THE IMMUNOLOGY OF MIND CONTROL – EXPLORING THE RELATIONSHIP BETWEEN THE MICROBIOME AND THE BRAIN - PART 1

Maria Karsas
Greg Lamb
Robin J Green
Department of Paediatrics and Child Health, University of Pretoria
Email | mkarsas@hotmail.com

ABSTRACT

In this series of articles, the relationship between the human species and the human gut microbiome will be evaluated to determine if it is symbiotic, parasitic or somewhere in between. The possibilities, based on animal studies, are explored and compared to studies in human beings. In particular, close attention is paid to the relationship between the gut microbiome and the central nervous system, especially its effect on human behaviour. This relationship is termed the 'microbiome–gut–brain axis'. The gut microbiome has an influence on stress (both acute and chronic), anxiety, loneliness and depression, through a number of pathways. It has also been associated with the development of neurodegenerative diseases, such as Alzheimer's and Parkinson's, with associated cognitive decline. The concept of 'mind control' of human beings by organisms in the microbiome is relatively new, but has been demonstrated with multiple examples in the animal kingdom. Therefore, it is not surprising that certain components of the microbiome have also been associated with the development of schizophrenia. Since the common treatments used for these conditions are not equally effective in all patients, it is vital for clinicians to explore other avenues to be used as therapeutic targets. Recent research has also evaluated the impact of vitamin D and olfaction on the brain, and its possible use as adjunctive therapy. The gut microbiome, in particular, requires further research to aid in the development of future therapies for certain conditions. Animal studies in this regard have shown promising results, but human studies are infrequent, often with disappointing results. Randomised control trials in human beings are required to prove or disprove the effects of the gut microbiome on complex psychiatric diseases.

Key words: immunology; mind control; microbiome; brain; relationship

INTRODUCTION

Both a species, and individuals of that species, are greatly affected by social behaviour. Social behaviour is regulated by complex neurological and biochemical processes as well as by underlying brain structures.[1] Similarly, normal social behaviour may be disrupted by neurological disorders such as depression, stress, social anxiety disorders, autism and schizophrenia, among many others.[1]

The human body contains a sizeable and diverse community of microbial cells, with their genetic material, collectively known as the 'microbiome'.[2] A new concept in modern science links gut microbiota to the potential to modulate the brain and behaviour.[1] This concept has been termed the 'microbiota–gut–brain axis'.[1] The gastrointestinal tract is the point of communication between the gut microbiota, the immense network of millions of neurons in the body and the body's largest concentration of immune cells.[3]

Literature suggests the microorganisms in the gut microbiome outnumber human host cells in the body by 100:1, whereas microbial genes of the gut microbiome outnumber human host genes by approximately 150:1.[4,5] 'We are thought to be more microbiome than human',[6] however, this does not automatically suggest a correlation between microbiome number and influence on human behaviour.[6]

It may not be surprising however that the gut microbiota can impact various areas of the host's physiology.[3] In addition, not only human physiology but human behaviour may very well be influenced by parasites and bacteria in our gut microbiome, where perturbations may result in individuals behaving in an odd and unpredictable manner.[6] The fact that bacteria effectively engage in mind control should not come as a surprise. If the weight of the microbiome organ is the same as that of our brains, then it is plausible that over millions of years microbiota have learned to know us so well that they may be able to affect

every part of our dispensations, driving us, for example, to go out and find them food or help them reproduce.[7]

Mind control is a real and prevalent threat to human beings. It is already used by many organisms on their hosts in the animal kingdom. For example, the *Cordyceps* fungus infects ants, causing them to travel to treetop canopies where they die. The fungus then reproduces and its offspring float down to the forest floor to infect more ants.[6] *Dicrocoelium dentriticum* causes ants to climb to the tops of grass blades, in order to enhance their chances of being eaten.[8] Nematomorph worms cause their cricket hosts to kill themselves by jumping into water and drowning so that the worms can return to their natural habitat; *Paragordius tricuspidatus* has a similar effect on grasshoppers.[6,8] Parasitic trematodes infect snails and make their eyeballs bulge and change colour – to blue, yellow and red – so that birds may better see them and then peck off their eyestalks, allowing the trematodes to complete their lifecycles in the bird's guts. These horrors are not restricted to invertebrates alone.[6] The intestine is densely populated with commensal bacteria that interact directly with protozoan parasites, and are able to influence their behaviour. Protozoa living in human blood or tissue may be affected by the interplay between the gut microbiome and the host's immune system and metabolism.[9] The mind-altering influence of the microbiome is a result of a long history of co-evolution, rather than malicious manipulation of the host's behaviour. However, it has been suggested that the gut microbiome is the puppeteer Gepetto, while the brain is Pinocchio, its puppet.[8]

