REVIEW

Diet and the Microbiota–Gut–Brain Axis: Sowing the Seeds of Good Mental Health

Kirsten Berding,[1] Klara Vlckova,[1] Wolfgang Marx,[2] Harriet Schellekens,[1,3] Catherine Stanton,[1,4] Gerard Clarke,[1,5] Felice Jacka,[2,6,7,8] Timothy G Dinan,[1,5] and John F Cryan[1,3]

[1]APC Microbiome Ireland, Cork, Ireland; [2]Deakin University, iMPACT – the Institute for Mental and Physical Health and Clinical Translation, Food & Mood Centre, School of Medicine, Barwon Health, Geelong, VIC,Australia; [3]Department of Anatomy and Neuroscience, University College Cork, Cork, Ireland; [4]Teagasc Food Research Centre, Moorepark, Fermoy, Cork, Ireland; [5]Department of Psychiatry and Neurobehavioural Sciences, University College Cork, Cork, Ireland; [6]Centre for Adolescent Health, Murdoch Children's Research Institute, Parkville, VIC, Australia; [7]Black Dog Institute, Randwick, NSW, Australia; and [8]College of Public Health, Medical & Veterinary Sciences, James Cook University, Douglas, QLD, Australia

ABSTRACT

Over the past decade, the gut microbiota has emerged as a key component in regulating brain processes and behavior. Diet is one of the major factors involved in shaping the gut microbiota composition across the lifespan. However, whether and how diet can affect the brain via its effects on the microbiota is only now beginning to receive attention. Several mechanisms for gut-to-brain communication have been identified, including microbial metabolites, immune, neuronal, and metabolic pathways, some of which could be prone to dietary modulation. Animal studies investigating the potential of nutritional interventions on the microbiota–gut–brain axis have led to advancements in our understanding of the role of diet in this bidirectional communication. In this review, we summarize the current state of the literature triangulating diet, microbiota, and host behavior/brain processes and discuss potential underlying mechanisms. Additionally, determinants of the responsiveness to a dietary intervention and evidence for the microbiota as an underlying modulator of the effect of diet on brain health are outlined. In particular, we emphasize the understudied use of whole-dietary approaches in this endeavor and the need for greater evidence from clinical populations. While promising results are reported, additional data, specifically from clinical cohorts, are required to provide evidence-based recommendations for the development of microbiota-targeted, whole-dietary strategies to improve brain and mental health. *Adv Nutr* 2021;12:1239–1285.

Keywords: diet, microbiota, brain, behavior, mental health, mechanisms, gut–brain axis, nutrition

Introduction

The human body harbors trillions of microbes [including bacteria, viruses, archaea, lower and higher eukaryotes, and fungi (1)] belonging to hundreds of different species, of which the vast majority reside in the gut. Recent decades have seen an exponential increase in our knowledge of the impact of the gut microbiota on various aspects of human health, including brain health (2). Moreover, it has become clear that diet is one of the key factors involved in shaping the gut microbiota, having marked effects on microbial diversity, as well as the abundance and metabolic capacity of specific microbes (3–5). In addition, there has been an increasing emphasis on the role of dietary habits in supporting optimal mental health (6–8).

Recently, the concept of *psychobiotics* has emerged, describing exogenous factors that influence the microbiota (e.g., via probiotics, prebiotics, diet) with bacterially mediated positive effects on mental health (9–12). It is evident that the consumption of Western-style diets rich in processed, fried and sugar-rich foods and low in plant foods with their constituent fiber and polyphenols can lead to the loss of microbial diversity and function as well as the extinction of important beneficial microbes and expansion of opportunistic pathogens (13, 14), with far-reaching consequences for human health. It is also recognized that using healthy diets to positively modulate gut–brain communication holds possibilities for both the prevention and treatment of common mental disorders (15). There are emerging studies that focus on the impact of supplementation with single food items, such as fruits and vegetables high in prebiotic fibers, showing some promising results in modulating microbiome–host interactions (16). While such approaches are important in advancing our understanding of how a specific food impacts human microbiota and health and could lead to the discovery of new functional foods, humans consume a combination of food groups with every meal and studying single foods could overlook the potential synergistic effect dietary components might have, not just on overall health,

but also on microbiota diversity and composition (17). Thus, the study of whole-dietary approaches represents a more realistic path to the development of new dietary interventions and could inform national healthy eating guidelines and policies.

In this narrative review, we summarize the current state of the literature triangulating diet, microbiota, and host behavior/brain processes. Additionally, potential mechanisms underlying the diet–microbiota–brain interrelationship are discussed. Recent advances highlighting the individual's microbial profile as a key determinant for the response to a diet intervention are also reviewed. It is envisioned that increasing knowledge in this area will ultimately lead to the development of microbiota-targeted nutrition approaches to mental health.

Impact of Diet on Microbiota Composition and Function

What is the gut microbiota?

Due to advances in sequencing technology and bioinformatics, there has been an increasing understanding of the impact of diet on microbiota composition (18, 19). Bacteria are taxonomically classified into phyla, classes, orders, families, genera, species, and strains. To date, 25 different phyla, ∼2000 genera, and 5000 species have been identified (20). Among the 25 phyla, the most dominant include *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Cyanobacteria*, *Fusobacteria*, *Proteobacteria*, and *Verrucomicrobia* (21), with the *Bacteroidetes* and *Firmicutes* phyla constituting 70–90% of the total healthy human gut microbiota (22). Genera within the *Firmicutes* phylum include *Clostridium*, *Lactobacillus*, *Bacillus*, *Enterococcus*, and *Ruminococcus*, whereas the *Bacteroidetes* phylum predominantly consists of the *Bacteroides* and *Prevotella* genera. *Bifidobacterium* is the main representative genus in the *Actinobacteria* phylum (23).

More than 1000 species of bacteria have been identified in the human gut, although a person on average only carries 160 species (24, 25). While controversies around the specifics of a "healthy microbiota" remain, it has been suggested that it can be defined by resistance (ability to resist perturbations) and resilience (return to baseline state) (26). Similarly, microbial richness (number of microbes) and diversity (the amount of different microbes, i.e., α-diversity) are often associated markers of a healthy microbiota (27). Additionally, certain bacterial genera can be regarded as beneficial symbionts, meaning they live in a mutually beneficial relationship with the human host. At the same time, other bacterial genera have been classified as potential pathogens and an imbalance in the ratio of these bacteria could increase the disease susceptibly of the host. Although this may vary within the specific host context, bifidobacteria and lactobacilli species are generally regarded as the "good" bacteria and are commonly used in probiotic supplements, whereas species like *Escherichia coli*, strains within the *Clostridium* genus, and LPS-forming taxa such as *Enterobacteriaceae* have been linked to disease states and symptomology (28–30). Likewise, the relation between the two dominant phyla, expressed as the *Firmicutes:Bacteroidetes* ratio, has been associated with several pathological conditions (31, 32), although the association with obesity is still being debated (33). One factor that reflects the difficulties of defining a healthy microbiota is the high variability observed between individuals. Thus, rather than defining a healthy microbiome based on the presence of specific microbes, it has also been suggested that the presence of key microbial functions, described as the "functional core," could be more important in defining a healthy microbial state (4, 26). This means that metabolic functions can be performed by different microbes, so that in individuals with a different microbiota composition the same microbial functions can be exerted. Likewise, the existing unknowns in the human microbiota make the definition of a healthy microbiota challenging. Although significant advances in sequencing technologies have been made in the last decade, some taxa and strain-level diversity as well as functionality remain unexplored in current microbiota studies (20). This strain-level diversity may be important in determining the associations of a specific bacterial genus with health or disease, which has been a focus of debate within the *Prevotella* genus (specifically *P. copri*) (34).

Diet and the gut microbiota

The core gut microbiota in adulthood is relatively stable, but environmental factors have been identified that can shape the gut microbial community (23, 35, 36). Both short- (37)

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Address correspondence to JFC (e-mail: j.cryan@ucc.ie).
Abbreviations used: ASD, autism spectrum disorder; BBB, blood–brain barrier; BCFA, branched-chain fatty acid; BDNF, brain-derived neurotrophic factor; CMC, carboxymethylcellulose; CNS, central nervous system; C-section, Caesarean section; GABA, γ-aminobutyrate; GF, germ-free; GLP-1, glucagon-like peptide 1; GPCR, G-protein-coupled receptor; HDAC, histone deacetylase; HMO, human milk oligosaccharide; HPA, hypothalamic–pituitary–adrenal; MAC, microbiota-accessible carbohydrate; NMDA, *N*-methyl-D -aspartate; NU-AGE, European Project on Nutrition in Elderly People; OTU, operational taxonomic unit; P80, polysorbate-80; PYY, peptide YY; TGR5, Takeda G protein-coupled receptor 5; TMA, trimethylamine; TMAO, trimethylamine *N*-oxide; 5-HT, serotonin.

TABLE 1 Overview of dietary components influencing the microbiota composition

Dietary factors with positive effects on microbiota		References
Mediterranean diet[1]	↑ Microbial diversity and health-promoting bacterial taxa (i.e., *F. prausnitzii*, *Roseburia*, *B. adolescentis*, *B. longum*, *Prevotella*)	(38–41)
Plant-based diet[1]	↑ Microbial richness and biodiversity Predominant phyla *Bacteroidetes* and *Actinobacteria* Enrichment in *Prevotella* bacteria ↑ *Bifidobacterium*, *Lactobacillus*, *Ruminococcus*, *E. rectale*, *Roseburia*, *F. prausnitzii*, *Anaerostipes* ↓ *Clostridium sensu stricto*, *C. perfringens*, *C. histolyticum*, *Odoribacter*	(42–50)
Fruits and vegetables[1,2,3]	↑ Microbial diversity and function Shift in the abundance of bacterial phyla Growth of beneficial bacteria ↓ Potentially harmful bacteria	(51–55)
Fermented foods[1,2]	Positive effects through ingestion of microbes and microbial metabolites ↑ Beneficial microbes (e.g., *Bifidobacterium*)	(56–59)
Nuts[1]	"Prebiotic effect" on the genus level ↑ *Firmicutes* genera, including some butyrate-produces (e.g., *Faecalibacterium* and *Roseburia*), *Clostridium* and *Dialister*	(60–62)
Fiber and prebiotics[1,2]	Depending on type of dietary fiber; generally ↑ bacterial diversity and abundance of beneficial microbes Potential predominance of *Prevotella*:*Bacteroides* ↑ Beneficial bacteria (i.e., *Bifidobacterium*, *Lactobacillus*, *Akkermansia*, *Faecalibacterium*, *Roseburia*, *Bacteroides*, *Prevotella*) ↓ Potentially pathogenic bacteria (e.g., *Enterobacteriaceae*)	(63–79)
Plant-based protein[1]	↑ *Bifidobacterium*, *Roseburia*, and *Lactobacillus* ↓ Pathogens such as *B. fragilis* and *C. perfringens*	(37, 80)
MUFAs/PUFAs[1]	↑ Beneficial bacteria, including butyrate producers (e.g., *Lactobacillus*, *Lachnospira*, *Roseburia*, and *Bifidobacterium*)	(81, 82)
Polyphenols[1,2,3]	"Prebiotic"-like effect has been described ↑ Symbionts and ↓ potential pathogens	(83–87)
Dietary factors with negative effects on microbiota		
Western diet[1,2]	Potential extinction of beneficial microbes with long-term consumption Dominance of *Bacteroides* taxa ↑ *Firmicutes*:*Bacteroidetes* ratio and *Proteobacteria* (potentially mucosa-associated pathogens) ↓ Protective SCFA-producing bacteria	(13, 14, 88–91)
Animal-based protein[1,2,3]	Specific microbial changes are observed in relation to different type and source of protein ↓ Beneficial butyrate producing bacterial groups (*Roseburia*, *E. rectale*) ↑ *Firmicutes* and ↓ *Bacteroidetes* ↑ Potential detrimental gut microbes (e.g., *Enterococcus*, *Streptococcus*, *Turicibacter*, and *Escherichia*)	(37, 92–94)
Saturated fatty acids[1,2]	↓ Total bacterial abundance, microbial diversity and richness ↑ Proinflammatory bacteria (e.g., *Alistipes, R. gnavus, Bilophila wadsworthia*)	(95–98)
Sweeteners[1,2,3]	Ambiguous findings dependent on the type of sweetener and administered dose Sucralose could induce microbial profile that promotes negative health effects	(99–106)
Emulsifiers[2]	Detrimental effects have been reported Microbial changes induced by emulsifiers could contribute to inflammatory diseases ↑ *Dorea*, *Bacteroides*, *Burkholderia*, *Clostridium*, *Veillonella*, and *Anaeroplasma*	(80, 107–109)

[1]Data available from human studies.
[2]Data available from animal studies.
[3]Data from in vitro studies; arrows represent generally reported increases or decreases in the literature.

and long-term (3) dietary habits have been recognized as one of the drivers of microbial composition and diversity and the impact of both individual nutrients and dietary patterns on the microbiota have been extensively explored. The dietary factors influencing the gut microbial community are summarized in **Table 1**. Although some generalizations about the impact of diet on microbiota composition can be made, recent work also suggests that the diet–microbe interaction is highly personalized and dependent on the baseline microbiota present (110), indicating that dietary interventions may need to be tailored to one's individual baseline microbiota (19).

