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Chapter title:

Microbiome - A Key Regulator of Body-Brain Interactions

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Chapter Summary

The gut microbiota, consisting of trillions of microorganisms, plays a critical role in regulating host physiology, including metabolism, immune responses, and brain function. This chapter examines the microbiota-gut-brain axis, a multifaceted bidirectional communication system connecting gut microbial activity with central nervous system processes through immune pathways, metabolic byproducts, and neural circuits like the vagus nerve. The evolution of the gut microbiota throughout an individual's life—from early developmental influences like birth mode and antibiotic use to changes associated with aging and neurodegenerative conditions—highlights its dynamic nature. The chapter reviews experimental approaches and microbiome-based interventions, to demonstrate the influence of the gut microbiota on neurological conditions such as autism spectrum disorder, anxiety, and Alzheimer's disease. Finally, it emphasises the importance of advancing microbiome-targeted therapies, integrating emerging technologies, and clinical trials to develop personalised strategies for enhancing brain health through gut microbiome modulation.

Introduction

The human gastrointestinal tract hosts trillions of microorganisms, collectively known as the gut microbiota, which have co-evolved with humans and profoundly influence various aspects of host physiology, including metabolism, immunity, and brain function (Cryan et al., 2019). This chapter examines the intricate dynamics of the microbiota-gut-brain axis, a bidirectional communication network linking the gut microbiota with brain function through direct and indirect pathways including immune modulation, tryptophan metabolism, vagus nerve activity, the enteric nervous system, and microbial byproducts. The chapter underscores the role of the gut microbiota as a reservoir of bioactive compounds that significantly affect host physiology and behaviour. Microbe-host interactions are in a symbiotic relationship that evolves throughout life, from early developmental stages influenced by birth mode and antibiotic use to age-related changes in microbial diversity linked to neurodegenerative diseases. Understanding these changes will be crucial for developing targeted microbiota-based interventions.

Studying the microbiome-gut-brain axis involves diverse methodologies and experimental approaches from germ-free and antibiotic-treated preclinical models to interventions using prebiotics, probiotics, synbiotics, and postbiotics (Cryan et al., 2020) see Fig. 1). These studieses have shed light on the microbiome's role in conditions such as autism spectrum disorder, attention-deficit hyperactivity disorder, anxiety, depression, obesity, and neurodegenerative diseases like Parkinson's and Alzheimer's disease. Factors such as diet and lifestyle significantly modulate the microbiome-gut-brain axis, influencing susceptibility to neurological disorders (Ross, Patangia, et al., 2024; Schneider et al., 2024a). These findings open avenues for microbiome-targeted therapies aimed at restoring balance and improving brain health.

Future research should focus on elucidating the mechanisms underlying microbiome-brain interactions and developing microbial-based therapies for neuropsychiatric disorders. Integrating systems biology with longitudinal and randomised controlled trials will be essential for translating these findings into clinical practice, ultimately leading to precision therapeutic strategies that enhance brain health through gut microbiome modulation.

The Gut-Brain Connection

Over two millennia ago, Hippocrates, often hailed as the father of modern medicine, reportedly proclaimed, "All disease begins in the gut". Although the authenticity of the quote remains debated, the underlying wisdom continues to significantly influence the field of medicine since including the emergence of new fields like nutritional psychiatry (Cryan et al., 2020; Dinan et al., 2021; Marx et al., 2022). This chapter embarks on a journey through history and science to explore the connections between the gut, digestion, and overall health, with a particular focus on the microbiome-gut-brain axis.

The journey into the mysteries of digestion began in the early 19th century with a fortuitous event involving the Canadian fur trader Alexis St. Martin. A gunshot wound left St. Martin with a fistula, creating a unique opportunity for Dr William Beaumont, a U.S. Army surgeon, to study human digestion in an unprecedented way (Beaumont, 1833). Beaumont's meticulous observations and experiments, which included inserting food directly into St. Martin's stomach through the fistula and analysing gastric secretions, provided groundbreaking insights into the digestive process. He discovered that emotional states, such as anger and irritation, could significantly impact digestion, hinting at the complex interplay between the brain and the gut. This early work laid the foundation for the concept of the brain-gut axis.

Following Beaumont's pioneering work, other scientists, including Charles Darwin and Claude Bernard, advanced the understanding of physiology (Ayala, 2009; Bernard, 1878, 1949 (Originally 1865); Darwin, 1859). Bernard's experiments with rabbits elucidated the process of fat digestion and the role of the pancreas. He introduced the concept of the "milieu intérieur," emphasising the necessity of a stable internal environment for healthy functioning, the cornerstone of homeostasis. Inspired by Beaumont, Ivan Pavlov developed the Pavlov pouch (LeDoux, 2003; Pavlov, 1897), a method to study digestive processes in canines. Pavlov's work on classical conditioning illustrated how external stimuli could affect internal physiological processes, reinforcing the concept of the brain-gut connection.

Such historical work laid the foundation for understanding the brain-gut connections' pivotal role in maintaining health and addressing disease. The advent of brain imaging technology in the 1980s revealed the bidirectional nature of a brain-gut axis, showing that gut distension activates crucial brain pathways, which are often heightened in conditions like irritable bowel syndrome (IBS) due to disruptions in the microbiota-gut-brain axis (Bonaz & Bernstein, 2013; Mayer, 2000). Additionally, the microbiota-gut-brain axis is recognised as a central component in mammalian interoception (Craig, 2009).

The Microbial Ecosystem: Allies in Health and Disease

More recently the critical role of the trillions of microbes residing on our bodies and in our gut, collectively known as the human microbiota has begun to emerge (Cryan et al., 2019). The human gut microbiota refers to the community of microorganisms themselves that reside in the gut, whereas the gut microbiome refers to the collective genomes of all the microorganisms which includes bacteria, viruses, fungi, and other microbes. In humans, the gut microbiota is one of the most well-studied communities, and it plays a key role in digestion, immune function, and even brain health through the microbiota-gut-brain axis.

Advances in sequencing technology and bioinformatic pipelines have enabled scientists to sequence these microbes and understand their vast contribution to our physiology (Bastiaanssen et al., 2019; Bastiaanssen et al., 2021; Bastiaanssen et al., 2022; Coelho et al., 2022; Human Microbiome Project, 2012; Sonnenburg & Sonnenburg, 2019). As a result and although the precise composition of a healthy gut microbiota is still debated (Joos et al., 2024), the gut microbiome is now recognised as a key player in regulating our immune system, metabolism, and even mental health.

Studies utilising germ-free animals, rodents that have grown up without exposure to any microbes, have shown that the absence of the gut microbiota affects many elements of health, including brain development and behaviour (Castillo-Ruiz et al., 2023; Desbonnet et al., 2015; Jaggar et al., 2020; Sens et al., 2023). Experiments introducing specific bacterial strains to animals and observing resultant behavioural changes have demonstrated the significant influence these microbes have on the brain (Bravo et al., 2011; McKernan et al., 2010; Savignac et al., 2014). Human studies have mirrored these findings, highlighting the microbiota's potential to impact mental health and cognitive functions (Kullberg et al., 2024; Tian et al., 2023). Indeed, large collaborative initiatives like the Human Microbiome Project, MetaHIT, the American Gut Project, the Dutch microbiome project, along with significant gut microbiota cohort analyses, have been crucial in mapping the gut microbiome at a population scale, providing foundational data that has informed subsequent? Studies focused on its role in mental health conditions such as depression, anxiety, and cognitive decline (Cotillard et al., 2022; Group et al., 2009; Lane et al., 2024; Li et al., 2014; Lopera-Maya et al., 2022; McDonald et al., 2018).

Microbiota Evolution: A Co-Dependent Partnership in the Holobiont

To truly appreciate the role of the microbiota in host health, it is essential to consider its evolutionary context. Host organisms have never existed without their microbial friends, co-evolving, becoming mutually dependent for survival (Nagpal & Cryan, 2021a). There has never been a time when mammals, including humans, existed without their microbial inhabitants (Bordenstein & Theis, 2015). Moreover, the brain has always received signals from the gut (Stilling et al., 2014). This co-evolutionary relationship is best described by the concept of the holobiont, which views the host and its symbiotic microbiota as a single ecological unit. This perspective has led to the hologenome theory of evolution, proposing that the holobiont and its combined genetic material act as a unit of evolutionary selection (Theis et al., 2016; Zilber-Rosenberg & Rosenberg, 2008). The hologenome theory highlights that genetic variation within the holobiont is driven by both the host genome and its associated microbial genome. This variation is further enhanced by the vertical and horizontal transmission of different microbial populations, including from parent to offspring and through social interactions, allowing optimal adaptation to environmental changes, such as diet, stress, and temperature (Walter & Hornef, 2021). For instance, initial vertical transmission of maternal microbiota during birth and susequent breastfeeding ensures that offspring acquire and establish critical microbial populations for immune and metabolic development (Sonnenburg & Backhed, 2016). Horizontal transmission, on the other hand, occurs through interactions within social groups, such as grooming or shared food sources and environments, contributing to microbiota diversity and resilience (Moeller et al., 2016). This theory may also explain complex biological phenomena, including behaviours that promote social interactions among holobionts, thereby facilitating greater transmission of microbiota and enhancing genetic diversity (Archie & Tung, 2015). Such transmission and assembly mechanisms reinforce the dynamic interplay between microbiota and host evolution, highlighting their collective role in shaping biological and behavioural traits.Understanding these evolutionary links between microbiota and the brain is crucial for studying human biology and the broader animal kingdom. With this in mind, it is easier to understand how our microbial symbionts have significantly influenced brain development, physiology, and behaviour throughout evolution.

The Bi-Directional Microbiota-Gut-Brain Axis: A Complex Communication Network With this information, researchers now refer to the bidirectional communication network connecting gut microbes to our brain, both directly and indirectly, as the microbiota-gut-brain axis, which integrates the enteric and central nervous systems. This connection explains how the gut can influence brain function and vice versa. Where early research focused on digestive functions and satiety (Konturek et al., 2004; Rinaman, 2010), more recent work has explored the axis's impact on higher-order cognitive and psychological processes and behavioural mechanisms (Davidson et al., 2024; Hung & Margolis, 2024; Ritz, Bastiaanssen, et al., 2024). Disruptions in the microbiota-gut-brain axis have been linked to various disorders, including IBS (Mayer et al., 2023; Wilmes et al., 2021), inflammatory bowel disease (IBD; (Michaudel et al., 2023; Schneider et al., 2023), and mental health conditions like anxiety and depression (Audet, 2021; Dalile et al., 2024; Diaz Heijtz, 2024; McGuinness et al., 2024; Ross, Mayer, et al., 2024). The concept of psychobiotics—including probiotics that can influence mental health—has emerged from these studies, offering new avenues for therapeutic interventions (Dinan et al., 2021). For example there is evidence that alterations in the gut microbiota composition under cold temperatures can regulate norepinephrine release in the intestine and brown adipose tissue in Brandt's voles, thereby contributing to the modulation of energy intake and thermal homeostasis during winter (Ge et al., 2018).

The chapter "**Noradrenaline regulation of brain-body communication**" in this book provides an in depth exploration of the effects of Noradrenaline and highlights its role as a key integrator of

information processing between the brain and body. This adrenergic network is vital to the execution of a wide range of physiological and behavioural functions, most notably the fight-or-flight response to threats.

From Gut to Brain and Back: Decoding the Communication Pathways

The intricate relationship between the gut microbiota and the brain is facilitated by various pathways of communication, ranging from neural networks to small molecule signalling systems. Understanding these pathways is crucial to comprehending how the microorganisms in our gut can significantly influence our brain and behaviour.

The Autonomic Nervous System: Orchestrating Gut-Brain Symmetry

The ANS is a complex network of neurons that control bodily functions such as breathing, heartbeat, and digestion without conscious effort (Jänig, 2006). The ANS consists of the sympathetic and parasympathetic branches and works closely with the enteric nervous system (ENS) and the central nervous system (CNS) to maintain physiological homeostasis (Wehrwein et al., 2016). The ANS communicates bidirectionally with the gut microbiota, influencing gut motility, permeability, secretion, and immune responses (Goehler et al., 2005; Sharkey & Mawe, 2023). These communications are essential for processing visceral information and responding to various stimuli, ensuring rapid changes in gut physiology. The sympathetic branch of the ANS typically prepares the body for stressful or emergency situations by initiating the "fight or flight" response, which can influence gut motility and secretion through the release of neurotransmitters like norepinephrine (Kaelberer et al., 2020). Conversely, the parasympathetic branch, which includes the vagus nerve (see below), supports the "rest and digest" functions, promoting digestion and reducing stress responses.

The ANS also interacts with the hypothalamic-pituitary-adrenal (HPA) axis (see below), creating a comprehensive network for integrating signals from the gut microbiota and maintaining overall physiological balance (Cussotto et al., 2018). This intricate interplay between the ANS, HPA axis, and gut microbiota ensures that the body's response to internal and external stimuli is well-coordinated and adaptive.

The Vagus Nerve: A Superhighway for Gut-Brain Signals

The vagus nerve (10th cranial nerve) is the primary conduit for communication between the gut and the brain (Fulling et al., 2019). Comprising mostly afferent fibres, it collects information from visceral organs and sends it to the brain directly, and quickly. The vagus nerve plays an important role in regulating gut function, including motility and secretion (Grundy et al., 2006). It also modulates inflammatory responses through the vago-vagal anti-inflammatory reflex loop, influencing conditions like IBD and functional gastrointestinal disorders (FGIDs) (Pavlov & Tracey, 2005). The vagus nerve's extensive innervation allows it to detect changes in the gut environment, such as the presence of bacterial metabolites, stretch, or chemical signals. It transmits these signals to the nucleus tractus solitarius (NTS) in the brainstem, which then relays information to other brain regions involved in autonomic control and emotional regulation, such as the hypothalamus, amygdala, and prefrontal cortex. Furthermore, the vagus nerve's efferent fibres carry signals from the brain back to the gut, modulating functions like gastric acid secretion, enzyme release, and gut motility (Bhattarai et al., 2018). This bidirectional communication is essential for maintaining gut-brain homeostasis and responding to changes in the gut environment.

The Enteric Nervous System: The Brain in Your Gut

The ENS, often referred to as the "second brain," is a network of neurons located in the walls of the gastrointestinal tract, specifically within the myenteric and submucosal plexuses (Benarroch, 2007). The ENS serves as a critical interface between the gut microbiota and the CNS, responding to microbial signals through direct interactions with microbial metabolites and indirect pathways involving hormones, immune mediators, and the vagus nerve (Hyland & Cryan, 2016). Indeed, recent advancements in high-throughput “omics” technologies, particularly single-cell RNA sequencing, have enabled the identification of specific expression signatures and potential subtypes of enteric neurons and glial cells in the ENS vulnerable to microbial signals (Dharshika & Gulbransen, 2023). The ENS influences gut functions such as motility and fluid movement and is involved in the development and maintenance of gut health. The ENS comprises the myenteric plexus (primarily controls gut motility), and the submucosal plexus (regulates secretion and blood flow). The ENS operates independent of the CNS but can also interact with it through autonomic pathways, allowing for coordinated responses to changes in the gut environment. Studies involving germ-free animals have shown that the absence of a gut microbiota leads to significant abnormalities in the ENS, highlighting the microbiota's role in ENS development and function (De Vadder et al., 2018; Obata & Pachnis, 2016; Wu & Wu, 2012). During development, the gut microbiota plays a critical role in shaping the ENS by influencing the proliferation, differentiation, and maturation of enteric neurons (Obata & Pachnis, 2016). Microbial metabolites such as short-chain fatty acids (SCFAs) and bile acids can modulate ENS activity, affecting gut motility and barrier function (Aburto & Cryan, 2024; O'Riordan et al., 2022).

Spinal Pathways: Conveying Gut Distress to the Brain

Neural signalling from the gut to the brain involves both the vagus nerve and spinal pathways. Painful and non-painful stimuli are conveyed through different routes, with non-painful signals predominantly mediated by vagal innervation and painful stimuli by spinal splanchnic innervation (Rea et al., 2021; Vermeulen et al., 2014). These pathways ensure the brain receives comprehensive information about the gut's status, allowing for appropriate physiological responses. Pain and discomfort from the gut are transmitted through spinal afferent pathways to the brain, where they are processed and integrated with other sensory information (Vermeulen et al., 2014). These pathways involve the dorsal root ganglia and the spinal cord, which relay signals to brain regions such as the thalamus, hypothalamus, and cerebral cortex. Understanding these spinal mechanisms is crucial for comprehending how gut disturbances, such as inflammation or injury, can influence brain function and behaviour.

