profiles, also show reduced BDNF expression in the hippocampus and cortex of germ free "*gnotobiotic*" mice, and this was specifically associated with increased anxiety and progressive cognitive dysfunction [26, 32].

Relevance of HM in pathophysiology of AD

The host is exposed to the pathogenic microbes and symbiotic gut microbiota during their lifetime. Symbiotic gut microbiota composition is able to modulate the immune system, because metabolic dysfunction in aging facilitates obesity. Microbiota and host exposure to pathogens and commensals may play crucial role in progression of degenerative disorders. The implication of gut microbiome in AD is shown in Figure 2.

Modulation of neurotransmitters by bacteria

Members belonging to Gram-positive facultative anaerobic or microaerophilic *Lactobacillus*, and anaerobic *Bifidobacterium* species possess a unique capability of metabolizing glutamate to produce gamma aminobutyric acid (GABA). GABA is the major inhibitory neurotransmitter in the CNS and its signaling dysfunctions are linked to anxiety, depression, and cognitive impairment including AD [21,31,35-37]. Increased level of GIT γ-aminobutyric acid appears to correlate with increased GABA levels in CNS, but the systemic pathways that contribute to this linkage between gut and brain require additional study [38,39]. Glutamate is the most abundant excitatory neurotransmitter in the human CNS and is recognized by the *N*-methyl-D-aspartate (NMDA) receptor that regulates synaptic plasticity and cognition. These data suggest the possibility of an interaction between neurotransmitters and HM.

Neurotoxin generated by resident microbes or environmental pathogens

Emerging studies indicate that the HM has highly interactive and symbiotic host microbiome signaling systems which allow HM to contribute to the regulation of multiple neuro-chemical and neuro-metabolic pathways [19].

Neurotoxins, BMAA is a neurotoxic amino acid normally incorporated into the polypeptide chains that constitute brain proteins. Elevated levels of BMAA have been reported in the brains of patients with amyotrophic lateral sclerosis [40], the Parkinson dementia complex of Guam, and AD [41]. Neurotoxins like saxitoxin and anatoxin, generated by Cynobacteria, may further contribute to neurological disease, especially when the intestinal epithelial barrier of the GIT

becomes significantly more permeable due to aging process [41,42]. Ability of bacteria to produce and recognize neurochemicals that are exactly analogous in structure to those produced by the host nervous system allow them to affect the neuro-signaling.

Bacterial Amyloids

Amyloid is considered as a major secretory product of microbes contributing to the pathophysiology of the human central nervous system (CNS). However, recent research has shown that these proteins are also expressed on bacterial and fungal cell surfaces and might contribute to immune response. Aβ42 peptides have the property to initiate a pattern of expression of inflammatory genes similar to classical immune and inflammatory response induced by infectious agents such as bacterial lipopolysaccharide (LPS) [43,44]. The diseases having accumulated amyloid as pathological feature, also involve a marked inflammatory response at sites of amyloid deposition, mediated by microglial cells. Microglial cells recognize abnormal forms of amyloid and initiate a phagocytic or "clearance" response through Toll like receptor 2 (TLR2) [45-47].

The factors released by gut [45, 48] may potentially modulate or alter amyloidosis, neurochemistry, and neurotransmission in CNS. The contribution of the gut microorganism and bacterial amyloid to protein misfolding and amyloidogenic diseases such as AD has been hypothesized and bacterial components such as endotoxins are often detected within the senile plaque lesions that characterize the AD brain. Interestingly, the extracellular 17.7kDa amyloid precursor contains a pathogen associated molecular pattern (PAMP) that, like the Aβ42 peptide (one of the dominant Aβ peptide monomer), is recognized by the human immune system TLR2[45,48,49].

Altered autoimmune response

The HM regulates autoimmune responses that can impact homeostatic metabolic and neural signaling functions within the CNS while constraining the host immunity to foreign microbes, including viral infection and xenobiotics [21,50]. Neurological disorders have been significantly associated with altered autoimmune responses. An increased incidence of auto immunity, exposure to pathogens both prenatal and postnatal, are common in disorders as diverse as anxiety, autism, depression, obsessive compulsive disorder, schizophrenia, PD, and AD. This suggests that differences in exposure and genetic vulnerability toward HM mediated auto immunity may be significant determinants in the course of age related neurological disease [21,50-54].

MicroRNA (miRNAs) modulation is also considered as a mechanism through which gut microbiota show its impact on the regulation of host physiology. CSF and extracellular fluid of AD patients contains miRNAs as the most abundant nucleic acids. The significant increase of miRNA-9, miRNA-125b, miRNA-146a, and miRNA-155 have been detected in AD CSF compared to age matched controls. Primary human neuronal-glial (HNG) cell co-cultures stressed with AD derived ECF also displayed an up-regulation of these miRNAs[55].

