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Feeding gut microbes to nourish the brain: unravelling the diet–microbiota–gut–brain axis

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The prevalence of brain disorders, including stress-related neuropsychiatric disorders and conditions with cognitive dysfunction, is rising. Poor dietary habits contribute substantially to this accelerating trend. Conversely, healthy dietary intake supports mood and cognitive performance. Recently, the communication between the microorganisms within the gastrointestinal tract and the brain along the gut–brain axis has gained prominence as a potential tractable target to modulate brain health. The composition and function of the gut microbiota is robustly influenced by dietary factors to alter gut–brain signalling. To reflect this interconnection between diet, gut microbiota and brain functioning, we propose that a diet–microbiota–gut–brain axis exists that underpins health and well-being. In this Review, we provide a comprehensive overview of the interplay between diet and gut microbiota composition and function and the implications for cognition and emotional functioning. Important diet-induced effects on the gut microbiota for the development, prevention and maintenance of neuropsychiatric disorders are described. The diet–microbiota–gut–brain axis represents an uncharted frontier for brain health diagnostics and therapeutics across the lifespan.

Human brain health occurs along a continuum with optimal functioning at one end, and neuropsychiatric disorders of neurocognitive and emotional dysfunction at the other, with transient states of flux in between. This spectrum signifies that an increased understanding of brain functioning in both non-clinical and clinical samples is necessary for developing interventions during healthy or transient phases that could delay or prevent the progression into clinical manifestation, with the ultimate goal of reversing the observed increased prevalence of neuropsychiatric disorders[1]. One identified factor contributing to this trend is poor dietary habits[2]. Indeed, healthy dietary intake has been linked to improved mood and cognitive performance, and the concept of nutritional psychiatry has emerged into the mainstream[3].

Recently, the gut microbiota, the multitude of microorganisms residing within the gastrointestinal tract, including bacteria, viruses, fungi, protozoa and archaea, has become an exciting and rapidly developing area of research in the context of mental health. The bidirectional communication between the gut microbiota and brain along the gut–brain axis represents a promising therapeutic target to improve brain health. Although the gut microbiota is altered via several genetic, health and environmental factors[4], host diet is among the most powerful and accessible means to modulate gut microbiota composition and function[5].

Colonization of the host gastrointestinal tract with microorganisms begins at birth and is influenced by a variety of factors, not least of which is mode of feeding. Breastfed infants, instead of formula-fed

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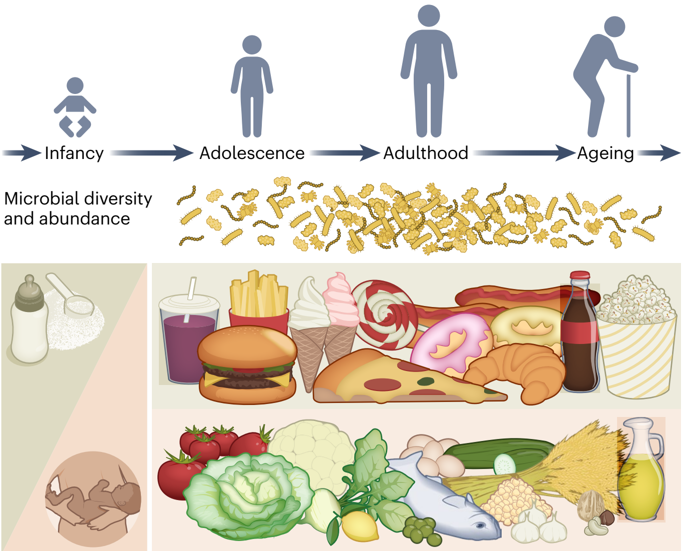

Fig. 1 | Lifespan nutrition. Overview of dietary patterns and gut microbiota composition across the lifespan. Colonization of the gut microbiota begins at birth with early feeding approaches such as breastfeeding or bottle-feeding showing distinct effects on gut microbiota composition. During childhood and adolescence, the combination of dietary factors and environmental factors lays the foundation for a healthy microbiota such that foods reminiscent of the Mediterranean diet show positive effects, while high-fat/high-sugar foods characteristic of the Western diet exert negative effects. Although gut microbiota composition is relatively stable by adulthood, dietary interventions have been shown to alter gut microbiota composition and function. Malnutrition and malabsorption of nutrients in older people are associated with less gut microbial diversity, but dietary interventions like the Mediterranean diet can enrich the gut microbiota.

infants, display an increased abundance of beneficial *Bifidobacteria* that is maintained during the period of infancy[6]. During childhood, optimal dietary practices combined with environmental effects build on these foundations to maintain a healthy gut microbiota into adulthood (Fig. 1). Poor dietary habits (for example, sweetened beverages, sweets and convenience meals) are associated with decreased relative abundances of *Bifidobacteria*, *Prevotella*, *Blautia* and *Roseburia*[7]. During adolescence, greater intake of high-fat, high-sugar, ultra-processed foods (UPFs) in mice decreases species richness, an indicator of the gut microbiota, which is often also reduced in numerous disease states[8–11]. Despite the relative stability of gut microbiota composition in adulthood, acute[12] and chronic[13] dietary manipulations reliably modify individual gut microbiota composition and function. A landmark study, based on gut microbiota sampling of healthy humans for 17 days, showed that diet explained 44% of the total variation in day-to-day variability from the same donor[14]. Moreover, individuals transitioning from an animal-based to a plant-based diet, or vice versa, displayed substantial alterations in gut microbiota composition within a mere 24 hours[12]. Finally, malnutrition and malabsorption coincide with loss of gut microbial diversity and cognitive function in older people[15,16].

The covariance between gut microbiota composition and host nutrition across the lifespan, alongside observations that diet rapidly shifts the gut microbiota, demonstrates the profound relationship between diet, the gut microbiota and associated signalling to the brain. Given this relationship, an expansion of the microbiota–gut–brain axis to include diet is now warranted.

In this narrative review, we provide support for a diet–microbiota–gut–brain axis by describing the effects of various dietary factors on the gut microbiota. We further describe diet and gut microbiota effects on emotion and cognition in humans and translational models where human data are sparse. Possible mechanistic pathways through which the diet–microbiota–gut–brain axis operates are explored. To advance future research on the diet–microbiota–gut–brain axis, we highlight potential opportunities provided by this framework with a focus on methodology to build the evidence base, establish mechanisms and determine causality.

Dietary patterns and the microbiota

The modulation of gut microbiota composition and function, and consequently its impact on brain and behaviour, is critically dependent on dietary influences. Both clinical and preclinical data highlight the considerable impact of different dietary components and patterns on gut microbiota composition and mood in individuals without diagnosed mood disorders per se[17]. However, it is currently unclear whether the effects of whole diets or specific dietary components on the gut microbiota drive changes in overall brain function or emotion, or if these effects occur independently of our gut microorganisms.

Different dietary patterns have been shown to dictate distinct gut microbiota composition patterns, with individuals adhering to an animal-based diet exhibiting signature compositional and functional traits compared to individuals following a vegetarian diet[18]. The Western diet and the Mediterranean diet are the main diets studied in relation to their influence on the gut microbiota and subsequent health outcomes. The Western diet is generally high in sugar, salt and fat, and has been linked to metabolic disorders. High-fat diets have been reported to alter Bacteroidota, increase Pseudomonadota and Bacillota, potentially negatively impacting brain function[19,20]. Dietary sugar and fat have been shown to impact the number of bacterial cells present in the faeces and the gut bacterial profile of mice where dietary fat was the primary factor driving obesity, diabetes progression and inflammation[21].

The Mediterranean diet, on the other hand, is rich in cereals, nuts, legumes and vegetables. Studies have shown that the Mediterranean diet associates with a lower risk of depression, possibly due to dietary polyphenols[22], and alters the gut microbiota[23–26]. Investigating individual dietary components can further yield valuable information about potential driving effects of dietary patterns like the Western and Mediterranean diets on the gut microbiota and brain.

Macronutrients

Carbohydrates. Carbohydrates constitute a large portion of the human diet. Carbohydrates include starch and sugars that undergo enzymatic degradation (glucose, fructose, sucrose and lactose). Alterations in staple carbohydrate intake can rapidly impact the composition of gut microbiota in just one week, and different carbohydrate sources exert distinct effects on the gut[27]. Diets rich in glucose, fructose and sucrose have been linked to a substantial increase in *Bifidobacterium* levels, coupled with a significant reduction in *Bacteroides*[28]. Mice subjected to a fructose-rich diet exhibited significant elevations in *Coprococcus*, *Ruminococcus* and *Clostridium*, along with a decrease in the Clostridiaceae family[29]. Another recent study unveiled intricate sex-dependent effects of dietary interventions, where an unexpected susceptibility among female mice to unfavourable metabolic outcomes was associated with low-carbohydrate diets such as the ketogenic diet[30], potentially owing to the decreased intake of fibre that supports both blood glucose regulation and the gut microbiota.

As the main energy source for gut microorganisms, undigested dietary fibres, largely from fruits and vegetables, are key components for a healthy gut microbiota. Fructooligosaccharides and galactooligosaccharides, inulin and pectins undergo fermentation by gut microorganisms in the distal colon, influencing the intestinal environment. Consequently, many prebiotics (Table 1) consist of undigested carbohydrates known to elicit beneficial effects on the gastrointestinal tract by promoting the growth of a healthy gut microbiota[5].

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Table 1 | Key definitions and preclinical methodologies in studying the microbiota–gut–brain axis

Key definitions of dietary components that target the gut microbiota.	
Term	**Definition**
Fermented food	Foods made through desired microbial growth and enzymatic conversions of food components[230]
Prebiotic	A substrate that is selectively utilized by host microorganisms conferring a health benefit[231]
Probiotic	Live microorganisms, which when administered in adequate amounts, confer a health benefit on the host[232]
Postbiotic	Preparation of inanimate microorganisms and/or their components that confer a health benefit on the host[233]
Synbiotic	A mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host[234]
Psychobiotic	Targeting the microbiome for brain health benefits[235]
Preclinical techniques to assess mechanism and causality in gut microbiota research.	
Term	**Definition**
Germ-free	Animals, usually rodents, bred in germ-free conditions and devoid of microorganisms, are contrasted with conventionally colonized controls that lack pathogenic microorganisms (that is, specific pathogen-free animals)[236]
FMT	Transfer of complete gut microbiota via faecal transplant from donor (human or animal) that possesses phenotypes of interest into an animal recipient. Physiological and behavioural changes in the recipient are assessed to determine likeness to donor[228,237].
Antibiotic administration	Administration of antibiotics to alter or deplete gut bacteria.

Protein. Protein is a vital dietary component, serving as the primary source of amino acids crucial for neurotransmitter synthesis and brain health. Indeed, dietary protein is the only source of essential amino acids (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine) that we cannot synthesize ourselves. The origin of the protein source, whether plant-based or animal-based, can also influence gut microbiota diversity[31]. For example, plant-based protein diets correlate with higher microbiota diversity, compared to high-fat, high-sugar diets[32]. A plant protein-rich diet elevates short-chain fatty acid (SCFA; gut microbial-derived metabolites) and branched-chain amino acid (valine, leucine and isoleucine) levels, which has been shown to promote health[31]. For instance, pea protein consumption increases SCFAs linked to anti-inflammatory effects and mucosal barrier maintenance[33].

Animal-based products can rapidly shift the gut microbiota community within 48 hours of ingestion, affecting between-sample beta diversity[34]. Animal-based protein-rich diets enhance *Bacteroides* abundance due to their role in initial protein proteolysis in the gut[35,36]. Children who consumed high amounts of animal protein exhibited increased *Alistipes* and *Bacteroides*, aligning with the higher protein intake[12]. Interestingly, clinical data link elevated *Alistipes* in the gut microbiota to depression[37,38]. Longer-term increased consumption of animal-based proteins may detrimentally affect the gut microbiota[39], warranting further research to elucidate the underlying mechanisms of protein-based diet components on gut microbiota and its metabolites. Moreover, sulfidogenic bacteria, such as *Bilophila wadsworthia*, are associated with inflammation, and are seen to increase with diets high in animal-based fat[40]. Compared to plant-based proteins as part of a vegan diet, an intervention with animal-based proteins as part of a ketogenic diet for 2 weeks had a larger impact on microbial composition and function. Specifically, the ketogenic diet downregulated pathways associated with amino acid metabolism and biosynthesis and upregulated branched-chain amino acids[41]. Research investigating the differences between plant-based and animal-based proteins on health, including the gut microbiota, is rapidly developing and may soon inform personalized nutrition plans for different disease states, but more understanding of long-term effects from adherence to each diet is needed first.