Macronutrients

Gut microbes are involved in the digestion, absorption, metabolism, and transformation of undigested macronutrients, extracting beneficial and bioactive compounds for the human host. Each macronutrient affects the microbial profile in a different way, due to the specialized functionality of microbial taxa. Variations in macronutrient ratios, amounts, and types are large drivers of the effect on microbiota composition (111), with specific microbes thriving on selective macronutrients, thereby increasing their abundance.

Dietary fiber

The most extensively studied macronutrients for shaping the gut microbiota are carbohydrates, specifically dietary fiber. The European Union regulation 1169/2011 defines dietary fiber as

> "carbohydrate polymers with three or more monomeric units, which are neither digested nor absorbed in the human small intestine and belong to the following categories: edible carbohydrate polymers (I) naturally occurring in the food as consumed and (II) obtained from food raw material by physical, enzymatic or chemical means with a beneficial physiological effect demonstrated by generally accepted scientific evidence, or (III) edible synthetic carbohydrate polymers which have a beneficial physiological effect demonstrated by generally accepted scientific evidence" (112).

Another well-studied type of dietary fiber is the prebiotic, which is defined as "a substrate that is selectively utilized by host microorganisms conferring a health benefit" (113). It is important to note that whereas most prebiotics can be classified as dietary fiber, not all dietary fibers are prebiotics. Prebiotics are generally fermentable, which is not true for all dietary fibers. Examples of prebiotics include pectins, inulin, fructooligosaccharides, and galactooligosaccharides.

It is generally accepted that the consumption of a high-fiber diet promotes an increase in bacterial diversity and leads to a bloom in the growth of beneficial bacteria (i.e., *Bifidobacterium* sp., *Lactobacillus* sp., *Akkermansia* sp., *Faecalibacterium* sp., *Roseburia* sp., *Bacteroides* sp., and *Prevotella*) as well as a reduction in potentially pathogenic bacteria (e.g., *Enterobacteriaceae*) (63–70, 114–116). More specifically, the chemical properties (e.g., polymerization, solubility, and viscosity) of different fibers determine the location of metabolism within the gastrointestinal tract, leading to specific microbial changes in response to their ingestion. For example, supplementation studies demonstrated that wholegrain products containing β-glucans (soluble nonstarch polysaccharides) support the growth of lactobacilli and bifidobacteria in humans (71) and rats (72), whereas intact cereal fibers (e.g., wholegrain cereals, barley fiber, wheat bran, and rye fiber) increase the abundance of *Actinobacteria*, *Bifidobacterium*, *Clostridium*, *Lachnospira*, *Akkermansia*, and *Roseburia* in humans (63, 65, 66, 73). Human consumption of resistant starch led to significant increases in *Bifidobacterium*, *Faecalibacterium*, and *Eubacterium*, while decreasing some *Ruminococcus* strains (74, 75). The solubility of a fiber also determines the impact on the microbial profile. Compared with insoluble fiber, soluble fiber seemed to have a more pronounced effect on the microbial composition and diversity in a piglet model (76). Nevertheless, insoluble, nonfermentable fiber such as cellulose, a prominent source of fiber in fruit and vegetables, can be metabolized by cellulose-degrading microbes (such as *Ruminococcus* and *Fibrobacter*), influencing their abundance as well as the abundance of bacteria using the solubilized products (e.g., oligosaccharides and polysaccharides) through cross-feeding (117). In animal studies, cellulose was shown to increase microbial richness (77) and change the microbiota composition, with a higher abundance of *Peptostreptococcaceae*, *Clostridiaceae*, *Akkermansia*, *Parabacteroides*, *Lactobacillus*, *Clostridium*, *Eisenbergiella*, *Marvinbryantia*, *Romboutsia*, *Helicobacter*, *Enterococcus*, or *Desulfovibrio* (77–79) and lower *Sutterellaceae*, *Lactobacillaceae*, or *Coriobacteriaceae* (77, 79).

Besides changing microbial composition, different dietary fibers also influence microbial enzymatic capacity and metabolite concentration. Chemical properties such as solubility and fermentability determine the degree and location of microbial fermentation as well as the type of metabolite produced (76). Soluble, fermentable fiber can increase microbial enzymatic capacity to degrade complex carbohydrates and produce health-promoting SCFAs, namely acetate, propionate, and butyrate (114, 118). SCFAs, specifically butyrate, have been implicated in gastrointestinal (main energy source of colonocytes, supporting gut barrier function) and metabolic (glucose homeostasis, lipid oxidation) health, exert anti-inflammatory and immunomodulatory properties, and can influence central functioning (as outlined in detail below) (119, 120). Numerous intervention studies in humans show that reducing the consumption of carbohydrates and wholegrain cereals lowers the abundance of important butyrate-producing bacteria, including the probiotic bifidobacteria, as well as SCFAs themselves (121–123). While insoluble fiber does not have a pronounced effect on SCFA production, alterations in the linoleic acid, nicotinate and nicotinamide, glycerophospholipid, glutathione, and sphingolipid pathways as well as the valine, leucine and isoleucine metabolic pathways were observed in response to insoluble fiber (e.g., cellulose) intake (78, 79).

Dietary lipids and fatty acids

Although most fatty acids are absorbed in the small intestine, dietary lipids and fat also exhibit a marked impact on the microbial profile. Whether these alterations are beneficial or harmful depends on the type of fat. Different degrees of saturation have been reported to differentially shape microbial composition. For example, high SFA intake has been shown to be associated with reduction in total bacterial abundance in humans (95) and in microbial diversity and richness (95, 96), as well as an increase in proinflammatory bacteria (e.g., *Bilophila wadsworthia*) (96–98) in mice. In humans, healthier polyunsaturated fatty acids (e.g., omega-3 PUFAs) promote the growth of beneficial bacteria, including butyrate producers such as *Lactobacillus*, *Lachnospira*,

Roseburia, and *Bifidobacterium* (81), and are correlated with higher microbial diversity as well as taxa from the families *Lachnospiraceae* and *Ruminococcaceae* (82). Besides the degree of saturation, chain length also determines the impact of fatty acids on the gut microbiota. Results from animal studies show that medium-chain fatty acids (7–12 carbons) increase the abundance of *Bifidobacterium*, *Bacteroides*, and *Prevotella* and decrease the abundance of *Clostridium histolyticum* or *Helicobacter* (119, 124–126). Long-chain fatty acids (13–18 carbons), on the other hand, alter the abundance of *Blautia*, *Clostridium*, *Coprococcus*, *Dialister*, *Lactococcus*, *Roseburia*, or *Bacteroides* (119, 127–129) in animal models. While a recent controlled feeding study in Chinese adults showed that adopting a higher-fat, lower-carbohydrate diet led to unfavorable changes in gut microbiota, fecal metabolomic profiles, and plasma proinflammatory factors (130), the fat type administered was primarily soybean oil, limiting conclusions about other types of dietary fat intake in humans. Indeed, there is currently a dearth of human interventions investigating the impact of amounts and different types of dietary lipids on the gut microbiota and associated metabolites, representing an important gap in the literature.

The benefits of ω-3 (n–3) fatty acids for central functioning range from enhanced memory, mood, attention, and cognitive performance to a reduced risk of developing depression and regulation of stress sensitivity (131–138). While most of these benefits can be linked to PUFA involvement in brain membrane structure, function and signal transduction, modulation of neurotransmitter turnover, neurogenesis, or anti-inflammatory and anti-apoptotic effects (139), the notion that PUFAs could be considered prebiotics (140) suggests another indirect mechanism through microbial alterations. Indeed, ω-3 fatty acids have been proposed to restore the eubiotic state in pathological conditions by increasing the beneficial bifidobacteria and decreasing enterobacteria, which in turn supports an anti-inflammatory environment through the production of SCFAs and suppression of endotoxemia (81, 141). This cascade of events in turn could have upstream effects on brain and behavior, specifically in inflammation-related disorders such as depression. Indeed, in an animal model, specific microbial changes (e.g., increased abundance of *Lactobacillus* and bifidobacteria and altered ratio of bifidobacteria to enterobacteria) associated with ω-3 fatty acid supplementation were closely related to changes in behavior (142).

Protein and amino acids

The source, concentration, and amino acid balance of dietary protein are primary factors influencing the composition, structure, and function of gut microbes. In human intervention studies, animal-based protein elicits a more pronounced effect on microbiota composition than plant-based protein (37). In mice, animal-based protein increases potential detrimental gut microbes, e.g., *Peptostreptococcaceae*, *Ruminococcaceae*, *Enterococcus*, *Streptococcus*, *Turicibacter*, or *Escherichia* (92), and plant-based protein boosts the abundance of *Bifidobacterium*, *Roseburia*, and *Lactobacillus* and lowers the abundance of pathogens such as *Bacteroides fragilis* and *Clostridium perfringens* (37, 42, 80). More specifically, the different sources of animal-based protein have been associated with distinct changes in the relative abundances of specific bacteria. For example, using rats and in vitro studies with human fecal inoculum, it was demonstrated that chicken protein could increase *Actinobacteria*, *Bifidobacterium*, and *Bacteroides*, whereas beef protein was linked to elevated levels of *Proteobacteria* and *Oscillibacter* and decreased *C. perfringens* and *C. histolyticum* (93, 94). Additionally, different amounts of protein intake have varying effects on microbial abundance. In a piglet model, reduction of protein concentration in the diet resulted in decreased bacterial richness and *Clostridium_sensu_stricto_1* abundance, whereas *Escherichia–Shigella* abundance increased and moderate protein restriction was associated with elevated *Peptostreptococcaceae* (143). Lastly, microbial metabolites are also affected by the amount of protein consumed. Switching to a high-protein, low-carbohydrate diet reduces the abundance of butyrate-producing bacteria and increases colonic protein fermentation and metabolites detrimental to health, such as branched-chain fatty acids (BCFAs) and concentrations of phenylacetic acid and *N*-nitroso compounds (121).

Micronutrients

Vitamins and minerals.