It is important to note that these data are largely based on animal studies (insects and small animals) or correlative analysis in patient populations. Additional research, in the form of randomised control trials is required in order to make conclusions regarding this hypothesis in human beings.[7]

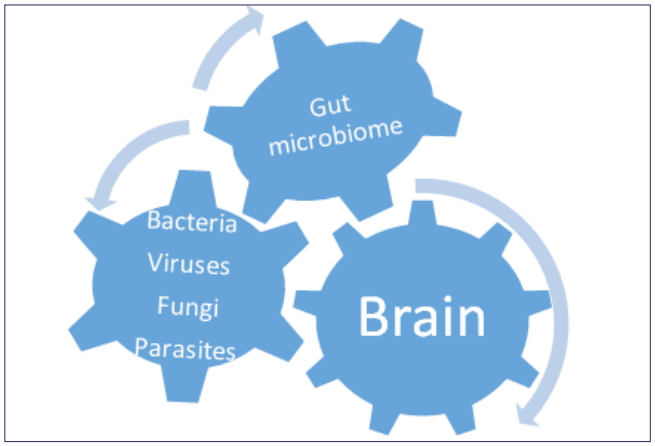

Figure 1: The symbiotic spectrum poses the question whether the relationship between the gut microbiome and the brain is mutualistic, commensalistic or parasitic in nature, or possibly a combination of all three.[8]

Only two bacterial divisions are prominent in the gut microbiome: the anaerobic gram-negative Bacteriodetes and gram-positive Firmicutes.[4,5,7] Interestingly, only 20–30% of microbes in the human colon can be cultured.[10] In order to test specific hypotheses, the medical community realised other techniques were required to fully assess the microbial function and diversity, as well as its potential effects.[11] Therefore multiple advances in analytic techniques (such as 16S rRNA sequencing, single-cell genome sequencing, metagenomic sequencing, cultivation, metabolomics, among others) have been employed in order to better characterise the diversity of the gut microbiome. This is because different bacterial species, including fungi, protozoa and viruses, vary in number and diversity throughout development as well as among different human populations.[2,4,10,11] These new techniques will aid in our understanding of the sites, pathways and molecular mechanisms within the gut–brain axis as well as establish new roles for the microbiome in health and disease; a still controversial issue in literature.[11,12]

The gut microbiome is often referred to as the 'forgotten organ'.[13] Our initial understanding of the gut microbiome and its effects relied upon the germ theory of disease postulated by Louis Pasteur, focusing on microbes as agents of disease. However, new ways of thinking and discussing concepts of microbiology have emerged looking at the commensalistic and/or symbiotic relationship of the gut microbiome rather than simply its parasitic realtionship.[11]

The gut microbiota's signature may be seen in several aspects of behaviour and in several neurological and metabolic disorders. These disorders affect social behaviour both directly and indirectly in various ways: via neural (vagus and the enteric nervous system), immune (cytokines), metabolic (short-chain fatty acids) and endocrine (cortisol) pathways.[1]

Microbiota produce neuroactive molecules which may affect the gut epithelial barrier and eventually the brain. The gut microbiota strongly influence the autonomic nervous system, via the enteric neurons and vagus nerve, to relay messages to the brain. They can alter the function of the hypothalamic-pituitary-adrenal (HPA) axis resulting in the release of cortisol, which alters gut permeability and barrier function and, ultimately, change the composition of the gut microbiome. They also play a role in the development of the immune system, and may control cytokine release through lymphocyte activation. This may have paracrine or endocrine actions.[1]