Bacterial infections can amplify pain signalling and induce long-term plastic changes in spinal nerve signalling by directly activating sensory afferents and modulating inflammation (Chiu et al., 2013). This heightened pain response, known as central sensitisation, is similar to long-term potentiation in the hippocampus, where neurotransmitters like glutamate and peptides such as substance P enhance synaptic transmission, leading to abnormal pain processing (Yu et al., 2016). Notably, *Lactobacillus reuteri* (DSM 17938) has been found to reduce spinal nerve firing in response to gut stimuli (Perez-Burgos et al., 2015).

Immune Interplay: Linking Gut and Brain Health

The gut is also home to a dense concentration of immune cells that continuously interact with the local microbes (Ratsika et al., 2023). The immune system, through the release of cytokines and chemokines, plays a significant role in gut-brain communication (Macpherson et al., 2023). These immune cells detect and respond to microbial-associated molecular patterns (MAMPs), such as

lipopolysaccharides (LPS) from Gram-negative bacterial outer membranes and peptidoglycan (a polysaccharide, consisting of sugar and amino acids, that is a component of bacterial cell walls) layers from bacterial cell walls (Gonzalez-Santana & Diaz Heijtz, 2020). The recognition of these microbial patterns is mediated by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and nucleotide-binding oligomerisation domain-containing proteins (NODs) (Li & Wu, 2021). For example, TLR4 specifically recognizes LPS, leading to downstream immune responses, while NOD1 and NOD2 are involved in detecting peptidoglycan-derived molecules. This coordinated detection of microbial components is crucial for maintaining the balance between the host and the gut microbiota, preventing harmful pathogens from breaching the gut barrier. Recent research has shown that a diverse gut microbiota is essential for proper functioning of microglia, the brain's resident immune cells, which are involved in neuroinflammatory responses and synaptic remodelling (S. Zhang et al., 2024).

The adaptive immune system comprises B and T lymphocytes, which provide a more specific and long-lasting immune response. Microbial metabolites such as SCFAs can modulate immune cell function, promoting anti-inflammatory responses and maintaining gut barrier integrity. For example, microbial metabolites can stimulate the production of regulatory T cells, which help suppress excessive immune responses and prevent inflammation (Caffrey et al., 2024). This modulation of the immune system by the gut microbiota is essential for preventing chronic inflammation and maintaining overall health (Fung, 2020). Indeed, various types of gut-innervating neurons influence intestinal mucosal immunity, dictating immune cell responses to neural signals during host defence and inflammatory processes providing a potential therapeutic target to address intestinal diseases (Yang et al., 2023).

One study investigated the microbiota-gut-brain axis using the dextran sodium sulphate (DSS) induced colitis in mice, demonstrating that gut inflammation leads to pro-inflammatory immune responses that can negatively impact brain myelination, oxidative stress, and oxygenation (Boles et al., 2024). This suggests that gut inflammation not only disrupts intestinal health but also contributes to neuroinflammatory processes, potentially affecting cognitive and neurological function. A key player in this interaction is microglia that play a major role in regulating the integrity of the blood-brain barrier (BBB). The BBB is crucial for maintaining CNS function and homeostasis but becomes compromised with systemic inflammation, where gut-derived cytokines and other inflammatory mediators can disrupt BBB integrity, leading to neuroinflammation. This can further be exacerbated with age, contributing to various age-related neurodegenerative disorders, such as Alzheimer’s disease (Aburto & Cryan, 2024).

Different dietary interventions (vegan/ ketogenic) can also modulate both gut microbiota composition and immune pathways, further influencing brain health (Boscaini et al., 2022). For instance, the ketogenic diet has been reported to enhance adaptive immune pathways, which may exert neuroprotective effects by reducing inflammation and promoting regulatory immune cell populations. In contrast, the vegan diet primarily promotes innate immune responses, particularly in antiviral immunity, highlighting the potential for tailored nutritional interventions to significantly influence host immunity and microbiota composition (Link et al., 2024). These findings underscore the potential for dietary strategies to modulate the microbiota-gut-brain axis, improve neuroinflammation, and mitigate the cognitive consequences of gut inflammation.

The brain can modulate peripheral inflammation by communicating with distinct populations of vagal neurons, manipulation of which can suppress pro-inflammatory responses while enhancing anti-inflammatory states (Jin et al., 2024). GABAergic signalling in the brain was shown to be crucial for regulating neuroinflammation-induced synaptic dysfunction, where inhibitory postsynaptic currents in glutamatergic neuronal activity was increased alongside excessive microglial activation (Jiang et al.,

2022). Such neuroimmune function can be modifiable by diet. Prebiotic-enriched diets can reverse age-related immune priming, reduce monocyte infiltration into the brain, and decrease the activation of microglia offering a potential route for management of neuroinflammatory conditions (Boehme et al., 2020). A recent probiotic study in a diet-induced obese mouse model using *Bacteroides uniformis* CECT 7771 revealed that *B. uniformis* improved glucose tolerance and insulin secretion through adaptive immunity mechanisms that do not require the bacteria to be viable, while its viability was essential for preventing weight gain, indicating distinct pathways through which a probiotic can influence energy homeostasis and immunity (Romani-Perez, Lopez-Almela, et al., 2024)

Stress Pathways: The HPA Axis and Microbiome Interactions

Upon encountering a stressor, the hypothalamus initiates the stress response by releasing corticotropin-releasing factor (CRF), which stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH), which then prompts the adrenal glands to release glucocorticoids, such as cortisol, into the bloodstream (Wu et al., 2021). These hormones help the body adapt to stress by mobilising energy reserves and modulating immune responses. The HPA axis is a key neuroendocrine system that coordinates the body's response to stress. The gut microbiota can influence the HPA axis, as evidenced by studies showing exaggerated stress responses in germ-free animals (Clarke et al., 2013; Lyte et al., 2020; Sudo et al., 2004). The HPA axis interacts with other pathways of communication, including the vagus nerve and the immune system, forming a complex network that regulates the body's stress response and maintains homeostasis.

The HPA axis is tightly regulated by feedback mechanisms that involve glucocorticoid receptors in the brain and other tissues. Dysregulation of the HPA axis, as seen in chronic stress or psychiatric disorders, can lead to altered immune function, metabolic disturbances, and changes in gut microbiota composition (Audet, 2019; Sheng et al., 2020). A recent pilot study investigated the association between gut microbiota composition and HPA axis reactivity in 34 healthy human infants by measuring salivary cortisol before and after a heel stick and conducting 16S rRNA amplicon sequencing to identify bacterial taxa (Rosin et al., 2021). It revealed a moderate positive correlation between α-diversity and cortisol reactivity at one month of age. Additionally, specific genera such as *Staphylococcus*, *Prevotella*, and *Lachnospiraceae* may be linked to cortisol responses, suggesting the microbiome's role as a mediator in the microbiome-gut-brain axis during infancy and highlighting the potential for manipulating gut microbes to enhance stress-response systems. Understanding the interplay between the HPA axis and the gut microbiota is essential for developing interventions to restore balance in stress-related disorders.

Hormonal Gatekeepers: Enteroendocrine Cells and Microbiota Influence

Enteroendocrine cells (EECs) are dispersed throughout the gut epithelium and can detect changes in the gut environment through their apical surface, which is exposed to the gut lumen. Upon detecting nutrients or microbial metabolites, EECs release hormones and neuropeptides into the bloodstream, or locally within the gut, to regulate various functions (Sharkey & Mawe, 2023). For example, enteroendocrine L cells release glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) in response to nutrient intake, which are involved in the regulation of appetite and glucose homeostasis (Zheng et al., 2024). GLP-1 and PYY act on hypothalamic and vagal afferents to reduce appetite and promote satiety helping to regulate body weight and energy balance. They also influence insulin secretion and glucose homeostasis, playing a crucial role in metabolic health. GLP-1 and PYY are also influenced by bacterial metabolites like SCFAs, which activate G-protein-coupled receptors such as FFAR2 (GPR43) and FFAR3 (GPR41) on enteroendocrine L cells, triggering hormone secretion (Larraufie et al., 2018). SCFAs can also enhance L-cell activity by modulating cellular energy metabolism, promoting the release of GLP-1

and PYY into the bloodstream (O'Riordan et al., 2022). The gut microbiota can significantly affect EEC cells activity, thereby impacting host metabolism and behaviour. Recent work has explored the role of specific proteins secreted by *Akkermansia muciniphila* in improving metabolic health (Yoon et al., 2021) *A. muciniphila*-derived P9 improved metabolic health by enhancing GLP-1 secretion and reducing insulin resistance in mice. Further, pasteurised *A. muciniphila* can benefit metabolic health, suggesting live bacteria may not be essential for therapeutic effects (Plovier & Cani, 2017).

Enterochromaffin cells produce the majority of the body's serotonin, which is involved in regulating gut motility, secretion, and pain perception (Sharkey & Mawe, 2023). Enterochromaffin cells not only transduce noxious stimuli and induce visceral hypersensitivity following activation but also contribute to persistent pain and anxiety-like behaviours, with significant sex differences in their engagement (Bayrer et al., 2023). Not only do these gut cells produce and respond to serotonin, but so do bacteria along with gamma-aminobutyric acid (GABA), and catecholamines (Wiley et al., 2021). These neuroactive molecules play critical roles in host mood, behaviour, and cognition. For instance, certain gut bacteria can modulate serotonin production, influencing the expression of tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis (Hata et al., 2017). GABA is an inhibitory neurotransmitter that is produced by some gut bacteria and can affect gut motility and signalling to the brain (Mazzoli & Pessione, 2016). Bacterial production of GABA can influence host behaviour, as evidenced by studies showing that GABA-producing probiotics can reduce anxiety-like and improve depression-like behaviours in animal models (Yu et al., 2020). Indeed, one study explored the impact of a GABA-producing *Bifidobacterium* strain on gut microbiota composition and metabolic activity in mice (Tames et al., 2024). Administering this GABA-producing strain lead to a distinct modulation of the gut microbiota compared to non-GABA-producing strains.

GABA plays also an important role in glucose metabolism and regulation. Within the (ventromedial) hypothalamus, GABA(A) receptor activity plays a key role in regulating glucagon release by the pancreas during hypoglycaemic events. The chapter "**Brain-body communication in glucose metabolism**" in this book explores the roles of different brain regions in glucose homeostasis and their connections to pancreas and liver through the sympathetic and parasympathetic nervous systems.

Catecholamines like norepinephrine and dopamine are also produced by certain gut bacteria and can interact with host cells to influence various physiological processes (Lachmansingh et al., 2023). Gut microbiota can influence resilience and susceptibility to stress-induced psychopathologies, where mice susceptible to stress exhibited higher baseline and stress-induced levels of epinephrine and norepinephrine, alongside significant shifts in gut microbial composition, suggesting that microbial profiles may play a critical role in modulating the sympathoadrenal stress response (Tanelian et al., 2022). These studies highlight the complex communication network within the microbiota-gut-brain axis.

Metabolic Mediators: How Microbial Molecules Shape Brain Function

SCFAs such as acetate, propionate, and butyrate, are primarily produced by microbial fermentation of non-digestible dietary fibres, and have been implicated in various host processes, including gut health, immune function, and brain physiology (O'Riordan et al., 2022). These metabolites can be absorbed by the gut epithelium and enter the bloodstream, where they can exert systemic effects on the host. SCFAs can influence brain function indirectly by modulating the immune system and directly by crossing the blood-brain barrier (BBB) and affecting neuronal activity (Dalile et al., 2019). In the brain, SCFAs can affect neuronal function by modulating neurotransmitter synthesis and release, influencing BBB integrity and brain energy metabolism, and acting as histone deacetylase inhibitors to regulate gene expression (Knox, Aburto, Tessier, et al., 2022; Knox et al., 2023; Stachulski et al., 2023). Studies

have shown that SCFAs can ameliorate stress-induced alterations in the brain and behaviour, highlighting their potential role in microbiota-gut-brain communication (Dalile et al., 2024; Dalile et al., 2020). In the gut, SCFAs help maintain barrier integrity by promoting tight junction assembly and mucus production (Ma et al., 2022). They also modulate immune responses by influencing the activity of various immune cells, including regulatory T cells and macrophages, promoting an anti-inflammatory environment (Liu et al., 2023). Therapeutically, engineered bacterial biosensors are capable of sensing SCFA concentrations produced by gut microbes (Serebrinsky-Duek et al., 2023). By utilising genetic circuits that respond inversely to SCFA levels, the researchers created systems that not only quantify SCFA absence but also deliver therapeutic cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), highlighting their potential as diagnostic and therapeutic tools for gut-related disorders.

Recently, a cranberry extract rich in (poly)phenols and oligosaccharides was given to 28 human subjects, revealing a significant bifidogenic effect and an increase in butyrate-producing bacteria after just four days of supplementation (Lessard-Lord et al., 2024). In particular, participants with a Prevotella-rich microbiota experienced an increase in butyrate-producing *Faecalibacterium* following cranberry extract supplementation. In fact, recent data from two large population-based cohorts in the Netherlands and Finland revealed that individuals with a higher relative abundance of butyrate-producing bacteria had a significantly reduced risk of hospitalisation or mortality due to infections, indicating that gut microbiota composition may play a protective role against severe infections in the general population (Kullberg et al., 2024). Indeed, reductions in butyrate-producing bacteria and butyrate production were linked to early changes in the microbiome-gut-brain axis that preceded Alzheimer's disease-related neuropathology and cognitive deficits in a mouse model (Chilton et al., 2024). Moreover, oral administration of tributyrin, a butyrate prodrug, mitigated these declines and delayed the onset of AD symptoms, suggesting that enhancing butyrate synthesis may be a promising therapeutic approach for AD prevention and treatment.

Bile Acids (BAs) are essential for absorbing dietary lipids and fat-soluble vitamins from the gut (Guzior & Quinn, 2021). Synthesised in the liver from cholesterol, primary BAs such as cholic acid and chenodeoxycholic acid aid lipid digestion and are recycled back to the liver. Beyond their digestive roles, BAs are potent signalling molecules, influencing lipid, cholesterol, and glucose metabolism, as well as energy balance and immune homeostasis through receptors like farnesoid X receptor (FXR) and G-protein-coupled bile acid receptor (TGR5) (de Aguiar Vallim et al., 2013). Studies have revealed bidirectional communication between the host bile system and gut bacteria, impacting gut-brain signalling (Lavelle & Sokol, 2020). BAs limit bacterial overgrowth in the small intestine through antimicrobial effects and activate FXR signalling to induce antimicrobial genes, protecting the gut epithelium from microbial invasion and inflammation (Long et al., 2017). Gut bacteria, including *Lactobacillus* and *Bifidobacterium*, express bile salt hydrolase enzymes which can deconjugate bile acids, enhancing their survival in the gut (Degirolamo et al., 2014), (Long et al., 2017). This microbial activity increases BA diversity in the host, affecting metabolism and weight regulation.

BAs are crucial for maintaining the gut barrier and regulating immune responses, which are essential for gut and brain function and health. TGR5 activation by BAs has anti-inflammatory effects and helps maintain epithelial integrity by modulating the gastrointestinal immune system (Sarathy et al., 2017). Alterations in gut microbiota composition that change BA profiles can impact microbiota-gut-brain axis signalling, particularly through inflammatory pathways. Deficient BA deconjugation in a mouse model of autism spectrum disorder (ASD) was linked to impaired intestinal barrier function and behavioural changes, highlighting the importance of bile-metabolising capacities of specific probiotic strains such as *Bifidobacterium* and *Lactobacillus* (Golubeva et al., 2017). The probiotic VSL#3 enhances BA

deconjugation and upregulates hepatic BA synthesis via the FXR/FGF15 pathway (Degirolamo et al., 2014). Further, FXR/FGF signalling in the ileum can suppress hypothalamic neurons involved in glucose regulation, improving glucose tolerance in obese mice (S. Liu et al., 2018). Interestingly, BAs function as natural pheromones in mice, with the olfactory system distinguishing between male and female faeces based on BA composition, suggesting a direct role in gut-brain communication (Doyle et al., 2016). In certain liver diseases, individuals often experience cognitive impairment, also seen in a bile duct ligation rodent model. Here, bile duct ligation mice develop cognitive symptoms early, before the onset of cirrhosis or liver failure, including memory loss, BBB disruptions, and hippocampal network destabilisation. This was reversible with BA (obeticholic acid) treatment restoring memory, preventing neuronal damage, and reversing cellular senescence in these mice (Gee et al., 2023). A pilot feasibility study investigating bile acid metabolites during the perinatal period, revealed significant temporal variations and associations with mental health (Kimmel et al., 2022). Notably, changes in secondary bile acid levels, particularly ursodeoxycholic acid, correlate with microbial diversity and are linked to psychiatric history, suggesting that bile acid dynamics may play a crucial role in perinatal mental health adaptations.