Vitamins and minerals are important cofactors in the synthesis and metabolism of neurotransmitters as well as in the energy metabolism of neurons. It is well appreciated that the gut microbiota can synthesize certain vitamins, most notably vitamin K and B-group vitamins [e.g., cobalamin (B_{12}), folate, and riboflavin (144, 145)], some of which might be directly absorbed. Because vitamins and minerals are mostly absorbed in the upper gastrointestinal tract and usually only small amounts will reach the colon (146), studying the impact of these nutrients on the colonic microbiota in humans is challenging and some inconsistent results have been reported (147). Nevertheless, there is now accumulating evidence that the vitamins that reach the distal colon can serve as an important nutrient source for resident microbes (148). A recent systematic review summarizing the evidence available from human and animal studies on the impact of vitamin D on the gut microbiota suggests that vitamin D status or supplementation can modulate microbiota composition; but with inconsistent data, especially from human studies, no trend is emerging yet (147). Although the current state of the literature does not allow us to draw conclusions on the influence of vitamins on specific taxa, their bidirectional relation has been suggested to play a key role in maintaining the abundance of symbionts as well as overall intestinal homeostasis (149–151). For example, the synergistic effect between vitamins D and A and the microbiota could be important in the regulation of immune function and maintaining intestinal barrier function (150, 152).

Similar to vitamins, minerals and trace elements actively interact with the gut microbiota in a symbiotic relationship (153). Because many gut bacteria require minerals for growth and survival (154), both deficiencies and excesses in some minerals have been linked to microbial imbalances and increased proliferation and fitness of pathogenic microbes (155). For example, iron supplementation in a cohort of Kenyan children increased the abundance of pathogens such as *Bacillus cereus*, *Staphylococcus aureus*, *Clostridium difficile*, *C. perfringens*, and *Salmonella*, potentially contributing to gut inflammation (156), whereas other studies have demonstrated beneficial or no effects of excess minerals on the microbiota composition in humans (157). Thus, more studies are needed to decipher the impact of differing mineral states on the microbiota, especially in healthy populations.

Polyphenols.

The phytochemical class of polyphenols broadly encompasses flavonoids (i.e., flavanones, isoflavones, anthocyanidins) and nonflavonoids (i.e., stilbenes, lignans, and tannins). Polyphenol-rich foods include fruit and vegetables, cocoa, spices, whole grains, nuts, and extra virgin olive oil, as well as beverages such as red wine, coffee, and green tea (158). Approximately 90–95% of polyphenols are not absorbed and thus can be degraded by intestinal microbes (83). Many health benefits have been associated with the consumption of polyphenols, including neuroprotective effects, mainly through their anti-inflammatory and antioxidative properties (159, 160), improved cognitive performance in an elderly population (161) and healthy young adults (162), as well as attenuated corticosterone and proinflammatory cytokine release and alleviated depressive-like behavior in animal models (163). Emerging observational studies have reported an association between increased dietary intake of polyphenols and lower rates of depression (164, 165). For example, a prospective analysis of the Nurses' Health Study ($n = 82{,}643$ women) reported that total and subclasses of polyphenols found in citrus fruit were associated with a lower incidence of depression (164). A recent animal study of early life stress also showed improved depressive- and anxiety-like behavior and reduced corticosterone levels while also modulating microbial diversity and composition, specifically in microbes associated with microbiota–gut–brain axis pathways (166). Thus, changes in the microbiome might be an underlying mechanism whereby polyphenols improve mental health. In a recent human intervention study, flavonoid-rich orange juice reduced depressive symptoms significantly compared with flavonoid-low orange cordial and enriched bacterial genera belonging to the *Lachnospiraceae*, *Bifidobacteriaceae*, and *Bacteroidaceae* families (167). Interestingly, the abundance of *Lachnospiraceae_uc*, which was positively correlated with the serum brain-derived neurotrophic factor (BDNF) concentration (which is often decreased in patients with major depression disorder and contributes to the effectiveness of antidepressants) in the depressed cohort, increased after the flavonoid treatment (167). Thus, it could be suggested that increased flavonoid consumption elevated the abundance of *Lachnospiraceae_uc*, which in turn restored BDNF levels and reduced depressive symptoms.

A vast body of animal and in vitro literature is available thematizing the effect of polyphenols on the microbial community (4). Fewer data are available from human cohorts and most studies investigated the impact of whole foods containing polyphenols rather than individual phenolic compounds (4). Polyphenols display a "prebiotic-like" effect, increasing the growth of beneficial bacterial strains, such as bifidobacteria and lactobacilli, while reducing the number of potential pathogens, such as *C. perfringens* and *C. histolyticum* in a dose-dependent manner (83, 84). Some common bacterial changes can be observed with polyphenols, but specific microbes can also be associated with specific phenolic compounds. *Bacteroides*, *Clostridium*, and *Staphylococcus* species were reported to decrease and the *Prevotella* group, *Blautia* and *Faecalibacterium prausnitzii* increase with cocoa (mainly flavonols) consumption (85), whereas coffee polyphenols [i.e., phenolic acids (chlorogenic acids)] were directly associated with the abundance of *Bacteroides* and high coffee consumption resulted in higher levels of *Bacteroides–Prevotella–Porphyromonas* in an observational study (86). Red wine (especially rich in resveratrol, a stilbene) was associated with increased α-diversity and *Barnesiella*, *Phascolarctobacterium*, and *Prevotellaceae*_NK3B31 abundance (87). Microbial metabolism of curcumin, a lipophilic polyphenol found in turmeric, resulted in metabolites with antioxidant, anti-inflammatory, and neuroprotective properties as well as promotion of beneficial bacterial strains (168).

Sweeteners.

Artificial (e.g., aspartame and saccharine) and natural (e.g., stevia) nonnutritive sweeteners are now commonly used in the food industry to reduce the amount of sugar present in food. Due to the known impact of diet on the gut microbiota, an increasing number of studies are investigating the consequences of the intake of sweeteners on the gut microbiota composition (for detailed reviews refer to 169, 170). Although earlier human studies indicated detrimental effects on microbial diversity and composition (99, 100) and a more recent study linked consumption of nonnutritive sweeteners to a "dysbiosis" [an increasingly redundant term in microbiome research (171)] and a decrease in butyrate concentration (172), some reports have concluded that no clear effects of sweeteners on the microbiota can be established (170) or that only some sweeteners (e.g., saccharin, sucralose, and stevia) impact the microbial profile (173). Thus, specific effects on the microbiota are still being elucidated and most likely depend on the chemical attributes of the different sweeteners and the concentration that reaches the colon (169). For example, aspartame and saccharine are mostly degraded and absorbed in the upper intestinal tract, whereas it has been estimated that 85% of sucralose can reach the colon, and steviol glycosides (i.e., stevia) arrive in the colon intact and require bacterial metabolism (169).

Sucralose (i.e., Splenda) administration has been reported to elicit microbial changes (e.g., decreased total bacterial abundance; increase in *Firmicutes*, *Proteobacteria*, *Turicibacter*, *Roseburia*, *Akkermansia*, *Clostridiaceae*, *Christensenellaceae*, and *Clostridium symbiosium*; decrease in *Ruminococcus*, *Streptococcus*, *Dehalobacterium*, *Erysipelotrichaceae*, and bifidobacteria), specifically in animal models (101–103). Interestingly, some of these microbial alterations have been proposed to induce some of the negative health effects associated with the consumption of sweeteners, such as glucose intolerance (100) and chronic inflammation (101). In a small human study with healthy volunteers, however, short-term intake of sucralose did not elicit major changes in the gut microbiota composition (104). Some of these discrepancies could be attributed to the limited metabolism of sucralose by the microbiota (174) and different dosages of sucralose, as well as the duration of sucralose exposure.

Despite possessing antibacterial and antifungal properties and being metabolized by microbial enzymes, mostly from the *Bacteroides* group (175, 176), only a limited number of studies have investigated the effect of stevia, or its main chemical compound, steviol glycoside, on the gut microbiota. In vitro studies suggest that steviol glucoside could inhibit the growth of probiotic bacteria such as *Lactobacillus reuteri* (105), but could also exert bacteriostatic effects on pathogens such as *E. coli* (177); however, another in vitro experiment did not find alterations in diversity or composition after incubation with steviol glycosides (106). Evidence from human trials is lacking, but a recent rat study showed that low-dose stevia (Rebaudioside A) consumption over 9 wk starting from early life reduced members of *Bifidobacteriaceae* and *Lactobacillus intestinalis* and increased abundance of *Bacteroides thetaiotaomicron* and *Akkermansia muciniphila*. Interestingly, the stevia intervention also seemed to impact appetitive behavior through the mesolimbic reward system, as evidenced by a reduction in tyrosine hydroxylase and dopamine transported in the nucleus accumbens (178).

Emulsifiers.

Emulsifiers [carboxymethylcellulose (CMC), polysorbate-80 (P80), arabinogalactan, carrageenan] are food additives that are highly prevalent in the Western diet and commonly used to alter the flavor and improve the texture, stability, and shelf life of foods. Mostly negative effects of emulsifiers on both host physiology and gut microbiota have been demonstrated using animal models (179), and it has even been suggested that microbial alterations induced by emulsifiers could contribute to chronic inflammatory diseases, including obesity, metabolic syndrome, gut inflammation, and colon cancer, potentially by promoting pathogen translocation (107, 108). Importantly, it has been shown that emulsifier consumption by germ-free (GF) animals (107) and animals with a highly restricted microbiota (180) did not elicit the same detrimental health effects, suggesting that microbial modulation may be required for the adverse effects of emulsifiers on host health. Some specific, potentially sex-dependent, microbial changes have been linked to emulsifier consumption in mice, such as increased *Porphyromonadaceae*, *Helicobacter*, *Campylobacter jejuni*, *Salmonella*, and *Clostridium* cluster XI as well as a decrease in *Bacteroides* abundance (181). In female mice, CMC increased *Anaeroplasma* and P80 increased the relative abundance of the *Proteobacteria*, *Clostridium*, and *Burkholderia*, whereas in male mice CMC enriched *Dorea* abundance and P80 treatment enriched *Bacteroides*, *Burkholderia*, *Clostridium*, and *Veillonella* abundance (109).

Food groups

Fruits and vegetables.

The impact of individual food groups on the gut microbiota, including fermented foods, fruit and vegetables, and nuts, has also been an area of investigation. A detailed review of the effects of individual fruit and vegetables on the gut microbiota has recently been provided (16). Several human and animal studies have indicated that consumption of fruit and vegetables leads to increased microbial diversity and function, a shift in the abundance of bacterial phyla, growth of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*, and reduction in potentially harmful bacteria, including *E. coli* and *Enterococcus* (51–55). Some of these benefits could be associated with so-called microbiota-accessible carbohydrates (MACs), such as oligosaccharides, pectin, cellulose, inulin, lignans, and resistant starches, as well as polyphenols, which are biotransformed by certain bacteria, and may inhibit the growth of pathogenic bacteria and stimulate beneficial bacteria, as described in detail above in *Polyphenols* (16).

Nuts.

Similarly, nuts, which are commonly consumed in plant-based diets as well as the Mediterranean diet, are rich in nutrients such as fiber, unsaturated fatty acids (e.g., PUFAs), and bioactive compounds [e.g., antioxidants (tocopherols), polyphenols, and phytosterols] with a potential prebiotic effect on the microbiota composition (60, 182, 183). A recent systematic review and meta-analysis of randomized controlled trials on the effect of nut consumption on gut microbiota concluded that nut consumption shapes the microbiota at the genus level (e.g., increases in *Clostridium*, *Dialister*, *Roseburia*, and *Lachnospira*, decrease in *Parabacteroides*); however, the specific effects depend on the type and amount of nut consumed and the duration of the intervention (184). For example, in a randomized, controlled, crossover study, daily consumption of 42 g of walnuts for 3 wk in healthy volunteers increased the relative abundances of *Firmicutes* genera, including some butyrate producers (e.g., *Faecalibacterium* and *Roseburia*) as well as *Clostridium* and *Dialister* (61). On the other hand, an 8 wk intervention with 56.7 g of almonds in young adults revealed an increase in α-diversity measures and a decrease in *B. fragilis* abundance (62).

