Research Article

THE IMMUNOLOGY OF MIND CONTROL: EXPLORING THE RELATIONSHIP BETWEEN THE MICROBIOME AND THE BRAIN (PART III)

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ABSTRACT

Part three of this four-part series continues to evaluate the relationship between the human species and the human gut microbiome. It focuses on whether their relationship is symbiotic, parasitic or somewhere in between. The possibilities, based on animal studies, are explored and compared to scientific facts proven in human beings. In particular, close attention is paid to the relationship between the gut microbiome and central nervous system, and the effect this has on human behaviour. This relationship is termed the 'microbiome–gut–brain axis'. Through a number of pathways, the gut microbiome has an influence on stress (both acute and chronic), anxiety, loneliness and depression, as well as on odour and attraction. It has also been associated with the development of neurodegenerative diseases such as Alzheimer's and Parkinson's, and with associated cognitive decline. Since the common treatments used for these conditions are not equally effective in all patients, it is vital for clinicians to explore other avenues that could be used as therapeutic targets. The gut microbiome, in particular, requires further research in order to aid the development of future therapies for certain conditions. The concept of the organisms in the microbiome controlling the mind of human beings is relatively new, but such control has been demonstrated through multiple examples in the animal kingdom. Animal studies in this regard have shown promising results, but human studies are infrequent and often present disappointing results. Randomised control trials in human beings are greatly needed, either to prove or to disprove, the effects of the gut microbiome on complex psychiatric diseases.

INTRODUCTION

The brain should no longer be viewed as an immune-privileged organ, and advances in immunology require integration into the pathogenic pathways of a variety of neurodegenerative conditions.[1] Neurodegenerative diseases are characterised by a slow but progressive loss of neurons in the central nervous system (CNS), resulting in specific brain-function deficits.[2] Since the common treatments for these conditions are not equally effective in all patients, clinicians must explore other avenues as therapeutic targets. Part three of this series will evaluate the relationship between the development of neurodegenerative diseases – specifically Alzheimer's disease (AD) and Parkinson's disease (PD) – the cognitive decline associated with them, and the gut microbiome.

COGNITION AND COGNITIVE DECLINE

Cognition – a general term that encompasses thought processes which contribute to memory and learning – is affected by numerous disorders of the CNS such as autism, depression, schizophrenia and AD. Furthermore, it is widely known that the neuronal pathways involved in cognition are strongly influenced by chronic stress experiences early in life, experiences that have a negative impact on cognitive function later in life. The potential contributions of gut microbiota to cognitive development (and decline) also need to be considered.[3] This article focuses on the connection between the microbiome, cognitive decline and age-related changes in physiology: ageing is associated with progressive changes in the motility of the gastrointestinal tract, immune function weakness, defects in the gut–blood barrier, and defective protein folding. These changes have a marked impact on gut microbiome diversity and therefore may be linked to age-related neurodegeneration.[4]

The decreased microbial diversity in the elderly can be observed in two phenomena: phyla levels and short-chain fatty-acid (SCFA) production. The two dominant phyla in younger age groups, *Firmicutes* and *Bacteriodes*, do remain prominent in older age, but possible changes in their ratios occur. An age-related decrease in SCFA production also occurs. The fatty-acid butyrate is especially important in maintaining colonic epithelial

integrity and inflammation.[5] These changes in phyla ratio and SCFA production are consistent with the theory of 'inflamm-aging', which associates chronic low-grade inflammation with various age-related pathologies, including cognitive decline.[5,6] This theory further suggests that ageing is associated with a global reduction in one's capacity to cope with a variety of stressors, and a concomitant progressive heightening in pro-inflammatory status.[6]

Fatty acids in the brain (namely, arachadonic and docosahexaenoic acids) have been shown to have an influence on depression, anxiety, and learning and memory, as they play a vital role in neurogenesis, protect against oxidative stress and may even alter neurotransmission. Recent evidence has shown that *Bifidobacterium breve* supplementation in mice increases brain fatty-acid levels.[7] Further research is required to ascertain how microbiota control fatty-acid production.