Lipids. Lipids include phospholipids, sterols and fats of which further comprise monounsaturated (for example, oleic acid), polyunsaturated (for example, linolenic ω-3 and linoleic ω-6 fatty acids) and saturated fatty acids (for example, palmitic acid). Dietary fats are predominantly absorbed in the small intestine, but a small percentage of fatty acids reach the colon intact to interact with gut microbiota. Increased intake of saturated fats is linked to cognitive impairment and mental health disturbances, with inverse effects for unsaturated fatty acid intake[42]. The quantity and saturation of fat similarly exerts unique effects on gut microbiota. In mice, saturated fat in the form of lard reduced bacterial diversity and abundance of *Bacteroides*, *Turicibacter* and *Bilophila* while increasing systemic inflammation compared to mice fed fish oil rich in polyunsaturated fatty acids. Faecal microbiota transplantation (FMT; Table 1) from fish oil-fed donor mice to recipient mice protected against lard-induced weight gain and inflammation with the enrichment of *Akkermansia* speculated to underlie these protective effects[43,44]. Moreover, certain bacteria have been shown to reduce serum cholesterol levels. Individuals housing microorganisms that form coprostanol—a compound formed from the microbial reduction of cholesterol in the intestines—exhibit significantly lower faecal cholesterol and serum total cholesterol levels[45].

Micronutrients and other dietary factors

Micronutrients. The gut microbiota synthesizes vitamin K and most of the water-soluble B vitamins. In some instances, microbial-derived vitamins are estimated to supply as much as 86% of daily reference intake in the case of pyridoxine/vitamin B_6 but only as little as 0.78% of pantothenic acid/vitamin B_5 (ref. 46). Interestingly, supplementation has been shown to increase microbial diversity, richness and SCFA production[47], indicating the mutual relationship between diet and gut microbiota composition. Additionally, vitamins A and D maintain intestinal barrier integrity necessary for responding to immune challenges[48,49]. Similarly, minerals and trace elements are required for the growth and survival of several gut bacteria[50], while deficiencies or toxicities promote the enrichment of pathogenic bacteria that evoke gut inflammation[51]. Micronutrient deficiencies are associated with poorer cognitive performance and emotional disturbances, and supplementation restores these functions[52–54].

Fermented foods. Despite existing for several millennia, fermented foods, specifically those containing live bacteria (for example, sauerkraut, kombucha and yoghurt), have sparked renewed interest in their potential probiotic, prebiotic, postbiotic and synbiotic properties (Table 1)[55]. Several ingested fermented foods survive passage through the digestive tract to increase gut microbial diversity[56]. Increased abundance of *Lactobacillus* has been reported following brief, 2-week administration of kefir[57], fermented soy[58] and yoghurt[59]. Moreover, a variety of fermented food intake such as yoghurt, kefir and kombucha increased gut microbial diversity compared to a high-fibre diet[56] and habitual non-consumers[17]. Similarly, regular consumption of kimchi and sauerkraut alters microbial metabolites[60], indicating the capacity for fermented foods to modulate microbial function.

Fermented foods have also shown a neuromodulatory effect on cognition and mood. The majority of the cognitive research has been conducted in older populations with fermented foods showing the potential to protect against age-related cognitive decline[61]. However, improvements in memory[57] and alterations in activity of prefrontal brain regions associated with cognitive performance in healthy younger adults[62] have been observed following administration of fermented dairy beverages. Recently, we have shown that a diet comprising a variety of fermented foods combined with foods rich in fibre improved perceived stress in a healthy population and altered microbial function[63]. Improvements in cognitive performance and mood from fermented foods may be driven by increased gut microbial diversity and subsequent production of metabolites that alter signalling to the central nervous system (CNS), but more research is needed to assess the underlying mechanisms and to verify the benefits in pathological states.

Dietary xenobiotics

Dietary xenobiotics are foreign compounds introduced through diet that are not naturally produced by the body. Dietary xenobiotics supplemented in food products by manufacturers with the intent to increase nutrient or flavour profiles, alter texture and/or to prolong shelf life are hallmarks of the modern Western diet. For example, plant sterols are frequently incorporated into foods, particularly those with elevated saturated fat content, to mitigate adverse health effects. The absorption rate of plant sterols in the intestines is 2–3%[64], and the remaining residues undergo biotransformation by colonic microorganisms. Using in vitro fermentation techniques, a plant sterol-enriched milk beverage decreased cholesterol conversion rate and the proportion of *Erysipelotrichaceae* species and increased the abundance of phylotypes associated with butyrate-producing *Eubacterium hallii*[65]. Food additives such as emulsifiers, preservatives and non-nutritive sweeteners (for example, saccharin, sucralose, stevia or aspartame) typically constitute UPFs. The positive relationship between intake of UPFs and risk for mood disorders is speculated to be partially mediated by UPF effects on the gut microbiota[66]. Indeed, specific taxonomic signatures can be observed in regular consumers of UPFs[67], alongside a broader association with reduced microbial diversity[68]. Experimental evidence evaluating the distinction between 'healthier' and 'less healthy' UPFs is needed to understand potential diverging effects on the gut microbiota[11].

An understudied area of research is the investigation of cooking methods on the gut microbiota. Increased intake of heterocyclic amines produced by high-temperature cooking of meat and fish is associated with a potentially detrimental increased abundance of Pseudomonadota and Verrucomicrobiota and *Streptococcus* and *Eubacterium*[69] and decreased Akkermansiaceae[70]. The tendency for heterocyclic amines to induce intestinal inflammation, alter the dopaminergic system and incur oxidative damage in the hippocampus suggests further detrimental effects on emotional and cognitive processes, particularly memory, despite the lack of direct evidence[71,72]. Intriguingly, microbial strains, such as *Eubacterium hallii*, exert protective effects against the carcinogenic and pro-inflammatory effects of heterocyclic amines, highlighting their potential to improve physical health and possibly brain health.

Polyphenols such as flavonoids, tannins and phenolic acids are commonly found in plant-derived products such as coffee, tea, cocoa and berries. The beneficial effects of polyphenols on the brain and body are well established[73]. Many polyphenols accumulate in the large intestine and are extensively metabolized by gut microbiota, producing metabolites with potential bioactive properties to improve cognition and emotional well-being. Given the increased popularity of complementary and alternative medicine approaches, research investigating dietary xenobiotics such as herbal supplements is likely to surge. For example, berberine, a plant-derived pentacyclic isoquinoline alkaloid, has been shown to interact with gut microbiota reducing blood glucose and lipid levels and microbial diversity, while increasing butyrate-producing bacteria[74,75]. More interventional studies assessing the impact of dietary xenobiotics on gut–brain signalling in both healthy and clinical samples are necessary to evaluate their efficacy as an alternative approach to treat neuropsychiatric disorders.

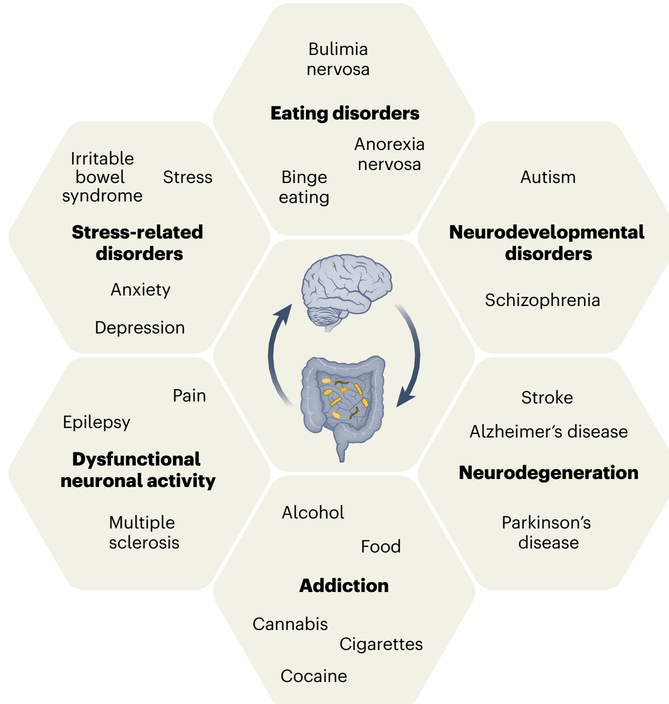

Fig. 2 | Implications for neuropsychiatric disorders. A summary of neuropsychiatric disorders where there is evidence for the involvement of the diet–microbiota–gut–brain axis. This relationship suggests that the diet–gut microbiota interplay may play a role in the aetiology, maintenance and treatment of each disorder.

Diet–microbiota–gut–brain axis and neuropsychiatric disorders

Several studies have demonstrated that manipulation of the gut microbiota either transiently through antibiotic depletion or in germ-free rodents across the lifespan (Table 1) alters cognitive and emotional processing in rodents[4]. In healthy humans, adherence to the Mediterranean diet and consumption of fermented foods alters gut microbiota composition/function and improves cognitive and emotional processing[76,77]. Generally, a healthy diet rich in fibre, polyphenols, unsaturated fatty acids and fermented foods enriches and diversifies beneficial bacteria and their associated metabolites, which nourish the brain via communications pathways outlined in the following sections. Conversely, dietary components associated with the Western diet that are low in fibre and micronutrients while high in sugar and saturated fat promote peripheral and central inflammation, increasing the expansion of opportunistic pathogens and susceptibility to infection[76]. It is therefore likely that poor dietary habits and their effects on the gut microbiota might be involved in the pathogenesis of neuropsychiatric disorders (see Fig. 2 for an overview).

Eating disorders

Eating disorders, including anorexia nervosa (AN), bulimia nervosa and binge-eating disorder, are marked by disruptions in eating behaviours. As such, eating disorders are positioned to provide the most insight about diet and gut microbiota interactions. Little is known about the link between gut microbiota and binge-eating disorder and bulimia nervosa, but high-fat, high-sugar foods that are rapidly consumed in large quantities in both disorders have been observed to reduce bacterial diversity, which was linked to detrimental changes in metabolic output in rodent models[78]. Conversely, AN is the most researched disorder within the context of the gut microbiota. Characterized as underweight via chronic food restriction and/or compensatory behaviours (for example, laxative use, purging), the gut microbiota is increasingly being recognized as a key regulator of AN[79]. A recent study showed elevation in metabolites associated with food restriction (for example, indole-3-propionic acid), and these metabolites were found to mediate the gut microbiota–AN relationship. FMT from human donors with AN to germ-free mice resulted in induction of AN-like profiles such as slower weight gain over time and altered expression of hypothalamic genes related to appetite and energy expenditure[80]. Interestingly, elevated levels of *Methanobrevibacter smithii*, a bacterium responsible for harvesting energy from food, has been observed in individuals with AN[81], likely as an adaptive mechanism to compensate for low-calorie diets, highlighting potential protective properties of gut microbiota. The gut microbiota also adapts to nutritional habits of the host as evidenced by the fact that high-calorie refeeding interventions for AN increased bacterial diversity compared to pre-intervention levels[82]. These data suggest that remodelling of the gut microbiota through eating habits indicative of the eating disorder, at minimum, coincides with disease progression/remission but may also play a leading role in different stages of the disorder[83]. In addition, further studies investigating whether baseline microbiota composition predisposes individuals to aberrant eating behaviours are now warranted.

Anxiety and depression

As the discipline of nutritional psychiatry emerges, a role for diet in both the pathological mechanisms and treatment options is developing. Emotional eating, a maladaptive coping mechanism in some individuals with anxiety and depression, often comprises high-fat/high-sugar foods[84] that confer deleterious effects on gut microbiota. In some individuals with anxiety and depression, however, food intake is restricted, which is also associated with alterations in gut microbiota as previously discussed. The hyperphagic and hypophagic tendencies observed in anxiety and depression malnourish and/or deprive the gut microbiota and subsequent communication to the brain, potentially exacerbating psychological symptoms. Observational and dietary intervention studies have highlighted the positive impact of a Mediterranean diet on mood[85–88], but gut microbiota readouts are needed for mechanistic insight. Strikingly, a combination of fermented foods and dietary fibre improved perceptions of stress and altered lipid and tryptophan metabolism in healthy adults[63], but these effects need to be replicated in samples with clinical anxiety and/or depression.

Schizophrenia

It has been suggested that inflammation, introduced either during the prenatal period or via postnatal environmental exposure, is a risk factor for the development of schizophrenia and influences symptom severity[89,90]. Severe famines such as the Dutch Hunger Winter of 1944–1945 and the Chinese famine in the 1950s, which lead to a deficiency in micronutrients including folate, essential fatty acids, retinoids, vitamin D and iron, were associated with increased risk for schizophrenia in offspring[91]. In rodents, a maternal high-fat diet during the later gestational phase reduced striatal dopamine levels, and offspring exposed to the maternal high-fat diet displayed schizophrenia-like symptoms[92]. While this study lacked inflammatory readouts, the detrimental consequences of high-fat diets on inflammation and the gut microbiota are well documented[93]. Remarkably, FMT from individuals with schizophrenia, in addition to inducing schizophrenia-like behaviours, altered lipid metabolism in serum and the hippocampus of germ-free recipient mice[94]. These results suggest an adaptation of the gut microbiota to dietary fat intake, but the full history of the donors with schizophrenia is not available to test this hypothesis. Thus, maternal or postnatal dietary malnourishment through underfeeding or overfeeding can induce inflammation, likely partially mediated by gut microbiota, which elevates the risk for development of schizophrenia.