Certain gut bacteria synthesise neurotransmitters, as well as approximately 20 neuropeptides produced in enteroendocrine cells. These neuropeptides serve as secondary brain messengers, regulating cognition and mood. They include calcitonin, corticotropin-releasing factor, substance P, pancreatic polypeptide, vasoactive intestinal polypeptide (VIP), glucagon-like-peptide-1 (GLP-1) and somatostatin, neuropeptide Y and peptide YY. The latter two play a vital role in energy homeostasis.[14] Neuroactive bacterial metabolites of dietary fibres, namely, short-chain fatty acids such as propionate and butyrate (among others), may also modulate behaviour and

TABLE I: POTENTIALLY HARMFUL AND BENEFICIAL BACTERIA OCCURRING IN THE GUT (ADAPTED FROM GHAISAS, MAHER & KANTHASAMY[19])

POTENTIALLY HARMFUL BACTERIA		POTENTIALLY HARMFUL OR BENEFICIAL BACTERIA	POTENTIALLY BENEFICIAL BACTERIA	
Production of enterotoxins	*Clostridia*	*Firmicutes*	*Bifidobacterium*	Aid in Digestion
Pathogen-producing toxins	*Staphylococcus*	*Bacteroides*	*Lactobaccilus*	Antitumor Activity
	Proteus	*Escherichia coli*	*Eubacterium*	Production of short-chain fatty acids
	Pseudomonas aeruginosa	*Enterobacteriaceae*	*Fusobacterium*	
		Veillonella	*Campylobacter jejuni*	Potential tumour marker

the brain by increasing peptide YY secretion. This reduces gut motility, resulting in enhanced absorption of nutrients and harvesting of energy. It is further linked to the development of diabetes and obesity, both diseases with social implications.[1]

The gut also communicates with the brain via hormone signalling pathways which activate the release from enteroendocrine cells of gut peptides (namely, ghrelin, galanin, orexin, leptin and gastrin) that may act directly on the area postrema of the brain. The response to these gut peptides has been linked to changes in anxiety, the sleep–wake cycle and sexual behaviour. Galanin plays a role in HPA-axis modulation in response to stress and has been shown to have deleterious effects on cognition, thereby acting as a link between stress, anxiety and memory. It has therefore been suggested that galinergic drugs should be considered as a therapeutic option for certain psychopathologies. Ghrelin similarly acts in the brain to mediate anxiogenesis and increases memory retention. The pancreatic polypeptide-fold family (pancreatic polypeptide, peptide YY and neuropeptide Y) have actions on a number of organs. Peptide YY and neuropeptide Y have been shown to have anxiolytic effects in rats, whereas the latter has also been implicated in obesity and feeding, memory retention, anxiety, depression and neuronal excitability. Lu et al, demonstrated the effect of low leptin plasma levels in rats exposed to chronic stress. Treatment of these rats with leptin reversed the behavioural changes, with associated neuronal activation in the limbic structures, particularly the hippocampus. Studies on diabetic mice have shown similar antidepressant effects of leptin.[3] Few randomised control trials have assessed the role of the gut microbiome in disease, therefore conclusions in this regard are difficult.[11]

Interestingly, mitochondria are thought to originate from bacteria via early formation of endosymbiotic relationships in the evolutionary history of eukaryotes. Cross-reactivity of mitochondria and immunological responses to the gut-microbiome constituents may have harmful effects on mitochondrial function through a process of molecular mimicry. This process plays a role in the inflammatory basal ganglia disorder, Sydenham's chorea and in rheumatic fever.[15]

Diet also plays a role in the gut-microbiome composition. In adults consuming Western diets, high in protein, sugar and fat, *Firmicutes* are the dominant phylum; whereas *Bacteroides* are more common in those individuals consuming fibre-based, agrarian diets.[10,14] Western diets contribute to gut-microbiome dysbiosis as well as reduced short-chain fatty acid production from fibre fermentation, contributing to a reduced anti-inflammatory role.[14] However, one mouse study revealed a 'protective effect' of a high-fat diet (reducing depressive and anxiety behaviours in chronic stress). This demonstrates the complex interactions and casual relationships between stress, diet and the microbiome–gut–brain axis.[7]

The gut microbiome is a dynamic entity that evolves continuously throughout the host's lifespan and reaches some stability only after the first three years of life.[2] The gastrointestinal tract is sterile in utero but is rapidly colonised at birth, primarily from maternal contact.[16] The composition of the early-infant microbiota is highly dynamic and unstable, but of low diversity.[17] The diversity and number of bacteria increase throughout early childhood, and are sensitive to a wide variety of factors such as infection, diet, stress and pharmacological interventions (such as antibiotic use), which result in both short-term and long-term sequelae to the host.[2,16,18] The resultant dysbiosis may impact both general and mental health negatively.[18] Of note, is the fact that it is becoming increasingly apparent that bacteria are required for normal brain development as well as brain function in adulthood.[7]