Pulses.

Pulses, which include beans, lentils, and chickpeas, are the edible seeds from legume plants. This food group often serves as a protein source in plant-based diets and is also rich in folate, iron, PUFAs/MUFAs, and specific phytochemicals, as well as dietary fiber. This nutritional content of pulses was also associated with changes in the gut microbiota composition and metabolite production. A recent systematic review concluded that significant changes can be observed after pulse consumption, but that results are inconsistent, especially in humans (185). For example, higher percentages of *Bifidobacterium* sp. and *Lactobacillus casei*/*L. bifermentum* sp. and lower percentages of *Clostridium* cluster XI and I/II were associated with chickpea intake in humans (186), whereas pinto beans had minimal effects in a population with premetabolic syndrome, only lowering the abundance of *Eubacterium limosum* (187). More pronounced changes were observed with extracted pulse flour in animal models. In mice, navy bean and black bean flours increased the abundance of *Prevotella*, S24–7, and *Ruminococcus flavefaciens* and SCFA production, and decreased the abundance of *Ruminococcus gnavus*, *Oscillospira*, *Coprococcus*, *Lactococcus*, *Streptococcus*, *Coprobacillus*, *Parabacteroides*, *Adlercreutzia*, and others compared with the basal diet. Some bean-specific changes were also observed, with black bean flour increasing α-diversity and navy bean flour decreasing the abundance of the potential pathogen *C. perfringens* (188).

Fermented foods.

Fermented foods (including sauerkraut, kimchi, kefir, dry fermented sausage, yogurt, cheese, kombucha, and miso), defined as foods or beverages produced through controlled microbial growth, containing both probiotic microbiota (most commonly *Lactobacillus*, *Streptococcus*, *Lactococcus*, and *Leuconostoc*) and yeast as well as microbial metabolites (189, 190), have been consumed by humans for centuries; however, their popularity has recently surged, leading to new investigations into their effect on host microbiota and health, including mental health (191, 192). Unsurprisingly, the ingestion of "living" fermented foods, increasing the numbers of microbes in the diet $\leq$10,000-fold, has the potential to modulate the intestinal microbial profile (193, 194). For example, significant increases in *Bifidobacterium* abundance were observed after kimchi consumption in obese women (56) and fermented soybean milk resulted in a decrease in coliform organisms and *C. perfringens* as well as increases in *Bifidobacterium* and *Lactobacillus* (57). In a recent mouse study, kefir administration increased the abundance of *L. reuteri*, *Eubacterium plexicaudatum*, and *Bifidobacterium pseudolongum*, and decreased *Lachnospiraceae bacterium* 3_1_46FAA, *Propionibacterium acnes*, and *Bacillus amyloliquefaciens*, and shifted the functional potential of the gut microbiota toward the production of neuroactive metabolites (58). In another recent human study, consumption of a fermented dairy drink for 4 wk increased the abundance of a few specific genera (e.g., *Holdemania*, *Gordonibacter*, *Lactobacillus*, an unclassified *Mollicutes* (RF-9), and two unclassified genera from *Clostridiales*), and enriched some functions of the resident microbes (195). Despite these promising results, a recent literature review concluded that not enough data are available yet to make inferences on any specific microbial patterns associated with a particular fermented food (196). The discrepancy could be attributed to variations in microbial composition between fermented products in a way that is difficult to predict. Nevertheless, larger clinical trials are needed to further decipher the impact of fermented food on resident microbes and health outcomes (196). In this effort, another recent study analyzing samples from 115 individuals in the American Gut Project showed that people who consumed fermented plants 1 or 2 times per week or once per day had a dose-dependent, significantly different gut community measured by β-diversity compared with nonconsumers. Additionally, an association between fermented food consumption and abundance of bacterial taxa (e.g., *Bacteroides*, *Pseudomonas*, *Dorea*, *Prevotella*, *Oscillospira*, *F. prausnitzii*, *Lactobacillus* spp.) as well as microbial functional profile was reported (59).

Whole diet

Although understanding the impact of single nutrients on microbiota composition has led to valuable advances in our understanding of the diet–microbiota interaction, it has been suggested that the diet should be considered as a whole, which is more reflective of general food consumption patterns and considers the potential synergistic or additive effects from nutrient interactions on the microbiota composition (197). Therefore, studies have started to profile the microbiota associated with certain dietary patterns, which are reviewed below.

Mediterranean diet.

The Mediterranean diet, characterized by high intake of fruits, vegetables, legumes, nuts, olive oil, and fish, and low consumption of red meat, dairy products, and saturated fats (198), has been well known for various health benefits, including mental health and cognition (199–202). More recent human intervention studies also support the beneficial impact of a Mediterranean diet on microbiota profiles. Greater microbial diversity as well as higher abundance of health-promoting bacterial taxa (i.e., *Clostridium* cluster XIVa, *F. prausnitzii, Roseburia*, *Eubacterium*, *B. thetaiotaomicron*, *Parabacteroides distasonis*, *Bifidobacterium adolescentis*, and *Bifidobacterium longum*) have been associated with consumption of the Mediterranean diet (38–40). Additionally, adherence to a Mediterranean diet was linked to beneficial microbiota-related metabolomic profiles, such as increased levels of SCFAs and reductions in BCFAs, bile acids, and trimethylamine *N*-oxide (TMAO) (38, 40, 41).

Plant-based diets.

Plant-based diets, including vegetarian and vegan diets, are dietary patterns rich in fruit, vegetables, legumes, nuts, and seeds; they may include seafood but are free of animal

products, including meat, eggs, and dairy products. Although the specific microbial composition depends on the degree of adherence to a plant-based diet, generally favorable microbial patterns have been observed. Important evidence was specifically provided by earlier studies comparing the microbiota composition from children living in Burkina Faso (largely vegetarian diet) with those living in Italy consuming a typical Western diet (43). Higher microbial richness and biodiversity was observed in children living in Burkina Faso. More specifically, these children had a microbial profile specialized for indigestible polysaccharide metabolism, enriched in *Bacteroidetes* and *Actinobacteria*, with *Prevotella*, *Xylanibacter*, and *Treponema* exclusively represented in their microbiota compared with children from Italy. On the other hand, *Firmicutes* and *Proteobacteria* were more abundant in Italian children, with an overrepresentation of *Enterobacteriaceae* (e.g., *Shigella* and *Escherichia*). In adults, a study comparing the microbiota from people living in rural Africa with that of African Americans living in the USA also revealed that the largely vegetarian diet in rural Africa was associated with predominance of *Prevotella*, *Succinivibrio*, and *Oscillospira*, and increased total and butyrate-producing bacteria, whereas the microbiota of African Americans was enriched in potentially pathogenic bacteria such as *Escherichia* and *Acinetobacter* (44). Although these differences could also be attributed to other environmental factors, studies comparing vegetarians with nonvegetarians revealed similar microbial profiles. Thus, characteristic patterns in the gut microbiota for these types of diets include high bacterial richness, increased numbers of *Bifidobacterium*, *Lactobacillus*, *Ruminococcus*, *Eubacterium rectale*, *Roseburia*, *Prevotella*, *F. prausnitzii*, and *Anaerostipes*, but lower abundance of *Clostridium sensu stricto*, *C. perfringens*, *C. histolyticum*, and *Odoribacter* (42, 45–49). Nevertheless, the data regarding the impact of plant-based compared with animal-based diets on the microbiota are still not conclusive, as evidenced by a human study indicating that the microbial composition was only modestly different between vegans and omnivores (110). However, considerable variations were observed in the bacterial metabolome, suggesting that diet as a substrate may play a larger role in determining microbial metabolite production than in the microbial composition itself. Indeed, in humans omnivorous, vegetarian, or vegan diets are related to differential microbial synthesis of proteins and metabolites; vegetarian and vegan diets were associated with higher levels of enzymes involved in tumor suppression, whereas omnivores had the highest levels of detrimental microbial metabolites, such as phenolic and indole derivatives, and TMAO (50).

Western diet.

It is generally accepted that a Western, omnivore-type diet, high in saturated fat, animal protein, and refined carbohydrates but inadequate amounts of dietary fiber shifts the composition of the microbiota to a more disease-associated type (203). Long-term consumption of a Western diet in humans and animals can lead to the extinction of beneficial microbes, decrease bacterial diversity, and drive the microbiota to a predominant *Bacteroides*-driven enterotype (13, 14, 116, 88). Likewise, an increased *Firmicutes:Bacteroidetes* ratio (41) and decreases in protective SCFA-producing bacteria (e.g., *F. prausnitzii*) (89, 204) are often observed. More recently, a small pilot crossover study in humans showed a detrimental impact on the gut microbiota and associated metabolites within 4 d of adopting a Western-style diet, with increases in bile-tolerant microbes, including *Collinsella*, *Parabacteroides*, and *B. wadsworthia*, as well as increases in TMAO and decreases in the metabolites indole-3-lactic acid and indole-3-propionic acid (205). Similar to the Western diet, high-fat diets in animal studies reproducibly change gut microbial community structure, decreasing the overall microbiota diversity and beneficial bacteria (e.g., *A. muciniphila*, *Bifidobacterium*, *Lactobacillus*, and *Lactococcus*) and increasing the *Firmicutes:Bacteroidetes* ratio and the abundance of *Enterobacteriales*, *Clostridium* cluster XVIa, *Mollicutes*, and *B. wadsworthia* (90, 91, 206).

Ultraprocessed foods (sugary beverages, snacks, and fast foods), a hallmark of the Western diet, are formulations ready for consumption, made from refined substances, are calorie-dense, and rich in saturated fat, with added simple sugars, salt and other additives; they are consistently associated with poor health outcomes, including depression (207). These food components are detrimental to the microbiota and some studies have described consequences of ultraprocessed food consumption for gut microbial composition (208). For example, the abundance of *Dialister*, *Coprococcus*, *Megasphaera*, *Oscillospira*, and *Blautia obeum* seemed to be most abundant in relation to the intake of processed food in humans (209). There is also increased concern due to the rising prevalence of children consuming these ultraprocessed foods and the ramifications in the child's development, including the microbiota, as links between ultraprocessed food consumption and microbiota composition have been reported. For example, members of the *Lachnospiraceae* family (related to *Clostridium clostridioforme*, *C. bolteae*, *C. celerecrescens*, or *C. sphenoides*), *Ruminococcus*, and *Bacteroides* were negatively associated with processed food groups (e.g., processed meat and savory snacks), whereas *Lachnospiraceae* (*Fusicatenibacter saccharivorans*), *Blautia*, and *Clostridium* were positively associated with processed food consumption in children (210).