Interestingly, both peripherally applied Aβ42 peptides and NF-κB regulated pro-inflammatory miRNAs are able to induce AD-type changes within brain cells in culture, including the dysregulation of innate immune and pro inflammatory signaling [56-58]. Studies have also reported the involvement of miRNAs in response to bacterial pathogens and viral infection, namely in mammalian cells [59]. These micro RNAs, including miR-146, miR-155, miR-125, are commonly modulated by bacterial infection and contribute to immune responses protecting the organism against overwhelmed inflammation. This suggests a mechanism through which commensal bacteria could impact the regulation of the barrier function and intestinal homeostasis.

Potential neurotropic microorganism in AD

The potential pathogenic microbes contributing to aging and subsequently to AD have been recognized [8,60,22,61-63]. Some bacteria are neurotropic by nature and are able to influence the nerves tissue by the production of bacterial amyloid, lipoproteins and other microbial triggers that can activate the microglial TLR2s, subsequently inducing cytokine production, inflammation, phagocytosis and innate immune defense responses that impact CNS homoeostasis and drive neuropathology. It has been observed that the TLR2/TLR1 complex can recognize biofilm associated amyloids produced by *Firmicutes*, *Bacteroidetes*, and *Proteobacteria* [48].

THE GUT-BRAIN AXIS

The enteric microbiota interacts with the host to form essential relationships that govern homeostasis in a healthy individual whereas dysbiosis make important contribution in disease pathology [24].

This has been established by identifying complex series of highly interactive and symbiotic host microbiome signaling systems that mechanistically interconnect the GIT, skin, liver, and other organs with CNS [18,64]. The bidirectional signaling between GIT and brain is vital for maintaining homeostasis and is regulated at the neural (both central and enteric nervous systems), immunological and hormonal levels. Perturbation of these systems results in alterations in the stress-response and overall behavior[65].

Neuronal signaling pathways has structural, metabolic, protective functions thus contributing to a number of extra-intestinal immune-mediated diseases. However they remain incompletely understood [18,64]. Neural connections involve the central and autonomic nervous systems. The brain can upset the gut and vice versa. The central nervous system (CNS) communicates with the intestine through gut-brain axis, comprising of the hypothalamic-pituitary-

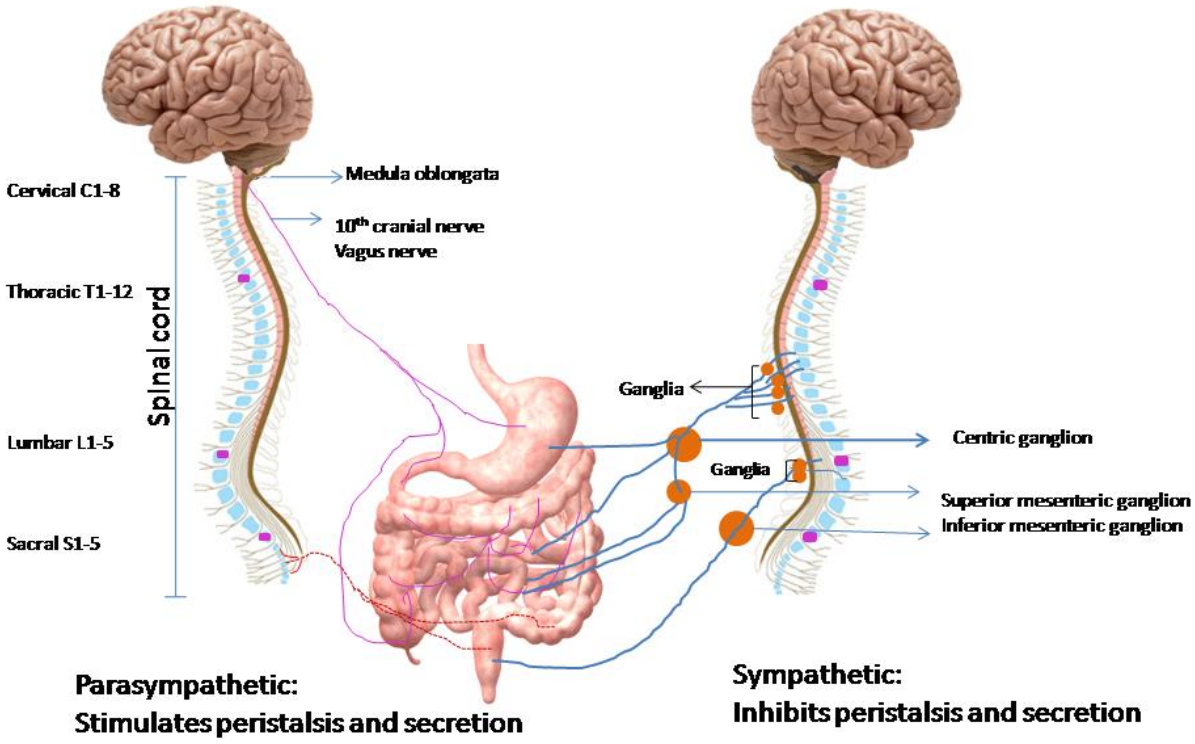

Figure 3. Communication between gut, gut microbiota and brain. Possible outcomes of their effect on each other influencing overall homeostasis.

adrenal axis and, in a gut context, the enteric nervous system (ENS). The autonomic nervous system (ANS) consists of three components: the sympathetic (noradrenergic) and parasympathetic (cholinergic) systems, which originate in the CNS (with cell bodies in the brainstem and spinal cord), and the enteric system [66] (Figure 3).