STRESS

Stress is defined as an acute threat to an organism's homeostasis. An adverse event or stressor, whether physical or psychological, will result in a cascade of physiological, emotional and behavioural reactions to allow the organism to cope with the situation. Chronic, severe, uncontrollable stressors, however, may trigger maladaptive changes in brain structure and function, with potential long-term effects on physical and mental well-being.[2]

The HPA axis is significantly involved in both mental and physical well-being of individuals. Positive and negative social

interactions have a marked impact on both the activity and the reactivity of the stress circuits. Gut microbiota have an impact on the HPA axis and vice versa, and this ultimately impacts social behaviour.[1] Research from both animal and human studies has shown that emotional stressors can negatively impact gut microbiota.[7,20]

As mentioned, gut microbiota can both directly and indirectly influence the stress circuits. Direct influence on the central nervous system (CNS) functioning occurs through neuronal activation of the stress circuits. The first point of contact for these microbiota is the gut lumen and the neurons of the enteric nervous system. These sensory neurons are less excitable in germ-free mice than their specific pathogen-free counterparts, whereas colonic neuron excitability may be enhanced by the probiotic bacterium *Lactobacillus reuteri*. Messages from the gut are then relayed to the brain via the vagus nerve. Direct central circuitry activation in the paraventricular nucleus of the hypothalamus has been observed in germ-free mice following oral administration of a non-infectious strain of *E coli* and *Bifidobacterium infantis*, demonstrating that pathogenic or commensal bacteria can alter the electrophysiological properties of enteric neurons and provide messages to the brain to which it, accordingly, reacts.[1] Sudo et al, demonstrated that germ-free animals had exaggerated HPA axis activation in response to stress, and that this hyper-response was reversed by reconstitution of animal faeces with a single bacterial strain, namely, *Bifidobacterium infantis*, but was further aggravated by enteropathogenic *E coli*.[3]

It is important to note that the germ-free model has several limitations. Researchers should therefore be cautious to extrapolate findings from these studies in germ-free mice to human beings.[12] Germ-free mice are delivered surgically and are transferred directly and raised in sterile isolators with no microbial exposure.[7,12] This gives rise to a wide range of differences in gut and brain biochemistry, HPA-axis response, metabolic function and social behaviour between germ-free and control animals (the latter of which have normal or pathogen-free flora and are reared by normally colonised mothers).[12]

Both acute and chronic stress activate the stress circuits indirectly and lead to modulation of the HPA axis.[1]

ACUTE STRESS

With regard to acute stress, a recent study revealed that the absence of gut microbiota in stress-sensitive rats aggravated the HPA and behavioural responses to acute stress. Germ-free rats had 2.8-fold higher serum corticosterone concentrations than their specific pathogen-free counterparts. The germ-free rats also had decreased glucocorticoid receptor mRNA expression in the hippocampus and increased corticotrophin-releasing hormone mRNA expression in the hypothalamus, indicating the exacerbation of neuroendocrine and behavioural responses to acute stress in the absence of gut microbiota. Germ-free mice exposed to restraint stress also demonstrated a significantly high corticosterone and adrenocorticotrophic hormone response, which was reversed after they received a probiotic bacterium, *Bifidobacterium infantis*.[1] This gives weight to the finding that a decrease in *Bifidobacterium* and *Lactobacilli* was observed under conditions of nervous-emotional and restraint stress.[1]

In studies observing the effects of maternal separation stress, neonatal stress in rats was shown to lead to an altered gut–brain axis as well as to alterations in the gut–microbiome composition. These effects were reversed by probiotics. Decreased numbers of *Lactobacilli, Campylobacter spp*. and *Shigella spp.* have been seen in conditions of maternal separation stress. It is important to note that the stress response circuitry at birth is functionally immature and develops alongside bacterial colonisation throughout the postnatal period, therefore being vulnerable to changes in the gut microbiome.[1]