Indoles are a group of tryptophan-derived metabolites produced by gut microbes (Lee et al., 2015; Turner et al., 2006). They play a critical role in gut-brain interactions, impacting host physiology through various mechanisms (Roager & Licht, 2018). Indole also impairs locomotion and induces anxiety-like behaviour in mice via dose-dependent activation of the locus coeruleus, highlighting its role in gut-brain communication (Mir et al., 2024).Further, chronic indole production by the gut microbiota amplifies emotional responses to chronic mild stress in male mice and enhances catecholamine biosynthesis in the adrenal medulla, highlighting its role in stress susceptibility (Mir et al., 2020). Indole, along with indoleacetic acid and indolepropionic acid, influence the gut's immune and neuroendocrine systems by acting on the aryl hydrocarbon receptor (AhR) (Zelante et al., 2013). The AhR is a ligand-activated transcription factor that is responsive to a broad range of physiological ligands, including microbial metabolites such as indole and other tryptophan derivatives (Barroso et al., 2021). By engaging AHR, indoles modulate immune functions and contribute to maintaining mucosal homeostasis, which may protect against inflammation (Cervantes-Barragan et al., 2017).

In addition to their peripheral effects, indoles have been shown to influence brain health through gut-brain communication. Indolepropionic acid, for instance, has been associated with neuroprotective effects, particularly in reducing oxidative stress and inflammation, processes implicated in neurodegenerative diseases such as Alzheimer's disease (Sun et al., 2022). Furthermore, indoles may indirectly modulate neurotransmitter systems by supporting the intestinal barrier and reducing systemic inflammation, thereby preventing inflammation-induced disruptions in brain function (Loh et al., 2024). Recent work found that oral tryptophan supplementation in healthy individuals enhances AhR activation and increases microbial indole and host kynurenine pathway metabolites in the small intestine, suggesting potential for therapeutic application in managing small intestine inflammation (Rueda et al., 2024).

Indoles also support intestinal barrier integrity through pregnane X receptor (PXR) signalling, potentially reducing intestinal permeability (Bansal et al., 2010). This enhanced barrier function may have downstream effects on the brain, as gut barrier dysfunction is increasingly linked to neuroinflammation and behavioural changes. Moreover, indole stimulates the release of gut hormones like GLP-1, hinting at their influence on metabolic health (Chimerel et al., 2014). Moreover, gut epithelial Gpr35 can regulate depressive-like behaviour in mice, via alterations in microbial tryptophan metabolism, specifically decreasing indole-3-carboxaldehyde (IAld) and increasing indole-3-lactate (ILA), which have opposing effects on neuroplasticity in the nucleus accumbens (Cheng et al.,

2024). Supplementing IAld alleviated depressive symptoms in mice and was found to be depleted in individuals with major depressive disorder (MDD), highlighting its potential as a biomarker and therapeutic target for depression. By connecting microbial metabolites to both local and systemic processes, indoles underscore the integral role of gut-derived molecules in maintaining gut and brain health.

Peptidoglycans are recognised by the host's immune system and can influence brain function (Gonzalez-Santana & Diaz Heijtz, 2020). These molecules can cross the BBB and affect neurons directly, suggesting a direct link between gut bacteria and brain function (Arentsen et al., 2017). Research has shown that peptidoglycan recognition proteins (such as pattern recognition receptors including Toll-like receptors and nucleotide-binding oligomerisation domain-containing proteins (NODs)), are involved in both immune responses and behaviour, highlighting the significance of microbial components in gut-brain communication (Medzhitov, 2007; Takeda & Akira, 2004). These receptors initiate immune responses upon recognising microbial components, leading to the release of cytokines and other immune signalling molecules. Studies have shown that peptidoglycans can modulate neuronal function and behaviour by interacting with receptors in the brain (W. Xu et al., 2023). For instance, NOD1 and NOD2 receptors, which recognise specific peptidoglycan motifs, are expressed in various brain regions and can influence neuronal activity and synaptic plasticity (Clarke et al., 2010; Gabanyi et al., 2022; Kawai & Akira, 2009; Schneider & Thaiss, 2022). Further, peptidoglycans were recently shown to play a key role in the interactions between neonatal gut microbiota, systemic inflammation, and brain development (Morin et al., 2025). Elevated circulating peptidoglycan levels were observed suggesting that systemic inflammation combined with disrupted gut microbiota (due to Cesarean section delivery) facilitates the translocation of peptidoglycans into the bloodstream, potentially influencing microglial activation, brain connectivity, and myelination, ultimately contributing to neurodevelopmental deficits (Morin et al., 2025).

Understanding the role of peptidoglycans in gut-brain communication could provide crucial insight into how microbial components contribute to neurological and psychiatric disorders. It also highlights the potential for targeting these pathways in therapeutic strategies for brain-related conditions. The maternal intake of a multispecies probiotic revealed the role of bacterial peptidoglycan in neurodevelopment (Siegler Lathrop et al., 2024). Specifically, the expression of the proton-coupled oligopeptide transporter 1 (PepT1), which facilitates the transport of peptidoglycan motifs, was significantly increased in the prefrontal cortex of male offspring exposed to the probiotic.

Microbial extracellular vesicles are nanoscale particles released by gut bacteria that play a pivotal role in the microbiota-gut-brain axis (Mandelbaum et al., 2023). These vesicles can traverse biological barriers, including the blood-brain barrier, facilitating direct communication between gut microbiota and the central nervous system. Microbial extracellular vesicles carry various bioactive molecules, such as proteins, lipids, and nucleic acids, which can modulate immune responses and influence brain function (Kang et al., 2023). For instance, they can interact with immune receptors on glial cells, leading to the production of cytokines and inflammatory mediators, thereby impacting neuroinflammation and potentially contributing to neurological disorders.

Beyond the role of diet in shaping the gut microbiota and influencing metabolic and neuropsychiatric health, dietary components also interact with key appetite-regulatory peptides that link metabolism to behaviour. Ghrelin and GLP-1, two critical peptides involved in energy balance and feeding behaviour, not only regulate food intake but also play a role in reward processing and addictive behaviours. This is covered in more detail in the chapter "**The connection between the appetite-regulatory peptides ghrelin and GLP-1 and alcohol use disorder"** where we explore the involvement

of these peptides in alcohol use disorder, shedding light on how metabolic signals influence substance-related behaviors and revealing potential therapeutic targets for addiction.

Microbiota-Gut-Brain Axis: Lifespan Dynamics and Clinical Implications

The microbiota-gut-brain axis is a dynamic system that evolves throughout our lives (Lynch et al., 2023). Small daily variations in microbiota composition are normal, but significant changes occur at different life stages. These transformations can be viewed as sensitive periods where the microbiota is highly influential on overall health and responsive to external factors, potentially offering therapeutic opportunities (Ratsika et al., 2023).

In early life, the *in utero environment* is understood to be sterile see: (Kennedy et al., 2023). Initial colonisation happens at birth, significantly shaping the microbiota's development (Roager et al., 2023). Early-life gut microbial succession follows conserved patterns globally, with a decline in *Bifidobacterium* and an increase in *Faecalibacterium prausnitzii* and other taxa as infants transition from breastfeeding to solid foods (Fahur Bottino et al., 2025). The gut microbiota then evolves rapidly in infancy, dominated by certain bacterial families, and reaches adult-like diversity within 1-3 years, influenced by diet and weaning (Palmer et al., 2007; Yatsunenko et al., 2012). Early life factors, including birth mode (Korpela & de Vos, 2022), diet (McEvoy et al., 2024), and antibiotic use (Desbonnet et al., 2015), impact long-term health, with emerging research suggesting that early microbiota manipulations can alter developmental and health trajectories. Early-life infections, antibiotic use, stress, and various biomarkers—including infant microbiota and cord serum metabolites— have been linked to development of neurodevelopmental disorders like intellectual disability and autism purporting the possibility to establish a foundation for early-life prediction and intervention strategies (Ahrens et al., 2024).

The neonatal gut is enriched with neurotransmitters like serotonin, which are derived from both host cells and specific gut bacteria. Certain gut bacteria contribute to serotonin production that can inhibit monoamine oxidase A, reducing serotonin breakdown, supporting local signalling pathways (Sanidad et al., 2024). This modulation of serotonin levels can contribute to shaping the neonatal immune system, promoting long-term immune tolerance toward dietary antigens and commensal bacteria. This process is critical for preventing excessive inflammatory responses and establishing immune homeostasis in neonatal mice (Sanidad et al., 2024). These findings highlight the critical role of gut-derived serotonin in shaping T cell responses and promoting immune tolerance during early development. Focus is also shifting to the early-life gut virome, where temperate bacteriophages may influence immune responses independently of the gut's bacterial population, particularly in the development of asthma ("Beyond bacteria: early-life gut virome link with childhood asthma development," 2024; Leal Rodriguez et al., 2024).

During adolescence, significant hormonal and brain changes coincide with shifts in social behaviour, diet, and exposure to new experiences, making this a vulnerable period for mental health issues (Carbia et al., 2023; Ratsika et al., 2023). Although few studies have directly compared adolescent and adult microbiota, early research indicates gradual transitions rather than distinct adolescent profiles (Agans et al., 2011; Hopkins et al., 2001). Positive lifestyle factors—such as parental care?, school engagement, healthy nutrition, and physical activity—can counteract genetic risks associated with accelerated brain aging in adolescence (Petrican et al., 2024). Longitudinal analysis revealed that genetic vulnerability and lifestyle factors uniquely influence functional neurodevelopment, particularly

in brain regions associated with emotional regulation, cognitive control, and stress responses. However, distinct microbiota trajectories between sexes emerge at puberty, driven by hormonal changes such as increased levels of sex hormones like oestrogen and testosterone (Korpela et al., 2021). These hormonal shifts can differentially shape the gut microbiota, influencing microbial composition, diversity, and function, which may contribute to sex-specific vulnerabilities to mental health disorders during adolescence. Diet and metabolic outcomes in adolescents correlate with microbiota composition (Kemp et al., 2024), suggesting further research is needed. Preclinical studies show that gut microbiota interventions during adolescence can influence long-term cognitive and behavioural outcomes, supporting the idea of adolescence as a sensitive period for microbiota-gut-brain interactions (Lynch et al., 2023).

Ageing brings a decline in various bodily functions and an increased prevalence of diseases, with notable changes in gut physiology affecting microbiota composition (Cruz-Pereira et al., 2023; Zhou et al., 2022). The stability of the adult gut microbiota deteriorates with age, influenced by diet and physical activity. Although studies show conflicting results regarding specific microbial taxa associated with ageing, decreased microbiota diversity is generally linked to adverse outcomes and unhealthy ageing (Ghosh et al., 2022). Some taxa, like *Bacteroidetes* and *Faecalibacterium prausnitzii*, are associated with reduced frailty and better health in the elderly (Ghosh et al., 2022; Lim & Nam, 2023).

The BBB is disrupted with ageing, likely involving altered function of microglia in regulating BBB integrity leading to accelerated decay in ageing and neurodegeneration (Knox, Aburto, Clarke, et al., 2022). This disruption is further influenced by gut microbiota-derived metabolites, such as SCFAs and tryptophan metabolites, which can modulate microglial function and BBB permeability. Age-related changes in microbiota composition may exacerbate BBB dysfunction, linking gut health to brain ageing and the progression of neurodegenerative disorders (S. Zhang et al., 2024).

The ageing gut microbiota contributes to "inflammaging," a state of chronic low-grade inflammation that accelerates aging and disease development (Fransen et al., 2017). Studies indicate that the gut microbiome plays a role in regulating neuroimmunity, with implications for therapeutic interventions targeting age-related cognitive decline and neurodegeneration (Boehme et al., 2021). Dietary interventions and caloric restriction have shown potential in modulating the gut microbiota to promote healthy aging, with some studies even suggesting that transferring microbiota from young to older individuals can extend lifespan (Boscaini et al., 2022). Intriguingly, dietary restriction in aging mice at risk for cognitive impairment following anaesthesia and surgery may alleviate cognitive dysfunction induced by anaesthesia/surgery by modulating gut microbiota (Ren et al., 2024). Reduced neuroinflammation in hippocampal microglia and enhanced neuronal repair and regeneration were noted. These insights suggest that dietary strategies could serve as innovative therapeutic approaches for managing the ageing brain.

Overall, the microbiota-gut-brain axis is crucial at various life stages, influencing health and disease outcomes. Understanding these dynamics offers opportunities for targeted interventions to improve health across the lifespan.

Shaping the Axis: Genetic, Environmental, and Lifestyle Factors

The interplay between the gut microbiota and the brain, is influenced by various factors including genetics (Otaru et al., 2024), diet (including pre-, pro-, and synbiotics) (Schneider et al., 2024a),

environment (Matsuzaki et al., 2023), exercise (Ni Lochlainn et al., 2024), medications (Cussotto, Clarke, et al., 2021), and birth delivery mode (Dinan et al., 2022; Selma-Royo et al., 2024). Each of these elements can significantly impact both brain function and the composition of the gut microbiota, leading to a range of physiological and behavioural outcomes. Next, we will examine these factors, exploring their known effects and potential areas for future research.

How Genes and Epigenetics Drive Gut-Brain Communication

The influence of genetics on the microbiota-gut-brain axis is an emerging field of study (Goodrich et al., 2014). Host genetics play a crucial role in shaping the gut microbiota, with evidence suggesting a significant correlation between genetic makeup and microbial composition (Zhernakova et al., 2024). Studies on monozygotic twins have shown a higher similarity in gut microbiota compared to dizygotic twins, indicating a genetic component in microbiota composition (McEvoy et al., 2024). For instance, the family *Christensenellaceae* is highly heritable and associated with a lower body mass index, highlighting the gut microbiota's role in mediating genetic influences on phenotypes (Waters & Ley, 2019).

Epigenetics, involving changes in gene expression without altering the DNA sequence, also plays a part in this axis. The gut microbiota can influence gene expression through mechanisms such as histone deacetylase (HDAC) activity. Inhibition of HDAC has been shown to reverse stress-induced behaviours in animal models, suggesting that microbial modulation of gene expression could impact brain function and behaviour (H. Liu et al., 2018). Additionally, noncoding RNAs, particularly microRNAs (miRNAs), are crucial mediators in this interaction by regulating post-transcriptional gene expression. miRNAs modulate a wide range of biological processes, including neural development, synaptic plasticity, and immune responses, all of which are influenced by the gut microbiota (Moloney et al., 2019). miRNAs regulate gene expression and have been linked to neuropsychiatric disorders (Chen et al., 2017; Moloney et al., 2018). Research in germ-free mice has demonstrated that the gut microbiota affects miRNA expression in brain regions like the amygdala and prefrontal cortex, further underscoring the microbiota's role in gene regulation and brain health (Chen et al., 2017).

MicroRNAs can also modulate gut-brain connections. As discussed in the chapter ***"MicroRNA Fine-Tune Brain and Body Communication in Health and Disease,"*** ongoing research is actively investigating the role of miRNAs originating in the gut and brain in contributing to various disease states.

How Birth Shapes the Microbiome: Vaginal Delivery vs. C-Section

The mode of delivery at birth is a significant determinant of an infant's initial microbiota (Zachariassen et al., 2021). Vaginal delivery allows for the transfer of maternal vaginal microbiota to the newborn, whereas C-section bypasses this exposure, leading to initial colonisation by skin and environmental bacteria. C-section delivery delays the transmission of beneficial maternal microbiota to infants, resulting in altered colonisation patterns, reduced early acquisition of key species like *Bifidobacterium longum*, and increased susceptibility to long-term health issues (Selma-Royo et al., 2024). However, breastfeeding plays a critical role in mitigating these effects by promoting the growth of beneficial bacteria and supporting gut and immune development, highlighting the importance of breastfeeding support and potential microbiota restoration strategies for C-section infants (Korpela & de Vos, 2022; Selma-Royo et al., 2024). Vaginally delivered infants typically have a microbiota similar to their mothers vaginal microbiota, rich in important commensal bacteria such as *Bifidobacterium* and *Lactobacillus*. In contrast, C-section delivered infants often have a less diverse microbiota, with higher levels of

Staphylococcus spp. and lower levels of important commensals like *Bacteroides* (Lynch et al., 2023; Shao et al., 2019).

These early differences can have long-term health implications. C-section delivery has been associated with an increased risk of developing conditions like obesity, type 1 diabetes, asthma, and allergies (Cabre et al., 2022). Additionally, C-section-born infants may have a higher risk of neonatal infections (Miller et al., 2020). Although these microbiota differences tend to diminish over time, the initial colonisation can have lasting effects on immune development and disease susceptibility (Dinan et al., 2022; Morais et al., 2020). C-section born individuals can display an increased psychological vulnerability to stress and lower positive affect, along with altered immune profiles, suggesting a potential lasting impact of delivery mode on psychological responses (Dinan et al., 2022).