Impact of Microbiota on the Brain and Behavior

In the past decades, the microbiota has emerged as a key player in regulating brain processes and behavior, via a bidirectional communication referred to as the microbiota–gut–brain axis (2). In particular, studies using GF animals that demonstrated aberrant behavior and neurochemical profile were critical in establishing the link between the gut microbiota and brain development and processes (211–217). In addition, the microbiota plays numerous essential roles

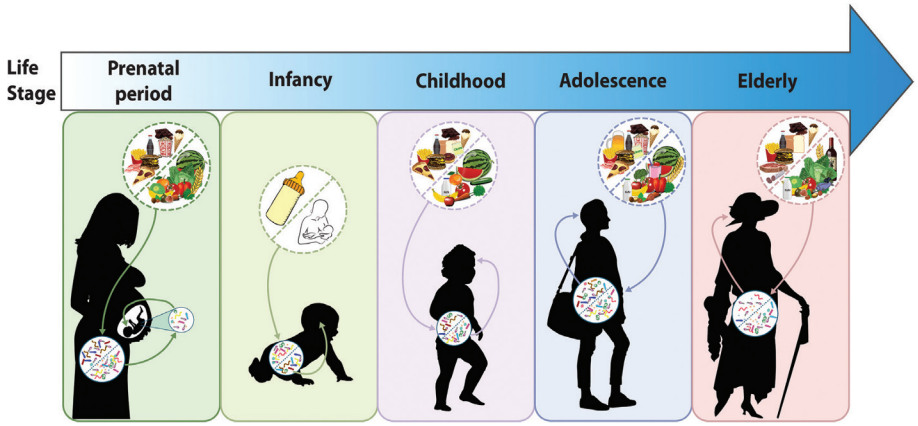

FIGURE 1 Diet and the microbiota–gut–brain axis at the extremes of life. Diet could influence the microbiota–gut–brain axis across the lifespan. During the prenatal period, maternal diet influences cognitive development of the offspring, potentially through some microbiota-mediated mechanisms. In infancy, breast or formula feeding majorly impact the microbiota composition. Emerging research is suggesting that this could affect brain and behavior. The timing of the "weaning response" could be important in driving the development of the microbiota–brain interaction. Continued development of the microbiota–gut–brain axis during childhood and adolescence could mark additional sensitive periods during which healthy dietary intake might be important for proper development of the axis. In elderly individuals the microbiota again undergoes changes, which could be driven partly by dietary intake. These changes in microbiota could be linked to frailty, "inflamm-aging" and cognitive function.

in normal neurodevelopment as well as the development of the hypothalamic–pituitary–adrenal (HPA) axis to regulate stress responses in animal models (218, 219). Establishing direct links between the gut microbiota and brain function in humans is more difficult and of correlational nature. In a recent human brain imaging study, correlations were made between gut microbiota composition and brain activity patterns in patients with amnestic mild cognitive impairment (220). Additionally, correlations have been established between the abundance of specific bacterial taxa and disease symptoms, such as autism spectrum disorder (ASD) (221).

Additional evidence for the microbiota–brain connection comes from both animal and human studies linking the direct administration of beneficial microbes, probiotics, to behavioral and cognitive changes in the host. Animal studies have demonstrated that administration of probiotics (e.g., *Lactobacillus plantarum*, *L. rhamnosus*, *B. longum*) can have anxiolytic and antidepressive effects (222, 223) and can impact aspects of cognitive function (224). Similarly, recent meta-analyses and systematic reviews reported promising, although preliminary, evidence for the potential of probiotics to improve anxiety, depression, and subjective stress in human populations (225–228). On the other hand, another recent meta-analysis and systematic review concluded that the current evidence from human trials does not support the efficacy of probiotics, prebiotics, and fermented food in affecting cognitive function, although the quality and quantity of the available data limit firm conclusions (229); for example, there is lack of studies investigating the same strain of probiotic or type of prebiotic, and probiotic- and prebiotic-specific effects are often observed.

Diet Microbiota–Gut–Brain Axis at the Extremes of Life

Microbial colonization of the intestinal tract is a successive process throughout the course of life. Especially in the first years of life the microbial community is dynamic and some bacteria that become part of the adult microbiota already colonize the gut during the first months of life (230–232). Although continued development of the microbiota in adolescence has been indicated in some studies, a core, albeit individualized, microbial profile develops in adulthood that is relatively stable and resilient in the absence of extreme external stressors (e.g., dietary changes or antibiotic treatment) (233–235). With increasing age, the microbiota can become more fluid once again, which is associated with frailty and accelerated aging (23, 233, 236). Several factors are known to influence microbial composition at different stages of life, including genetic factors, mode of delivery [vaginal birth or Caesarean section (C-section)], gestational age, exercise, medication use, living environment, and diet (237–240). There is increasing interest in studying the effect of dietary manipulation of the microbiota–gut–brain axis at different stages of life (241). Here, we provide a brief overview of existing evidence of the diet–microbiota–gut–brain axis from the prenatal period to the elderly. A graphical representation is provided in **Figure 1**.

Prenatal period

During the prenatal period, maternal factors, including diet, not only influence the offspring's microbial profile but may also exert lasting effects on infant cognition and behavior. Adequate maternal nutrition is key to the development of the growing fetus and nutrient inadequacies are established causes for neurological abnormalities (e.g., low folate intake

and neural tube defect). Likewise, in nonhuman primates, an unhealthy diet during pregnancy has been linked to poorer cognitive outcomes, enhanced stress responses, and behavioral disruptions in the offspring (242), and human observational studies also link maternal diet during pregnancy to child emotional and cognitive outcomes (243). In recent years, evidence from animal models suggests that the gut microbiota could be an underlying factor linking maternal diet to neurodevelopment (244–246). Investigations into the effect of high-fat or Western diets revealed that some diet-induced shifts in the microbial profile mediated behavioral and cognitive impairments in the offspring (244–246), while very recent experimental data show that maternal microbial modulation of brain development may occur via the action of microbial metabolites (247).

At birth, neonates are exposed to the first large number of microbes that colonize the gastrointestinal tract and differences in the microbiota composition based on birth mode have been reported. Thus, naturally born infants are exposed to the mother's vaginal bacteria, whereas babies born by C-section are first introduced to bacteria of the mother's skin, the hospital environment, or the healthcare workers (237). Although these differences can dissipate a few weeks or months after birth (248), it has been suggested that some microbes acquired during the first years of life will be important residents of the adult microbiota (249). Likewise, some other studies suggest that the impact of C-section on the microbial profile can last up to age 4 (250). These microbial alterations (e.g., depletion in *Bifidobacterium*) associated with C-section delivery could have permanent effects on behavior and cognition; however, some of these microbial and behavioral alterations could be reversed by supplementation with a prebiotic mixture (galactooligosaccharide, fructooligosaccharide), suggesting that microbiota-targeted diet interventions could be used to alleviate some of the negative effects associated with C-section (251).

Infancy

Critical windows or sensitive periods during brain development, in which the microbiota can have long-lasting effects on behavior, neurochemistry, and brain morphology, have been identified in animals (219). Animal studies have shown that this early exposure to microbes is essential for neurodevelopment and that some behavioral effects related to a missing or altered microbiota cannot be reversed later in life or can only be reversed during a specific period of time (218, 245, 252). Thus, there is a growing emphasis on the diet–microbiota–gut–brain axis in early life. Indeed, the first 1000 d has been seen to be critical for programming later health, including brain health (253).

Following birth, colonization of the infant gut is majorly determined by the early feeding mode, with distinguishable microbial compositions between breast- and formula-fed infants (254, 255). Generally, breast-fed infants harbor a less diverse and species-rich microbiota that is dominated by *Bifidobacterium* species, whereas the microbiota of formula-fed infants is functionally more similar to that of an adult and is often enriched in microbial taxa such as *Klebsiella*, *Enterococcus*, *Peptostreptococcaceae*, *Akkermansia*, *Veillonella*, and *C. difficile* (256, 257). Thus, various intrinsic factors of breast milk influence the developing microbiota. Human milk harbors a unique microbial community, including commensal, mutualistic, and probiotic bacteria, some of which can be found as first colonizers of the neonatal gut (258, 259). Additionally, prebiotic human milk oligosaccharides (HMOs) can be fermented by the resident microbes, promoting the growth of beneficial bacteria (260). Although other bioactive compounds present in breast milk, such as immunoglobulins, antibodies, antimicrobial peptides, and lactoferrin, can have microbiota-independent benefits for the infant, mediation of health benefits [such as lower incidence of immune and gastrointestinal diseases, obesity, and type 2 diabetes, as well as improved cognitive function (261, 262)] through the assembly of a healthy microbiota has been suggested (263–265). While the composition of the infant gut microbiota at a young age has been associated with subsequent cognitive development and behavioral outcomes later in infancy (266, 267), whether these relations are mediated by breast-feeding and early dietary intake is still being investigated. Supplementation with oligosaccharides from birth in a mouse model modulated the microbiota composition and diversity, increased saccharolytic and decreased proteolytic fermentation while also resulting in improved social and anxiety-like behavior (268), suggesting that consumption in early life of prebiotics, such as HMOs, supports normal neurodevelopment by altering the microbial richness, composition, and enzymatic activity. Although human data are limited to date, the relative abundance of the dietary fiber-linked *Prevotella* in infants at 12 mo was recently associated with child behavioral dysregulation at 2 y of age (269).

Additionally, the timing of weaning or introduction of solid foods has been studied as an important factor for the proper development of the microbiota–host interaction, specifically the immune system, a key pathway of the gut–brain communication. Altering the timing of weaning could result in a pathological imprinting of the immune response and increased susceptibility to later immunopathologies (270). In piglets, early weaning stress impairs intestinal barrier function (271) and increases inflammation (272) and oxidative stress (273). In human studies, early introduction of solid food was associated with a higher risk of obesity (274, 275) or immunological diseases (276). Due to the known profound effects of the microbiota on host development, accelerated maturation of the gut microbiota has been proposed as a contributing pathway to the detrimental effects of early weaning on host processes (275). Indeed, animal studies demonstrated that early exposure to some dietary components shifted the microbiota composition, which could favor systemic inflammation and influence the brain, such as altering blood–brain barrier (BBB) permeability (277).

Childhood and adolescence period

Encouraging healthy eating habits during childhood and adolescence is crucial for developing healthy eating in adult life (278, 279), thereby laying a foundation for overall well-being and the establishment of a healthy, mature microbiota. Microbiota underdevelopment due to inadequate nutrition can have overarching consequences. Transfer of fecal samples from undernourished children to GF mice elicited metabolic and immune dysregulations in the mouse model similar to those observed in the human host, suggesting that the manifestations of malnutrition could in part be attributed to the absence of certain beneficial microbes (280). Besides physiological repercussions, an immature microbiota as a consequence of undernutrition in early childhood has been proposed to be causally related to neurological abnormalities (281). Supplementing children with moderate acute malnutrition with a microbiota-directed complementary food prototype shifted the microbiota as well as markers of neurodevelopment toward that of healthy children, indicating that the immature microbiota is causally linked to unhealthy growth and development, but can be rescued by microbiota-targeted food therapy (282).

Although it was previously believed that, with the introduction of solid foods, the microbiota is "matured" and resembles that of an adult, some studies suggest that it undergoes additional development during adolescence (283, 284). Adolescence is also a critical time period for neuroanatomical change and maturation, which translates into behavioral development, including cognitive function, social cognition, and executive function (285, 286). These extended maturations can pose an additional sensitive period for microbial priming of the maturing adolescent brain and provide opportunities to improve adolescent mental well-being (219, 287). Thus, dietary intake could be an important driver of healthy microbiota–brain communication. Unhealthy eating or dieting with failure to meet recommended intake of fruits and vegetables and excess intake of fat or high-sugar foods and drinks can be characteristic of the adolescent period (288–290). Findings from human cohorts point to the importance of adequate nutrition and diet quality for adolescent brain and mental health (291, 292). Although the interplay between diet, gut microbiota, and the brain during this period of development is largely unstudied, one study demonstrated that ω-3 fatty acid and vitamin A supplementation reversed microbial disturbance and impairments in novel object recognition, as well as alterations in hippocampal and prefrontal cortex BDNF levels elicited by social instability stress in an animal model (293). In a mouse model of adolescence, exposure to a cafeteria diet for 21 d resulted in decreased species evenness (measured by the Shannon diversity index) and abundance of *Roseburia*, *Turicibacter*, and *Enterorhabdus*, and, although no behavioral manifestations were observed, altered gene expression involved in neuroimmunity and neurotransmission in the prefrontal cortex and amygdala (294).