Autism spectrum disorder

Children with autism exhibit general fear and/or rejection towards new or unfamiliar foods, alongside consumption of fewer fruits, vegetables and protein, but greater intake of high-carbohydrate and/or high-fat foods (for example, white bread, pizza and ice cream)[95,96]. Although variations in gut microbiota composition and functionality have been linked to autism spectrum disorder (ASD)[97], recent reports suggest that this relationship is better explained by the impact of host nutritional intake on the gut microbiota. A metagenomic analysis of 247 stool samples from donors with ASD revealed that diet homogeneity patterns reduced microbial diversity to a greater degree than direct associations between ASD diagnosis[98]. On the other hand, a recent meta-analysis showed an interaction between the gut microbiota, ASD and diet[97]. However, more information is needed to understand how nutrition-mediated gut microbiota alterations affect various ASD phenotypic behaviours[99]. Nevertheless, these results suggest that nutritional patterns across all neuropsychiatric disorders should be analysed in gut microbiota studies to capture potential mediating and moderating factors that might go undetected.

Epilepsy

Diet has long been used to manage symptoms in some types of epilepsy, for example, ketogenic diet-based treatments for drug-refractory epilepsy[100]. Increased abundance of specific strains protects against seizures[101]. Children with drug-refractory epilepsy who were responsive to the ketogenic diet increased overall microbial diversity and butyrate levels with specific decreases in relative abundance of genera such as *Bifidobacterium*, *Akkermansia*, Enterococcaceae and *Actinomyces*[96]. The therapeutic mechanism of action is speculated to be the production of ketones that inhibit apoptosis and reduce oxidative stress[102], but more research is needed to understand how the gut microbiota interacts with this mechanism.

Dementia and Alzheimer's disease

Dietary habits, specifically greater intake of meat, butter, high-fat dairy products, eggs and refined sugar are associated with greater risk for dementia or Alzheimer's disease (AD)[103]. Conversely, supplementation of vitamin D and curcumin alongside adherence to the Mediterranean diet has been shown to delay the onset of AD[104]. Targeting the gut microbiota through fermented food administration improved cognitive function in adults with milder cognitive impairment and adults with AD[58,105]. Moreover, adherence to a modified Mediterranean diet altered gut microbiota composition that correlated with cerebrospinal fluid biomarkers of AD such as β-amyloid ($A\beta_{42}$) and tau-p181 in adults with mild cognitive impairment[106]. Similarly, improvements in cognitive performance following 12-month adherence to the Mediterranean diet in pre-frail older people was associated with diet-induced alterations of butyrogenic taxa[77]. These randomized controlled trials provide robust evidence for a diet–microbiota–gut–brain axis.

Attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder (ADHD) carries a high prevalence of comorbid obesity[107]. Moreover, children with ADHD have significantly lower serum concentrations of chromium, magnesium and zinc[108]. An increased abundance of *Eggerthella* and *Faecalibacterium*, genera linked to dopamine metabolism and inflammation, respectively, has been consistently shown across multiple studies comparing control and ADHD microbial profiles[109]. Notably, foods associated with an inflammatory response and blunting of dopaminergic activity with chronic intake (that is, sugar, candy and soda) are associated with increased prevalence of an ADHD diagnosis, while the inverse is shown with fibre-rich foods (that is, fruits, vegetables, pasta and rice)[110]. It remains to be seen if the baseline microbial capacity to produce and absorb micronutrients, in addition to metabolizing sugar products, alters ADHD onset/prognosis. Evidence linking gut microbiota to metabolic processes in healthy and clinical samples provides tentative insights into this possibility.

Diet–microbiota–gut–brain axis and metabolism

The diet–microbiota–gut–brain axis is implicated in the predisposition, aetiology and progression of metabolic disorders. Indeed, distinct taxonomic and/or functional profiles have been observed between healthy controls and individuals with metabolic disorders, including obesity, type 2 diabetes and metabolic dysfunction-associated steatotic liver disease[111]. At a peripheral level, the gut microbiota contributes to energy balance by influencing absorption of lipids in the small intestine and by harvesting energy from undigested carbohydrates and proteins for the formation of fermentation-dependent microbial metabolites. Microbial-derived metabolites, such as SCFAs from fibre and bile acids from cholesterol breakdown, can activate receptors on enteroendocrine L cells to stimulate the release of anorexigenic hormones glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), which then promote satiety via signalling to the nucleus tractus solitarius (NTS) and hypothalamus[112]. Microbe–brain signalling may also impact central regulation of food intake and satiety and, therefore, metabolic processes. Indeed, in rodents, SCFAs can act on the hypothalamus to directly control feeding[113]. These SCFAs further influence metabolic health by promoting intestinal gluconeogenesis and thus modulating glucose homeostasis in both the periphery and the hypothalamus. In a landmark study, it was found that blood glucose response varied significantly between different meal compositions, even within meals deemed 'healthy' and 'unhealthy', and that individual gut microbiome composition explained this variability[114], directly implicating microbiota in glucose regulation.

Intriguingly, some bacterial proteins mimic satiety hormones such as α-melanocyte-stimulating hormone to further control hunger[115]. Although the gut microbiota can synthesize neurotransmitters traditionally involved in appetite control, including dopamine, serotonin, acetylcholine, noradrenaline and GABA (gamma-aminobutyric acid), their signalling routes from the periphery to the brain are less understood. Nevertheless, by modulating gastrointestinal physiology, such as motility in the case of serotonin, these peripheral neurotransmitters can influence hunger/satiety. Indole, a microbial metabolite produced from tryptophan, may be correlated with connectivity between key brain reward areas, body weight and self-reported food addiction and anxiety in healthy adults[116], providing tentative evidence for the effects of gut-synthesized neuromodulators on the brain.

It is now clear that energy balance is maintained through interactions between homeostatic and hedonic processes. Rodent data suggest a role for the gut microbiota in the regulation of food reward. FMT (Table 1) from diet-induced obese mice into naive mice induced hedonic behavioural responses and altered dopaminergic activity reflective of obese donor mice[117]. In humans, it was recently shown that synthetic dietary fibre in the form of inulin supplemented daily for 2 weeks decreased brain activation in reward-related brain regions for high-calorie food stimuli, effects that correlated with increased levels of SCFA-producing bacteria, in adults with overweight[118]. These results indicate that the gut microbiota regulates energy balance, beyond homeostatic effects, and that fibre could improve reward hypersensitivity.

A causal role of the gut microbiota in obesity has been questioned, largely owing to the failure to translate preclinical findings in human interventions[112,119]. Preclinical studies have indeed demonstrated a link between the gut microbiota and obesity such that germ-free and antibiotic-treated mice have lower adiposity compared to control mice, despite higher energy consumption and expenditure[120,121]. However, when the mice are not germ-free (that is, conventional) and are, therefore, more reflective of humans, FMT from obese mice fails to alter body fat or weight in recipient mice[122]. These null results are consistent with human FMT data, which predominantly show no alteration in body weight, despite showing an improvement in other metabolic indicators such as triglycerides, fasting glucose and blood pressure[123]. More research is needed to understand these discrepancies. It is tempting to speculate that it could be explained by stronger effects of the gut microbiota on homeostatic processes of energy metabolism than hedonic processes, thus sparing effects on food intake, but more research is needed to test this hypothesis.

The high comorbidity between neuropsychiatric and metabolic disorders[124], coupled with divergences in gut microbiota composition, may be, at least partially, explained by diet-induced effects on gut microbiota signalling to the brain. This may be particularly relevant for immunometabolic dysregulation in depression.

Mechanisms of action

There are several pathways of bidirectional communication through which the diet–microbiota–gut–brain axis coordinates cognition and emotion in healthy and clinical states. Figuring prominently are both local interactions within the gut and distal connections reaching to the brain[4]. See Fig. 3 for an overview.

Bacterial metabolites

Since microbial by-products resulting from the breakdown of food by microorganisms have been proposed as a key player in the communication between the microbiota and the brain, there is a growing interest in utilizing these metabolites as potential therapeutic treatments[125].

SCFAs. Gut microbiota-derived metabolites, particularly SCFAs (predominantly acetate, propionate and butyrate) constitute over 95% of gut-derived microbial metabolites. Although SCFAs primarily originate from microbial fermentation of host-indigestible dietary fibres, endogenous SCFAs can be derived from microbial protein breakdown, host metabolism of long-chain fatty acids and pyruvate, fermented foods and alcohol consumption[126]. SCFAs have been implicated in gastrointestinal function, blood pressure regulation, circadian rhythm regulation and (neuro)immune function[127]. Notably, alterations in faecal SCFA levels have been associated with AN[128], Parkinson's disease (PD)[129], obesity[130], chronic psychosocial stress[131] and ASD[132], suggesting a strong link between SCFAs and microbiota–gut–brain axis related disorders. In PD, altered SCFA levels have been observed in both humans and animal models. Oral SCFA administration induced PD-related deficits and neuroinflammation in an α-synuclein mouse model[133]. This contrasts with findings from human studies showing decreased SCFA-producing bacteria and SCFA levels in individuals with PD[129]. Addressing this deficit, propionate treatment promoted dopaminergic cell survival in an in vitro PD mouse model[134]. Additionally, amyloid uptake in humans was positively associated with blood acetate levels and negatively associated with blood butyrate levels[135].

Once absorbed by the host, SCFAs serve as a crucial metabolic fuel where they are utilized in the synthesis of glucose and lipids as energy for the host[136]. The metabolism of SCFAs involves diffusion through epithelia via specific transporter proteins, with subsequent participation in mitochondrial β-oxidation and the Krebs cycle, providing energy to colonocytes, as well as acting as substrates for gluconeogenesis, and cholesterol synthesis[137]. SCFAs not metabolized by colonocytes enter portal circulation, with a small fraction reaching peripheral tissues where they contribute to energy metabolism and physiological regulation, potentially influencing insulin sensitivity and appetite.

The metabolism of SCFAs involves diffusion through epithelia or with specific transporter proteins, with subsequent metabolism in the Krebs cycle as an energy source. Acetate is found in the cerebrospinal fluid, while propionate and butyrate's direct impact on brain physiology remains uncertain[138]. SCFAs, predominantly butyrate, propionate and acetate, also exert epigenetic functions by inhibiting histone deacetylases and influencing histone acetylation and crotonylation, with butyrate being the most potent inhibitor of class I and IIa histone deacetylases. SCFAs can also directly engage with and activate extracellular G-protein-coupled receptors, including free fatty acid receptor (FFAR) 2, FFAR3 and hydroxycarboxylic acid receptor 2. Notably, FFARs

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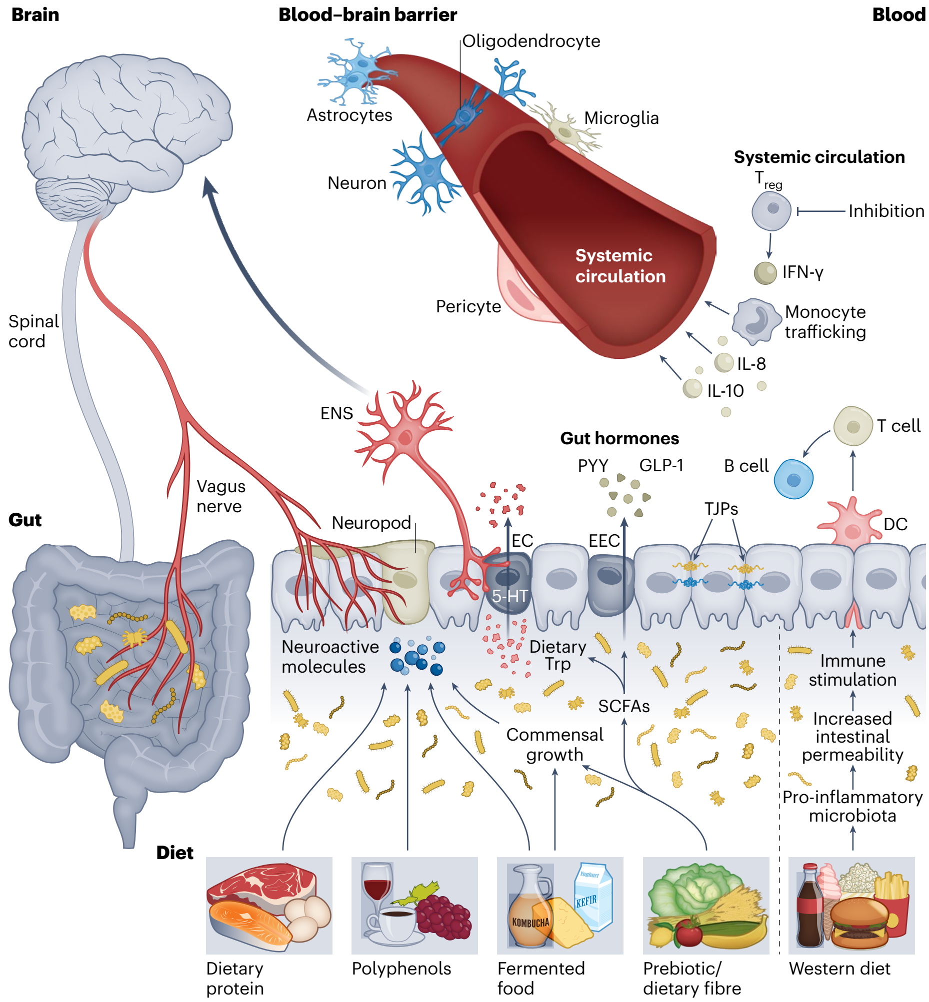