Studies on germ-free mice have shown that commensal gut microbiota are essential to membrane electrical activity, namely, the excitability of the sensory neurons in the gastrointestinal tract, ion fluxes and action potentials. Therefore, gut microbiota are involved in bidirectional signalling exchange between the gut microbiome and the CNS, in the enteric nervous system, in the autonomic nervous system and also in the neuroendocrine and neuroimmune systems.[8] The varying combinations and strains of species of bacteria among human populations may contribute to human biochemical individuality or genetic vulnerability and on an impact on resistance to disease.[9]

Miklossy published a review in 2011 demonstrating that oral bacteria, particularly oral spirochetes (obligate anaerobes), were present at seven times higher density and variety in the brains of patients with AD, when compared to cognitively normal controls.[10,11] Furthermore, one longitudinal study conducted at the University of Kentucky explored the potential for using oral bacteria in blood as a predictive tool for cognitive decline. The study found that increased baseline serum-antibody levels, particularly for the oral anaerobes *Prevotella intermedia* and *Fusobacterium nucleatum*, correlated with cognitive deficits.[10,12] Also of interest in relation to oral hygiene and cognitive decline, are a Swedish study of monozygotic twins as well as a study of North American nuns, both of which found a statistically significant correlation between tooth loss and the development of dementia risk.[13,14] An American study corroborated the assumption of these studies that tooth loss is a rough indicator for poor oral hygiene; it did so by showing that dentate individuals who did not brush their teeth daily had a 22–65% increased risk of developing dementia compared to those who brushed their teeth three times daily.[10,15]

Inadequate sleep also increases the risk of age-related cognitive decline: preliminary data suggest a possible relationship between sleep quality, gut-microbiome composition and cognitive flexibility in healthy older adults. Better sleep quality was associated not only with increased proportions of *Verrucomicrobia* and *Lentisphaerae* in the gut microbiome, but also with better cognitive scores – suggesting that improved microbiome health may buffer against sleep-related cognitive decline in older adults.[16]

Studies of Western-style diets with a high energy intake have also shown an association between such diets and cognitive impairment, increased anxiety-like behaviour and hippocampal-dependent memory inhibition.[17,18] Diets high in animal fat and protein are associated with a higher number of *Bacteroides*; high-fibre diets are associated with *Prevotella*, and plant-based diets have higher numbers of *Bacteriodes* and *Firmicutes*.[19] Bacteria and a high-fat diet interact to promote pro-inflammatory changes in the gut.[17]

High-fat diets change the gut microbiome composition and result in significantly increased concentrations of lipopolysaccharide and endotoxin. These increased levels result in increased intestinal permeability. This chronic gut inflammation is characterised by the infiltration by macrophages of adipose tissue during obesity. This results in increased TNF-α secretion from hypertrophied adipocytes, which leads to immune-cell alteration (such as TH1 cells, B cells, neutrophils and mast cells), with subsequent M1 activation of macrophages. The additional associated secretion of chemo-attractants (MCP-1, MIF) and cytokines (TNF-α, IL-1β, IL-6) drive immune cells, namely, T cells, dendritic cells and macrophages, into adipose tissue. This results in a chronic low-level systemic inflammation, which in turn leads to neuroinflammation. Persistent systemic inflammation triggers and sustains neuroinflammation.[17]

Neuroinflammation is associated with a variety of neurodegenerative diseases in several brain regions, including the hippocampus and the cerebellum.[1,17] This results in the up-regulation of amyloid beta and neurofibrillary tangles, synapse/neuronal degeneration, atrophy of the grey-matter volume and resultant progressive cognitive decline with memory and learning impairment.

It is important to note that the hippocampus is strongly linked to food-related behaviour. It controls feeding behaviour via the detection and integration of energy-state signals through memory and encodes information regarding food experiences. The hippocampal-dependent memory inhibition therefore vitally