In mice, the impact of early-life gut microbiota alterations due to C-section delivery reveal that C-section delivery leads to an excessively diverse microbiota too early in life, which triggers an inflammatory immune response, disrupts gut epithelium structure, and alters mucus production (Barone et al., 2023). Importantly, transferring the microbiota from mice born by C-section into germ-free mice confirmed the causal relationship between the altered microbiota and increased inflammatory susceptibility. Further, supplementation with *Lactobacilli* restored resilience against inflammation, further highlighting the critical role of early-life microbiota-host interactions in shaping long-term health outcomes. Such disruptions have been associated with various neurological and psychiatric conditions, suggesting potential implications for brain health too.

In rats, offspring born via C-section to obese mothers exhibited greater weight gain and caloric intake, alongside altered expression of appetite-regulating neuropeptides, while those from lean mothers born by C-section had higher stress hormone levels and reduced expression of genes associated with fat metabolism (Cho et al., 2021). The findings indicate that C-section delivery affects obesity risk differently depending on maternal obesity status, and such alterations in the gut microbiota due to C-section delivery could have systemic effects influencing brain function and behaviour through the microbiota-gut-brain axis, although more work is needed.

Strategies to mitigate the impact of C-section on the microbiota include vaginal seeding, where vaginal microbiota are transferred to the newborn, maternal faecal microbiota transplantation, and supplementation with probiotics and prebiotics (Korpela & de Vos, 2022). A recent study investigated the impact of vaginal microbiota transfer (vaginal seeding) on neurodevelopment and gut microbiota composition in C-section delivered infants (Zhou et al., 2023). Results indicated that vaginal seeding significantly improved neurodevelopmental outcomes at 6 months of age; this also accelerated gut microbiota maturation and positively influenced various metabolic functions within 42 days post-birth. While these preliminary results highlight the potential of vaginal seeding to support neurodevelopment and microbiota composition in C-section-delivered infants, the authors note that further research is needed to establish the long-term safety and efficacy of this intervention. These findings do not currently support routine clinical implementation but underscore the need for more studies to assess the approach's feasibility and broader health implications.

Dietary Drivers of Microbiota-Gut-Brain Health

Diet is a critical factor influencing the microbiota-gut-brain axis (Berding et al., 2023; Ross, Mayer, et al., 2024; Schellekens et al., 2023). Different dietary patterns can significantly alter gut microbiota composition, affecting brain function and behaviour. The Western diet, high in sugar, salt, fat, and ultra-processed foods, is linked to negative health outcomes such as metabolic disorders and altered gut microbiota (McGuinness et al., 2024). This diet tends to decrease pro-health bacteria like *Bacteroidetes*

and increase negative gut microbes like Proteobacteria (Ross, Patangia, et al., 2024). Such shifts can lead to systemic inflammation and negatively impact brain health. Studies in mice have shown that a high-fat diet can drastically alter gut microbiota within 48 hours, indicating the rapid and profound effects of dietary changes (Fulling et al., 2020). Furthermore, HFD is associated with neuroinflammation, impaired blood-brain barrier integrity, and altered hippocampal plasticity, contributing to cognitive deficits and mood disturbances (Bruce-Keller et al., 2015). These effects are thought to be mediated through changes in gut microbiota composition, leading to systemic inflammation and increased permeability of the gut barrier and subsequent effects on the microbiota-gut-brain axis (de Paula et al., 2021).

The Mediterranean diet, rich in fruits, vegetables, whole grains, and healthy fats, is associated with numerous health benefits, including reduced risk of neurodegenerative diseases and improved mood (Bizzozero-Peroni et al., 2024; Conti et al., 2024; Park et al., 2024). Human studies have demonstrated that adhering to a Mediterranean diet can lower the incidence of depression and enhance cognitive function (Ross, Mayer, et al., 2024). A first of its kind randomised controlled trial provided evidence that a Mediterranean-style diet can significantly reduce depressive symptoms in individuals with moderate to severe depression (Jacka et al., 2017). Participants who improved their diet quality, with guidance from a dietitian, experienced notable mental health benefits, independent of weight changes. These findings highlight the potential of dietary improvement as an adjunctive strategy for managing depression in clinical settings.

The ketogenic diet, high in fat and low in carbohydrates, has been shown to benefit neurological conditions such as epilepsy and autism (Allan et al., 2024; Smolensky et al., 2023). This diet increases ketone bodies, which have neuroprotective effects, and alters gut microbiota composition to include important commensal bacteria like *Akkermansia* and *Parabacteroides* (Santangelo et al., 2023). These changes in gut microbiota composition and function are thought to contribute to the diet's therapeutic effects on brain health (Boscaini et al., 2022). One study examined the effects of low-carbohydrate diets, focusing on sex differences in metabolic responses and adipose tissue dynamics in mice (Smolensky et al., 2023). Although the ketogenic diet resulted in weight loss and reduced subcutaneous fat in males, it also revealed decreased insulin levels and increased ghrelin and Fibroblast growth factor-21 levels in both sexes, with female mice exhibiting unfavourable metabolic effects from the non-ketogenic moderate low-carbohydrate diet, suggesting a complex and sex-dependent response to these dietary interventions. Emerging evidence highlights the potential of the ketogenic diet as a therapeutic intervention for schizophrenia (Sarnyai et al., 2019). By providing ketone bodies as an alternative energy source, the diet compensates for glucose metabolism and mitochondrial dysfunction commonly observed in schizophrenia. Recent preclinical studies and case reports suggest that the ketogenic diet can restore synaptic communication, improve psychiatric symptoms, and mitigate metabolic side effects associated with antipsychotic treatment (Kraeuter et al., 2019). However, more rigorous randomised (Kennedy et al., 2007; Paoli et al., 2013)controlled trials are needed to validate these findings and explore its long-term safety and efficacy.

Carbohydrates, both digestible and indigestible, play a role in shaping gut microbiota, influencing body-brain interactions. Digestible carbohydrates, such as sugars, can increase certain commensal bacteria but may also contribute to metabolic disorders if consumed in excess (Lippert & Bruning, 2022). Indigestible carbohydrates, like dietary fibre, are fermented by gut bacteria into a variety of compounds including SCFAs, secondary bile acids, aromatic amino acid, neurotransmitters, and B vitamins. These metabolites support gut health and modulate brain function via anti-inflammatory properties and microbiota-gut-brain signalling pathways (Dalile et al., 2019; Grant et al., 2025). Indeed, SCFAs such as butyrate are known to cross the blood-brain barrier and influence neuroinflammation,

neurotransmitter production, and cognitive processes (Silva et al., 2020). Individuals with insulin resistance have increased levels of faecal carbohydrates, particularly host-accessible monosaccharides, which correlate with microbial carbohydrate metabolism and inflammatory cytokines (Takeuchi et al., 2023). This systemic inflammation associated with insulin resistance can also affect neuroinflammation and brain health, contributing to conditions such as cognitive decline and Alzheimer's disease (Arnold et al., 2018). By identifying gut bacteria linked to insulin resistance and demonstrating their potential to improve host insulin sensitivity in a mouse model, microbial carbohydrate metabolism could be a promising therapeutic target for addressing insulin resistance, such as with type 2 diabetes. Such interventions may not only address insulin resistance and type 2 diabetes but also alleviate the associated cognitive and neurological complications through microbiota-gut-brain and immune pathways linked to brain health.

Protein intake, whether from animal or plant sources, affects gut microbiota diversity and composition. Animal-based proteins tend to increase bacteria associated with protein fermentation, while plant-based proteins promote a more diverse microbiota (Bartlett & Kleiner, 2022). Indeed, omnivorous diet-associated microbes, influenced by meat consumption, were linked to inflammation and poorer cardiometabolic health, while vegan-associated microbes, enriched by plant-based diets, correlated with positive gut functions and improved cardiometabolic markers (Fackelmann et al., 2025). Vegetarian microbiomes displayed intermediate characteristics, with dairy consumption leaving a distinct microbial signature (Fackelmann et al., 2025). High-protein diets can enhance the production of SCFAs and branched-chain amino acids, which have various health benefits including anti-inflammatory effects and modulation of neurotransmitter synthesis (Awan et al., 2024; Mueller, Differding, Zhang, et al., 2021). However, excessive protein intake, especially from animal sources, may increase the risk of gut inflammation and metabolic disorders, which are linked to systemic inflammation and impaired brain function (Armet et al., 2022; Zhu et al., 2015). Indeed, dietary proteins from different sources are digested and utilised in the gut differently by the host and the gut microbiota (Awan et al., 2024). Some proteins were preferentially utilised by the microbiota, such as the alpha subunit of β-conglycinin found in soy, lectin and legumin J present in peas, ovalbumin in egg white, and cell wall proteins from yeast. These variations in protein utilisation can influence gut microbial metabolites, which in turn impact brain health through the microbiota-gut-brain axis. For example, specific microbial metabolites derived from protein fermentation, such as aromatic amino acids, are precursors for neurotransmitters like serotonin and dopamine, which are crucial for mood regulation and cognitive function (Strandwitz, 2018). This work highlights the significant differences in the fate of dietary proteins suggesting that these variations may contribute to the differential health impacts associated with different protein sources.

The type of fat consumed can influence gut microbiota, overall health, and brain function. Saturated and trans fats, common in a Western diet, are linked to negative changes in the gut microbiota composition and increased risk of cardiovascular diseases, increased inflammation, and heightened risk of neurodegenerative diseases (Martinez et al., 2017; Zhang & Gerard, 2022). In contrast, polyunsaturated fatty acids, such as omega-3 and omega-6, support the growth of commensal bacteria and have anti-inflammatory effects, and positively influence brain health (Leyrolle et al., 2022; Muth & Park, 2021). Omega-3 fatty acids, in particular, have been shown to improve cognitive function and reduce the risk of depression and other neuropsychiatric conditions. In particular docosahexaenoic acid and eicosapentaenoic acid, are critical for brain structure and function, as docosahexaenoic acid is a key component of neuronal membranes and synapses, contributing to neuroplasticity, neurotransmission, and cognitive function. For example, a recent study investigated the effects of various doses of eicosapentaenoic acid (an Omega-3 fatty acid) on inflammatory markers and depressive symptoms in a cohort of sixty-one unmedicated adults diagnosed with MDD and elevated

high-sensitivity C-reactive protein (hs-CRP) levels (Mischoulon et al., 2022). A higher dose of daily EPA daily led to significant improvements in response rates and a correlation between reductions in hs-CRP and decreases in depressive symptoms. These findings highlight the role of omega-3 fatty acids in modulating both inflammation and brain health, emphasising their therapeutic potential for mood disorders and cognitive decline.

A recent study noted, after identifying five dietary patterns, that global dietary patterns are more strongly associated with variations in the gut microbiome than individual dietary components, emphasising the importance of a holistic approach to dietary evaluation for understanding gut health and informing personalised dietary strategies (Cotillard et al., 2022).

Fueling the Axis: Impact of Prebiotics andFermented Foods

Prebiotics and fermented foods also play a crucial role in this field (Hutkins et al., 2025; Schneider et al., 2024a). Prebiotics are substrates selectively utilised by host microorganisms, conferring health benefits (Salminen et al., 2021). While many prebiotics are dietary fibres, such as resistant starch, inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS), not all fibres meet the criteria to be classified as prebiotics (F. Liu et al., 2017; Zhang et al., 2021). Prebiotics can also include non-fibre compounds, such as certain polyphenols and human milk oligosaccharides, which have been shown to positively influence gut microbiota composition and function, thereby modulating host health (Donoso et al., 2020; Ferrier et al., 2022; L. Zhu et al., 2024). These diverse prebiotics are found in sources like fruits, vegetables, grains, and human milk, each demonstrating unique effects on gut microbiota composition and metabolic activity.

The Western diet has led to a drop in prebiotic intake, along with a rise in inflammatory diseases and lifestyle disorders (Zhang et al., 2021). Supplementing with prebiotics has shown to reduce stress, anxiety, and depressive-like behaviour, positively influencing brain physiology and behaviour (Berding et al., 2023). The mechanisms of action for prebiotics involve altering gut microbiota composition, leading to increased production of health-promoting metabolites like SCFAs (Zhang et al., 2021). These changes can enhance hippocampal synaptic efficacy, general hypothalamic neuronal activity, and cognitive functions (Church et al., 2023; Rusch et al., 2023). The dietary fibre polydextrose showed significant improvements in cognitive flexibility and sustained attention in healthy female population (Berding et al., 2021). Although polydextrose supplementation did not alter microbial diversity, it did increase the abundance of *Ruminiclostridium* 5 and reduced inflammation suggesting a potential mechanism for improved gut-to-brain communication and behavioural modulation (Berding et al., 2021).

Fermented foods are products rich in microbes and bioactive metabolites that interact with the gut microbiota, influencing the microbiota-gut-brain axis and promoting mental and physical health (Balasubramanian et al., 2024; Marco et al., 2021). They have emerged as a promising avenue for enhancing mental health through their ability to modulate the gut microbiota (Schneider et al., 2024a). Rich in microbes and bioactive metabolites, these foods interact with the microbiota-gut-brain axis, influencing the various pathways mentioned previously, impacting brain function and emotional well-being (Schneider et al., 2024b). By harnessing the power of fermented foods, we can tap into their potential to shape the gut microbiome, bolster immune responses, and promote cognitive health. For example, a recent study with critically ill patients received escalating doses of kefir (fermented dairy product), with no reports of serious side effects, and a high adherence rate of 91% to the prescribed doses (Gupta et al., 2024). Although no significant changes in gut microbial diversity were noted, a marked improvement in the Gut Microbiome Wellness Index was observed, suggesting that kefir could positively influence gut

health in this vulnerable population. A similar study using kefir noted improvements in relational memory tasks combined with a significant increase in Lactobacillus levels (Cannavale et al., 2023).

From Probiotics to psychobiotics: Microbial Allies in Mental Health

Probiotics are live bacteria that confer health benefits to the host when ingested in adequate amounts, and interact with host microbiota and the intestinal epithelium (Gupta et al., 2024; Hill et al., 2014; Mazzone et al., 2024; Samara et al., 2022). They have been shown to improve metabolism, immunity, and even brain function. Indeed, recent work has identified the Lab4 multistrain probiotic as reducing IBS symptom severity, anxiety, and depression, along with improved stool consistency in a cohort of individuals with IBS (Mullish et al., 2024). Further, children with ASD provided with the probiotic *L. reuteri* demonstrated noteworthy improvements in social functioning across various assessments, although did not significantly affect overall autism severity or microbiota composition (Mazzone et al., 2024). A probiotic formulation featuring four *Bifidobacterium* strains and one *Lacticaseibacillus* strain was shown to facilitate the rapid transition toward a stable, term-like microbiome in extremely premature infants (Samara et al., 2022). Such work indicates that *Bifidobacterium* strains significantly influence microbiome maturation from an early age, contributing to a more interconnected microbial community and promoting an anti-inflammatory immune environment, thereby underscoring their role as key contributors to gut ecosystem development in this vulnerable population.

Research has documented probiotics' ability to modulate neurotransmission, neurogenesis, and neuroinflammation, impacting various disorders from depression to autism (Audet, 2021; Guzzetta et al., 2022; Mohle et al., 2016). For example, the probiotics *Lactobacillus plantarum* A7 and *Bifidobacterium animalis* delayed disease onset in an experimental autoimmune encephalomyelitis (EAE) animal model of Multiple Sclerosis (MS) (Salehipour et al., 2017). A marked inhibition of inflammatory cytokines and enhanced levels of regulatory T cells were noted, effectively promoting anti-inflammatory responses by favoring Treg differentiation.

A prebiotic or probiotic that, when ingested in adequate amounts, produces health benefits by positively influencing mental health and brain function through mechanisms such as modulation of the gut microbiota and its communication with the brain is called a psychobiotic (Slykerman et al., 2025). Probiotics like *Faecalibacterium prausnitzii* have demonstrated potential as psychobiotics, reducing anxiety and depression-like symptoms in animal models (Hao et al., 2019; Zhernakova et al., 2024). The ability of *F. prausnitzii* to produce butyrate under conditions of adequate dietary fibre highlights its therapeutic potential. However, its effects depend on the availability of specific substrates like dietary fibres or prebiotics and a conducive gut environment. Similarly, other psychobiotics may require specific conditions to produce bioactive metabolites, such as neurotransmitter precursors or SCFAs. Therefore, while the promise of probiotics for enhancing health is significant, it is essential to consider how factors such as dietary composition, availability of microbial substrates, and the complexity of the host's microbiota can influence their metabolic outputs, efficacy, and overall outcomes.