Fig. 3 | Mechanisms of action. Mechanisms of action: schematic overview of the several pathways of bidirectional communication through which the diet–microbiota–gut–brain axis impacts on cognition and emotion. Healthy dietary patterns, rich in fibre, fruits and vegetables, promote microbial diversity in the gut and the production of beneficial metabolites such as SCFAs. These metabolites can travel to the brain directly through the bloodstream, enhancing cognitive and emotional processing. Additionally, a healthy diet supports gut barrier integrity, preventing harmful substances from entering the bloodstream, and modulates the immune system to promote anti-inflammatory responses that benefit brain function. Neural pathways, such as signalling via the vagus nerve, also play a crucial role in transmitting signals from the gut microbiota to the brain. Conversely, the consumption of high-fat and high-sugar foods typical of the Western diet leads to a reduction in beneficial gut bacteria and increases the production of pro-inflammatory metabolites. This weakened gut barrier allows harmful substances to leak into the bloodstream, resulting in systemic inflammation that can negatively impact the brain. Inflammatory responses travel through the bloodstream and reach the brain, potentially affecting behaviour, cognition and emotional states. The schematic underscores the critical role of dietary choices in influencing mental health and cognitive function through these interconnected pathways involving gut microbiota and associated metabolic and inflammatory processes. DC, dendritic cell; EC, enterochromaffin; EEC, enteroendocrine cell; ENS, enteric nervous system; IFN-γ, interferon gamma; T_{reg} regulatory T cell; TJPs, tight junction proteins; Trp, trypotophan.

are prominently expressed on immune cells such as neutrophils, monocytes, and regulatory T lymphocytes within the intestinal mucosa[139]. SCFA diffusion through epithelial cells is facilitated by transporters such as the sodium-coupled monocarboxylate transporter[140] as well as the pH-dependent hydrogen-coupled monocarboxylate transporter (MCT) 1 and MCT4 (ref. 141). MCT1 is particularly important in SCFA uptake from the gut because its expression can be influenced by diet, such as with a high-resistant starch diet[142]. Additionally, MCT1 expression is highest in the caecum and colon, areas where SCFA absorption is most efficient[143]. Faster colonic transit times have been seen alongside reduced SCFA absorption, resulting in increased faecal SCFA content[144].

Butyrate has been studied for its role in enhancing learning and memory, reducing depressive-like behaviour and increasing sociability in mouse models. Acetate can be converted to acetyl-CoA, which drives increased histone acetylation, although such activity might not necessarily be a result of direct activity by gut microbiota-derived SCFAs. Preclinical work has demonstrated a reduction of depressive-like behaviour and stress responsiveness that was linked to psychosocial stress[131]. Additionally, direct administration of microbial metabolites can yield similar benefits for brain function[145]. However, data from human studies are limited due to potential challenges in administering microbial by-products directly. For instance, SCFAs administered directly to the colon via specialized pH-dependent capsules were found to mitigate cortisol response to psychosocial stress[146]. However, a 4-week psychobiotic diet (Table 1; high in prebiotic and fermented foods) had no effect on SCFA levels while reducing perceived stress[63]. Interestingly, colonic acetate was detected in the brain using positron emission tomography scanning, and both peripheral and central administration of acetate suppressed feeding in mice[113]. These data confirm future studies using human brain imaging and SCFAs are warranted.

Bile acids and taurine. Bile acids are known for their role in aiding the absorption of dietary lipids and lipid-soluble vitamins and are primarily synthesized in the liver from cholesterol, including cholic acid and chenodeoxycholic acid in humans, and cholic acid and α/β-muricholic acid in mice[147]. Following generation in the liver, bile acids are conjugated with taurine or glycine, and stored in the gall bladder, after which primary bile acids are released into the intestine to facilitate lipid digestion and are subsequently recycled back into the liver.

Taurine, which is a metabolite that primary bile acids can be conjugated with, itself is recognized for its important role as a microbial metabolite beneficial to health[148]. In particular, taurine can function as an agonist of glycine, $GABA_A$ and $GABA_B$ receptors in the brain, and thus has neuroprotective, anticonvulsant and cognitive-enhancing properties, where taurine supplementation could hold potential therapeutic value in managing various brain disorders, including AD, PD, epilepsy, ASDs, anxiety and depression[149].

Beyond their digestive function, bile acids have emerged as potent signalling molecules to the brain, from within the gut, influencing systemic lipid, cholesterol and glucose metabolism, as well as energy and immune homeostasis through the activation of nuclear farnesoid X receptor and plasma membrane TGR5 receptor[150]. Various major gut-associated microorganisms, including *Lactobacillus*, *Bifidobacterium* and Bacteroidetes taxa, express bile salt hydrolase enzymes, allowing them to de-conjugate bile acids from taurine and glycine[151]. Bile acids also play a crucial role in constraining bacterial population expansion in the gastrointestinal tract. Reduced luminal bile acid levels are associated with small intestinal bacterial overgrowth, inflammation activation and subsequent epithelial damage[152]. Bile acids can exhibit direct antimicrobial effects due to their membrane-solubilizing properties and, through farnesoid X receptor signalling, induce the expression of antimicrobial defence genes, safeguarding the gut from bacterial translocation[153]. Although initial evidence indicates that bile acids might serve as a conduit through which the microbiota can impact specific brain functions as a factor of diet, experimental findings have pointed to alterations in gut microbiota composition triggered by a Western diet that were linked to neuroinflammation and reduced synaptic plasticity due to changes in bile acid synthesis and impaired TGR5 signalling[154].

Metabolomic studies have revealed that in hepatic encephalopathy, abnormal increases in blood bile acids and ammonia, exacerbated by the apical sodium-dependent bile acid transporter protein, contribute to ammonia-induced brain injuries[155]. Inhibiting the apical sodium-dependent bile acid transporter protein in mouse models of liver disease effectively reduced these neurotoxic substances, offering potential therapeutic strategies for alleviating brain and liver damage. Further, a Western diet rich in fat and sugar was shown to impact cognitive function through dysregulated bile acid synthesis and dysbiosis, leading to systemic inflammation and microglial activation, reducing neuroplasticity[154]. By affecting bile acid receptor-regulated signalling in the brain and digestive tract, a Western diet exacerbated neuroinflammation and postsynaptic damage, thereby contributing to cognitive decline. Such work demonstrates how dietary choices affect metabolomic profiles, which in turn influence brain health, offering insights into potential therapeutic interventions, such as targeting bile acid transport mechanisms to reduce neurotoxic impacts.

Immune signalling

The gastrointestinal tract houses the highest concentration of immune cells in the body, which are in continuous communication with the food we eat. This exchange facilitates communication between the gut and the immune system by recognizing self-antigens and non-self-antigens[156]. Consequently, this primes the immune system to identify potential pathogens, including food-borne ones. In addition to providing a physical barrier, the epithelium contains various cell types such as enterocytes, secretory cells, chemosensory cells and gut-associated lymphoid tissue[157]. Enterocytes express innate immune receptors and can release cytokines and chemokines. The gut-associated lymphoid tissue uses lymphocytes for a more specific immune response with, for example, immunoglobulins. Chemosensory cells play a role in defence against helminths[158], while secretory cells are involved in releasing mucus, antimicrobials and neuroendocrine compounds from enteroendocrine cells[159]. Commensal (non-pathogenic) bacterial metabolites, including neuromodulators, bacteriocins, bile acids, choline and SCFAs, can modulate the immune system[160,161]. Growing evidence suggests that microbe–host interactions in the gut release various signalling molecules that can influence neural signalling, infiltrate the blood and lymphatic systems, and communicate with the brain[127].

Fundamentally, the immune system comprises two subsystems, both of which can be modulated by gut microorganisms: innate and adaptive/acquired. Innate immunity serves as the primary defence against potential infectious organisms, involving cells derived from the myeloid lineage. Whereas adaptive immunity elicits a specifically targeted response to pathogens, involving cells from the lymphoid lineage, such as B and T lymphocytes, and responds to specific bacterial antigens modulated by dietary components, suggesting potential therapeutic avenues. Understanding the microbiota's role in shaping immune–brain communication, particularly through the adaptive immune system, remains a crucial area for future exploration. In a 17-week study on healthy adults, one study investigated the impact of plant-based fibre and fermented foods on the microbiota and immune system[56]. The high-fibre diet increased microbiota-encoded glycan-degrading enzymes without altering cytokine response scores. High consumption of fermented foods raised microbiota diversity and reduced inflammatory markers. This example demonstrates the potential of dietary interventions, particularly fermented foods, in addressing microbiota diversity and inflammation issues in industrialized societies.

Microbial endocrinology

Microbial endocrinology is a critical concept shaping our understanding of the microbiota–gut–brain axis, bridging the gap from mere correlation to causation. At its core, this concept revolves around the shared neurochemical language between host and microorganisms. Landmark studies from the 1990s laid the groundwork by revealing that bacteria respond to host neuroendocrine signalling molecules, including noradrenaline and adrenaline, challenging prior beliefs about the gut–brain axis[162,163].

Catecholamines. Catecholamines, adrenal peptide hormones, are integral in the stress response and gut integrity, and play diverse roles in host physiology including triggering the fight-or-flight response, maintaining gut integrity and influencing behaviour and decision-making, while also promoting bacterial pathogenesis and growth[164]. This demonstrates a complex interplay in host–microbe cross-talk with notable clinical implications. Intriguingly, enteric nerves have the genetic machinery to synthesize dopamine and noradrenaline but lack the enzyme needed to convert noradrenaline into adrenaline. However, gut microorganisms harbouring the bacterial enzyme β-glucuronidase can convert host noradrenaline and dopamine from a biologically inactive to a biologically active form. Bacteria such as *Escherichia* and *Bacillus*, mirror host catecholamine production, underlining their shared biochemical language and potential impact on host physiology, emphasizing their shared biochemical language[165]. This interaction suggests that both host and gut microbiota contribute to a shared pool of biologically active catecholamines, affecting host physiology in ways that are not fully understood, highlighting an area ripe for further investigation into the impacts of bacterial catecholamines on human health.

Certain bacteria possess plasma membrane monoamine transporter and organic cation transporter proteins that can facilitate the

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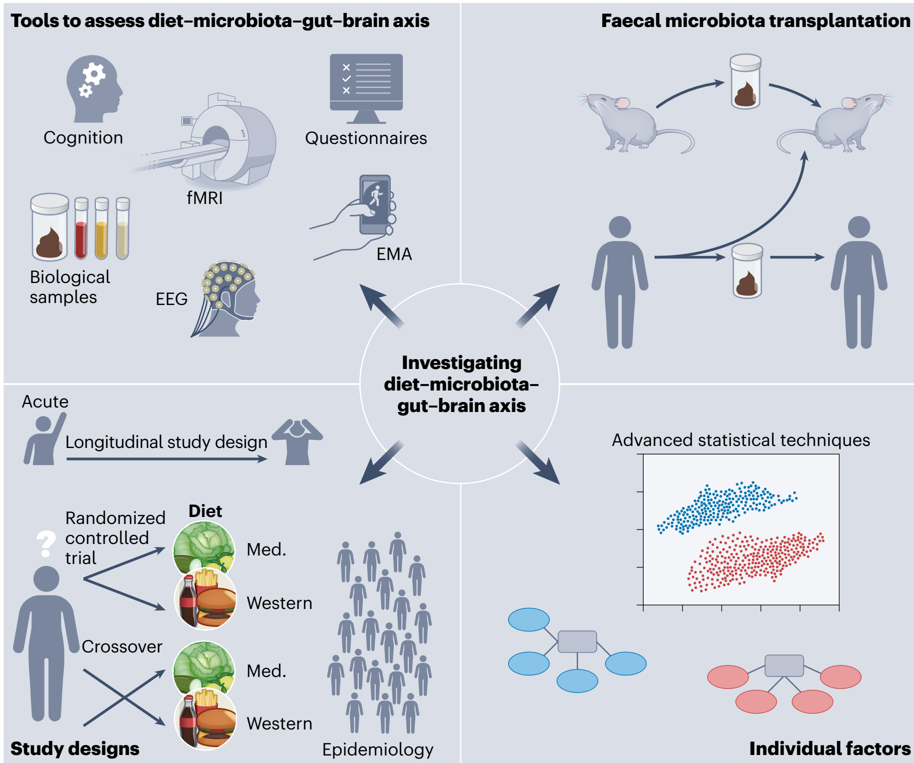

Fig. 4 | Investigating the diet–microbiota–gut–brain axis. Methods used to investigate the diet–microbiota–gut–brain axis in human and preclinical research. There is a need to understand both the acute and chronic effects of food intake on the microbiota–gut–brain axis. Multimodal assessments that measure brain function, behaviour and biological signalling in epidemiological, longitudinal and randomized controlled trials are needed. FMT methodology can develop a causal understanding of the diet–microbiota–gut–brain axis. Advanced statistical techniques can improve understanding of how individual factors such as baseline gut microbial composition interact with dietary habits and composition to influence behaviour. EEG, electroencephalography; EMA, ecological momentary assessment; Med, Mediterranean.

transfer of extracellular noradrenaline into the bacterial cell. Interestingly, the circulating concentration of noradrenaline in germ-free rodents is higher compared to conventional animals, and the lumens of the ileum, caecum and colon contain detectable levels of dopamine, noradrenaline and adrenaline[166].