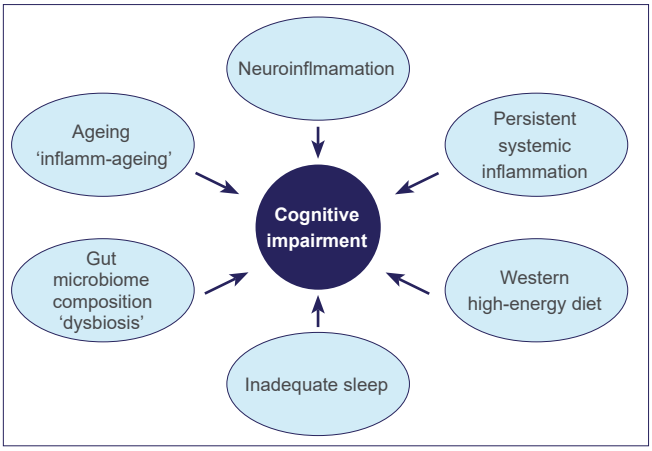

Figure 1: Factors affecting risk for cognitive decline

limits the response to environmental food-related cues, which results in excess energy intake. A dysfunctional hippocampus is a risk factor for obesity, leading to a vicious cycle.[17]

Researchers have proposed using anti-inflammatory drugs to combat the chronic neuroinflammatory process. However, limited studies have been conducted and clinical trials on the use of non-steroidal anti-inflammatory drugs have shown disappointing results.[1]

PARKINSON'S DISEASE

Treatments for neurodegenerative diseases in adults are delivering mixed results worldwide. This has led researchers to turn towards the gut microbiome for answers; a marked interest has developed in understanding its role in the context of PD.[19] Studies of mice have shown that enteric bacteria can regulate movement disorders through the deposits of unfolded protein in certain parts of the brain. These deposits are insoluble and promote neuronal apoptosis. AD and PD are types of amyloid disorder that are characterised by fluctuating manifestations. These diseases are cause for a growing health concern in an ageing population.[20]

The concept that patients with PD have low-grade gut inflammation has existed for some time: the colonic biopsies of PD patients reveal an increased mRNA expression of pro-inflammatory cytokines. This chronic low-grade inflammation may trigger blood–brain barrier leakiness, the activation of immune cells and subsequent neuroinflammation.[19]

The classic motor symptoms of PD (tremors, muscle rigidity, bradykinesia and impaired gait) are caused by the deposition of α-synuclein (αsyn) in dopaminergic neurons of the substantia nigra, leading to the subsequent death of these dopamine-generating cells.[20,21] Pathogenic bacteria release SCFAs into the peripheral circulation; they cross the blood–brain barrier and generate a pro-inflammatory environment in the brain through the activation of microglia. This dysregulated inflammation prevents the unfolding of certain proteins and accelerates their turnover and deposition in neurons.[20]

A wide variety of non-motor manifestations are also associated with PD: these involve the olfactory, cardiovascular, urogenital and gastrointestinal systems. Gastrointestinal manifestations (constipation, reflux, dysphagia, nausea and hypersalivation) often precede motor symptoms in the course of the disease.[21] In fact, gastrointestinal pathology precedes motor symptoms by years, which indicates that the peripheral nervous system (PNS) is involved before the CNS, and that pathology spreads from the gut to the brain via the vagal nerve.[22] Subsequently, αsyn aggregates have been found in the enteric and parasympathetic neurons of the gut.[21] This revelation has sparked much debate. The dual-hit hypothesis indicates that αsyn pathology is transmitted to the midbrain via two separate pathways: nasal (from the olfactory bulb to the temporal lobe) and gastric (through the enteric nervous system (ENS), secondary to the swallowing of nasal secretions via saliva). The disease may begin in the ENS and subsequently spread retrogradely to the CNS, or vice versa. The lesions in the ENS are not only thought