Other studies have revealed similar results, with an 18–26% increase in *Bacteriodes* and a 10-fold decrease in *Lactobacilli* and *Bifidobacterium* in stressed conditions; one study demonstrates a decrease in *Lactobacilli* with an increase in aerobic bacteria under conditions of emotional stress, food deprivation, acoustic stress and restraint conditions.[1] These studies identify the direct involvement of gut microbiota in stress, and clarify the microbiota's role in HPA-axis programming early in life as well as in reactivity to stress over an individual's lifespan.[1]

CHRONIC STRESS

Chronic stress and depression are rampant in modern life. Both may cause measurable brain shrinkage. More than 140 proteins in the brain are affected negatively by electromagnetic frequency exposures emitted by cellphones and other electronic devices. Technology has forced most individuals to be multitaskers. The brain, however, cannot concentrate on two things at once but rather toggles quickly back and forth between tasks, with resultant decreased attention span, ability to learn, short-term memory and overall mental performance.[20]

As if this were not enough, chronic stress is also associated with dysregulation of the HPA axis. Prolonged stress results in disruption of the integrity of the intestinal barrier, resulting in increased translocation of gut microbes and direct access to both neuronal and immune cells of the enteric nervous system. Exposure to specific chronic psychosocial stress in mice leads to an increase in *Clostridium spp* and a reduction in *Bacteroides spp*. Pre-treating rats with a probiotic, namely, *Lactobacillus farciminis,* has been found to attenuate the HPA-axis stress response by preventing impairment of the intestinal barrier.[1]

Up to 60% of gastrointestinal diseases are linked to stress. Due to globalisation, individuals with gastrointestinal conditions have high stress rates and suffer further from anxiety, stress and pain due to marked lifestyle changes that impact on their quality of life.[14] These individuals also have alterations to their gut microbiomes.[14] In patients with irritable bowel syndrome (IBS), studies have reported decreased proportions of *Bifidobactrium* and *Lactobacillus* species and increased levels of *Firmicutes* such as *Bacteriodetes*.[10]