GABA. Both humans and bacteria possess the ability to transform glutamate into GABA, a major inhibitory neurotransmitter in hosts, with species like *Escherichia* and *Lactobacillus* being identified as GABA producers[167]. These bacteria, often found in fermented foods rich in GABA such as Chinese pao cai, also have the capability to produce glutamate[168]. Intriguingly, the probiotic strain *Escherichia coli* Nissle 1917 has been shown to produce a GABA-containing analgesic lipopeptide that enhances GABA's ability to cross the epithelial barrier and activate sensory neurons, although it is uncertain if other gut microorganisms share this trait. While the role of bacterial GABA in the host intestinal lumen is unclear, studies using probiotics suggest potential analgesic effects via GABA-associated lipopeptides, opening avenues for understanding the influence of bacterial GABA on host–microbe cross-talk impacting intestinal inflammation and immune function[169]. Indeed, levels of *Ligilactobacillus murinus*, a GABA-containing lipopeptides-producing bacterium, are reduced in rodents exposed to prenatal stress as well as in individuals with irritable bowel syndrome[170]. The findings suggest that GABA-containing lipopeptides could potentially alleviate visceral pain in individuals with irritable bowel syndrome, offering the potential for personalized therapy development.

Research, including findings from the Human Microbiome Project, indicates that the gut microbiome contains the gene encoding glutamate decarboxylase, essential for converting glutamic acid to GABA, with certain bacterial strains like *Bifidobacterium dentium* showing potential therapeutic effects against visceral hypersensitivity in rats[171]. Bacteria also have receptors for detecting GABA, suggesting a reciprocal influence between host-produced GABA and microbial behaviour, as seen in the increased virulence of *Pseudomonas aeruginosa* when exposed to GABA. These observations highlight the complex interaction between glutamate, GABA and the gut microbiota, emphasizing the need for further research to decode these interactions and their implications for health and disease.

Histamine. Histamine, a biogenic amine derived from histidine, plays pivotal roles in mammalian physiology, including promoting wakefulness and the immune response, and is synthesized by various immune cells like mast cells in the gastrointestinal mucosa[172]. This synthesis pathway is shared by certain bacterial strains, which underscores a critical aspect of host–microbe communication, with mucosal mast cell activity influencing intestinal integrity and visceral pain. While histamine production by food spoilage bacteria is a well-known concern in food safety, its potential to interact with the host's nervous system through vagal afferents highlights a complex interplay[173]. The presence of histamine-producing bacterial species like *Morganella morganii* and *E. coli* in the human gut, equipped with the histidine decarboxylase gene, suggests a microbial capacity to influence host physiology[174]. Although the exact impact of microbial-derived histamine on the host is still being explored, studies indicate that histamine from *Lactobacillus reuteri* can suppress inflammatory responses and modulate gut immune functions through human monocytoid production of tumour necrosis factor via Toll-like receptor stimulation[175]. This relationship between histamine and host–microbe interactions opens additional avenues for understanding how microbial components might affect host health, indicating a multifaceted neuroendocrine–immune mediation in these interactions.

Serotonin and tryptophan. Serotonin, also known as 5-hydroxytryptamine (5-HT), which is crucial for host behaviour and gastrointestinal functions, has intricate ties to the gut microbiota with important implications for both the gut and the brain. Microbial impacts on host gastrointestinal serotonergic systems, highlighted by *Clostridium perfringens* modulation, suggests a microbial role in gastrointestinal motility and serotonin synthesis via host tryptophan hydroxylase 1 enzyme[176]. This influence is evident at baseline and following acute stress exposures[177]. The gut microbiota is also associated with hippocampal serotonin concentrations[178,179]. Tryptophan can be diverted away from 5-HT production into the kynurenine pathway, potentially impacting host mental health[180]. Microbial indole production from the bacterial metabolism of L-tryptophan derivatives further influences metabolic and gastrointestinal function in health and disease, including intestinal barrier integrity, inflammation and potentially even impacting host longevity[181,182]. Isatin, a metabolite of indole produced by both bacteria and the host, has been linked to anxiety-like behaviour in rodents[183] and is detectable in various host tissues, including human cerebral spinal fluid and the hippocampus. Elevated levels of isatin have been observed in individuals with bulimia nervosa[184]. Additionally, the gut microbiota contributes to the production of tryptamine from tryptophan, a monoamine akin to 5-HT that can modify colonic secretion and gut motility via the 5-HT-4 receptor[185]. Approximately 10% of the human population possesses the necessary gut microbiota decarboxylases for this reaction. While neuropharmacological and electrophysiological studies suggest tryptamine might activate postsynaptic receptors independently of 5-HT, its CNS function remains unclear.

A direct impact of diet on tryptophan metabolites in humans was uncovered when it was observed that consumption of a Mediterranean diet and a fast-food diet resulted in differential effects on tryptophan metabolites[186]. The Mediterranean diet increased indole-3-lactic acid and indole-3-propionic acid, and the fast-food diet decreased them, both of which have been associated with beneficial effects on neuronal cells. A diet enriched with tryptophan for 4 weeks increased brain activation in areas related to empathy during a social cognition task. While tryptophan did not significantly enhance emotion recognition overall, it did improve the recognition of positive emotions in older participants, suggesting its potential to mitigate age-related declines in social cognition[187]. Further, consuming a high-tryptophan diet for 4 days resulted in significantly more positive affect and reduced symptoms of depression and anxiety compared to a low tryptophan diet. These effects were possibly due to increased serotonin levels influenced by nutritional intake, aligning with evidence that dietary tryptophan, crossing the blood–brain barrier and converting to serotonin with the aid of vitamin B_6, can effectively ameliorate mood disorders[188]. Altogether, these findings support the hypothesis that dietary tryptophan can positively influence mood and affective disorders, distinct from earlier studies suggesting limited effects from nutritional tryptophan intake on mood states in healthy individuals.

TMAO. Trimethylamine *N*-oxide (TMAO) is a metabolite produced from the breakdown of dietary fish, meat and fat, with its precursor, trimethylamine (TMA), formed by gut microorganisms metabolizing choline, L-carnitine and phosphatidylcholine[189]. Elevated levels of TMAO, produced by gut microorganisms from choline metabolism, have been linked to an increased risk of vascular dysfunction, including stroke, leading to vascular cognitive impairment by affecting cholesterol metabolism, inflammation and oxidative stress, resulting in a strong association between TMAO and dementia, particularly in cerebrovascular disease[190].

TMA travels to the liver where it is oxidized to TMAO, which then enters systemic circulation, correlating with gut microbial composition. Studies have identified TMAO in the cerebrospinal fluid of both mice and humans, suggesting that circulating TMAO can influence the CNS[191]. High concentrations of TMAO in human cerebrospinal fluid imply that liver-derived TMAO can cross the blood–brain barrier increasing the risk of stroke[190], although the mechanism is unclear, and some TMAO in the brain may be synthesized locally due to the presence of the enzyme flavin-containing dimethylaniline monooxygenase 3 (FMO3). While high levels of TMAO are linked to cardiovascular diseases, obesity, diabetes and neurodegenerative disorders, including AD[189,192], TMAO may have neuroprotective effects within

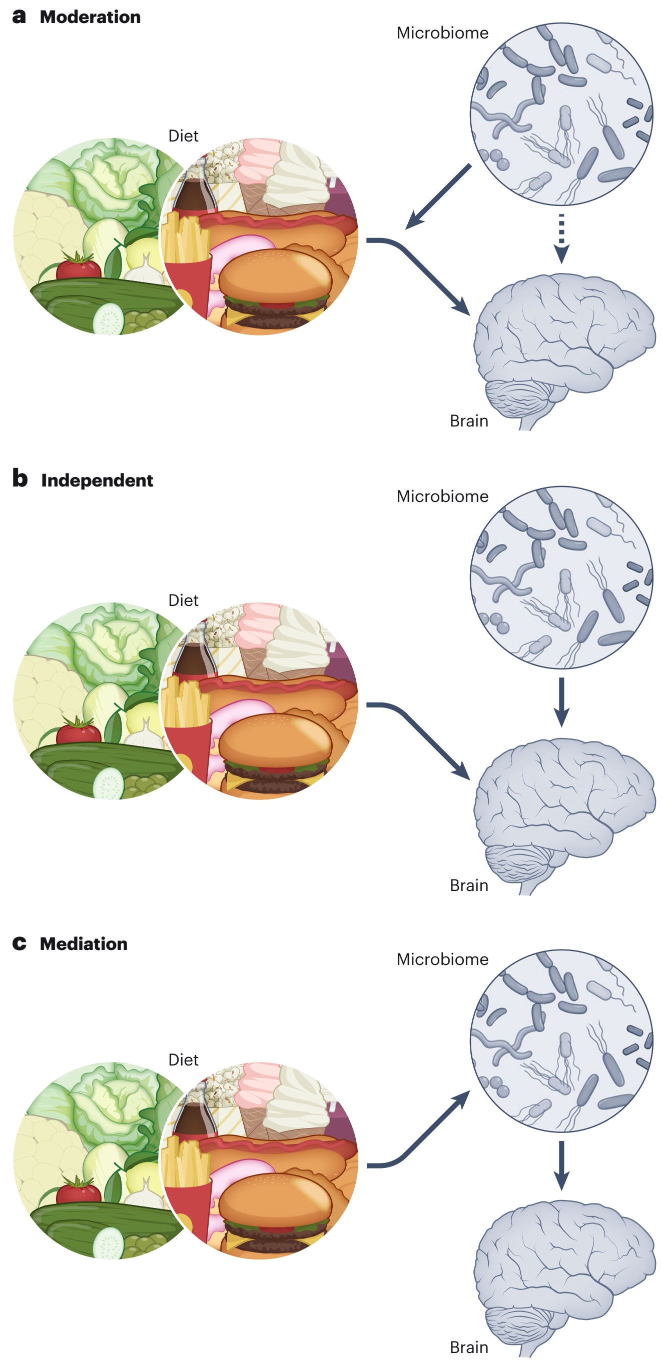

Fig. 5 | Gut microbiota as a potential mediator/moderator. a–c, Potential routes through which diet could mediate or moderate behaviour and cognition. The gut microbiota could shape the strength of the relationship between food and the brain (moderation; **a**), the gut microbiota and diet could influence the brain directly (independent; **b**) and the gut microbiota could explain the relationship been diet and the brain (mediation; **c**).

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Table 2 | Summary of interventional studies investigating the effect of whole diet approaches on microbiota and behavioural or cognitive outcomes in humans