Beyond pre- and probiotics: The Rise of Synbiotics and Postbiotics

Synbiotics are "a mixture comprising live microorganisms and substrate(s) selectively utilised by host microorganisms that confers a health benefit on the host" (Swanson et al., 2020). The synergistic action of synbiotics aims to improve the balance of gut microbiota, support digestive health, and potentially provide various health benefits beyond those offered by probiotics or prebiotics alone. Synbiotics have been the focus of some important recent research. A randomised controlled trial involving 153 infants

born via elective C-section were given a synbiotic or prebiotic-supplemented formula which showed significant differences in their gut microbiome development compared to vaginally born infants (Lay et al., 2021). Breastfed infants exhibited a more favourable hypoxic and acidic gut environment preventing the establishment of an unwanted microbiome. One study investigated the impact of a synbiotic supplement on metabolic syndrome components in patients receiving antipsychotic treatment (Basafa-Roodi et al., 2024). They concluded that the synbiotic significantly reduced waist circumference and HbA1c levels, while also preventing BMI increases compared to the placebo group, suggesting a potential role for the synbiotic in managing metabolic health in this population. These findings have implications for the microbiota-gut-brain axis, as improved metabolic health and reduced inflammation are linked to better brain function and mental health outcomes in schizophrenia. By modulating gut microbiota and lowering systemic inflammation, the synbiotic may indirectly support cognitive function and mood regulation, addressing both physical and mental health challenges associated with this condition.

Postbiotics are “preparation of inanimate microorganisms and/or their components that confers a health benefit on the host” (Salminen et al., 2021). These compounds can include SCFAs, peptides, and other metabolites that contribute to health benefits, such as supporting immune function, enhancing gut barrier integrity, and reducing inflammation (Braga et al., 2024; Salminen et al., 2021; Siciliano et al., 2021; Wang et al., 2024). Unlike probiotics, which are live microorganisms, postbiotics are not alive but still exert positive effects on the host's health. A recent study examining the postbiotic *Lactobacillus* LB, derived from heat-treated *Limosilactobacillus fermentum* and *Lactobacillus delbrueckii*, has been shown to enhance the growth of commensal bifidobacteria in both human faecal models and pure cultures, leading to improved metabolic outcomes such as increased acid production (Warda et al., 2021). Importantly, postbiotics may also play a role in brain health via the microbiota-gut-brain axis. For example, SCFAs, a class of microbial metabolites that may be delivered as part of a postbiotic preparation, have been shown to modulate microglial activation, reduce neuroinflammation, and influence brain plasticity, linking postbiotic activity to improved cognitive and emotional regulation (Dalile et al., 2019). Furthermore, GABA, a neurotransmitter critical for mood regulation and stress resilience, may act as part ofa postbiotic preparation since its levels in both circulation and the brain are influenced by gut microbiota composition. Recent findings suggest that both circulating and brain GABA levels are influenced by gut microbiota composition, positioning GABA as a potential mediator of the microbiota-gut-brain axis. Exploring GABA-producing microorganisms in the gut and dietary factors that enhance GABA production could lead to new therapeutic approaches for treating neurological and psychological disorders (Braga et al., 2024).

Environmental Influencers: Shaping Microbial Ecosystems

The environment we inhabit exerts a profound influence on our health outcomes and the composition of our gut microbiota (Gacesa et al., 2022; Matsuzaki et al., 2023; Sanmarco et al., 2022). Cross-cultural differences in health can often be traced back to environmental factors that shape our microbiome (Morais et al., 2024). Various members of the gut microbiota are involved in metabolising numerous environmental chemicals through enzymes such as azoreductase, nitroreductase, β-glucuronidases, sulfatases, and β-lyases (Claus et al., 2016; Walsh et al., 2020). Conversely, these chemicals can also modify the composition of the gut microbiota, impacting brain function and behaviour via the microbiota-gut-brain axis.

A notable example is bisphenol A, an endocrine-disrupting chemical used extensively in manufacturing plastic containers. Exposure to bisphenol A through diet has been shown to reduce the diversity of gut microbiota in rodents while increasing the abundance of *Proteobacteria* and *Helicobacteraceae* and decreasing *Clostridia* (Lai et al., 2016). Such alterations in microbiota composition could influence brain

function and behaviour. These changes in microbiota composition have been linked to altered microbiota-gut-brain axis communication. For example, increased *Proteobacteria* are associated with heightened intestinal inflammation, which can promote neuroinflammation through immune signalling pathways (Heinzel et al., 2024). Additionally, reductions in bacteria such as *Clostridia* through environmental factors may impair the production of SCFAs, which are critical for maintaining blood-brain barrier integrity and regulating brain neurochemistry (Chiu et al., 2020).

Heavy metals such as cadmium, mercury, arsenic, and lead are highly toxic and can disrupt immune function, damage DNA, and cause oxidative stress (Jomova et al., 2025). Exposure to these metals also alters gut microbiota composition in both animals and humans (Lu et al., 2014; Thompson et al., 2022; Zhang et al., 2015). Studies have shown that heavy metals administration to animals perturbs their gut microbiota and metabolomic profile, increasing levels of *Lactobacillaceae* and *Erysipelotrichaceae* while reducing *Lachnospiraceae* (Breton et al., 2013; Q. Zhu et al., 2024), a genera of bacteria associated with depression in humans (Radjabzadeh et al., 2022). This suggests a potential microbiota-gut-brain pathway for the mental health impact of environmental pollutants.

Another environmental factor that can affect the gut microbiota is pesticides, which are widely used in modern agriculture (Matsuzaki et al., 2023). Preclinical research has demonstrated that pesticides can negatively affect gut microbiota composition, leading to changes in host physiology and behaviour, including increased anxiety-like and depressive-like behaviours (Curtis et al., 2023; Yue et al., 2024). As a result, it is becoming ever more critical to investigate whether pesticide-induced alterations in gut microbiota are responsible for these behavioural impairments. In humans, occupational pesticide exposure has been associated with altered gut microbiome composition, including decreased microbial diversity and changes in specific bacterial taxa (Gois et al., 2023). Chronic, low-level dietary exposure to highly toxic pesticides like Paraquat and Chlorpyrifos has been shown to negatively affect the human gut microbiota, potentially increasing systemic inflammation, compromising gut barrier integrity, and contributing to metabolic disorders; a concern that has not been fully addressed by regulatory agencies (Gama et al., 2022). The PELAGIE study investigated the relationship between prenatal and early childhood exposure to pyrethroid insecticides and neurobehavioral outcomes in children (Viel et al., 2017). They found that prenatal exposure (e.g. via diet) to certain pyrethroid metabolites was associated with internalising difficulties, while childhood exposure correlated with externalising behaviour problems and impaired prosocial skills. These findings highlight the potential influence of long-term pesticide exposure on the human gut microbiome and its possible health consequences, including neurological impacts. Better monitoring and regulation of pesticide residues in food is desperately needed, particularly in developing countries, where exposure could lead to prolonged and harmful effects on gut and brain health.

Recently, researchers identified unusual phospholipids, termed MmDEACLs, produced by *Morganella morganii*, which incorporate the environmental micropollutant diethanolamine (DEA) (Bang et al., 2025). DEA is an industrial chemical produced on a massive scale and widely used in agriculture, consumer products, and manufacturing. DEA is a non-natural micropollutant that enters the environment in significant quantities and is incorporated into these microbial metabolites via a promiscuous cardiolipin synthase enzyme in *M. morganii*. These DEA-modified phospholipids activate TLR2/TLR1 receptors, inducing the release of pro-inflammatory cytokines, particularly IL-6, known to be associated with MDD and other inflammatory conditions. This mechanism highlights the role of gut microbial metabolites, chronic inflammation, and environmental pollutants in mental health disorders.

In the chapter *"**Beyond Infections: The Impact of Emerging Environmental Toxins on Maternal Immunity and Neurodevelopment**,"* the authors present evidence that early immune system disruptions may significantly contribute to neurodevelopmental disorders. Specifically, altered

immune responses during prenatal development—such as maternal immune activation (MIA) triggered by infections—have been linked to an increased risk of these disorders in offspring. Immune dysregulation, particularly elevated pro-inflammatory cytokines, can interfere with brain development and synaptic connectivity, resulting in lasting effects on brain function and behavior.

Exercise and the Axis: Enhancing Gut-Brain Health Through Movement

Exercise is well known for its benefits to overall health, including brain health (Nota et al., 2023). It influences brain structures and functions, such as neurogenesis in rodents. Exercise can counteract age-related declines in hippocampal neurogenesis, potentially reversing aging effects within brain structures (Nicolas et al., 2024; Wang et al., 2023). Despite extensive research on exercise and brain health, the impact of exercise on gut health and the microbiota-gut-brain axis is less understood. The PROMOTe trial, a randomised controlled study investigating the effects of prebiotic supplementation on muscle strength, function, and cognition in older adults, demonstrated that prebiotic supplementation improved cognitive function in older adults, particularly in memory tasks linked to Alzheimer's risk, but had no significant impact on muscle strength or function over 12 weeks (Ni Lochlainn et al., 2024). The prebiotic (inulin and fructo-oligosaccharides) effectively modulated the gut microbiome, increasing *Bifidobacterium* abundance. These findings highlight the potential of prebiotics for addressing cognitive frailty, though further research is needed to explore their role in muscle health.

Moderate exercise can positively affect gut microbiota diversity and composition (Noetel et al., 2024; Sanchez et al., 2017). It reduces stress, enhances immunity, and improves energy homeostasis by modulating the hypothalamic-pituitary-adrenal (HPA) axis, leading to lower cortisol levels, a critical marker of stress (Hillman et al., 2008; Ni Lochlainn et al., 2024; Noetel et al., 2024; Rodrigues et al., 2025). Additionally, exercise enhances immunity by increasing the circulation of immune cells, such as natural killer cells, and modulating the production of anti-inflammatory cytokines (Campbell & Turner, 2018). Exercise also improves energy homeostasis by influencing mitochondrial biogenesis and metabolic pathways that regulate glucose and lipid metabolism (Warren et al., 2020)

Studies in rodents have shown that voluntary exercise can significantly alter the balance of major bacterial phyla, such as Bacteroidetes and Firmicutes, preventing diet-induced obesity and normalising glucose tolerance (McNamara et al., 2021). Exercise increases commensal bacteria like *Lactobacillus* and *Bifidobacterium*, enhancing gut health and potentially influencing brain and behaviour.

Human studies have also highlighted the benefits of exercise on gut microbiota. For instance, the American Gut Project found that individuals who exercised more frequently had greater microbiota diversity, particularly in the Firmicutes phylum (Lane et al., 2024). Professional athletes have shown higher microbiota diversity compared to sedentary individuals, with an increase in the genus *Akkermansia*, associated with a healthier metabolic profile (Jie et al., 2021).

Regular physical activity positively correlates with increased microbiota diversity and specific bacteria. Studies involving various exercise regimens, including aerobic and resistance training, have shown modest but significant alterations in gut microbiota composition, suggesting that both exercise and diet drive gut biodiversity (Komulainen et al., 2021; Nota et al., 2023).

Pharmaceutical Impacts: How Medications Alter Microbiota

Antibiotics, although useful in the preclinical setting for studying the gut microbiota, are also widely used in agriculture and over-prescribed in human medicine, having a significant impact on natural ecosystems and the health of organisms, highlighting the need for a broader perspective on planetary

health and antibiotic use (Llor & Bjerrum, 2014; Manyi-Loh et al., 2018; Prestinaci et al., 2015). Antibiotics directly target the gut microbiota, but non-antibiotic drugs can also influence microbial composition and behaviour. Further, laxatives, antidepressants, and antihistamines, also significantly alter the gut microbiota (Cussotto, Clarke, et al., 2021; Cussotto, Walsh, et al., 2021; Rogers & Aronoff, 2016). These changes can impact drug pharmacokinetics and host health.

Polypharmacy, the concurrent use of multiple medications, has been associated with reduced microbial diversity (Ticinesi et al., 2017). Certain drug classes, such as proton pump inhibitors, antidepressants, and antipsychotics, have strong associations with specific gut bacteria (Cussotto et al., 2019; Imhann et al., 2016). Studies have shown that these medications can alter microbial gene expression related to drug metabolism, highlighting the need for careful consideration of polypharmacy and its impact on the microbiome (Bretler et al., 2019; Imhann et al., 2016; F. Xu et al., 2023). Preclinical exposure to SSRIs combined with maternal immune activation lead to changes in immune and serotonin signalling pathways (Zengeler et al., 2023). These disruptions not only affect placental physiology but also but also influence the maternal and foetal microbiota, result in sex-specific neurodevelopmental and behavioural alterations in offspring, through the microbiota-gut-brain axis.

Stress and the Axis: The Role of Microbiota in Resilience

Stress disrupts the normal homeostasis of an organism, triggering the HPA axis and resulting in cortisol release. Indeed, both traumatic and chronic stress can induce maladaptive changes that may increase vulnerability to gastrointestinal disorders and alter gut-brain communication, impacting neural and behavioural responses (Leigh et al., 2023). For example, chronic stress leads to HPA axis dysregulation and increased risk of various health issues, including anxiety and depression (Audet, 2019; Clarke et al., 2013; Lyte et al., 2020). However, the effects of acute stress are less understood, but stress has been shown to impair gut barrier function, disrupt enteric nervous system circuitry, and modify the gut microbiota (Chen et al., 2024; Gheorghe et al., 2024). Stress has been shown to impair gut barrier function, disrupt enteric nervous system circuitry, and modify the gut microbiota(Chen et al., 2024; Gheorghe et al., 2024). Stress-related disorders have significant economic impacts, highlighting the importance of understanding the microbiota-gut-brain axis in stress regulation. Numerous studies have demonstrated that stress-induced alterations in gut microbiota can influence brain function and behaviour (Berding et al., 2023; Garcia-Cabrerizo & Cryan, 2024; Ritz, Draper, et al., 2024). For instance, shifts in microbial composition, such as decreased *lactobacilli*, and increased Helicobacter pylori levels in mice, may contribute to changes in neurotransmitter production and inflammatory pathways, which directly affect gut-brain communication (Carabotti et al., 2015; Guo et al., 2009; Palomar et al., 2014) . Psychological stressors, such as maternal separation and overcrowding, have also been shown to change gut microbiota composition and disrupt microbial diversity, leading to altered brain signalling and behavioural outcomes (Chen et al., 2023; Nicolas, McGovern, et al., 2022). Prenatal exposure to maternal stress alters the gut microbiota composition and stress-response pathways in offspring, with these effects persisting across generations (Chen et al., 2023). Further, maternal HFD exposure can alter the offspring's gut microbiota and metabolite profiles, contributing to metabolic and neurodevelopmental changes (Dzamko, 2023; Nicolas, Leime, et al., 2022). These findings underscore the intricate interplay between stress, the gut microbiota, and brain health via the microbiota-gut-brain axis.

Maternal stress during pregnancy can alter the microbiota composition of offspring, affecting their stress response in adulthood (Block et al., 2022; Potter et al., 2023). Studies have shown that the transfer of maternal vaginal microbiota from stressed dams to non-stressed pups can alter their response to stress, suggesting that early-life microbial exposure plays a crucial role in stress regulation

(Jasarevic et al., 2021; Mueller, Differding, Ostbye, et al., 2021; Wei et al., 2022; Zhou et al., 2023). In utilising a probiotic *Lactocaseibacillus rhamnosus* HN001 for the treatment of postpartum mood and caregiving behaviours after stress during pregnancy in a rodent model, researchers have discovered a potential therapy for pregnant and postpartum women (Lonstein et al., 2024). This work noted a reduction in postpartum anxiety-related behaviours and altered neurotransmitter levels in the prefrontal cortex. It also impacted maternal behaviours and gut microbiota diversity.

Circadian Clocks and Microbial Rhythms: Timing the Axis

The circadian rhythm, a 24-hour cycle regulating bodily functions, interacts with the microbiota and influences health outcomes (Teichman et al., 2020). Modern lifestyles often disrupt circadian rhythms, leading to metabolic and psychiatric disorders. Indeed, the gut microbiota has been shown to regulate stress responsivity via the circadian system (Tofani et al., 2025). The interplay between circadian rhythm and the microbiota is being further explored in the context of obesity, cardiovascular disease, diabetes, psychiatric disorders, and neurodegenerative diseases.

The mammalian circadian clock operates through a feedback loop involving transcription factors such as CLOCK and BMAL1 (Altaha et al., 2022; Heddes et al., 2022). Disruptions in circadian rhythm can alter gut microbiota composition, affecting metabolic and brain health (Heddes et al., 2022; Minnebo et al., 2023; Zhang et al., 2023). Studies have shown that changes in light, diet, or microbiota can influence peripheral clocks, leading to dysregulation of the microbiome and host homeostasis. Indeed, the microbiome itself may help stabilise circadian rhythms in the host gut, buffering against rapid environmental fluctuations (Zhang et al., 2023).