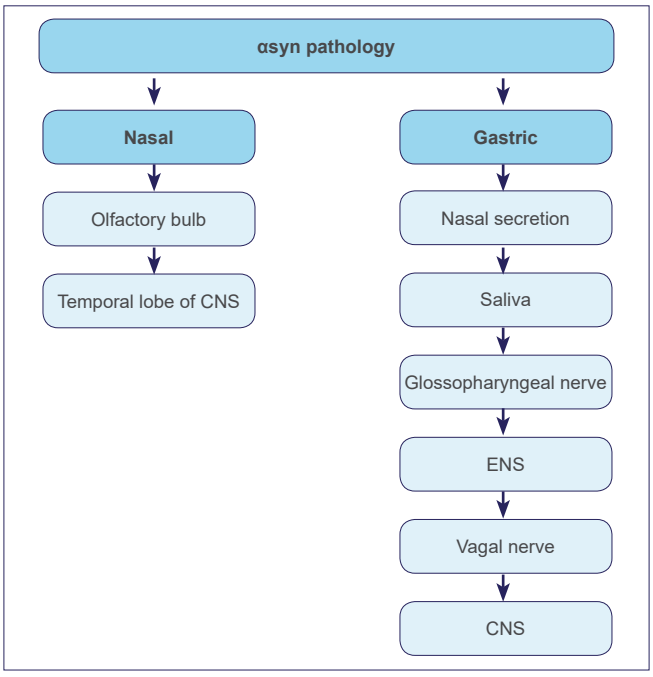

Figure 2: Alpha-synucleinopathy spread along the brain–gut axis (adapted from Sampson, Debelius & Thron and Mulak & Bonaz)

to affect the dopaminergic neurons, but are also suspected of being responsible for the digestive symptoms of PD. However, data available on the neurochemical and structural changes of enteric neurons are not yet complete.[21]

Prevotella is known to break down complex carbohydrates into SCFAs, with folate and thiamine as by-products. Patients with PD have decreased *Prevotella* numbers and have therefore reduced the production of these essential micronutrients. This results in both a decreased production of important vitamins and impaired gut-hormone secretion. These gut-microbiome changes could therefore have a direct effect on the CNS, although further studies are required before definitive conclusions may be made in this regard.[19]

PD has a defined clinical pattern, with gastrointestinal symptoms being followed by impaired olfaction and abnormal salivation. This step-wise march can be replicated by the Braak staging system, which shows increasing deposits of αsyn in the enteric nervous system, the motor nucleus of the vagus nerve, the olfactory bulb and the submandibular gland. All of these sites are exposed to the environment.[23] The analysis of urinary products of bacterial metabolism provides further evidence to support bacterial dysbiosis in the aetiology of PD.[24,25] Urinary indoxyl sulphate reflects small intestinal bacterial overgrowth (SIBO) and is consistently elevated in PD patients.[24] Similarly, microbial communities from faecal and mucosal specimens in PD patients are significantly different from those in control subjects.[26] Several studies have also shown a close relationship between nutritional status and neurodegenerative disease, reaffirming the interdependency between the brain and gastrointestinal function.[27] Nutritional assessment should, therefore, be included in the work-up of patients with PD. There is, however, inadequate

clinical evidence to make appropriate suggestions regarding nutritional advice for symptom reduction and improved health-related quality of life in this group of patients.[27]

SIBO is defined as a syndrome of malabsorption associated with an increased density of bacteria of more than 10^5 colony-forming units/mL of small intestinal aspirate and/or the presence of colonic-type species.[28,29] Predisposing factors for the development of SIBO are related to impaired gastrointestinal motility (caused by systemic diseases such as hypothyroidism and diabetes mellitus). Fasano et al found an increased prevalence of SIBO in PD patients without finding an increased prevalence of *Helicobacter pylori* when compared to healthy controls. *Helicobacter pylori* infection did, however, play a synergistic role with SIBO in the pathogenesis of motor fluctuations, with worsening unpredictable motor fluctuations that improved with *Helicobacter pylori* eradication.[28]

SIBO contributes towards the development and severity of motor complications in numerous ways. SIBO may impair drug absorption by changing chyme composition. Mucosal injury may lead to malabsorption secondary to loss of brush-border disaccharidases activity. Detrimental inflammatory effects on enterochromaffin-like cells further reduce gastric emptying. SIBO may impair levodopa absorption due to jejunal mucosal inflammation or as a result of partial metabolism of levodopa by bacteria.[28] The fact that bacterial overgrowth is significantly higher in the small intestine of PD patients, together with the predictable clinical pattern, suggests that dysbiosis may be central to CNS disease and that future treatment strategies may need to be adjusted accordingly.[28] Additional studies are required in this regard.