Population	Length of intervention	Diet	Cognitive, behavioural or neurochemical changes	Microbiota changes	Notes/refs.
Adults 18–85 years of age; mean 21.84 years *n*=26 (male (44%) and female (56%)) Belgium	2 weeks of (ITF) diet then, 18 days of normal diet	ITF rich diet: at least 9 g of ITF	Higher levels of satiety, hedonic attitude to salsify consumption, and intrapersonal emotional competence reported. A reduced desire to eat sweets and salty food that persisted after returning to regular diet.	Lasting reduction in α-diversity. PLS-DA analysis: 20 OTUs identified that discriminate for the ITF intervention. Increased levels of Actinobacteria, phylum and class, Actinobacteridae sublass, Bifidobacteriales order, Bifidovacteriaceae family, *Bifidobacterium longum* and Prevotellaceae. Reduced levels of unclassfied Clostridiales, *Oxalobacteraceae* (trend); *Alistipes* and *Oscillibacter*.	238
Adult women with obesity Diet group mean age 62 years Control group mean age 63 years *n*=44 Japan	8 weeks long with informational sessions every 2 weeks	A nutrition education programme that centred on the gut microbiome, emphasizing consumption of dietary fibre and fermented foods. Nutrition education resulted in an elevated consumption of dietary fibre, vegetable dishes and milk products.	Lower depression scores as measured by the Center for Epidemiologic Studies Depression scale. Higher self-rated health scores.	Increased α-diversity Shannon and Simpson indices. Increased levels of Lactobacillales, Streptococcaceae, *Streptococcus*, *B. bifidum*, *Streptococcus thermophilus* and *Veillonella parvula*. Decreased levels of Bacteroidetes, Bacteroidia, Bacteroidales, Bacteroidaceae and *Bacteroides*.	239
Aged population (~65 years of age) at risk for AD due to baseline cognitive impairment (MCI), or cognitive or subjective memory complaints. *n*=17 (*n*=11 with MCI and *n*=6 with normal cognition)	Randomized, double-blind, crossover: 6 weeks with a 6-week washout period	Comparison between the MMKD[240] developed for the study and the AHAD. MMKD characterized by macronutrient distribution with less than 10% of calories from carbohydrates (<20 g per day), 60–65% from fat and 30–35% from protein. MMKD includes extra-virgin olive oil and encourages consumption of fish, lean meats and nutrient-rich foods. AHAD comprises 55–65% of calories from carbohydrates, 15–20% from fat (<40 g/day) and 20–30% from protein. AHAD emphasizes ample intake of fruits, vegetables and carbohydrates for sufficient fibre, along with lean meats and protein. Daily multivitamin supplements for both groups.	No reported alterations in AD biomarkers following the intervention.	There were no strong effects on α- and β-diversity after dietary interventions. MMKD: Reduced levels of Bifidobacteriaceae and *Bifidobacterium* and *Lachnobacterium*; Increased levels of *Akkermansia*, Tenericutes and *Slackia*. Reduced gene families annotated to AD (PICRUSt-inferred predictions of metagenome) and in KEGG pathway associated with type 1 and type 2 diabetes and bacterial toxins. Reduction in acetate and increase in butyrate. AHAD: Reduction in *Bifidobacterium* only in individuals with MCI; increase in Tenericutes. Increase in acetate and decrease in butyrate.	After the MMKD: negative correlation between *Enterobacteriaceae*; and Tenericutes positive correlation between *Rikenellaceae*, *Parabacteroides* and Aβ_{42} in MCI cohort; positive correlation between *Sutterella*, observed OTUs and the Shannon index. Negative correlation in MCI cohort between RF39, F-tau and phosphor-tau, and *Mollicutes* After the AHAD: no positive correlations observed in MCI cohort. Negative correlation between Bacteroidaceae and Actinobacteria, as well as Aβ_{42}, Actinobacteria and phospho-tau[106]
Individuals with ulcerative colitis *n*=17	Crossover 2×4-week periods with a 2-week washout period in between	A comparison between a low-fat, high-fibre diet (with 10% of calories from fat, 1–5% from saturated fat, 5–9% from unsaturated fat, and an omega-6:omega-3 ratio of 3:1) and an 'improved regular American diet' (featuring increased intake of fruits, vegetables and fibre, with 35–40% of calories from fat, 10–11% from saturated fat, 25–29% from unsaturated fat, and an omega-6:omega-3 ratio of 20–30:1).	An increased quality of life was observed with both diets, characterized by a reduction in perceived limitations related to physical and emotional health, improved social functioning, diminished pain and an overall positive impact on general health.	β-diversity shifted after consumption of the low-fat diet with an increase in Bacteroidetes, Actinobacteria and *Prevotella*. *Faecalibacterium prausnitzii* was increased in the low-fat diet group compared to the 'improved regular American diet' group. Higher levels of tryptophan and the SCFA acetate, as well as lower levels of lauric acid, after low-fat diet consumption.	No correlations were identified between microbial compositions and psychological or behavioural outcomes[241].
Aged population (65–79 years of age) *n*=612 Controls: *n*=289 (65–79 years) Male *n*=145; female *n*=144 Intervention: *n*=324 (65–79 years) Male *n*=141; female *n*=182 A subset of the NU-AGE cohort, involving Italy, United Kingdom, the Netherlands, Poland and France	12 months: parallel group design	Customized Mediterranean diet (MedDiet): Participants were educated on how to choose a diet based on Mediterranean diet or control diet guidelines. Control diet cohort participants were provided with a leaflet containing national dietary guidelines.	Strict adherence to the dietary plan led to enhancements in overall cognitive function and episodic memory when compared to low adherence. Both groups exhibited an overall improvement in performance on the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery.	Greater adherence to the dietary plan resulted in a mitigated decline in microbial diversity. Machine learning identified 'diet-responsive' microorganisms, with 44 OTUs such as *F. prausnitzii*, *Roseburia hominis*, *Eubacterium* (*E. rectale*, *E. eligens* and *E. xylanophilum*), *Bacteroides thetaiotaomicron*, *Prevotella copri* and *Anaerostipes hadrus* showing an increase with the diet. Conversely, 45 OTUs, including *Ruminococcus torques*, *Collinsella aerofaciens*, *Coprococcus comes*, *Dorea formicigenerans*, *Clostridium ramosum*, *Veillonella dispar*, *Flavonifractor plautii* and *Actinomyces lingnae*, decreased with the diet. The diet elevated SCFAs and BCFAs and reduced secondary bile acids, p-cresols, ethanol and carbon dioxide.	Positive correlations were observed between enhanced cognitive function and taxa that increased with the diet[77].

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Table 2 (continued) | Summary of interventional studies investigating the effect of whole diet approaches on microbiota and behavioural or cognitive outcomes in humans

Population	Length of intervention	Diet	Cognitive, behavioural or neurochemical changes	Microbiota changes	Notes/refs.
Adults: 45–75 years of age Elevated systolic blood pressure ≥ 120 mm Hg (not on hypertensive medication)	8 weeks for each dietary phase (MedDairy and LFD)	MedDairy: Fresh fruits and vegetables, legumes, fish and seafood, nuts and seeds, whole-grain cereal products and selected white meats; limited or no consumption of: red/processed meat, cream, butter, sugary beverages and bakery items Recommended dairy consumption: 3–4 daily servings, with specific serving sizes for different types of products (for example, 250 ml low-fat milk, 40–120 g cheese, 200 g low-fat Greek yoghurt). LFD: Reduced fat intake, including breads, cereals, lean meat, legumes, rice, vegetables and fruit.	No taxa change associated with cognitive measures (planning, memory, attention, processing speed or ACE-R scores).	A modest decrease in microbial diversity was observed in the LFD group, but not in the MedDairy group. MedDairy resulted in significant increases in relative abundance of *Butyricicoccus* and significant decreases in *Collinsella* and *Veillonella*. Also, there were significant increases in Lachnospiraceae and *Streptococcus*, and reductions in Oscillospiraceae and Ruminococcaceae. Higher adherence to the MedDairy diet was associated with increased *Butyricicoccus*, which correlated with lower systolic blood pressure but increased fasting blood glucose. Reductions in *Collinsella* was associated with improvements in the cholesterol:high-density lipoprotein ratio and the MedDiet adherence score.	242
Aged population (65–79 years of age) *n* = 226	Cross-sectional: data from pre- and post-intervention periods combined; 7-day food record	Intervention group received individually tailored dietary advice to follow a Mediterranean-like diet	Cognitive function did not associate with gastrointestinal microbiota composition nor α-diversity.	29 nutrients and 10 food groups (including fresh fruits, nuts, seeds, peanuts, grain products and red/processed meat) were significantly correlated with gastrointestinal microbiota composition. Consumption of animal-based foods and higher BMI was positively associated with *Ruminococcus gnavus*, Streptococcus spp. and *Collinsella*, but inversely associated with *Akkermansia muciniphila*, uncultured Clostridiales I and II, and species related to *Sporobacter termitidis*. Consumption of fresh fruits, nuts, seeds, peanuts and vitamin C was associated with various genera from the Bacteroidetes phylum and Firmicutes, including *F. prausnitzii*, *Oscillospira guillermondii* and *E. rectale*. BMI was negatively correlated with α-diversity; fresh fruit, nuts, seeds and peanuts were positively correlated with α-diversity. Vitamin C, various minerals, forms of carbohydrate and plant protein were positively correlated with α-diversity included.	243
31 healthy adults aged > 55 years Male *n* = 14; female *n* = 17	20 weeks (8 weeks per arm; 4-week washout)	200 ml low-dose anthocyanin (5 mg/100 g) Queen Garnet plum nectar or raspberry cordial control	No significant changes	No significant differences were observed for *Bifidobacterium* and *Clostridium*. No biomarkers associated with Queen Garnet plum nectar consumption over the 8-week intervention arm.	244
24 healthy adults	2 weeks	1 × 8-fluid ounce container per day of fermented dairy: kefir	No effect on anxiety and depression scores; improved relational memory-associated task performance.	Increased levels of *Lactobacillus* and decreased *Phascolarctobacterium*	57
45 healthy adults	4 weeks	200 ml 2–3 times per day of sauerkraut, kefir or kombucha	Lowered perceived stress scores	No changes to either α- or β-diversity	63
36 healthy adult women: 18–55 years	4 weeks	125 g fermented milk product (with probiotic) twice a day	Reduced activity noted in primary interoceptive and somatosensory cortices, and precuneus; frontal, prefrontal and temporal cortices, parahippocampal gyrus and the periaqueductal grey.	No changes noted	62
100 adults with MCI	12 weeks	800 mg of *Lactobacillus Plantarum* C29-fermented soybean per day	Increased cognitive function	Increased faecal *Lactobacilli*	58

Table 2 (continued) | Summary of interventional studies investigating the effect of whole diet approaches on microbiota and behavioural or cognitive outcomes in humans

Population	Length of intervention	Diet	Cognitive, behavioural or neurochemical changes	Microbiota changes	Notes/refs.
23 adults: 18–70 years with fibromyalgia	34 weeks (8 weeks per arm; 8-week washout) randomized, double-blind crossover	CD and KD (*Triticum turgidum* subsp. Turanicum), KAMUT brand	CD: Negative correlations detected between Actinobacteria and WPI+SS score; as well as Erysipelotrichales and FSS score. KD: Positive correlation observed between Actinobacteria and TSS and FOSQ scores; between Verrucomicrobiae and WPI+SS and WPI scores; between candidatus Saccharibacteria and SS score; between Bacteroidales and SRSBQ score. Negative correlation between Bacteroidales and FSS score; and between Enterococcaceae and WPI score.	Both interventions did not significantly modify microbial composition, diversity or SCFA levels. CD was associated with a significant increase in *Turicibacter* spp., linked to body fat and positively correlated with butyrate. CD also decreased abundance of Bacteroidales and increased Erysipelotrichales and Verrucomicrobiae. KD significantly increased Saccharibacteria and Actinobacteria, along with a higher abundance of butyrate after the first arm. KD also increased the abundance of Actinobacteria and Saccharibacteria after the first arm.	245
276 adults: ≥65 years	6 months	Randomized, personalized oral dietary advice: increase protein intake to 1.2 g per kg body weight per day, and include at least one meal with ≥35 g protein; all without increasing total daily energy intake.	No baseline or intervention differences in SNAQ or VAS appetite scores between the groups. fMRI showed differential activation in several brain areas in response to food pictures or high-caloric food pictures versus non-food pictures. No significant differences in brain activation were found between the diet and control groups at follow-up for either of the tasks. ROI analyses at the 6-month follow-up revealed an increase in signal in the right insula in response to anticipating chocolate milk in the intervention group.	Intervention did not alter the microbiome compared to the control. α-diversity and β-diversity unaffected by diet. No significant changes in overall microbiota composition based on the Bray–Curtis dissimilarity measure or weighted UniFrac. Multilevel PCA of CLR-transformed data showed no significant effect of the dietary intervention. No significant effects on specific microbial species counts were observed using negative binomial linear mixed-effect models.	246
80 adults: 18–35 years (completed = 60)	16 weeks	Control: no nuts or fatty fish in diet. Intervention: one portion (approximately 56 g) per day of fresh pre-portioned walnuts	Academic stress decreased total protein levels in the control group, but walnut consumption alleviated this decrease. Walnut consumption significantly decreased salivary α-amylase levels at visit 2 compared to controls. Plasma cortisol levels did not show significant differences between the groups. Academic stress did not increase biomarkers of stress in participants.	α-diversity (Shannon index): Academic stress led to a significant decrease in gut microbiota richness and evenness in females, compared to the baseline; but no significant differences in gut microbiota diversity across all clinical visits. β-diversity (Bray–Curtis dissimilarity index): Pairwise PERMANOVA comparisons in females revealed dissimilarities in microbial communities between the control group at visit 1 and the treatment group at visit 2. No significant changes were identified in the relative abundance of *Bifidobacteria*, *Bacteroides* and *Lactobacillus*. Trend analysis revealed significant changes in the relative abundance of certain families (for example, Bifidobacteriaceae) and a near-significant main effect of treatment in Ruminococcaceae. Genus-level analysis (ANCOM): identified significant changes in relative abundance of *Ruminococcus* 1, *Ruminococcus* 2, *Alistipes*; *Ruminococcus* 1 and *Ruminococcus* 2 showed trends, with significant changes between visit 1 and visit 3 in controls; *Alistipes* showed a significant increase between visit 2 and visit 3 overall, with a significant main effect of time on abundance.	247

Table 2 (continued) | Summary of interventional studies investigating the effect of whole diet approaches on microbiota and behavioural or cognitive outcomes in humans