Elderly

At the other extreme of life, in elderly populations, the microbiota again undergoes a shift, affecting aspects of host health such as frailty, inflammatory status, and cognitive function (233, 234). In general, microbial diversity decreases and numbers of beneficial bacteria (bifidobacteria, lactobacilli, *Clostridium* cluster XIVa, *F. prausnitzii*) reduce, whereas facultative anaerobes and opportunists or even proinflammatory pathogenic bacteria (*Escherichia* spp., *Enterobacteriaceae* spp., *Bacteroides* spp., *C. difficile*, etc.) increase when compared with younger individuals (235, 295, 296). Diseases of cognitive decline, such as Alzheimer's disease and vascular dementia, are associated with aberrant microbial compositions when compared with healthy controls (297). Geography, living situation (long-term care facility or community), medication use, and other environmental factors, such as diet, can play a major role in the microbe–health interaction in the elderly. The well-established notion that a healthy diet is fundamental in preserving cognitive health (298) could thus partly be mediated by the association between diet, microbiota, and inflammation. Investigations into understanding these interactions are emerging. In an animal study, shifting the microbiota composition with inulin supplementation was able to reverse neuroinflammatory impairments associated with middle age (299). In the human European Project on Nutrition in Elderly People (NU-AGE) cohort, adherence to the Mediterranean diet in elderly subjects was associated with microbial taxa that were positively correlated with markers of healthy aging, including improved cognitive function (300). Thus, understanding how diet can be used to positively manipulate the microbiota and inflammation in advanced age could be an avenue to preserving cognitive performance.

From the existing literature, a clear interaction between diet and the microbiota–brain communication across the lifespan emerges. As an increasing number of studies are investigating this interplay, new findings will inform the development of early-life intervention strategies to minimize the detrimental effects of microbial disruptions on neurodevelopment and adolescent brain maturation and aid in guiding nutritional therapies for the elderly population to maintain cognitive and mental health.

Using Whole-Diet Approaches to Manipulate the Gut Microbiota and Behavior

Research in the last decade has shed light on the importance of adequate nutrition for mental health. There are now extensive observational data across many different countries and cultures linking healthy dietary patterns to a reduced risk of common mental illnesses, particularly depression (202), while emerging trial data show that improving dietary habits can improve depressive symptoms (301). Although the Mediterranean diet is the dietary pattern most studied in regard to health outcomes, including mental health (201), traditional dietary patterns from many parts of the world (e.g., the Norwegian and Japanese diets) also show protective associations (302, 303) and are correlated with reduced

risk of developing depression or Alzheimer's disease as well as a general slowing of cognitive decline (201, 304). On the other hand, poor dietary habits (such as the Western-style diet), intake of low-quality, processed, or high-fat/sugar foods and malnutrition (over- and undernutrition) can be related to poorer mental health (305, 306), impaired cognitive function (298), and increased risk of developing anxiety (307), depression (292, 308, 309), or other mental illnesses. These associations are observed across the age range, including in early adolescence, which represents the primary age of onset for mental disorders (292, 310).

Increasingly, mechanisms underlying this diet–brain connection are being deciphered. While the effects of probiotics and prebiotics on the microbiota and mood or cognition have been more widely studied (12), investigations into whole-food and diet approaches are scarce. A recent review has highlighted the benefits of whole fruit and vegetables, mostly attributed to their polyphenol and MAC content, on the microbiota and associated diseases, such as obesity and colonic inflammation (16). While some evidence from preclinical studies shows the triangular relation between diet, microbiota, and brain/behavior, similar studies in human populations are lacking and most clinical studies investigating the effect of diet on anxiety, depression or cognition did not explore microbiota compositional changes (199, 311, 312). A nonexhaustive list summarizing studies investigating the impact of whole-dietary approaches on gut microbiota, neurochemistry, and behavior from both clinical and preclinical studies is provided in **Table 2**.

Evidence from preclinical studies

To date, much research has focused on understanding the effect of unhealthy diets on the microbiota and brain processes. Feeding high-fat, high-sucrose, or high-caloric diets results in unfavorable changes in the microbiota composition (e.g., an increase in the abundance of *Firmicutes* and a decrease in the abundance of *Bacteroidetes*, and higher percentages of *Clostridiales* and *Bacteroidales*) with adverse effects on cognition and behavior, as evidenced by decreases in memory function, poorer cognitive flexibility, or hyperactive behavior, or altered social behaviors (313–315). Additionally, changes in neurochemistry (e.g., reduction in BDNF in the hippocampus), neuronal activity (e.g., increased c-Fos activity in the prefrontal cortex and amygdala), and signaling [e.g., altered γ-aminobutyrate (GABA)], increase in brain inflammation [e.g., increased microglia, expression of inflammatory genes, and glial fibrillary acidic protein (*Gfap*)] and gene expression related to neuroplasticity [e.g., *Bdnf*, Homer protein homolog 1 (*Homer1*), mammalian target of rapamycin (*mTOR*), and insulin-like growth factor 1 (*Ifg1*)] were associated with administration of these diets (316–319).

On the other hand, investigations into the potential benefits of healthy diets in mediating the microbiota–brain interaction are only recently starting to emerge. For example, in a recent study, alterations in microbial composition and metabolites that were associated with behavioral, neurochemical, and brain structural changes were observed after intermittent fasting in a diabetic mouse model (320). In another recent animal study, supplementation with the prebiotic β-glucan abrogated microbiota alterations and cognitive impairment as well as microglia activation and neuroinflammation induced by a high-fat, fiber-deficient diet (321). Importantly, the microbiota composition was rescued prior to cognitive changes and the positive effects of β-glucan were eliminated with antibiotic treatment (321), suggesting a potential causal relation between diet-induced microbial alterations and cognitive function.

While most studies report microbial and behavioral changes separately, some studies have attempted to correlate diet-induced alterations in microbial composition to behavioral outcomes. For example, differences in *Coprobacter* elicited by varying lengths of exposure to the cafeteria diet was identified as a predictor of performances in spatial recognition memory (322). Likewise, strong associations between increased behavioral reactivity and a microbial profile elicited by a high-starch diet, as well as more settled behaviors associated with microbes promoted by a high-fiber diet, were observed in horses (323). In juvenile rats, positive correlations between a diet-linked increase in *Lactobacillus* and mRNA expression of neuronal activation and serotonin (5-HT) receptors were described (316), suggesting that effects of diet on brain chemistry are mediated by certain microbes. Lastly, a recent study demonstrated that a microbiota composition induced by a high-fat diet and plasma metabolites linked to the microbiota were associated with and predictive of depressive-like behavior in rats (324). Interestingly, prior treatment with a probiotic (VSL#3, containing 3 strains of bifidobacteria, 4 strains of lactobacilli, and 1 strain of *Streptococcus*) was able to prevent diet-induced cognitive deficits in the hippocampal-dependent place recognition task and rescue specific bacterial taxa that were decreased by exposure to a cafeteria diet (317). Likewise, even short-term diet exposure (2 wk) shifted the microbiota composition in a way that was associated with inflammation-related pathways and memory deficits (325), indicating rapid effects on microbiota and brain function.

Evidence from human trials

While there is existing evidence from clinical interventions showing improvements in depression and anxiety symptoms following dietary manipulation (199, 311, 326), these studies have not, to date, collected gut microbiota data. Most human intervention studies have focused on probiotic and prebiotic supplementation to manipulate the microbiota and investigate the effect on brain function and mental health (327, 328). For example, *B. longum* 1417 modulated resting neural activity as well as neural responses to social stress, while supplementation with β-galactooligosaccharide reduced the salivary cortisol awakening response, a biochemical measure of stress, and improved emotional information processing (329), and an oligofructose-enriched inulin improved memory and mood in healthy volunteers (330). Fermented foods, rich in probiotics and prebiotics,

TABLE 2 Summary of interventional studies investigating the effects of whole-diet approaches on microbiota and behavioral or cognitive outcomes[1]

Reference	Population/animal	Diet	Length of intervention	Microbiota and metabolite changes	Cognitive/behavioral /neurochemical changes	Correlational or causal relationships
Human studies						
(331)	Healthy adults (18–85 y of age; mean 21.84 y) $n = 25$ [male (44%) and female (56%)] For microbiota analysis $n = 24$; behavior data for salsify $n = 16$ (only participants who were knowledgeable about it) Belgium	Inulin-type fructan (ITF)-rich diet (at least 9 g) Only hot meals for lunch and soup for dinner containing ITF-rich vegetables were provided (mean intake 15 g/d); examples of ITF-rich vegetables include Jerusalem artichoke, garlic, salsify, artichoke, and leeks	14 d of ITF diet followed by 18 d of regular diet	↓ α-Diversity (observed species index of richness), which remained lower after returning to baseline diet 20 OTUs (including *B. longum* subsp. *longum*, *Bifidobacterium pseudocatenulatum*, *B. bifidum*, *B. adolescentis*, and *Blautia* sp.) were identified that discriminate for ITF intervention ↑ *Actinobacteria*, phylum and class, *Actinobacteridae* subclass, *Bifidobacteriales* order, *Bifidobacteriaceae* family, *Bifidobacterium*, *B. longum* and *Prevotellaceae* ↓ Unclassified *Clostridiales*, *Lachnospiraceae*, *Oxalobacteraceae* (trend); *Alistipes* and *Oscillibacter* Most abundances returned to baseline levels, except for decrease in *Lachnospiraceae* species-like taxa, which remained decreased; *Oscillibacter* and *Prevotellaceae* did not return to baseline level, but appeared at intermediate concentration compared with baseline and directly after intervention No overall changes in microbial fermentation as measured by breath hydrogen (only subjects with highest ITF content in meal previous to testing day had ↑ breath hydrogen) No changes in kinetics of gas or SCFA production by time–substrate interaction	↑ Levels of satiety and ↓ desire to eat sweet, salty, and fatty food, which persisted after returning to regular diet ↑ Hedonic attitude to salsify consumption (trend) and intrapersonal emotional competence No changes in perceived stress scale (measured with Perceived Stress Scale); intention to eat more vegetables, leek, and salsify; (*Appetite-related feelings were measured on visual analog scale; hedonic attitudes were measured with 5-point Likert scale questionnaires; intrapersonal competence was measured with study-specific questions and short profile of emotional competence*)	No correlations between microbes and psychological/behavior outcomes reported
(332)	Obese[2] adult women [mean BMI 27.8 kg/m^2 (diet) and 27.3 kg/m^2 (control)] Mean age 62 y (diet) and 63 y (control) $n = 44$ (22 per group) Japan	Nutrition education program focusing on gut microbiome (dietary fiber and fermented foods) Nutrition education increased intake of dietary fiber, vegetable dishes, and milk products Intervention ↑ dietary fiber (15.0 vs. 18.6 g/d), vegetables (6.0 vs. 8.4 servings/d) and milk intake (1.4 vs. 2.9 servings/d) and ↓ frequency of snacking (5 vs. 4 times/wk) compared to control	8 wk (education sessions every 2 wk)	↑ Shannon and Simpson indices of α-diversity, *Lactobacillales*, *Streptococcaceae*, *Streptococcus*, *Bifidobacterium bifidum*, *Streptococcus thermophilus*, *Veillonella parvula* ↓ *Bacteroidetes*, *Bacteroidia*, *Bacteroidales*, *Bacteroidaceae*, and *Bacteroides*	↓ Depression score (measured by Center for Epidemiologic Studies Depression Scale) ↑ Self-rated health ↑ Subjective well-being score (but not significantly different between groups)	No correlations between microbes and psychological/behavior outcomes reported

(*Continued*)

TABLE 2 (*Continued*)