Gut microbiota have also been shown to modulate behaviour via fermentation products. One of these fermentation products – namely, D-lactic acid – has cognitive effects, with cognitive impairment associated with rising levels of D-lactic acid. SIBO is associated with increased D-lactic acid production and therefore subsequent cognitive decline.[7]

Various systemic diseases, including obesity and diabetes, show significant changes in both resident gut-microbiome composition and the host's gut homeostasis and metabolic processes.[19] Type 1 and type 2 diabetes mellitus, obesity and PD have been associated with dysbiosis of the gut.[25] Individuals with type 2 diabetes mellitus have been shown to have higher proportions of *Betaproteobacteria* than healthy individuals. This correlated with higher plasma glucose levels more than with body mass index (BMI), implying that *Betaproteobacteria* may be involved in glucose metabolism. Preliminary studies have also shown an increased association with type 2 diabetes mellitus and the development of PD. Although the mechanistic link between these conditions is unknown, both share pathophysiological mechanisms: chronic inflammation, oxidative stress and mitochondrial dysfunction.[19]

Since individuals with type 2 diabetes mellitus have a higher risk of developing PD, the effect of anti-diabetic drugs on PD has also been evaluated. An individual's risk of developing PD increases 2.2-fold when they are diagnosed with type 2 diabetes mellitus. However, with oral anti-hyperglycaemic agents, the risk is decreased to 1.3-fold. This suggests that oral anti-hyperglycaemic agents may have a protective effect against the development of neurodegenerative diseases such as PD.[19]

ALZHEIMER'S DISEASE

The gut microbiome has been shown to condition the host's immune system to foreign microbes while regulating autoimmune responses that can have an effect on neural-signalling and homeostatic metabolic functions.[8,9] The particular contribution of the gut microbiome and bacterial amyloid to misfolding and amyloidogenic diseases needs to be researched further.[8] AD has been associated with dysregulation of innate immune and auto-immune responses.[8] Some studies have suggested that differences in exposure or 'human biochemical individuality' and genetic vulnerability towards autoimmunity, mediated by the gut microbiome, may have a significant impact on the course of age-related neurological disease.[8,9]

The distinctive neuropathological features associated with AD include amyloid plaques and neurofibrillary tangles.[1,10] In many areas of the brain – namely, the hippocampus, the frontal, temporal and parietal cortices, and the cholinergic basal forebrain – these neurofibrillary tangles form amyloid-β peptides that are deposited as amyloid plaques. This results in the withdrawal of neurites, lost synapses and subsequent cell death.[10] The 'amyloid-cascade' hypothesis of AD suggests that amyloid-beta peptide accumulation is the primary influence on the inflammatory degeneration of neurons in the CNS and is possibly the driving factor for the pathogenesis of AD. The presence of bacterial lipopolysaccharides or endotoxin-mediated inflammation contributes greatly to amyloid neurotoxicity and, once formed, may induce a self-perpetuating sequence resulting in the amplification, aggregation and spreading of pathological protein assemblies.[30]

A wide variety of gut microbiome-resident species, including bacteria, viruses and fungi, generate significant quantities of functional lipopolysaccharides, amyloids and related microbial exudates. Therefore the human physiology is chronically exposed to a marked systemic burden of a wide variety of microbial amyloids.[30] This exposure becomes exceedingly important during the ageing process, during which the blood–brain barriers and gastrointestinal tract epitheliums become significantly more restructured and permeable.[25,30,31] This results in the CNS being more susceptible to microbes and/or their neurotoxins as well as to neurotoxins produced by environmental pathogens.[31]

There is a direct communication between the brain and the oronasal cavity via many nerves, particularly the trigeminal and olfactory nerves. The trigeminal nerve may act as a route of entry for oral bacteria into the brain in AD, because it has been shown to harbour Treponema. The 'olfactory hypothesis' introduced by Mann et al suggested that the olfactory tract is a possible entry route for pathogens which are able to trigger production of neurofibrillary tangles and amyloid plaques.[10]

The neurotrophins, the brain-derived neurotrophic factor (BDNF) and the nerve-growth factor are essential to maintaining cell viability and synapse connectivity, both of which are diminished in AD.[10] Amyloid protein is thought to possibly also be produced by human microbiota. This raises concern about the role of the gut microbiome in the induction of AD.[4]