Population	Length of intervention	Diet	Cognitive, behavioural or neurochemical changes	Microbiota changes	Notes/refs.
107 adults: 18–35 years (completed=60)	12 weeks	Control; FD; exercise (RS); FD-RS	Participants in the FD and FD-RS groups showed a significant reduction in the PRMQ, PM and RM scores after intervention. After baseline adjustment, the PRMQ, PM and RM scores of the FD and FD-RS groups were significantly lower than the control group. Short-term memory scores under the PM subscale decreased in the RS, FD and FD-RS groups. Long-term memory score under the PM subscale decreased in the FD-RS group. Significant decreases in short-term memory scores for the FD and FD-RS groups in the RM subscale and in the long-term memory score for the FD-RS group. After adjusting for baseline values, the improvement in short-term memory in the FD and FD-RS groups was significantly better than that in the control group. The long-term memory score in the FD-RS group was significantly lower than that in the control group. Environment-cued memory scores under the PM subscale were significantly lower in the FD and FD-RS groups compared to the control group after adjusting for baseline values. Self-cued memory scores in the RM subscale were improved in the RS, FD and FD-RS groups. Significant increases in the GEC, MI scores, working memory, plan/organize and organization of materials in the control group.	Community evenness index significantly improved in both the RS and FD groups after intervention. Microbial community diversity (Shannon index) and richness (number of observed features) did not change significantly within each group after the 12-week intervention. PCA and PERMANOVA showed no significant shift in the composition of microbial community at the OTU level within each group, but significant differences were observed among the groups at week 12. Firmicutes, Actinobacteriota, Bacteroidetes and Proteobacteria were the main affected communities, with Firmicutes being the most abundant. Bacillota:bacteroidota showed no significant changes in the three groups. RS intervention increased the relative abundance of Firmicutes and decreased Verrucomicrobiota. RS increased the relative abundance of *Eubacterium coprostanoligenes*, *Escherichia shigella* and *Faecalibacterium*. FD increased relative abundance of the NK4A214 group. Both RS and FD led to a significant decrease in *Lactobacillus* spp.; RS also reduced the relative abundance of Muribaculaceae.	244

WPI+SS=FM severity scale; WPI, widespread pain index; SRSBQ, sleep-related and safety behaviour questionnaire; FSS, fatigue severity scale; SS, symptom severity scale; TSS, tiredness symptoms scale; FOSQ, functional outcome of sleep questionnaire; SNAQ, simplified nutritional appetite questionnaire; VAS, visual analogue scale; PRMQ, prospective and retrospective memory questionnaire; PM, prospective memory; RM, retrospective memory; GEC, global executive composite; MI, metacognition index; MCI, mild cognitive impairment; ACE-R, Addenbrooke's cognitive examination; PLS-DA, partial least-squares discriminant analysis; PICRUSt: phylogenetic investigation of communities by reconstruction of unobserved states; BCFAs, branched-chain fatty acids; PCA, principle component analysis; CLR, centred log ratio; ROI, region of interest; fMRI, functional magnetic resonance imaging; PERMANOVA, permutational multivariate analysis of variance; ANCOM, analysis of compositions of microbiomes; OTU, operational taxonomic unit; ITF, inulin-type fructan; LFD, low-fat diet; MMKD, modified Mediterranean ketogenic diet; AHAD, American Heart Association Diet; MedDairy, Mediterranean Diet supplemented with adequate dairy; CD, control wheat diet; KD, Khorasan wheat diet; FD, fibre-rich diet; RS, rope skipping; FD-RS, fibre-rich diet with rope skipping; KEGG, Kyoto Encyclopedia of Genes and Genomes; BMI, body mass index.

normal physiological ranges, highlighting a dose-dependent relationship[193,194]. This body of work indicates not only detrimental effects, such as modulating lipid and hormonal homeostasis and promoting neuroinflammation, but also potential benefits, including protecting the blood–brain barrier, enhancing microtubule assembly and acting as a potential therapeutic approach in AD. The dose-dependent nature of TMAO's impact on the brain adds complexity to interpreting its relationship with cognition, which is further complicated by variations in circulating TMAO levels influenced by factors like age, diet and renal clearance[195]. Further research revealed how methylamines, linked to the microbiome, engaged directly with the mammalian blood–brain barrier, offering protection against inflammation, thereby preserving cognitive function[196].

It has been shown that TMAO plays a key role in forecasting and modulating obesity, glucose tolerance and host behaviour, while also enhancing insulin secretion and reducing metabolic stress[197]. Also, computational analyses have identified TMAO as a potential biomarker for neurodegeneration and cognitive decline[198], emphasizing the need for additional in vivo investigations. For example, a high-sugar and high-fat diet affected gut microbiota and, subsequently, brain physiology

Table 3 | Dietary approaches affecting gut microbiome and behavioural or cognitive outcomes in rodents

Diet	Outcomes	Refs.
Mouse		
50% LB	Reduced anxiety-like behaviour; enhanced working and reference memory in LB-fed CF1 male mice. Higher microbial diversity observed in the LB group including 12 unique genera discovered in the LB group (*Chthoniobacter*, *Alistipes*, *Dorea*, *Allobaculum*, *Staphylococcus*, *Proteus*, *Eggerthella*, *Gemella*, *Leuconostoc*, *Sarcina*, *Serratia* and *Turicibacter*) and 3 in the controls (*Erysipelothrix*, *Atopobium* and Bacteroidales)	248
Low-fat diet (10% of calories from fat) High-fat diet (60% of calories from fat)	Reduced Y-maze spatial recognition memory, and novel object exploration and recognition index in the novel object recognition test in SPF C54BL/6J male mice. Increased anxiety-like behaviour during the elevated plus maze task. Reduced hippocampal BDNF and phosph-CReP and nuclear factor-κB activation, as well as an indicator of activation of microglia through increased Iba1 expression. Increased Bacillota:Bacteroidota ratio as well as Proteobacteria and Deferribacteres, along with reduced Bacteroidetes and Tenericutes.	249
High-fat diet (60 kJ% from fat, 24kj% from carbohydrate, 16 kJ% from protein)	Increased depression-like behaviour with a disrupted circadian ingestion pattern in C57BL/6J mice. Decreased locomotor activity. β-diversity differed between high-fat diet and control animal groups. Increased α-diversity in the high-fat diet group with reduced levels of Bacteroidetes and increased levels of Firmicutes and Cyanobacteria.	250
High-fat/no-sucrose diet	Reduced digging and impaired cognitive function in BALB/cAnNTac mice. Differences in β-diversity with increased levels of Firmicutes, Ruminococcaceae, Lachnospiraceae, *Ruminococcus*, *Dorea* and *Oscillispira* but reduced levels of Bacteroidetes, S24–7 and *Anaeroplasma*.	251
High-sucrose/standard low-fat diet	Reduced anxiety-like and hyperactive behaviour. Correlations were reported between gut microbiome and behaviour, as well as BDNF levels and inflammatory markers.	251
High-fat (42%)/ high-sucrose (66%) diet	Differences seen in high-sucrose and high-fat diet-fed C57BL/6J mice in the water maze test. Mice on the high-fat diet had increased levels of Erysipelothrichales. Mice on the high-fat and high-sucrose diet had two genera in Clostridiales increased and three genera in Bacteroidales reduced. Mice on the high-sucrose-only diet were the only group to show the presence of *Enterococcus*, along with increased levels of Lactobacillales, *Lactobacillus* and *Lactococcus*. Control mice had the order Bacteroidales not present in any of the experimental groups; with the phyla Tenericutes, Mollicutes and Anaeroplasmatales presenting only in control animals. It was reported that higher Clostridiales levels were correlated with poorer performance for learning new platform location as well as searching closer to old platform location; lower Bacteroidales levels were correlated with lower proximity scores for the location of the old platform; and higher Lactobacillales levels were correlated with poorer performance on first probe trial of the water maze test.	252
High-fructose diet	No memory impairment was reported. Provision of the high-fructose diet for 8 weeks to C54BL/6N male mice altered microbial community structure but not α-diversity. Specifically, Bacteroidetes were reduced, Proteobacteria were increased with a trend reported for increased Firmicutes. Deferribacteraceae, Helicobacteraceae, Lachnospiraceae and Ruminococcaceae were all reported at higher levels in the high-fructose diet-fed mice. Total SCFAs were also reduced.	253
Magnesium-deficient diet	C57BL/6NBomTac male mice fed a magnesium-deficient diet displayed altered anxiety-like behaviour, and increased depressive-like behaviour. Control mice showed a correlation between the gut microbiome and anxiety-like behaviour.	254,255
High-amylose corn starch	Swiss Webster male mice on a diet of high-amylose corn starch (HA-7) displayed increased anxiety-like behaviour, as measured with an elevated plus maze test. No differences were noted in α-diversity or β-diversity	165
6:1 fat:protein ketogenic diet	A 6:1 fat:protein ketogenic diet fed to germ-free/SPF wild-type Swiss Webster mice reduced the threshold to seizure coupled with increased hippocampal glutamate and GABA levels. Further, α-diversity was reduced, along with increased levels of *A. muciniphila*, *Parabacteroides*, *Sutterella* and *Erysipelotrichaceae*. Germ-free status or SPF mice treated with antibiotics both abolished the anti-seizure effect of the ketogenic diet.	101
Fermented dairy: fermented glycated milk protein	C57BL/6 male mice; restoration of gut microbiome after intervention. Clustering of gut microbiota with intervention; decreased anxiogenic-like behaviour.	256
Fermented dairy: fermented with LAB	ICR mice; high dose of GABA fermented milk resulted in a difference in β-diversity, which differed significantly from medium-dose and low-dose groups; they also had higher levels of butyrate and spent more time in the centre of an open field test (reduced anxiety-like behaviour) with longer time sleeping.	257
Fermented dairy: fermented with kefir	C57BL/6J mice; increased diversity with kefir (UK4) gavage; repetitive behaviours were reduced; increased time spent in FUST with kefir as well as memory and spatial learning modulation.	258
Fermented dairy: fermented with kefir	BTBR T+ Itpr3tf/J mice; no changes to α-diversity or β-diversity; increased levels of Lachnospiraceae bacterium A2 and decreased Clostridiaceae with kefir. Reduced marble burying and enhanced social recognition; no impact on fear-dependent memory, anxiety or depression-related behaviours.	259
Fermented dairy: fermented with kefir	CD-1 male mice; microbiome rescue from lipopolysaccharide challenge with kefir; female mice with kefir were more immobile, with the opposite observed in male mice.	260
Fermented dairy: fermented with Tibetan yoghurt	APP/PS1 transgenic mice; increased levels of *Mucispirillum*, Firmicutes and *Ruminiclostridium*; decreased levels of Tenericutes, Proteobacteria, Deferribacteres and Bacteroidetes. Spent more time with the novel object and in target quadrant of NOR and MWM tests.	261

Table 3 (continued) | Dietary approaches affecting gut microbiome and behavioural or cognitive outcomes in rodents

Diet	Outcomes	Refs.
Mouse		
Fermented cereal (yeast-enriched beer)	3xTg-AD mice; gut microbiota restored with treatment; increased Tenericutes and Actinobacteria; decreased Proteobacteria and Sordariomycetes with treatment. Reduced hippocampal and PFC tumour necrosis factor expression; increased interleukin-4 and interleukin-10. Unaltered NOR; increased discrimination index with treatment.	262
Fermented grain	Albino mice; increased *Bifidobacterium* and decreased *C. perfringens*. Increased colonization of *Lactobacilus* and *Bifidobacterium* in the colon. Increased distance travelled on T-maze; equal time spent in open and closed arms in treatment group.	263
Red ginseng fermented with Bifidobacteria	C57BL/6 male mice; increased levels of Bacteroidaceae and Muribaculaceae; rescued stress and depression-like phenotype associated with an *E. coli* challenge stressor.	264
Intermittent fasting (24 h/24 h)	Diabetic male BKS.Cg-*Dock7*^{m}+/+*Lepr*^{db}/J mice on an intermittent fasting schedule of 24 h on and 24 h off demonstrated improvements in anxiety-like behaviour, locomotor activity and rescue of cognitive deficits, as well as enhanced spatial memory. Hippocampal neuroanatomical metrics were altered. Both α- and β-diversity were altered, with *Lactobacillus* and *Odoribacter* increased and *Enterococcus*, Enterococcaceae, *Streptococcus*, *Rummeliibacillus, Candidatus Arthromitus* and *Leuconostocaceae* reduced. 17 *Lactobacillus* OTUs were altered by the fasting regime. Specifically, *C. Arthromitus* and some unknown *Leucostocaceae* genera positively associated with cognition-associated blood glucose levels.	145
Rat		
Cafeteria	In female Sprague–Dawley rats fed a CCD, novel place recognition, which is a spatial recognition task, was reduced. Moreover, novel place recognition performance was a predictor of global microbiome composition. β-diversity differed significantly depending on diet; rats on a CCD or HTCD were more closely aligned than those on a control diet, although all three were different. Rats on a CCD were reported to have a lowered α-diversity. 16 OTUs were enriched in the CCD rats; 15 OTUs were enriched in the HTCD group. A correlation between Coprobacter_OTU66 and spatial recognition memory was reported in the control rats.	265
Galactooligosaccharide, polydextrose, lactoferrin, whey protein concentrate, milk fat globule membrane	Male Fisher rats (F344) on a diet mix of galactooligosaccharide, polydextrose, lactoferrin, whey protein concentrate and milk fat globule membrane-10 showed a decrease in anxiety-like behaviour, linked with an increase in total *Lactobacillus* spp. The microbial alteration positively correlated with *Cfos* mRNA expression in cingulate, infralimbic and prelimbic regions of the PFC and dorsolateral and dorsomedial striatum; as well as serotonin mRNA in the caudal dorsoventral aspect of the DRN and lateral amygdala.	266
Short-intermittent periods (2 h/day) of hypercaloric HFHS diet	A short-intermittent period (2 h/day) of hypercaloric HFHS diet fed to male Sprague–Dawley rats reduced social motivation when HFHS food access was restricted for a 23-h period; they displayed reduced social interaction before compared to after access and increased social investigation after access. They also showed impaired social and object recognition. While no difference in α-diversity was reported, there was a dissimilarity of microbiota β-diversity. Specifically, *Blautia*, *Ruminoccoceae*, *Phascolarctobacterium*, *Bifidobacterium*, Bacteroidales and *Allobaculum* were all increased.	267
Gerbil		
Fermented Chungkookjang (×2)	Mongolian gerbils; increased α-diversity; β-diversity clustered differently dependent on the intervention. Both Chungkookjang interventions rescued short-term memory deficits associated with artery occlusion; the CKJ1 intervention specifically protected against memory dysfunction.	268
Fermented Chungkookjang (×2)	Mongolian gerbils; increased Shannon index, *Bacteroidota* and *Clostridia*; increased passive avoidance test memory.	269
Equine		
High-fibre diet	Horses fed a low-fibre and high-starch diet (57% hay and 43% barley) spent less time feeding and more time resting. A positive correlation was reported between caecal and colonic amylolytic bacteria and performance in a sociability test; and between caecal lactate-utilizing and colonic amylolytic bacteria in a social novelty test.	270
High-fibre or high-starch diet	Ponies were reported to be more active and less settled (more nervous and unsure) when fed a high-starch diet. 85 OTUs were significantly altered as a result of diet; 20 OTUs were significantly different depending on diet.	271
High-fibre or low-fibre and high-starch diet	Crossbred horses fed a low-fibre and high-starch diet (56% hay and 44% barley) exhibited more blowing (exhaling through mouth) during a test of novelty seen as an anxiety-like alert behaviour. This correlated with higher concentrations of amylolytic and total anaerobic bacteria, as well as a higher abundance of Succinivibrionaceae.	272