The humoral components of the gut-brain axis consist of the hypothalamic-pituitary-adrenal axis, the entero-endocrine system and the mucosal immune system. The hypothalamic-pituitary-adrenal axis is responsible for stress responses, resulting in the release of corticosterone, adrenaline and noradrenaline. The specialized endocrine cells located in the epithelial lining of the gut produce hormones such as cholecystokinin and ghrelin, involved in regulating appetite and 5-hydroxytryptamine having multiple effects on gut and brain functions [67].

Studies comparing germ-free and conventional rats showed that the microbiota influences the number of gut endocrine cells and the release of biologically active peptides [68] providing a further mechanism by which the microbiota might influence behavior. The intestinal microbiota imprints and instructs the mucosal immune system throughout the life of the host [69]. The intestinal microbiota is able to influence immune activation at sites beyond the GIT and may affect host susceptibility to immune-mediated conditions [70]. The integrity of the adaptive immune system, and of T lymphocyte responses in particular, are crucial for normal learning and memory in the mouse[71]. A range of psychiatric disorders, including depression implicates the role of pro-inflammatory cytokines, including interleukin-4 (IL-4) and interferon-γ [35]. Studies have shown that manipulation of the gut microbial composition influences systemic cytokine levels in animals [72,73] and humans [74]. Administration of *B. longum* subsp. *infantis* str. 35624 improves depression-like behavior and induces increased secretion of IL-6 by peripheral blood cells in mice that are subjected to maternal separation [73]. Thus, it is possible, that alterations in the intestinal microbiota may influence behavior indirectly by affecting cytokine levels in the circulation and the brain.

Perturbed microbiota induced changes in brain chemistry and behavior, independent of vagus nerve demonstrates the role of microbe originated metabolite[75,76]. A recent study in mice showed that the microbiota exerts potential effect on the metabolomic profile of the host. The microbiota serves as a major source of both circulating organic acids and tryptophan metabolites[75,77]. GABA, which has been implicated in anxiety, has shown to be produced by commensal lactobacilli and bifidobacteria in human indicating that gut bacteria might influence behavior via the production of neurotransmitters [39]. Some gut bacteria are also able to produce other neurochemicals including noradrenaline, 5-hydroxytrypta-mine receptors (5-HT), dopamine and acetylcholine. The use

of these bacteria has been suggested for treatment of neuropsychiatric diseases [78]. Moreover, germ-free mice, when colonized with bacteria show a >2-fold increase in 5-HT and its metabolites owing to bacterial metabolism of tryptophan which in turn influence the brain and behavior [77]. Alterations in the microbial composition of the gut might result in changes in serum kynurenic acid (tryptophan metabolite) levels which acts as an antagonist at excitatory amino acid receptors, could thus modify central nervous system (CNS) excitation and behavior which has been implicated in major psychiatric illnesses, including schizophrenia [79].

Behavior in animals has been reported to be influenced by bacterial fermentation products, including lactic acid and propionic acid. In a study diet rich in fermentable carbohydrates fed to rat, revealed a strong correlation between d-lactic acid levels in the caecum and displaying anxiety-like behavior and impaired memory [80]. High fecal concentrations of propionic acid show correlation with anxiety in patients with IBS[81]. Interestingly carbohydrate malabsorption, has been associated with depression in females, which may result from increased substrate availability for bacterial fermentation [82]. Influence of the microbiota on the brain is, further evidenced by the observation that behavioral traits of donor mice can be adoptively transferred into adult germ-free mice of a different strain via the intestinal microbiota. Combining these observations, the metabolic products of the intestinal microbiota influence brain function and behavior in the host.

Conclusions

This review has presented a detail overview of our current understanding on the potential relevance of HM in pathophysiology of AD. To have an insights into the gut-brain crosstalk during infection, correlation of metabolic and neurological phenotypes with the HM profiles have been discussed. Further exploring the complex host microbiome relationships in healthy human brain vs. aging and during neuropsychiatric disease is necessary. Advanced technology such as high throughput sequencing and metagenomic technologies may further strengthen the suggested association with complex microbial ecosystems and may give rise to strategies to manipulate HM.

Conflicting Interests

The authors declare that they have no conflict of interests.

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