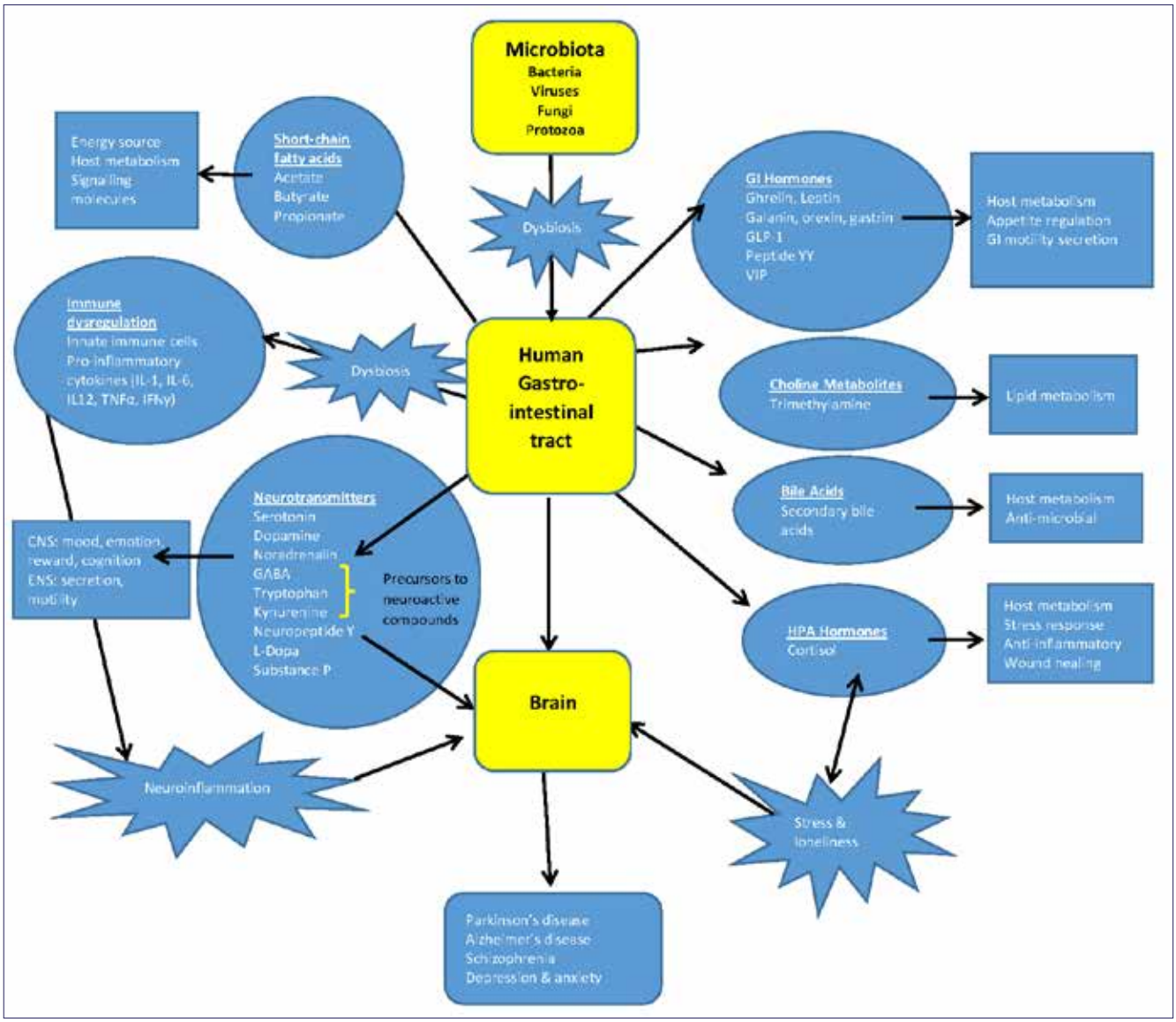

Figure 2: The microbiome gut–brain axis and its effects (adapted from Forsythe & Kunze,[3] Pandura et al,[14] O'Callaghan et al,[23] SJ functional medicine[24] and Ramezani & Raj[25])

ANXIETY

Anxiety and social behaviour are often inseparable. Social anxiety disorder (or social phobia) is an overwhelming and persistent fear of social situations that significantly impacts social behaviour. Gut microbiota seem to play a deceitful role regarding anxiety, with contradictory reports. Some studies have shown that germ-free mice have reduced anxiety-like behaviour, despite an elevated basal corticosterone level compared to their specific pathogen-free counterparts. However, other studies dispute these findings, revealing increased anxiety-like behaviours with associated increased corticosterone levels.[1]

Reconstituting the guts of germ-free mice with healthy microbiota in early life results in normalisation of elevated plus maze behaviour and some aspects of light/dark behaviour; however, reconstitution of the gut microbiome in adulthood fails to alter the anxiety-like phenotypic behaviour.[1] This suggests that gut microbiota contribute to developmental programming, and have an action during a developmental 'window of vulnerability' which subsequently may impact long-term physiological function.[3]

Antimicrobials also have an effect on the gut microbiome and anxiety-like behaviour. Oral administration of neomycin, bacitracin and antifungal pimaricin for seven days increases exploratory behaviour and decreases anxiety-like behaviour, a behavioural pattern similar to that seen in germ-free mice, however, this behavioural pattern returns to normal after a two-week rest period. This finding is further supported by a study documenting that germ-free mice treated with antibiotics demonstrated no behavioural changes.[1]

Prenatal and early postnatal life represents a critical period for the developmental trajectory of the brain, characterised by

rapid changes in neuronal and microbial organisation, and may be influenced by the gut–brain communication.[18,21] Problems relating to such communication during this critical period may result in an increased risk of mental illness and behavioural problems later in life.[18] This period is also, fascinatingly, a critical period for metabolic development.[21] Recent studies have shown that low-dose antibiotic exposure from birth to weaning age in mice led to an altered metabolic phenotype that persevered to adulthood. Interestingly, post-weaning antibiotic exposure had less of an effect on the adult phenotype.[21] This shows an increased vulnerability to gut dysbiosis in the early postnatal window, which may have long-lasting effects on mental health in adulthood.[18,21]