Reference	Population/animal	Diet	Length of intervention	Microbiota and metabolite changes	Cognitive/behavioral /neurochemical changes	Correlational or causal relationships
(333)	Older adults (mean age ~65 y) at risk of Alzheimer's disease (AD) due to baseline mild cognitive impairment (MCI) or cognitive/subjective memory complaints $n = 17$ [29% male, 71% female; $n = 11$ with MCI and $n = 6$ cognitive normal (CN)] USA	Modified Mediterranean ketogenic diet (MMKD; calories from macronutrient: <10% carbohydrate (<20 g/d), 60–65% fat, 30–35% protein; supplied with extra virgin olive oil, encouraged to eat fish, lean meats, and nutrient-rich foods) vs. American Heart Association Diet [AHAD; 55–65% carbohydrates, 15–20% fat (<40 g/d), 20–30% protein; plenty of fruit, vegetables and carbohydrates for adequate fiber, lean meats and protein sources] Daily multivitamin supplement in both groups	Randomized, double-blind, crossover design (6 wk with 6-wk washout period)	*Only changes after dietary intervention are listed* No strong effects on α- and β-diversity or bacterial abundance at phylum level MMKD: ↓ *Bifidobacteriaceae* and *Bifidobacterium* (more prominent in MCI patients), *Lachnobacterium*; ↑ *Akkermansia*, *Tenericutes*, and *Slackia* ↓ 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; slight ↓ in gene families associated with carbohydrate digestion and absorption and ↑ in lipid metabolism ↓ In acetate and ↑ in butyrate (lactate ↑ in CN, but slightly ↓ in MCI patients) AHAD: ↓ in *Bifidobacterium* only in MCI patients, ↑ in *Tenericutes* ↑ Acetate (only in MCI) and propionate and ↓ butyrate (lactate ↓ CN but ↑ MCI)	Changes in AD biomarkers postintervention were not reported	Post-MMKD: Negative correlation between *Tenericutes* and *Enterobacteriaceae*, and positive correlation between *Rikenellaceae*, *Parabacteroides* and *Lachnospiraceae* and Aβ42 in MCI patients; Positive correlation between observed OTUs, Shannon index, *Lachnospiraceae* and *Sutterella* and negative correlation between *Mollicutes* and ptau in MCI patients; in CN positive association between Aβ42 and *Oscillospira* In all subjects, positive correlation between *Bacteroidetes* and Aβ42:Aβ40 ratio; *Ruminococcus* and ptau and ptau:Aβ42 ratio; *Dialister* and Aβ42 and Aβ40; negative correlation between *Coriobacteriaceae* and Aβ42:Aβ40 ratio, *Roseburia* and tau, ptau and ptau:Aβ42 ratio; *Clostridiaceae* and Aβ42:Aβ40 ratio and lactate and ptau Post-AHAD: No correlations observed in MCI patients; negative correlation between *Actinobacteria* and *Bacteroidaceae* and Aβ42 and lactate and ptau in CN and *Actinobacteria* and ptau in all participants In all subjects, negative correlation between *Coriobacteriaceae* and Aβ42:Aβ40; *Mogibacteriaceae* and Aβ40; *Erwinia* and Aβ42; *Roseburia* and tau; *Phascolarctobacterium* and Aβ42; and *Oscillospira* and

(*Continued*)

TABLE 2 (*Continued*)

Reference	Population/animal	Diet	Length of intervention	Microbiota and metabolite changes	Cognitive/behavioral /neurochemical changes	Correlational or causal relationships
						ptau: Aβ42; positive correlation between *Erwinia* and ptau:Aβ42; *Roseburia* and Aβ40; *Phascolarctobacterium* and ptau:Aβ42; and *Oscillospira* and Aβ42
(334)	Patients with ulcerative colitis (mean age 42 y; average BMI 27) $n = 18$ (male 39%, female 61%) USA	Low-fat, high-fiber diet (10% of calories from fat, 1–5% from saturated fat, 5–9% unsaturated fat, ω 6:3 ratio 3:1) vs. improved standard American diet (increased fruit, vegetables, fiber: 35–40% of calories from fat, 10–11% from saturated fat, 25–29% from unsaturated fat, ω 6:3 ratio 20–30:1)	Crossover design (two 4-wk periods separated by 2-wk washout)	Shift in β-diversity after low-fat diet with ↑ *Bacteroidetes*, ↓ *Actinobacteria*, and ↑ *Prevotella* No change in β-diversity in improved American diet or between diets *F. prausnitzii* higher in low-fat vs. improved American diet Modest changes at family and genus level after improved American diet ↑ Acetate and tryptophan, ↓ lauric acid after low-fat diet	↑ Quality of life [measured by short inflammatory bowel disease (IBD) questionnaire] on both diets; ↑ through reduction in perceived limitations due to physical and emotional health, social functioning, pain, and general health measured by Short Form-36 Health Survey	Association between β-diversity and short IBD questionnaire
(300)	Elderly population (65–79 y of age) $n = 612$ ($n = 289$ control; 50% male, 50% female; $n = 324$ diet, 44% male, 56% female) subset of NU-AGE cohortMulticountry study (Italy, United Kingdom, Netherlands, Poland, France)	Diet education on tailored Mediterranean diet or control diet (CD; leaflet with national dietary guidelines)	12 mo (parallel group design)	Higher adherence to diet resulted in attenuated loss of microbial diversity Identified "diet-responsive" microbes by machine learning {DietPositive: 44 OTUs [e.g., *F. prausnitzii*, *Roseburia* (*R. hominis*), *Eubacterium* (*E. rectale*, *E. eligens*, *E. xylanophilum*), *B. thetaiotaomicron*, *P. copri*, *Anaerostipes hadrus*] increased with diet; DietNegative: 45 decreased (e.g., *Ruminococcus torques*, *Collinsella aerofaciens*, *Coprococcus comes*, *Dorea formicigenerans*, *Clostridium ramosum*, *Veillonella dispar*, *Flavonifractor plautii*, and *Actinomyces lingnae*) with diet ↑ SCFAs and BCFAs and ↓ secondary bile acids, *p*-cresols, ethanol, and carbon dioxide	High adherence to diet resulted in improvements in global cognition and episodic memory compared with low adherence (overall improvement in cognition in both groups with no between-group differences) (cognitive test battery included the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery) [from (335)]	Positive associations between improved cognitive function and DietPositive taxa (key species in gut microbial community)
Animal studies						
(336)	CF1 mice (male) 5 wk of age $n = 8$ per group	Regular pellet powder chow mixture (PP diet) 50% lean beef-supplemented diet (BD)	3 mo	↑ Microbial diversity in BD compared with PP 12 genera unique to BD group (*Alistipes*, *Allobaculum*, *Chthoniobacter*, *Dorea*, *Eggerthella*, *Gemella*, *Leuconostoc*, *Proteus*, *Sarcina*, *Serratia*, *Staphylococcus*, *Turicibacter*), and 3 unique to PP (*Atopobium*, *Bacteroidales*, *Erysipelothrix*)	↑ Working and reference memory in BD-fed mice; BD mice retained working memory longer ↓ Anxiety-like behavior in BD-fed mice	No correlations between microbes associated with diet and behavior outcomes reported

(*Continued*)

TABLE 2 (*Continued*)

Reference	Population/animal	Diet	Length of intervention	Microbiota and metabolite changes	Cognitive/behavioral /neurochemical changes	Correlational or causal relationships
(313)	BALB/cAnNTac mice 7 wk of age $n = 42$ ($n = 14$ per group)	High-fat/no sucrose diet High-sucrose/standard low-fat diet Control starch-based diet	9 wk	Difference in β-diversity in unweighted and weighted UniFrac between high-fat and sucrose and control In high fat: ↑ *Firmicutes*, *Ruminococcaceae*, *Lachnospiraceae*, *Ruminococcus*, *Dorea*, and *Oscillospira*; ↓ *Bacteroidetes*, S24–7, and *Anaeroplasma*	↓ Burrow-digging and impaired cognitive functioning in mice on high-fat diet ↓ Anxiety and hyperactive behavior in high-sucrose diet No difference in sucrose preference test No difference in BDNF levels in hippocampus or prefrontal cortex	Correlations between gut microbiota, behavior, BDNF, and inflammatory markers were reported for control group that did not receive experimental diet
(314)	C57BL/6J mice 8 wk of age $n = 18$ ($n = 6$ per group)	High fat (42% fat) High sucrose (66% sucrose) Normal chow diet	2 wk	Chow diet: ↑ *Bacteroidales*; *Tenericutes*, *Mollicutes*, *Anaeroplasmatales* only found in chow diet High-sucrose diet: ↑ *Lactobacillales*, *Lactobacillus*, and *Lactococcus*; *Enterococcus* only observed in high-sucrose group High-fat and -sucrose diet: ↑ 2 genera in *Clostridiales*; ↓ 3 genera in *Bacteroidales* High-fat diet: ↑ *Erysipelotrichales*	In reversal probe trial in water maze test, high-sucrose and high-fat searched closer to old platform location in reversal probe trial Less difference between naïve and delayed short-term memory trials in high-sucrose diet No difference in anxiety-like behavior, novel object or location recognition	Correlations were determined between bacteria and behavior outcomes that were significantly different between groups: Higher *Clostridiales* correlated with poorer performance for learning new platform location and with searching closer to old platform Lower *Bacteroidales* were associated with lower proximity scores for old platform location Higher *Lactobacillales* correlated with poorer performance on first probe trial
(337)	C57BL/6NBomTac mice (male) 8 wk old $n = 20$ ($n = 10$ per group); for microbiota: feces $n = 8$ (control) and $n = 6$ (diet) and cecum $n = 9$ (control) and $n = 6$ (diet)	Standard diet or Mg-deficient diet	6 wk	Difference in β-diversity ↓ Bacterial diversity in Mg-deficient diet (both feces and cecum)	Mg-deficient mice showed ↓ latency to enter light compartment (altered anxiety-like behavior)	Correlations between gut microbiota and anxiety-like behavior reported for control group
(338)	C57BL/6NBomTac mice (male) 8 wk old $n = 30$ ($n = 15$ per group); for microbiota: $n = 6$ (control) and $n = 7$ (diet)	Standard diet or Mg-deficient diet	6 wk	Microbial profile between dietary treatments differed in feces and cecum	↑ Immobility in Mg-deficient mice in forced swim test (depressive-like behavior) No difference in entries to center or activity in open-field test No differences in BDNF levels	Positive correlation between microbiota and hippocampal IL-6 after Mg-deficient diet Correlations between gut microbiota and depressive-like behavior reported for control group

(*Continued*)

TABLE 2 (*Continued*)