The rhythmicity of gut microbiota develops early on in life and is directly impacted by diet (Heppner et al., 2024). Different eating patterns, including meal frequency and timing, also influence the gut microbiome across various regions and niches of the colon (Minnebo et al., 2023). Although eating patterns moderately affect microbiome composition, time-restricted eating has an even more significant effect, increasing the abundance of commensal bacteria like *Bacteroides* and *Faecalibacterium* highlighting the importance of eating patterns in dietary intervention studies (Minnebo et al., 2023). Formula supplemented with the prebiotic GOS in a recent study examining the impact of diet on gut microbiota in infants, showed that the colonisation of the commensal *bifidobacteria* performed similarly to breastfed infants (Heppner et al., 2024). Intriguingly, circadian rhythmicity in gut bacterial communities and functional pathways became more pronounced with age, especially in both breastfed and GOS-supplemented infants.

Research in transgenic mice with disrupted circadian clock genes has demonstrated significant changes in microbiota composition, suggesting that circadian rhythm regulates microbiota function (Deaver et al., 2018; Voigt et al., 2016). Human studies have shown that disruptions such as jet lag and shift work can lead to arrhythmic gut microbiota, promoting metabolic imbalances (Dollish et al., 2024; Zhang et al., 2023). Using germ-free and antibiotic-treated mice, recent work revealed that tryptophan metabolism is highly responsive to a short acute stress event, with specific bacterial species involved in this metabolic process (Gheorghe et al., 2024). The gut's response to stress varies depending on the time of day and the makeup of the microbiota, resulting in significant changes to gut barrier function and tryptophan metabolism, particularly in the ileum and colon. These findings together highlight the importance of understanding the relationship between circadian rhythms, and the gut microbiota for potential therapeutic interventions.

The study of the microbiota-gut-brain axis is still in its early stages, but the insights gained so far underscore the profound impact of gut microbiota on overall health. As research progresses, the

potential for developing targeted therapies to address neurological and psychiatric disorders through microbiota modulation continues to expand, promising new avenues for improving mental health and well-being.

The Gut Microbiome in Health and Disease: Bridging Body-Brain Communication

As research into the microbiota-gut-brain axis has advanced, it has become increasingly evident that the microbiota is involved in a variety of psychological and neurological disorders. This includes conditions influenced by stress exposure, dysregulation of the HPA axis, and individual resilience to stress, all of which are impacted by the gut microbiota. The depth of evidence varies across disorders, from early-stage studies showing correlations between gut microbiota composition and clinical populations to more robust findings supporting a causal role of the microbiota in certain disease processes. Now, we will consider the involvement of the gut microbiota in disease.

Autism and the Microbiome: Bridging Gut and Brain Development

ASD encompasses a range of neurodevelopmental conditions characterised by significant social deficits, repetitive behaviours, anxiety, and cognitive disturbances (American Psychiatric Association, 2013; Hung & Margolis, 2024). ASD affects approximately 1 in 68 children globally, with a higher prevalence in males. The behavioural symptoms are linked to changes in neuroinflammation, neurogenesis, neurotransmission, and the production of hormones like oxytocin and vasopressin. Although traditionally considered a neurological disorder, there is growing evidence of gastrointestinal involvement, with about 70% of children with ASD experiencing gastrointestinal issues such as bloating, constipation, and diarrhoea (Madra et al., 2020).

Studies have noted alterations in the gut microbiota of children with ASD, including a reduction in commensal *Bifidobacterium* and an increase in potentially negative *Desulfovibrio* and *Clostridia* (Morton et al., 2023; Zuffa et al., 2023). These microbial imbalances are linked to disruptions in the microbiota-gut-brain axis, with potential impacts on neuroinflammation and neurotransmitter synthesis. One study found that the *Clostridium perfringens* β2 toxin gene (*cpb2*), which encodes for the clostridial toxin b, is more expressed in *Clostridium perfringens* from ASD children, possibly explaining some gastrointestinal symptoms and their downstream effects on behaviour via vagus nerve signalling (Gora et al., 2018). Interestingly, *Clostridium perfringens* has also been reported increased in children born by C-section (Mueller, Differding, Ostbye, et al., 2021). Although interventions targeting the microbe, such as probiotics or dietary changes, have shown promise, more rigorous clinical trials are necessary (Cull et al., 2022; Wang et al., 2021).

Preclinical studies have provided further insight into the microbiota-gut-brain axis in ASD. For example, Shank-3 knockout mice, which exhibit autistic-like behaviours, also show microbiota alterations and respond differently to probiotic treatment based on sex (Osman et al., 2023; Rein et al., 2024). The BTBR mouse model, another tool for studying ASD, demonstrates altered gastrointestinal physiology and microbiota composition (O'Connor et al., 2021; Sen et al., 2022; van de Wouw et al., 2021). Environmental factors, such as *in utero* exposure to Poly I or valproic acid, have been shown to induce autistic-like behaviours and microbiota changes in animal models (Adiguzel et al., 2022; Avolio et al., 2022; Prince et al., 2024).

Probiotic interventions in preclinical models have shown some success. For instance, *L. reuteri* has been found to improve social behaviour and increase oxytocin production in male Shank-3 knockout

mice, as well as significant improvements in social functioning in children with ASD (Mazzone et al., 2024; Tabouy et al., 2018). Similarly, *B. fragilis* has been shown to alleviate certain ASD-related behaviours in a maternal immune activation model (Buzun et al., 2024; Hsiao et al., 2013).

Microbial Influences in ADHD: Diet, Probiotics, and Beyond

ADHD is a neurodevelopmental condition marked by symptoms of inattention, hyperactivity, and impulsivity, either individually or in combination. Although research on the microbiome's role in ADHD is still in its infancy, diet has long been recognised as influential in managing ADHD symptoms (American Psychiatric Association, 2013; Bostock et al., 2017; Hontelez et al., 2021). A Western-style diet, characterised by high consumption of ultra-processed foods and sugars, has been suggested as a potential risk factor for ADHD, though evidence remains debated (Howard et al., 2011). Similarly, elimination diets, especially those excluding artificial food colouring, have shown positive effects on symptom management in some studies, but findings are not universally agreed upon and require further investigation (Gkougka et al., 2022).

As diet profoundly influences gut microbiota, this suggests that the microbiome could play a role in ADHD symptomatology (Wang et al., 2020). A study involving a small clinical cohort of adults and adolescents with ADHD found an increased presence of the genus *Bifidobacterium* when compared to healthy controls, which might affect dopamine precursors in the gut (Partty et al., 2015). Furthermore, a perinatal probiotic intervention has been shown to reduce the risk of an ADHD diagnosis in later childhood, indicating the potential for microbiota-based treatments for ADHD (Allahyari et al., 2024). A few-foods diet can substantially reduce ADHD symptoms in children, although the mechanisms behind this effect are not yet well understood (Hontelez et al., 2021). Looking at the effects of supplementing a probiotic in children with ADHD for eight weeks, those receiving probiotics showed significant reductions in total ADHD symptom scores and anxiety levels, suggesting that probiotics may offer beneficial effects on certain psychological symptoms in children with ADHD (Ahmadvand et al., 2021).

Depression and Microbiota: An Axis of Mood Regulation

MDD is marked by a persistently low mood, diminished interest or pleasure in activities, recurrent thoughts of death, and a range of cognitive and physical symptoms that can significantly impact the quality of life. MDD affects at least 4.4% of the global population and is also characterised by increased pro-inflammatory cytokines and HPA axis hyperactivation, along with a specific clinical diagnosis defined by established criteria in the DSM-5 (American Psychiatric Association, 2013; Marx et al., 2023). Effective treatments for depression can reduce these inflammatory responses and HPA axis activity (Gheorghe et al., 2022). The microbiota-gut-brain axis has been implicated in MDD, with preclinical studies showing that certain probiotic and prebiotic interventions can reduce depressive-like behaviours and inflammation (Audet, 2021; Bastiaanssen et al., 2020; Horne & Foster, 2018).

Human studies have identified differences in the faecal microbiota of MDD patients compared to healthy controls, though findings remain inconsistent (Green et al., 2023; Jiang et al., 2015). Enema-delivered FMT was found to be feasible, acceptable, well-tolerated, and safe, in a cohort of participants with MDD, showing high satisfaction and potential improvements in gastrointestinal symptoms and quality of life (Green et al., 2023). Some studies have reported reduced *Bifidobacterium* and *Lactobacillus*, while others have noted increased bacterial diversity or different bacterial populations (Brushett et al., 2023). One notable study involving over 1,000 individuals found that depression was associated with a lower abundance of *Faecalibacterium* and *Coprococcus*, bacteria involved in producing the SCFA butyrate, which is linked to higher quality of life (Nikolova et al., 2021; Val-Laillet

et al., 2018; Valles-Colomer et al., 2019). Probiotic interventions have shown promise in improving mood and depressive symptoms in some human studies. For example, *Lacticaseibacillus casei* has improved mood in elderly individuals, while a combination of probiotics has shown benefits in MDD patients (Akkasheh et al., 2016). However, not all studies have found significant effects, highlighting the need for more research.

Microbiota, depression, and Anxiety: Pathways to Calm

Anxiety often co-occurs with depression, and much of the evidence for the microbiota-gut-brain axis in anxiety comes from preclinical studies (Gyles et al., 2024). Germ-free mice, for example, show reduced anxiety-like behaviour and altered HPA axis responses (Lynch et al., 2024). One study highlighted a connection between gut microbiota composition and personality traits, including anxiety-related characteristics, where individuals with higher neuroticism, often linked to anxiety, exhibited reduced gut microbiota diversity and lower levels of commensal genera like *Faecalibacterium* and *Coprococcus* (Salia et al., 2025). Another study examining the role of gut microbiota in anxiety-like behaviours found that alterations in gut microbial homeostasis induced by chronic stress correlated with elevated anxiety levels in animal models (Chen et al., 2024). Such findings emphasise the importance of the microbiota-gut-brain axis, suggesting that microbial interventions may have therapeutic potential for anxiety disorders.

Interventional probiotic treatments have yielded mixed results in both animal models and human studies (Berding & Cryan, 2022; Cannavale et al., 2023; Lonstein et al., 2024; Mullish et al., 2024; Mysonhimer et al., 2024). One study that performed maternal administration of *Lactocaseibacillus rhamnosus HN001* from early pregnancy through postpartum, found that the probiotic reduced postpartum anxiety-related behaviours in rodents (Lonstein et al., 2024). The effects were associated with changes in prefrontal cortex dopamine and serotonin turnover and the prevention of postpartum reductions in gut microbiota diversity, highlighting the potential of probiotics in mitigating peripartum mood disorders through the microbiota-gut-brain axis. Further, prenatal intake of a multispecies probiotic formulation significantly influenced offspring neurodevelopment, with enduring sex-dependent effects; male offspring exhibited reduced anxiety-like behaviours, enhanced gut microbiota diversity, and an upregulation of anti-inflammatory and tight junction-related genes (Siegler Lathrop et al., 2024). Further, some probiotic strains have been shown to reduce anxiety in healthy individuals and those with chronic fatigue syndrome such as *Lactobacillus plantarum* DR7 which has been identified as a potential psychobiotic capable of alleviating anxiety and stress-related symptoms in a controlled clinical trials (Chong et al., 2019; Rudzki et al., 2019; Song et al., 2022; Wang et al., 2021). However, more translational research is needed to confirm these findings.

Dietary interventions for the treatment of depression and anxiety are also under investigation. A recent systematic review and meta-analysis of five randomised controlled trials explored the impact of a Mediterranean diet on alleviating depressive symptoms in adults with depression (Bizzozero-Peroni et al., 2024). Their findings concluded that adherence to the diet significantly reduced depressive symptoms compared to control conditions, although the overall risk of bias was moderate to high, and the certainty of evidence was low; thus, indicating that more rigorous, large-scale, and long-term trials are necessary to confirm the diets potential benefits for depression. One fascinating study investigated the connection between gut microbiota and cognitive function and depression in older adults with cognitive impairment (Kolobaric et al., 2024). Their work found that greater microbial diversity was associated with lower cognitive performance and higher depression levels, while certain bacterial abundances and metabolic activities were linked to future cognitive decline and increased depressive symptoms. They suggest that the gut microbiome could serve as a non-invasive biomarker and prognostic tool for cognitive and psychiatric health.

Post-Traumatic Stress Disorder (PTSD) and Microbiota: Stress Recovery Through Gut-Brain Modulation

PTSD is a severe anxiety disorder resulting from exposure to traumatic events that has been gaining attention as a potential target for microbiome-based strategies (American Psychiatric Association, 2013)Tanelian, 2022 #7712}. Although direct investigations into the microbiota's role in clinical PTSD are limited, preclinical and clinical evidence suggests that modulating the microbiota could influence stress responses (Khan et al., 2025). By comparing the bacterial composition of trauma survivors with probable PTSD to trauma-exposed controls without PTSD, one study found no significant differences in overall microbial community structure, but the probable PTSD group exhibited notable changes in specific bacterial taxa (Geier et al., 2024). *Prevotella* and *Ruminococcaceae* negatively correlated with negative mood and positively associated with hyperarousal, suggesting that the microbiome may mediate the diverse psychological outcomes following trauma and could inform personalised psychobiotic interventions based on symptom profiles (Geier et al., 2024). Further preclinical research utilising a mouse model of PTSD-like symptoms induced by single prolonged stress, found that affected animals exhibited increased anxiety-like and depressive-like behaviours, a disruption in gut microbiota composition, and altered intestinal health (Khan et al., 2025). A probiotic treatment improved commensal microbiota and reduced anxiety and depression, suggesting a potential therapeutic approach for PTSD symptoms linked to gut health. Further research into the human gut microbiome profile under chronic stress conditions is necessary to understand its potential impact on PTSD.

Gut-Brain Connections in Bipolar Disorder: A New Frontier

Bipolar disorder, another serious neuropsychiatric condition, has also been linked to microbiota alterations (American Psychiatric Association, 2013; McGuinness et al., 2024). Patients with bipolar mania are more likely to have been recently treated with antibiotics, which can disrupt gut microbial composition and potentially influence immune function and neuroinflammation (Yolken et al., 2016). Faecal microbiome analysis has shown decreased *Firmicutes*, particularly *Faecalibacterium*, a butyrate-producing genus, in bipolar patients (Nikolova et al., 2021). A compromised gut barrier, often referred to as “leaky gut,” may allow microbial metabolites and inflammatory molecules, such as LPS, to enter the bloodstream, triggering systemic inflammation and potentially exacerbating mood instability via neuroimmune pathways.

A recent systematic review revealed that higher consumption of ultra-processed foods is strongly associated with a range of adverse health outcomes, including bipolar disorder, although the quality of evidence varied from very low to moderate (Lane et al., 2024). This dietary pattern may contribute to chronic low-grade inflammation, oxidative stress, and metabolic disturbances, which are all increasingly recognised as key factors in mood disorders. Interestingly, a probiotic trial suggested that probiotic therapy could reduce rehospitalisation rates for patients recently discharged after mania (Dickerson et al., 2018). Such findings highlight the need for further research into microbiota-targeted interventions as an adjunctive strategy for bipolar disorder management, integrating dietary and probiotic therapies with conventional psychiatric treatments.

Microbial Profiles in Schizophrenia: Emerging Mechanisms

Schizophrenia is a severe psychiatric disorder marked by psychosis, cognitive dysfunction, and social withdrawal (American Psychiatric Association, 2013; Tian et al., 2023). There is evidence suggesting a role for the gastrointestinal tract and immune response in its pathogenesis (Tian et al., 2023; Vasileva et al., 2024). Research into the gut microbiota of individuals with psychosis, including schizophrenia, reveals significant differences in microbiota composition compared to controls, with potential

functional consequences (Murray et al., 2023). Although α-diversity did not consistently differ, β-diversity showed a marked contrast, indicating distinctive microbial profiles in those with psychosis (Nguyen et al., 2019). Notably, genera like *Bifidobacterium*, *Lactobacillus*, *Megaspheara*, and *Veillonella* are more prevalent in psychosis groups and are associated with metabolic pathways that influence inflammation and neurotransmitter function (Nguyen et al., 2021). This finding is surprising, as *Bifidobacterium* and *Lactobacillus* are typically associated with beneficial effects on gut and mental health, including anti-inflammatory properties and support for neurotransmitter function, making their increased prevalence in psychosis groups unexpected in terms of microbiota composition. These microbial patterns are also linked to behavioural and cognitive outcomes in both human and animal models, underscoring the microbiome's potential role in the pathophysiology of psychosis and schizophrenia (Basafa-Roodi et al., 2024; Misiak et al., 2024; Vasileva et al., 2024; Wei et al., 2024). Future research focusing on the functional impact of these microbial changes may offer new avenues for microbiome-targeted treatments for psychiatric conditions.

Further studies have found significant differences in the oropharyngeal microbiota of individuals with schizophrenia compared to healthy controls, including reduced microbial diversity and altered neurochemistry in germ-free mice receiving FMT from schizophrenic patients (Castro-Nallar et al., 2015; Wei et al., 2024). Although probiotic interventions have not yet demonstrated significant improvements in schizophrenia symptoms, some studies have reported alleviation of gastrointestinal issues (Lee et al., 2023). Further research is needed to explore the microbiota's role in schizophrenia and potential therapeutic interventions.