Some microorganisms in the gut microbiome, such as *Lactobacillus brevis* and *Bifidobacterium dentium*, are able to metabolise glutamate to produce gamma-amino butyric acid (GABA). GABA is the major inhibitory neurotransmitter of the CNS. Increased GABA in the gut is associated with increased CNS levels. CNS dysfunctions in GABA-mediated neurotransmission and neuromodulatory functions have been linked to the development of behavioural deficits, depression, anxiety, epilepsy and cognitive impairment, including AD.[8]

BDNF is also known to be essential in neuronal maintenance and survival and also has pleiotrophic effects on neuronal development, differentiation and synaptogenesis.[8,9] BDNF plays an important role in the synaptic plasticity that underlies neuronal circuit formation and cognition.[8,9] It has been found to be reduced in the serum and brain of patients with behavioural defects, anxiety, schizophrenia and AD.[8,9]

Interestingly, β-N-methylamino-L-alanine (BMAA), a neurotoxic amino acid not typically incorporated into polypeptide chains that form brain proteins, has been linked with intra-neuronal protein misfolding.[8] This is a hallmark feature of the resultant inflammatory neurodegeneration that is secondary to amyloid peptide-enriched senile plaque lesions which are characteristic of AD, prion disease, PD and amyotrophic-lateral sclerosis. BMAA has been shown to be a neurotoxin that depletes glutathione, targets NMDA glutamate and induces oxidative stress.[8,9] It has been postulated that BMAA is produced by the cyanobacteria of the gut microbiome. Gastrointestinal disease, malnutrition and stress are further associated with increased BMAA production.[9]

Approximately 95 per cent of human beings harbour the intensely neurotropic herpes simplex-1 (HSV-1) in their trigeminal ganglia. Whether this relationship between host and virus is symbiotic, neutral or detrimental remains controversial. The activation or re-activation of HSV-1, as well as other forms of endogenous virus, are stress-related; however, it is still unclear whether gut microbiome metabolites play a role in pathogenic activation mechanisms. Recent studies have linked the activation of endogenous HSV-1, or other neurotropic microorganisms, to neurological stressors that are further linked to inflammatory neurodegeneration, amyloidogenesis and progressive cognitive impairment.[9] It may also play a contributory role to the predisposition to, or the early development of, AD and schizophrenia.[9,31]

Chronic fungal infections, *Toxoplasma gondii* (*T gondii*), *Chlamydophila pneumoniae*, hepatitis C virus, cytomegalovirus and prion diseases have been shown to increase the risk of AD.[31] Cytomegalovirus has also been linked to schizophrenia,

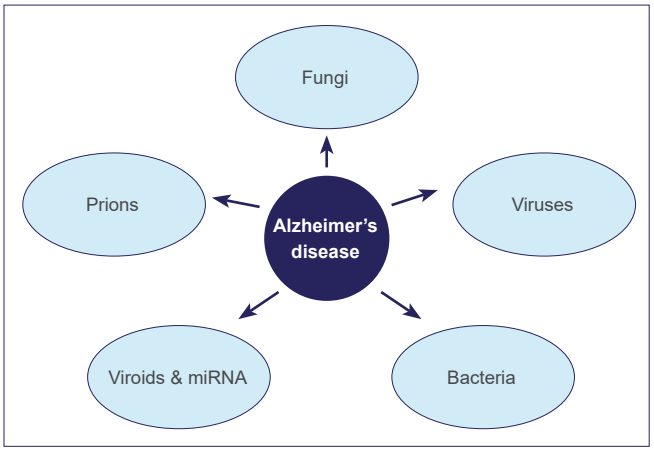

Figure 3: Potential contributing pathogenic microbes to the development of AD (adapted from Hill, Clement, Pogue, Bhattacharjee, et al)

depression and anxiety.[32] Prion diseases are self-replicating 'microbes' and amyloid-beta peptide 'prion-like' deposits induce widespread amyloidogenesis after inoculation into susceptible animal hosts.[31] *T gondii* has been shown to have strange effects on mice.[32,33] It causes them to lose their wariness of cats and cat urine, become more exploratory and spend increased time in daylight, therefore increasing their exposure to cats.[33] In human beings, *T gondii* causes males to be more aggressive and more jealous, and to indulge in riskier behaviour, while causing females to be more likely to commit suicide. *T gondii* has been associated with dementia, but also bipolar mood disorder, obsessive-compulsive disorder, autism and schizophrenia.[33]