NOR, novel object recognition; MWM, Morris water maze; LAB, lactic acid bacteria; ICR, Institute for Cancer Research; FUST, female urine sniffing test; SPF, specific pathogen-free; BDNF, brain-derived neurotrophic factor; GABA, gamma-aminobutyric acid; PFC, prefrontal cortex; DRN, dorsal raphe nucleus; LB, lean beef; CCD, continuous cafeteria diet; HTCD, half-time cafeteria diet; HFHS, high-fat and high-sucrose diet.

through changes in neurotransmitter metabolism, intestinal health and brain circular RNA profiles in mice[199]. Thus, it appears that diet-induced dysbiosis altered neurotransmitter secretion and degraded specific brain circular RNAs via microbial metabolites like TMAO, potentially aiding the development of therapeutic strategies for related pathologies.

Vagus nerve signalling

The vagus nerve is the 10th cranial nerve and serves as the primary connection between the gut and the brain. Comprising 80% afferent and 20% efferent fibres, vagal afferents tonically transmit vital information from the gastrointestinal, respiratory and cardiovascular systems (bottom-up), while also providing feedback to the viscera (top-down). These afferents in the gut can detect a diverse range of mechanical, chemical and hormonal signals[200]. The vago-vagal anti-inflammatory reflex loop, involving vagal efferents, plays a role in modulating pro-inflammatory cytokines and is linked to inflammatory bowel disease. Sensory vagal fibre cell bodies in the nodose ganglia in the brainstem synapse on various brainstem nuclei including the NTS[201].

Multisynaptic pathways ascending from the NTS link visceral information directly with the entire brain, eliciting for example, emotional and behavioural responses driven by the gut, and hence through diet. Thus, the NTS coordinates the integration of interoceptive feedback transmitted via the vagus nerve, acting as a hub for diet–microbiota–gut–brain signalling. Studies suggest gut bacteria use vagal afferents to influence emotional and behavioural responses, emphasizing the vagus nerve as a conduit for microbiota–brain signalling[202].

The role of the vagus nerve in regulating food intake has long been recognized. Preclinical studies have provided evidence suggesting that shifts in the gut microbiota induced by diet can disrupt communication between the gut and the brain via the vagus nerve[200]. High-fat/high-sugar diets can alter gut microbiota abundances leading to intestinal inflammation, increased intestinal permeability, heightened microglia activation and vagus nerve remodelling[203,204], which was suppressed by antibiotic treatment, indicating the mediating role of the gut microbiota on adverse effects of a high-fat diet on vagal signalling[204].

Another study has suggested that the palatability of energy-dense foods high in fats and sugars can influence dietary choices[205]. It is apparent that post-ingestive nutritional signals, through the gastrointestinal infusion of fats and sugars, activate distinct and separate neurons within the vagus nerve, ultimately conditioning flavour preferences and driving overeating, indicating separate gut–brain circuits for fat and sugar[205]. This work elegantly demonstrates how engaging separate but interconnected reward circuits in the brain modulates desire and motivation to consume nutrient-rich foods, promoting overeating, underscoring the complexity of dietary behaviours and their impact on obesity.

Endocrine signalling

Enteroendocrine cells constitute a mere 1% of epithelial cells in the gastrointestinal tract yet wield considerable influence over gut homeostasis. Among these, enteroendocrine L cells and enterochromaffin cells stand out, notably populating the distal small and large intestines where diverse bacterial taxa thrive. Postprandially, enteroendocrine L cells orchestrate the release of GLP-1 and PYY, powerful anorexigenic hormones shaping eating patterns[206]. These peptides act as messengers, engaging with local gut neurons, vagal afferents and the CNS, particularly the brainstem and hypothalamus, to stimulate satiation and inhibit eating. Recent insights into synaptic connections between L cells and the enteric nervous system reveal a previously underestimated speed and precision in gut–brain signalling[207]. In the proximal gut, L cells respond to luminal nutrients, like carbohydrates and long-chain fatty acids, conducting a postprandial surge in GLP-1 and PYY. In the distal gut, L cells respond to bacteria-derived metabolites, including SCFAs and secondary bile acids, which choreograph signals that persist between meals, supported by the ongoing bacterial fermentation of undigested nutrients. The delicate balance of GLP-1 and PYY secretion, crucial for controlling food intake, body weight and metabolism, is disrupted in individuals with obesity[208]. Chronic dietary interventions using prebiotics or probiotics showcase the gut microbiota's role in maintaining metabolic health. Certain dietary fibres and probiotic strains have shown to be instrumental in enhancing GLP-1 and PYY production, underscoring the profound impact of bacterial metabolites and diet on metabolic well-being.

Autoantibodies targeting appetite-regulating hormones, such as α-melanocyte-stimulating hormone, hint at an evolutionary mimicry, giving gut bacteria a tool to manipulate host food intake[115]. The discovery of the caseinolytic protease B heat-shock protein in gut commensal *E. coli* further affirms this symbiotic dance, influencing appetite and satiety[209]. Enterochromaffin cells produce serotonin from dietary tryptophan. Gut bacteria, particularly spore-forming clostridia, induce colonic serotonin synthesis, impacting gut functions like intestinal transit[176]. The interplay involves bacterial metabolites, such as secondary bile acids and lipopolysaccharides, offering insights into the diet–gut–microbiota dialogue.

HPA axis

The hypothalamic–pituitary–adrenal (HPA) axis is a cornerstone neuroendocrine system vital for stress response modulation and has been implicated in microbiota–gut–brain axis function. Importantly, the HPA axis is modifiable by probiotics[210,211] and prebiotics[212]. Specifically, germ-free mice have a hyper-responsive HPA axis, marked by elevated corticosterone (murine equivalent of cortisol) levels in response to stress[179,213], and humans with IBS display heightened cortisol responses, coupled with microbiota alterations, emphasizing the reciprocal regulation between the microbiome and the HPA axis[214].

Dietary interventions have demonstrated the ability to regulate HPA axis activity. In humans, supplementation with vitamin C, fish oil or polyphenol-rich dark chocolate led to reductions in cortisol levels and subjective stress measures[215]. Additionally, adopting a whole-foods diet, particularly with increased dietary carbohydrate intake, improved salivary cortisol levels in overweight or obese women[216]. Thus, there is growing interest in targeting HPA axis activity through microbiota-directed dietary interventions. Some studies suggest that the gut microbiota may play a role in the nutritional modulation of stress responses[217]. For instance, in a preclinical study, supplementation with milk fat globule membrane and prebiotics attenuated HPA axis dysregulation and cognitive dysfunction induced by early-life maternal separation while also influencing microbiota composition[218]. Similarly, in another animal model of chronic unpredictable social stress, prebiotic administration normalized stress-induced alterations in microbiota and corticosterone levels[219].

Investigating the diet–microbiota–gut–brain axis: towards mechanisms and causality

A fundamental gap in understanding the diet–microbiota–gut–brain axis is determining the biobehavioural processes that occur between consumption of a food item and its effects on emotional and cognitive functioning (see Fig. 4 for an overview). The acute effects of food intake on behaviour in humans can be investigated by combining brain neuroimaging techniques such as functional magnetic resonance imaging and electroencephalography recording with behavioural assessments of mood and cognitive performance[220–222]. Biological samples (that is, blood, saliva, urine and faeces) should also be collected to determine mechanisms of action. Due to the prolonged transit time of food metabolism, assessment of the gut microbiota via faecal sampling lacks feasibility and precision for acute insights. Instead, serum samples for the determination of SCFAs[223] and urine samples for metabolomics before and after food intake can elicit more real-time information. Another methodological limitation is the accurate and convenient assessment of food intake. Common approaches include self-report methods such as food diaries, 24-h dietary recalls and food frequency questionnaires, but reliance on memory and bias in reporting are important threats to accuracy, despite being convenient to administer[224]. Objective measures such as nutritional biomarkers are ideally supplemented with self-report measures, but their expense and complexity in analysis are current limitations[225]. Moreover, some foods, such as fermented foods, do not yet have specific biomarkers[226]. However, the recent development of bioinformatic pipelines to estimate dietary intake from metagenomic sequencing of stool samples is an encouraging area of research that may mitigate some of the current issues in assessing food intake[227].

The effects of chronic food intake on the microbiota–gut–brain axis are also poorly understood. Longitudinal intervention designs with multiple samplings of the gut microbiome can provide essential time course data about when diet alters microbial composition/function and if these effects are enduring. Multimodal, longitudinal designs can also be utilized to follow cohorts before disease onset to understand

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the role of the diet–microbiota–gut–brain axis in the pathogenesis of neuropsychiatric disorders and/or in symptom severity. Preclinical research utilizing established methods that ascertain causality (Table 1) can be incorporated to provide insights that are not practical in humans. Specifically, back-translation with FMT methodology in animal models is among the most powerful tools in determining causality in microbiome research[228]. Randomized controlled trials with dietary interventions in clinical populations can also provide information as to whether diet-induced effects on gut microbiota are maintenance factors for some population subsets. Furthermore, such data could uncover the possibility for alternative therapeutics to attenuate brain dysfunction, including a combination of prebiotics/probiotics and personalized dietary plans. Therefore, it is possible that the gut microbiota is a mediating or moderating factor in explaining the relationship between diet and brain health (Fig. 5). As evidenced throughout, individual gut microbiota composition and functionality can be vulnerable or protective against poorer dietary intake. Utilizing Mendelian randomization, a method used in epidemiology to assess causal relationships between risk factors and health outcomes, it is possible to reveal causal connections between the gut microbiome and blood metabolites. Such causal insights can shed light on the mechanistic links within the complex network of diet, gut microbiota and metabolic health[229]. Incorporating sophisticated statistical models[229], including structural equation modelling and discriminant analyses in large datasets with multimodal measures, may determine risk factors, including the capacity of individual gut microbiota to metabolize dietary products, that predict disease onset and phenotype, while providing additional evidence for the diet–microbiota–gut–brain axis.

Summary and conclusion

It is now well established that the gut microbiota communicates with the brain along the microbiota–gut–brain axis to influence mood and cognition of the host. We can now add diet as a key regulator of this axis as nearly all ingested items undergo a degree of metabolism by the gut microbiota. This evolutionary and relevant relationship between diet and gut microbiota composition and function may partially explain both the beneficial and detrimental effects of diet on brain functioning. This intricate triangulation between diet, gut microbiota and brain health further suggests a diet–microbiota–gut–brain axis that can be exploited to support cognitive and mental health for healthy individuals and to prevent and manage impairments in individuals with neuropsychiatric disorders (Tables 2 and 3).

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Author contributions

E.S., G.C. and J.F.C. conceptualized the article. E.S. and K.J.O. drafted the manuscript. All authors contributed to interpretation, editing and finalization of the manuscript.

Competing interests

E.S. has received an honorarium from Janssen Sciences Ireland UC as an invited speaker. K.J.O. has received honoraria from Sanofi Genzyme and Danone. G.C. has received honoraria from Janssen, Probi and Apsen as an invited speaker, is in receipt of research funding from Pharmavite, Reckitt, Tate and Lyle, Nestle and Fonterra, and has received payments as a consultant from Yakult, Zentiva and Heel Pharmaceuticals. J.F.C. has received research funding from IFF, Nutricia and Kerry Foods and has been an invited speaker at meetings organized by Bromotech & Nestle.

Additional information

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