Gut Disturbance in Anorexia Nervosa: Targets for Recovery

Anorexia nervosa is one of the psychiatric illnesses with the highest mortality rates and has a profound impact on quality of life. It is characterised by a distorted body image leading to severe food intake restriction, significant weight loss, hyperactivity, and hypothermia (American Psychiatric Association, 2013). The exact aetiology of anorexia nervosa remains unclear, and there are no effective medications currently available. Recent evidence, however, suggests a potential involvement of gut microbiota, identifying it as a possible target for intervention (Andreani et al., 2024; Fan et al., 2023). One longitudinal analysis involving adolescent inpatients diagnosed with anorexia nervosa revealed that microbiota composition changed significantly during acute starvation and weight recovery, suggesting that specific microbial profiles at admission may predict treatment outcomes and potential hospital readmission (Andreani et al., 2024). Faecal samples collected before and after clinical treatment from patients with eating disorders and non-eating disorder controls were characterised revealing that, while weight improvements were observed, the gut microbiota in anorexia nervosa patients post-treatment remained significantly different from non-eating disorder controls (Fouladi et al., 2022). Notably, pre-treatment anorexia nervosa microbiota signatures showed increased fermentation pathways and reduced carbohydrate degradation capabilities compared to controls underscoring the intricate microbial communities in AN patients that warrant further investigation.

Addiction and the Microbiota: New Avenues for Intervention

Addiction is classified as a chronic relapsing disorder characterised by compulsive engagement in harmful behaviours despite adverse consequences (American Psychiatric Association, 2013). Studies have mainly focused on the impact of substance abuse on gut microbiome, particularly alcohol, which has been shown to alter gut microbiota, increase intestinal permeability, and promote hepatic inflammation (Garcia-Cabrerizo et al., 2021). Probiotics like *L. rhamnosus* GG have been found to mitigate some of these effects (Tette et al., 2022). Other substances, including tobacco, opioids, and methamphetamine, also alter gut microbiota, affecting intestinal permeability, inflammation, and

metabolic processes (Garcia-Cabrerizo & Cryan, 2024). Recent preclinical work has shown that depletion of gut microbiota can significantly alter reward responses, diminishing the effects of cocaine while enhancing the reward derived from social interactions (Garcia-Cabrerizo et al., 2023). These findings suggest that targeting the microbiota in conjunction with promoting social engagement may offer an effective strategy for reducing the negative impacts of drug use, offering a potential therapeutic avenue, but requires further exploration.

Obsessive-Compulsive Disorders (OCD) and the Gut Microbiota: Compulsions in Context

Speculation about the involvement of the gut microbiota in OCD is growing, although current research is limited. Stress and antibiotic exposure, both of which affect microbiota composition, are proposed mechanisms potentially coinciding with the onset of OCD symptoms (American Psychiatric Association, 2013). Although the literature on this connection remains limited, emerging evidence suggests that changes in the gut microbiota and high rates of bowel syndromes may be prevalent among OCD patients, particularly featuring an increase in pro-inflammatory bacterial species and a decrease in butyrate producers (Domènech et al., 2022; Turna et al., 2020). One study revealed significant reductions in α-diversity in OCD alongside notable differences in β-diversity across various taxonomic levels, with specific genera such as *Pseudomonas* and *Streptococcus* being less prevalent in OCD patients (Kang et al., 2023). Additionally, the microbial composition differed between early-onset and late-onset OCD, particularly regarding *Corynebacterium* and *Pelomonas*, highlighting the potential role of the microbiota-gut-brain interaction in the disorder's pathophysiology and underscoring the need for further longitudinal studies.

Transplanting faecal microbiota from first-episode, drug-naive OCD patients and healthy controls into antibiotic-treated specific pathogen-free mice revealed that colonisation with OCD-associated microbiota induced significant behavioural deficits, including anxiety-like and compulsive-like behaviours, along with altered neuronal morphology and function in the medial prefrontal cortex (mPFC) and inflammation in both the mPFC and colon (Y. D. Zhang et al., 2024). Metabolomic analyses identified elevated levels of succinic acid in OCD-colonised mice, which negatively impacted neuronal activity and contributed to inflammation, suggesting that gut microbiota may influence brain function through succinic acid signalling. Additionally, manipulation of dimethyl malonate showed neuroprotective effects, indicating potential therapeutic avenues for addressing OCD through gut-brain interactions.

Pre- and probiotics have been shown to influence compulsive behaviours, suggesting potential therapeutic benefits in future OCD treatments. One study investigated the effects of a multi-strain probiotic formulation on OCD-like behaviours in rats induced by quinpirole, revealing that the probiotic treatment effectively reduced compulsive behaviours and anxiety-like phenotypes (Ghuge et al., 2023). Probiotic administration also normalised inflammatory markers and neurotransmitter levels in the frontal cortex while promoting commensal gut microbiota changes, including increased abundance of *Allobaculum* and specific *Bifidobacterium* species.

Longitudinal human studies are needed to clarify the gut microbiota's role in OCD symptomatology. Future evaluations of OCD should include comprehensive gastrointestinal assessments, addressing factors like physical comorbidities, nutritional habits, bowel movements, fluid intake, and exercise patterns, all of which influence gut health. Treatment implications indicate that understanding gastrointestinal issues can guide medication choices, such as using SSRIs or tricyclic antidepressants based on the presence of irritable bowel syndrome symptoms.

Microbial Drivers of Obesity: Targets for Intervention

Obesity is a major public health issue that is often fuelled by diets high in fat and sugar that disrupt the balance between energy intake and expenditure, and is associated with a range of serious health problems and centrally regulated disorders like depression and anxiety (González-Muniesa et al., 2017; Romani-Perez, Liebana-Garcia, et al., 2024). This dietary pattern shapes the gut microbiota, affecting neuroendocrine and immune functions within the intestine, which in turn influences gut-brain pathways that regulate appetite and metabolism (Boscaini et al., 2022). These interactions can elevate inflammation and disrupt metabolic processes, further promoting disease. Obesity has been associated with an altered gut microbiota composition, often characterised by an increased ratio of *Firmicutes* to *Bacteroidetes*(Ley et al., 2005). At a more specific taxonomic level, studies have reported elevated abundances of genera such as *Lactobacillus* and *Clostridium* (within Firmicutes) and reduced levels of *Bacteroides* and *Prevotella* (within Bacteroidetes) (S. F. Clarke et al., 2012). These imbalances have been shown to impact metabolic pathways, such as those involved in energy harvest and short-chain fatty acid production, and can be modulated through dietary interventions (Tremmel et al., 2017; Turnbaugh et al., 2008; Turnbaugh et al., 2009). The gut microbiome plays a crucial role in the central regulation of food intake, and its composition is notably influenced by diet (Marungruang et al., 2020; Medawar et al., 2024). Moreover, the microbiota-gut-brain axis is emerging as an essential factor in obesity, as changes in gut microbiota can affect metabolic functions and energy homeostasis signalling through vagal afferent neurons (Daly et al., 2011).

Bariatric surgery is a notable intervention for morbid obesity that significantly alters the composition (diversity and abundance) of host gut microbiota, enhancing hormonal and inflammatory profiles, reducing adiposity, and improving insulin sensitivity (Aron-Wisnewsky & Clement, 2014; Ribeiro et al., 2021). Research indicates that this surgical approach can lead to increased microbial diversity and altered composition, particularly with higher levels of *Gammaproteobacteria* and *Verrucomicrobia*, alongside a reduction in *Firmicutes* (Ulker & Yildiran, 2019). Further findings have suggested that an FMT from post-bariatric surgery mice to germ-free animals can result in decreased fat mass and body weight (Liou et al., 2013). Additionally, gut-derived peptides such as ghrelin and oxyntomodulin, which are influenced by the gut microbiome, show potential as therapeutic targets for obesity treatment (Tschop et al., 2001; Wallace Fitzsimons et al., 2019). Another study in humans looked at the impact of bariatric surgery on cortical morphometry in obese individuals, examining changes in brain grey and white matter associated with food intake and cognitive-emotional regulation (Liu et al., 2019). Results indicated significant reductions in fasting plasma ghrelin, insulin, and leptin levels post-surgery, along with structural changes such as decreased cortical thickness in the praecuneus and increased thickness in various frontal and temporal regions, which were linked to weight loss. These findings suggest that bariatric surgery may promote structural recovery in brain areas involved in executive control and self-referential processing, supporting the idea that weight loss can lead to beneficial changes in brain morphology.

Probiotics and prebiotics are also being explored as potential interventions to restore normal microbiome-mediated gut-brain signalling and treat obesity (Schellekens et al., 2021; Torres-Fuentes et al., 2017). Indeed, one study investigated the anti-obesity potential of *Bifidobacterium longum* APC1472, demonstrating that supplementation led to decreased body weight and fat accumulation in high-fat diet-induced obese mice (Schellekens et al., 2021). Although the human trial did not show significant changes in body mass index or waist-to-hip ratio among healthy overweight/obese participants, it revealed a beneficial effect on fasting blood glucose levels, suggesting the potential of *B. longum* APC1472 as a valuable supplement for addressing specific obesity-related markers. Advances in understanding these diet-microbe-host interactions highlight potential microbiome-based

interventions, like faecal microbiota transplants, probiotics, and other biotherapeutics, which may offer promising avenues to address obesity, although significant knowledge gaps remain.

Irritable Bowel Syndrome (IBS) and the Axis: Decoding Gut-Brain Dysfunction

IBS is a prevalent disorder of gut brain interaction (DGBIthe), previously regarded a functional gastrointestinal disorder, significantly impacting patients' quality of life and often presents with comorbid behavioural and psychological factors, including altered bowel habits, abdominal pain, bloating, and excessive flatulence (Enck et al., 2016). It often coexists with various psychosocial and environmental factors, making microbiota-gut-brain interactions a focal point in IBS research (Rodino-Janeiro et al., 2018). IBS is officially classified as a disorder of the microbiota-gut-brain axis, suggesting that diet-microbiota interactions may play a role in its core symptoms (Collins, 2014; Quigley, 2018; Wilmes et al., 2021). As a result, the microbiota-gut-brain axis is a prime target in IBS (G. Clarke, J. F. Cryan, et al., 2012). A crucial mechanism in IBS is the serotonin signalling pathway, which regulates gastrointestinal functions, including secretion and motility; alterations in serotonergic function and tryptophan metabolism have been noted in IBS patients (G. Clarke, D. P. McKernan, et al., 2012; Clarke et al., 2009). Mono-colonisation of germ-free mice with *Ruminococcus gnavus* resulted in enhanced gastrointestinal transit and colonic secretion, by stimulating serotonin production through the catabolism of dietary phenylalanine and tryptophan into metabolites like phenethylamine and tryptamine (Zhai et al., 2023). Further, altered levels of microbial metabolites like SCFAs have been reported in patients with diarrhoea-predominant IBS (Tian et al., 2020). Significantly higher levels of propionate and butyrate were found in the serum of these IBS patients suggesting that elevated serum levels of propionic and butyric acids may be linked to the onset and progression of diarrhoea-predominant IBS. Indeed, partial mechanistic function of the FMT may be to significantly increase levels of butyrate improving IBS symptoms (El-Salhy et al., 2021).

Emerging microbial and diet-based treatments for IBS show promise, with some studies highlighting the efficacy of probiotics like *L. acidophilus* and *B. longum* in alleviating stress-related gastrointestinal symptoms (Ait-Belgnaoui et al., 2018; Diop et al., 2008; Simren et al., 2010). Other research indicates that *B. longum* may improve mood in IBS patients, although inconsistent results have been reported with different probiotic strains (Crouzet et al., 2013; Dapoigny et al., 2012; De Palma et al., 2017; Pinto-Sanchez et al., 2017). The proposed mechanism for these benefits includes anti-inflammatory effects, which may also explain the positive outcomes associated with dietary interventions such as the low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet, known to reduce gastrointestinal distress by limiting certain fermentable carbohydrates (Whelan et al., 2018). Recent work investigating efficacy of a multi-strain probiotic on symptom severity in female patients with IBS showed significant reductions in the symptom severity, anxiety, and depression, along with improvements in bowel habits (Mullish et al., 2024). Although the overall diversity of the faecal microbiota remained largely unchanged, specific microbial differences were noted, suggesting that daily supplementation with this multi-strain probiotic could be a beneficial option for managing IBS symptoms in women. Intriguingly, a recent GWAS study identified six genetic loci associated with IBS that are linked to mood and anxiety disorders and are expressed in the nervous system (Eijsbouts et al., 2021). A strong genome-wide correlation was observed between IBS risk and traits such as anxiety, neuroticism, and depression, suggesting that shared pathogenic pathways underlie these conditions, rather than anxiety simply causing abdominal symptoms, highlighting the need for further investigation into the mechanisms of altered brain-gut interactions in IBS. Additionally, FMT from non-IBS individuals to those with IBS has gained popularity as a treatment option, although the overall efficacy remains a subject of ongoing investigation (El-Salhy et al., 2021; Johnsen et al., 2018; Verstockt et al., 2018).

Pain Disorders and the Microbiota: A Gut-Brain Perspective

Pain can be categorised as nociceptive, inflammatory, or pathological, with mechanisms and treatment targets varying across types (Colloca et al., 2017; Millan, 2002). Nociceptive pain typically arises from tissue damage and is well understood, while the mechanisms behind visceral pain, neuropathic pain, and chronic pain remain complex and challenging to address therapeutically (Felice et al., 2015; Lagomarsino et al., 2021). Conditions like fibromyalgia, migraines, and gastrointestinal pain often involve intricate interactions between the nervous system and underlying pathophysiological changes, complicating the development of effective treatments (Drewes et al., 2020; Woolf et al., 1998). Gastrointestinal pain is prevalent in conditions like irritable bowel syndrome, Crohn's disease, and pancreatitis; it presents a diagnostic challenge due to overlapping autonomic and somatic symptoms. Complex mechanisms, including peripheral and central sensitisation and autonomic nervous system involvement, contribute to gastrointestinal pain. Treatment varies based on pain type and underlying disorder, potentially involving pharmacological, behavioural, or surgical approaches.

Research into the role of gastrointestinal microbiota in pain response has predominantly focused on nociceptive and inflammatory disorders, particularly those affecting the gut, such as inflammatory bowel disease (IBD) and FGIDs (Holzer et al., 2017; Rea et al., 2017). Chronic visceral pain is a common symptom in these conditions, indicating a shared pathophysiological pathway regulated by both central and peripheral mechanisms, often referred to as disorders of the microbiota-gut-brain axis (Mayer et al., 2023; Pusceddu & Gareau, 2018). Studies have identified altered gut microbiota profiles in patients with chronic visceral pain, revealing decreased levels of commensal genera like *Bifidobacterium* and *Lactobacillus*, and shifts in the Firmicutes-to-Bacteroidetes ratio (often associated with metabolic health) although the causative relationships between microbiota changes and pain experiences remain unclear (G. Clarke, D. P. McKernan, et al., 2012; Manor et al., 2020).

Research has indicated that modifying gut bacteria through diet, probiotics, or antibiotics could reduce symptoms in some chronic pain patients, although much remains to be clarified about the microbiome's impact on pain mechanisms (Baldi et al., 2022; Simren & Tack, 2018; Tuck et al., 2022). Prebiotic, probiotic and FMT therapies have shown promise in treating gastrointestinal pain and associated symptoms, although outcomes can vary significantly among individuals (Basso et al., 2018). In fact, the prebiotic dietary inulin fibre was shown to influence the composition of murine gut microbiota, altering levels of microbiota-derived metabolites such as bile acids, leading to type 2 inflammation in the intestines and lungs (Arifuzzaman et al., 2022). This work highlights the role Inulin may play in promoting allergic inflammation and signalling host defence mechanisms.

Although FMT has been effective in some patients with *C. difficile* infections, the results for IBD treatment have been mixed, with reports of clinical remission rates varying widely (Green et al., 2020; Wei et al., 2022). Similarly, the efficacy of probiotics in managing pain related to arthritis and other inflammatory conditions is still being investigated, with current evidence inconclusive (Kragsnaes et al., 2018; Lin et al., 2023; Lowe et al., 2018). As the field progresses, further clinical trials are essential to clarify the effectiveness of microbiota-based interventions for visceral pain and to explore the mechanisms through which the gut microbiota may influence pain pathways, potentially offering new therapeutic avenues for managing chronic pain syndromes.