Dietary manipulation of the gut microbiome and future personalisation of medicine may improve the clinical management and outcomes of brain disorders such as AD.[1] Future AD disease therapies may also involve probiotic approaches, particularly as a prophylactic tactic prior to the diagnosis of mild cognitive impairment or early AD.[9] Many antibacterial dietary components have been associated with reducing the risk of AD. Foodstuffs with proven antibacterial activity include garlic, olive oil, curcumin and honey. Many of these 'protective' foodstuffs also have anti-inflammatory properties that are thought to help in the prevention of AD progression, though clinical trials have shown disappointing results in this regard.[10]

The brain is an organ with a high metabolic rate, and therefore oxidative stress is a common phenomenon in its neural tissue. Antioxidant enzymes are endogenous but need exogenous nutrients for proper functioning.[5] Epidemiological studies researching the association between the dietary intake of antioxidants – particularly vitamins A, C and E (and trace minerals copper, selenium, zinc and manganese) and polyphenols (found in vegetables, fruit and plant-derived foods and beverages) – and cognitive decline, have shown inconsistent results.[5] One large randomised control trial (RCT) on long-term supplementation with extra-virgin olive oil revealed a significant improvement in episodic memory and verbal fluency and a decreased incidence of mild cognitive impairment.[5]

The relationship between the gut microbiome and the immune system is a fundamental aspect of the pathogenesis of obesity and obesity-related disorders. Increasing evidence has linked obesity to an increased risk of AD, as a result of more structural brain changes such as altered white matter and increased age-related brain atrophy. These findings have been shown in longitudinal data from the Framingham Heart Study. Significant literature has emphasised the vital role that the hippocampus plays in obesity-associated cognitive dysfunction. The metabolic syndrome results in neurocognitive impairment secondary to the long-term effects of poor metabolism. Mean grey-matter cerebral blood flow was shown to be 15 per cent reduced in individuals with metabolic syndrome when compared to that of controls. However, even short-term metabolic impairments have been associated with smaller hippocampal volumes and cognitive decline. Obesity has also been associated with increased levels of reactive oxygen species that promote cognitive impairment.[17]

For future clinical management of AD and related neurodegenerative disorders with inflammatory and immune components, therapeutic approaches should include anti-inflammatory, anti-bacterial and/or antiviral medication directed towards the health and homeostasis of the microbiome.[1,8,31]

CONCLUSION

Gut microbiota play a crucial role in the bi-directional interaction between the CNS and the intestines.[34] There is a long history of co-evolution between human beings and the microorganisms in our gut microbiome. This co-evolution may have effects on mental and physical health. The effects of imbalances in gut microbiota composition at different stages of life, and their subsequent short- and long-term impact on behaviour and brain modulation, require extensive consideration.[7] However, premature conclusions in extrapolating these findings to human beings should be avoided.

The extrapolation of findings in studies based on laboratory animal models to human beings is unwise because laboratory animals live under abnormally hygienic conditions. Animals living in less hygienic conditions, and human beings, encounter different immune responses. Human beings also exhibit cognition and adaptive behaviour that is different from other species.

More studies (including carefully designed translational and clinical studies) need to be conducted to investigate the aftermath of imbalances in gut microbiota composition. Investigations also need to be launched into possible avenues of prevention and treatment in the clinical sector to avoid long-term or permanent