Probiotics are live microorganisms that assist in the maintenance of a natural balance of gut microbiota and, when administered in adequate amounts, confer a health benefit on the host.[1,10] They have been widely used in the treatment of IBS.[10] *Lactobacillus rhamnosus* ingestion affects the brain at both a molecular and a behavioural level, and has been reported to have anxiolytic properties leading to decreased despair-like behaviour. At a molecular level, *L rhamnosus* alters the mRNA expression of both $GABA_A$ and $GABA_B$ receptors in several brain regions. These receptors are associated with depression and anxiety. Ingestion of *Bifidobacterium breve* in mice increases fatty-acid concentrations (namely, arachadonic and docosahexaenoic acid) in the brain. These fatty acids are known to have an effect on depression, anxiety and memory. The combination of *B longum* and *L helveticus* used in a clinical trial of healthy subjects revealed a reduced serum cortisol level and improved psychological effects, with a reduction in depression and anxiety. Other studies have shown similar results.[1]

The evidence from human studies regarding the manipulation of the gut microbiome with prebiotics and antibiotics is inconclusive. A small meta-analysis in patients with inflammatory bowel disease (IBD) treated with probiotics suggested a small therapeutic effect; however, it is unclear as to whether gut-microbiome alterations arise from primary alterations at the gut-microbial interface or as a subsequence of changes in the brain-to-gut signalling.[12]

TABLE II: GUT BACTERIA PRODUCE ACTIVE METABOLITES FOR THE HUMAN ORGAN SYSTEM[22]

BACTERIUM IN GUT MICROBIOME	ACTIVE METABOLITE PRODUCED
Lactobacillus and *Bifidobacterium*	Gamma-aminobutyric acid (GABA)
Escherichia coli, Bacillus and *Saccharomyces*	Norepinephrine
Bacillus and *Serratia*	Dopamine
Candida, Streptococcus, Escherichia and *Enterococcus*	Serotonin

Enteric infections with pathogenic bacteria also affect the microbiota–brain–gut axis. Mice infected with *Trichuris muris* demonstrate increased anxiety-like behaviour with associated decreased hippocampal levels of brain-derived neurotrophic factor (BDNF) mRNA, increased levels of pro-inflammatory cytokines and an increased plasma kynurenine : tryptophan ratio. Both tryptophan and BDNF have established roles in anxiety and in other neurological processes. Ingestion of *Bifidobacterium longum* assisted in normalisation of behaviour and BDNF mRNA in these mice, but had no effect on kynurenine or cytokine levels. Lyte et al, and Gareau et al, were able to document similar results with *Citrobacter rodentium. C rodentium* infection resulted in anxiety-like behaviour seven to eight hours post-infection.[1]

A possible avenue of exploration regarding adjunctive treatment for anxiety is reconstitution of the gut microbiome from healthy individuals via faecal transplantation. The behaviour of germ-free mice after faecal transplantation has shown that these mice acquired a behavioural profile similar to that of the donor. This provides evidence that microbiota strongly drive individual behaviour, and may be considered therapeutic targets for stress and anxiety.[1]

CONCLUSION

Gut microbiota play a crucial role in the bidirectional interaction between the CNS and the intestines.[10] The long history of co-evolution between humans and the microorganisms in our gut microbiome may result in a mind-altering influence on the host's behaviour, and may impact various areas of cognition. 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, need considerable consideration.[1] Germ-free mice have been shown to have disruptions in the development of brain mechanisms in relation to the HPA axis, hyperalgesia, behaviour and associated brain biochemistry. Premature conclusions regarding the extrapolation of these findings to human beings should be avoided.[10]

More studies (including carefully designed translational and clinical studies) need to be conducted to investigate the aftermath of these imbalances, as well as possible avenues of prevention and treatment in the clinical sector in order to avoid long-term or permanent effects.[1] Infant studies are of particular importance to ascertain the effects of alterations in the gut microbiome early in life on brain development, as well as gut–brain interactions and assess whether interventions aimed at reducing gut dysbiosis can alter these effects.[12]

The hygiene or microbiota hypothesis for allergic disease, and the possible association between gut microbiota and psychiatric conditions, as well as obesity, also need consideration, as do the relevance of probiotic or commensal strain exposure to certain inflammatory conditions, such as rheumatoid arthritis, asthma, IBD and chronic obstructive pulmonary disease (COPD), all of which have strong associations with mood disorders and depression.[3] Further studies in human beings are essential prior to any conclusive remarks regarding the effect of the gut microbiome on complex psychiatric disorders can be made.[7]

DECLARATION OF CONFLICT OF INTEREST
The authors declare no conflict of interest.

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