Parkinson's Disease (PD) and Microbial Contributions to Neurodegeneration

PD, a progressive neurodegenerative disorder, is characterised by cognitive and motor impairments, and gut discomfort, which often precedes motor symptoms (Poewe et al., 2017). Disturbances in the gut microbiome are believed to play a role in neurodegeneration, particularly since constipation—a

common non-motor symptom—can precede a PD diagnosis by many years (Abbott et al., 2001). Key features of PD include not only dopaminergic neuron loss and α-synuclein accumulation but also neuroinflammation (Dzamko, 2023). Much research has demonstrated that α-synuclein, associated with PD pathology in the brain, is also found in the gut's nerve fibres and ganglia (Hilton et al., 2014). Preclinical models have indicated that gut microbiota may facilitate α-synuclein aggregation and impede the clearance of protein aggregates (Sampson et al., 2016), while evidence suggests that α-synuclein might travel from the gut to the brain via the vagus nerve, a crucial pathway for gut-brain communication (Holmqvist et al., 2014). Studies have shown that truncal vagotomy could lower PD risk and prevent the gut-to-brain spread of α-synucleinopathy in animal models (Kim et al., 2019; B. Liu et al., 2017). Human studies have identified distinct microbial profiles in PD patients, indicating potential biomarkers for early diagnosis and new therapeutic targets (Stagaman et al., 2024). However, there remains no consensus on a specific microbial pattern linked to PD, highlighting the need for caution due to small study sizes and a lack of longitudinal data.

A Taiwanese study identified significant differences in microbiota composition between PD and non-PD patients, particularly a reduction in the commensal genus *Prevotella* across diverse populations (Lin et al., 2019). Increased levels of *Akkermansia muciniphila* have also been observed in PD patients, though its role remains ambiguous and may be associated with heightened constipation (Romano et al., 2021). Collectively, reduced SCFA-producing bacteria and elevated *A. muciniphila* may contribute to PD pathology, emphasising the microbiome's involvement in disease progression. FMT from PD patients to germ-free mice has induced PD-like symptoms, and antibiotic treatment has shown symptom improvement in preclinical models (Koutzoumis et al., 2020; Sampson et al., 2016). Future research should focus on microbiota composition across various stages of PD, including the prodromal phase, to better understand how specific bacterial changes can alter SCFA profiles and influence neuroinflammation in the brain.

Alzheimer’s Disease (AD) and the Microbiota: Insights into Cognitive Decline

AD, the leading cause of dementia, is linked to β-amyloid plaques and tau protein abnormalities in the brain (Knopman et al., 2021). There is growing evidence for a microbial origin of AD, with bacteria and viruses potentially playing roles in its pathogenesis. Alterations in gut microbiota have been observed in AD patients, and preclinical studies have shown that probiotics can mitigate cognitive deficits and inflammation. Emerging evidence indicates a potential microbial origin for AD, suggesting that negative microbes may play a role in its development and progression (Grabrucker et al., 2023; Itzhaki et al., 2016; Lathe et al., 2023). Studies have found a correlation between increased *Bacteroides* and higher levels of β-amyloid and tau in AD mouse models, with gut alterations characterised by reduced microbial diversity and increased negative bacteria in AD patients (Cattaneo et al., 2017; Jia et al., 2024; Vogt et al., 2017; Zhuang et al., 2018). Further, alterations in gut microbiota following antibiotic use can modulate neuroinflammation and influence Aβ deposition in mouse models of AD (Minter et al., 2017). One recent study identified a gut microbiome-brain axis in AD, showing that an imbalance of *Clostridium* and *Bacteroides* correlated with β-amyloid burden (Zha et al., 2025). Supplementation with *Bacteroides ovatus* or its metabolite lysophosphatidylcholine reduced Aβ pathology, improved cognitive function, and inhibited ferroptosis via activation of the orphan receptor GPR119 in AD mouse models. These findings suggest that gut microbiota-derived metabolites (e.g. lysophosphatidylcholine) could offer novel therapeutic avenues for AD by modulating neuroinflammation, lipid peroxidation, and neurodegeneration.

FMT from healthy individuals has shown promise in modulating the gut microbiome and reducing Aβ aggregates and tau pathology in AD mouse models (Kim et al., 2020). Although some clinical trials report cognitive improvements with probiotic treatment, results have been inconsistent, particularly

in severe cases of AD (Agahi et al., 2018; Akbari et al., 2016; Tamtaji et al., 2017). (Zha et al., 2025)Nonetheless, psychobiotic therapy presents a potential adjunctive treatment for AD, and ongoing research aims to elucidate the underlying mechanisms and identify biomarkers for early detection. The exploration of microbiota-based interventions continues to be a compelling area of study with the potential to transform the understanding and management of AD.

Stroke, Brain Injury, and the Gut: The Role of Microbiota in Recovery

Inadequate blood flow to the brain, leading to cell death, is a defining characteristic of stroke and a common consequence of brain injury (Campbell et al., 2019). Research has indicated that peripheral and systemic factors, particularly an enhanced inflammatory response, can exacerbate outcomes following a stroke (Brea et al., 2021). A recent study involving Chinese patients revealed significant depletion of commensal gut microbes, such as *Bacteroides*, *Prevotella*, and *Faecalibacterium*, alongside an increase in opportunistic pathogens like *Enterobacter* and *Megasphaera* in individuals with stroke or transient ischemic attacks (Yin et al., 2015). Notably, patients with severe strokes exhibited a higher abundance of Proteobacteria compared to those with milder strokes. Further, levels of trimethylamine-N-oxide (TMAO), a low molecular weight microbial metabolite primarily generated from the metabolism of dietary substrates, strongly correlated the development of numerous diseases, including stroke, other cardiovascular conditions, diabetes, certain cancers, and neurological disorders (Gatarek & Kaluzna-Czaplinska, 2021). Using FMT from low- and high-TMAO-producing human subjects into germ-free mice, research demonstrated that both TMAO generation and stroke severity were transmissible traits (Zhu et al., 2021). This FMT conveyed functional deficits in pro-inflammatory T-cell trafficking and increased ischemic lesion volume.

Comparing germ-free mice to recolonised and conventional specific pathogen-free mice another study showed that bacterial colonisation significantly reduced stroke volumes and enhanced cerebral expression of cytokines along with increased microglia and macrophage cell counts, contributing to improved stroke outcomes (Singh et al., 2018). Notably, this microbiome-mediated neuroprotection is lost in lymphocyte-deficient mice, indicating that lymphocyte-driven protective neuroinflammation, regulated by the microbiome, plays a crucial role in the brain's response to stroke. The use of broad-spectrum antibiotics before ischemic injury resulted in poorer outcomes, correlating with decreased trafficking of IL-17+ γδ T cells and reduced neuroinflammation at the ischemic site (Benakis et al., 2016).

Conversely, probiotic supplementation, such as with *C. butyricum*, has shown potential neuroprotective effects in traumatic brain injury models by enhancing intestinal barrier integrity and promoting the secretion of intestinal GLP-1, suggesting that pre- and probiotic treatments could mitigate some of the complications associated with stroke and cerebral ischemia (Li et al., 2018; Sun et al., 2016). Although some findings indicate promise for the use of probiotics and prebiotics, the current research is limited, and more work is needed.

Microbial Modulation in Multiple Sclerosis: Hope for Therapies

MS is an autoimmune disorder of the central nervous system characterised by motor deficits, blurred vision, and sensory changes that occur suddenly, often with few prodromal signals (Dendrou et al., 2015; Filippi et al., 2018). Given the immune basis of MS, there is growing interest in therapeutic interventions targeting the gut microbiota (Cantoni et al., 2022; Schumacher et al., 2024). Notably, FMT from MS patients into mice resulted in the development of autoimmune encephalomyelitis, a hallmark symptom of MS (Berer et al., 2017; Cekanaviciute et al., 2017), while germ-free mice showed resistance to this condition, indicating the influence of gut microbiome on disease expression. In

particular, the presence of gram-positive segmented filamentous bacteria and an increase in *Akkermansia* were correlated with symptom development, while reduced levels of the anti-inflammatory species *Parabacteroides* distasonis were observed in MS patients (Cekanaviciute et al., 2017).

Looking at the complex interplay between the gut microbiome, immune system, metabolism, and diet in MS a six-month longitudinal multi-omics analysis involving 49 participants, found that MS patients exhibited significant alterations in gut microbiota composition (Cantoni et al., 2022). Specific microbes (including *B. thetaiotaomicron*) correlated with disease severity, alongside perturbations in blood metabolome pathways related to fatty acid metabolism and inflammation. Such findings suggest that the gut microbiota significantly contributes to MS pathophysiology and may be responsive to dietary interventions, warranting further research into targeted microbiota therapies.

Huntington's Disease: Gut Microbiota as a Therapeutic Target

Huntington's disease, caused by a mutation in the Huntingtin gene, leads to progressive motor, cognitive, and psychiatric decline (McColgan & Tabrizi, 2018). Altered gut microbiota-derived metabolites have been observed in early Huntington's disease, indicating potential microbiota-based interventions (Kong et al., 2020). Research in preclinical models suggests that microbiota may influence disease progression and symptomatology. Ultrastructural analysis of myelin plasticity and oligodendroglial dynamics in the BACHD mouse model of Huntington's disease revealed that germ-free BACHD mice exhibited alterations in myelin thickness and reduced levels of myelin-related proteins compared to specific-pathogen-free mice (Radulescu et al., 2019). They also reported a decrease in mature oligodendrocytes in the prefrontal cortex, indicating that the absence of gut microbiota can affect myelin characteristics which highlights the adaptive properties of myelination in response to gut microbial changes.

In summary, the microbiota-gut-brain axis is a burgeoning field of research with implications for a variety of diseases, as well as psychological and neurological disorders. Although there is substantial evidence from preclinical studies, more rigorous and large-scale clinical trials are needed to establish effective microbiota-targeted therapies for these conditions.

Toward the Future: Translating Microbiome Science into Therapy

The exploration of the gut microbiota as a key regulator of body-brain interactions has unveiled a transformative understanding of how gut microbes influence both physical and mental health. This chapter has demonstrated that the microbiota-gut-brain axis represents a dynamic, bidirectional communication network that affects a variety of physiological and neurological processes. Through historical perspectives, cutting-edge research, and advanced methodologies, we now appreciate the profound roles that gut microbes play in immune function, metabolism, and brain health.

Evidence from both preclinical and clinical studies underscores the significant impact of gut microbes on conditions ranging from gastrointestinal disorders to neuropsychiatric and neurodegenerative diseases. The identification of microbial pathways and metabolites, such as short-chain fatty acids and neurotransmitter-like molecules, provides insight into how the gut microbiome communicates with the brain. These microbial signals traverse multiple pathways—including the autonomic nervous system, immune system, and endocrine signalling—to influence cognition, mood, and behaviour.

As we move forward, it is clear that future research must focus on unravelling the complexities of these communication pathways and the intricate relationships between the host and its microbial symbionts leveraging the range of preclinical model systems (Nagpal & Cryan, 2021b). Advances in sequencing technologies and bioinformatics, along with the development of germ-free animal models and faecal microbiota transplantation, have equipped researchers with powerful tools to explore the causal mechanisms underpinning microbiota-brain interactions. This knowledge lays the groundwork for new therapeutic strategies targeting the microbiome to treat a wide range of disorders.

In conclusion, the microbiota-gut-brain axis offers tremendous potential for understanding the interplay between the brain and body. The ability to modulate this axis through diet, probiotics, prebiotics, and other microbial interventions opens the door to personalised medicine that enhances health across the lifespan. The convergence of microbiome science with neurobiology, immunology, and psychiatry promises to revolutionise how we approach disease prevention and treatment, positioning the microbiome at the forefront of modern medicine's quest to improve brain and body health.

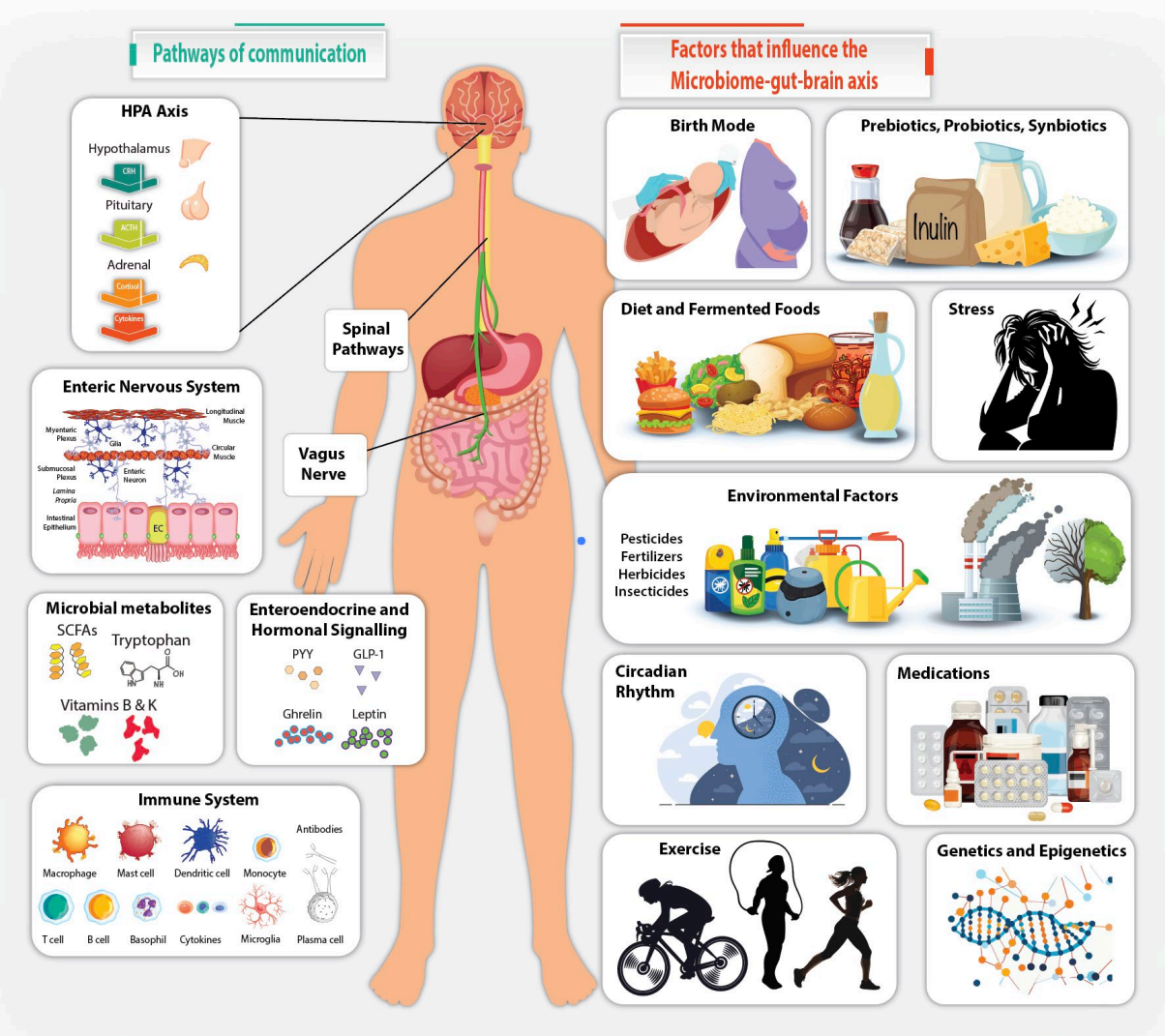


Figure 1: The Microbiota-Gut-Brain Axis. Here we illustrate the complex interactions between the gut microbiota and the brain, highlighting the bidirectional communication that occurs via multiple pathways, including the hypothalamic-pituitary-adrenal (HPA) axis, the enteric nervous system, spinal pathways, and the vagus nerve. Key modulators of this axis include microbial metabolites (such as short-chain fatty acids and tryptophan), immune system mediators, and enteroendocrine hormones (like GLP-1, PYY, ghrelin, and leptin). The right side of the figure presents factors that influence the gut microbiota, including birth mode (vaginal vs. Caesarean), the intake of prebiotics, probiotics, and synbiotics, diet (particularly fermented foods), and exposure to stress, environmental chemicals (pesticides, fertilizers, herbicides, insecticides), circadian rhythm disturbances, physical activity (exercise), medications, and genetic and epigenetic factors. These elements collectively contribute to the regulation of gut-brain communication, potentially impacting health and disease.

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Conflicts of Interest

JFC has spoken at conferences organized by Mead Johnson, Ordesa, and Yakult, and received research funding from Reckitt, Nutricia, Dupont/IFF, and Nestle. GC received honoraria from Janssen, Probi, Apsen and Boehringer Ingelheim; research funding from Pharmavite, Fonterra, Tate and Lyle, Nestle and Reckitt; and is or has been a paid consultant for Yakult, Zentiva and Bayer Healthcare. KJOR *received honoraria from Sanofi Genzyme and Danone.* This support did not influence or constrain the contents of this manuscript. JN and MRA report no conflicts.

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