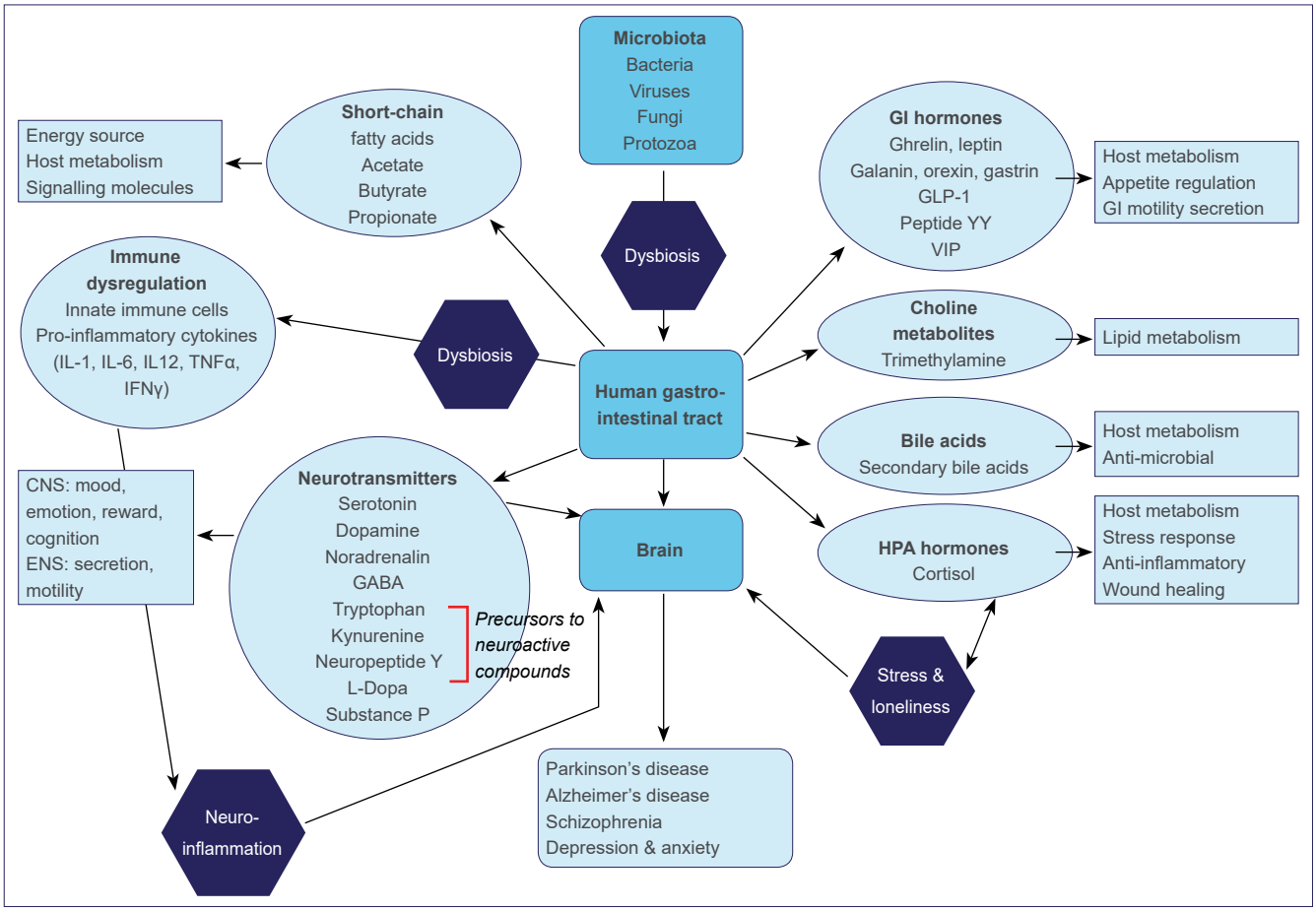

Figure 4: The microbiome–gut–brain axis and its effects (adapted from Forsythe & Kunze; Panduro, Rivera-Iniguez, Sepulveda-Villegas & Roman; O'Callaghan, Ross, Stanton & Clarke and Ramezani & Raj DS)

effects.[7] Infant studies are of particular importance, first, to ascertain the effects of alterations in the gut microbiome early in life on brain development and gut–brain interactions and, secondly, to assess whether interventions aimed at reducing gut dysbiosis can alter such effects.[35]

Several other areas need further consideration. These include obesity, the hygiene or microbiota hypothesis for allergic disease and the possible association between gut microbiota and psychiatric conditions. Of further relevance is the role of probiotic or commensal strain exposure to certain inflammatory conditions – such as rheumatoid arthritis, asthma, inflammatory bowel disease (IBS) and chronic obstructive pulmonary disease – all of which have strong associations with mood disorders and depression.[36] Further studies in human beings are therefore essential before any conclusive remarks, regarding the effect of the gut microbiome on complex psychiatric disorders, can be made.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

This article has been peer reviewed.

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