Reference	Population/animal	Diet	Length of intervention	Microbiota and metabolite changes	Cognitive/behavioral /neurochemical changes	Correlational or causal relationships
(339)	Horses 11–19 y old $n = 6$	High-fiber (HF) diet (100% hay) vs. low-fiber, high-starch (HB) diet (57% hay, 43% barley) (crossover study)	3 wk of HF diet, 5 d transition period, 3 wk HB diet, 3 wk HF diet (without transition)	↑ Concentration of total anaerobic, amylolytic and lactate-utilizing bacteria in colon after HB diet (no difference in cecum); cellulolytic bacteria not different in colon	↓ Time feeding and ↑ time resting during HB diet No difference in sociability or novelty test or in percentage of time spent vigilant and looking outside the stall	Positive correlation between cecal and colonic amylolytic bacteria and duration of vigilance in sociability test, between cecal lactate-utilizing and colonic amylolytic bacteria and time spent in vigilance during novelty test
(325)	Sprague–Dawley rats (male) Age not reported $n = 12$/group	Diets enriched in sugar, SFAs or PUFAs (matched for energy, micronutrients and percentage of energy available from protein and carbohydrate)	2 wk (energy-matched CD 3 d prior to start of treatment)	Differential effect of diet at class, order, family, genus and OTU level; 89 taxa (16 control; 24 PUFA; 12 SFA; 37 sugar) contribute to differences among diets For example, *Lactobacillus* different between PUFA/sugar and control/SFA diet; *Alloprevotella* enriched in control; *Clostridium sensu stricto* in SFA; *Ruminococcaceae* unclassified in PUFA; *Porphyromonadaceae* unclassified in sugar	↓ Exploration ratio of SFA and sugar diets in place recognition task compared with control; PUFA rats higher exploration ratio compared with SFA and sugar diet ↓ Exploration time in place recognition task in all 3 experimental groups compared with control Collectively a difference in hypothalamus gene expression between SFA and PUFA; ↓ expression of *NfκBia* expression in experimental diets in hypothalamus (other inflammatory markers were not affected); trend for ↓ appetite-regulating genes (*Pomc* and *Npy*) in PUFA diets No difference in object recognition task No difference in hippocampal gene expression (including *Bdnf*) or hypothalamic BDNF expression	Associations between microbiota and memory are reported, some specifics for different type of diet (e.g., in *Lachnopiraceae* family OTU40 was positively correlated with place memory for sugar comparison; in *Ruminococcaceae* family OTU57 was responsive to fat and correlated negatively with place memory)
(340)	Swiss–Webster mice (male) 4 wk old $n = 48$ (16 per group)	Normal corn starch (NCS) High-amylose corn starch (HA-7) High-amylose corn starch modified with 10% octenyl succinic anhydride (OSHA-7)[Experimental diets are high in resistant starch (RS)]	6 wk	No difference in α- and β-diversity More temporal changes in control than resistant starch diet RS-fed mice: stable abundance of *Bacteroidetes* and *Firmicutes*; alterations in *Verrucomicrobia*, *Bacilli*, *Actinobacteria*, and spirochetes OSHA-7 diet: ↓ in *Actinobacteria* and *Lactobacillus*; ↑ *Clostridia* HA-7 diet: ↑ *Bifidobacterium, Sutterella*, and *Clostridia*; ↓ *Lactobacillus*	HA7-fed mice ↓ in number of entries to open arm and time spend in open arm in elevated plus maze (↑ anxiety-like behavior) HA-7 and OSHA-7 mice ↓ exploration of open field ↑ Corticosterone in NCS and OSHA-7 mice	No correlations between microbes associated with diet and behavior outcomes reported

(*Continued*)

TABLE 2 (*Continued*)

Reference	Population/animal	Diet	Length of intervention	Microbiota and metabolite changes	Cognitive/behavioral /neurochemical changes	Correlational or causal relationships
(316)	Fisher rats F344 male Juvenile (24 d old) $n = 6–8$ per group	Test diet: galactooligosaccharide, polydextrose, lactoferrin, whey protein concentrate milk-fat globule membrane-10	4 wk	↑ Total *Lactobacillus* spp.	c-Fos mRNA ↑ in prefrontal cortex and amygdala and ↓ in amygdala ↑ BDNF mRNA in infralimbic subregion of PFC, but not in hippocampus ↑ mRNA expression of *Glun1* subunit of NMDA receptor in all subregions of PFC ↓ mRNA of *Glun2b* subunit of NMDA receptor in PFC ↓ Anxiety-like behavior	Positive correlation between diet-induced increase in *Lactobacillus* and increase in c-Fos mRNA expression in cingulate, infralimbic and prelimbic region of PFC and dorsolateral and dorsomedial striatum; Positive correlation between *5-ht1a* mRNA in caudal dorsoventral aspect of dorsal raphe nucleus and *5-ht2c* in lateral amygdala
(315)	Sprague–Dawley rats (male) 21 d of age$n = 32$ ($n = 8$ control; $n = 8$ hypercaloric high-fat and high-sucrose diet (HFHS); $n = 16$ sample animals for social memory and interaction)	Control: normal rodent chow Short intermittent periods (2 h/d) of HFHS diet	4 wk	No difference in α-diversity Dissimilarity of microbiota based on β-diversity ↑ *Blautia*, *Ruminococcaceae*, *Phascolarctobacterium*, *Bifidobacterium*, *Bacteroidales*, and *Allobaculum*	↓ Social motivation when no access to HFHS diet for 23-h period (less social interaction pre- compared with post-food access in HFHS diet and increased social investigation post-food access in HFHS diet) Impaired social and object recognition in HFHS diet No effect on social odor preferences of odor recognition memory ↓ *Maoa*expression in PFC and hippocampus and ↓ *Comt* and *Bdnf* in PFC in HFHS diet	Correlations were observed between behaviors and biological measures Associations between microbiota and social behavior were tested pre-dietary exposure
(341)	SPF wild-type Swiss Webster miceGF wild-type Swiss Webster miceMale and female 3–4 wk old Sample size ranged per test from 3 to 25	6:1 fat:protein ketogenic diet (KD) vs. vitamin- and mineral-matched CD	14 d	↓ α-Diversity. ↑ *Akkermansia muciniphila*, *Parabacteroides*, *Sutterella*, and *Erysipelotrichaceae* in KD ↑ *Allobaculum*, *Bifidobacterium* and *Desulfovibrio* in CD	↑ Seizure threshold after KD ↑ Hippocampal GABA and glutamate levels in diet- and microbiota-mediated seizure protected groups	Metabolomics revealed that microbiota modulates metabolomic response to KD and that seizure protection is associated with microbiota-dependent alterations in ketogenic γ-glutamylated amino acids Germ-free status and antibiotic treatment abolish antiseizure effect of KD Colonization with *A. muciniphila* and *Parabacteroides* restores seizure protection in antibiotic-treated mice fed KD Transplantation of KD microbiota confers antiseizure effect in absence of KD (this is abrogated after

(*Continued*)

TABLE 2 (*Continued*)

Reference	Population/animal	Diet	Length of intervention	Microbiota and metabolite changes	Cognitive/behavioral /neurochemical changes	Correlational or causal relationships
						return of microbiota to CD profile unless treated with *A. muciniphila* and *Parabacteroides*)
(317)	Sprague–Dawley rats (male) Age not reported $n = 10$/group	Cafeteria (Caf) or chow diet	25 d of diet Treatment with vehicle, low (2.5×10^9 bacteria) or high (2.5×10^{10} bacteria) dose of VSL#3[3] started 2 wk prior to initiation of diet	↓ Microbial diversity (observed OTUs and Shannon's diversity) after Caf diet ↑ In 137 taxa (e.g., *Blautia*, *Bacteroides*, *Phascolarctobacterium*, *Parasutterella*, *Erysipelotrichaceae*) and ↓ 394 taxa (e.g., *Butyrivibrio*)	↑ Genes related to neuroplasticity (*Bdnf*, *Homer1*, *mTOR*, *Igf1*), inflammation genes (*Gfap*), *5-ht1a*, *mGlur5*, *Mapk8*, and *Mapk10*, glucocorticoid receptor *Nr3c1*, *Glut3*, *C-Jun*, *Jak2*, and *Nod2*, and ↓ *Ikbkb*, *5-ht2c* after Caf diet Deficits in place recognition task ↓ Antioxidant-related and fat metabolism-related pathways No effect on anxiety-like behavior	Overall correlation between gut microbial profile and object memory and neuroplasticity genes (not specifically performed for Caf diet group only)
(342)	C54/BL/6N mice (male) 4 wk old $n = 60$ (30 per group)	Standard diet High-fructose diet	4 wk all on diet; half of either group treated with antibiotics for another 4 wk	8 wk of high-fructose changed microbial structure of community but not α-diversity ↓ *Bacteroidetes* and ↑ *Proteobacteria* and trend for ↑ *Firmicutes*; ↑ *Deferribacteraceae* (*Mucispirillum*), *Helicobacteraceae* (*Helicobacter*), *Lachnospiraceae*, and *Ruminococcaceae* ↓ Total SCFA, acetate, propionate, and butyrate High-fructose diet induced thinning of intestinal mucosa, epithelium, muscularis mucosae, loss of crypts and glands, edema in lamina propria, and infiltration of inflammatory cells	↑ TNF-α, IL-1β, and IL-6 ↑ Iba1+ microglia (whole hippocampus) ↓ NeuN + neurons and doublecortin (DCX)+ newborn neurons and GFAP + astrocytes in hippocampal dentate gyrus in high-fructose diet; No memory impairment	Antibiotic treatment inhibited upregulation of IL-1β, TNF-α, and IL-6 mRNA and increase in Iba1+ microglia, and suppressed GFAP+ astrocyte increase in high fructose but did not affect decrease in NeuN+ and DCX+ neurons
(318)	SPF C54BL/6 J mice (male) 5 wk old $n = 8$/group	Low-fat diet (10% of calories from fat) High-fat diet (60% of calories from fat)	9 wk	In high-fat diet: ↑ *Firmicutes:Bacteroidetes* ratio, *Proteobacteria*, *Deferribacteres* ↓ *Bacteroidetes* and *Tenericutes*	In high-fat diet: Impaired spatial recognition memory in Y-maze ↓ Novel object exploration and recognition index (recognition memory impairment) ↑ Anxiety-like behavior (more time in open arms in elevated plus maze) In hippocampus: ↓ BDNF and phosphorylation of CREB, NFκB activation, ↑ Iba1 (activation of microglia)	In vitro follow-up experiments suggest that LPS components from Gram-negative bacteria in fecal lysate from high-fat diet might damage neuronal cell function observed in vivo

(*Continued*)

TABLE 2 (*Continued*)

Reference	Population/animal	Diet	Length of intervention	Microbiota and metabolite changes	Cognitive/behavioral /neurochemical changes	Correlational or causal relationships
(323)	Welsh section A ponies 18 mo old $n = 10$	High-fiber (HF) or high-starch (HB) diet (crossover design)	14 d	↓ Diversity, richness and ↑ variance in HB vs. HF diet, but not statistically significant 85 OTUs significantly affected by diet and 20 OTUs showed significant difference depending on diet (e.g., ↓ *Ruminococcaceae*, *Christensenellaceae* and ↑ *Streptococcus* in high-starch diet)	Ponies are more reactive and less settled on high-starch diet (↑ number of times pace was changed, less time standing and less time investigating surroundings, ponies were more tense, nervous, unsure)	Strong correlation between pace change and microbiota associated with HB diet as well as between investigating and microbiota associated with HF diet
(319)[4]	C57Bl/6J mice (male) 8 wk old $n = 156$ (total)	High-fat diet (HFD, 60 kJ% from fat, 24 kJ% from carbohydrate, 16 kJ% from protein) or control (12 kJ% from fat, 65 kJ% from carbohydrate, 23 kJ% from protein) diet	8 wk	Differences in β-diversity between groups. HFD: ↑ α-diversity (Shannon and Simpson indices); ↓ *Bacteroidetes* and ↑ *Firmicutes* and *Cyanobacteria* LEfSe analysis identified several other microbial differences between diets (total of 39 taxa enriched in HFD and 16 enriched in CD) ↓ Myeloperoxidase after high-fat compared with CD LEfSe analysis identified PICRUSt predictions of metagenomic alterations enriched in each diet (e.g., tryptophan, sphingolipid, aspartate, and glutamate pathways)	HFD: ↑ depression-like behavior (↓ sociability, sucrose preference, self-care); disruption in circadian ingestion pattern, ↓ in horizontal and vertical locomotor activity Prefrontal cortex and striatum: change in lactate (involved in energy metabolism) and GABA (neuronal signaling) Hypothalamus and hippocampus: ↓ in *Nyp*	No correlations between microbes associated with diet and behavior outcomes reported
(343)	Adult crossbred horses (male) 13–21 y old $n = 6$	High-fiber (HF) diet (100% hay) vs. low-fiber and high-starch (HB) diet (56% hay and 44% barley) (crossover design)	30 d HF diet, 5 d gradual transition, 23 d HB diet	↑ Concentration of amylolytic and total anaerobic bacteria in HB diet; ↑ abundance of *Succinivibrionaceae* in HB diet	↑ Frequency of blowing (exhaling through mouth) in novelty test in HB diet (alert type of behavior associated with anxiety) No difference in other behavioral tests	Positive correlation between: amylolytic bacteria and frequency of blowing; Shannon index and frequency of moving; *Succinivibrionaceae* (genus *Succinivribrio*) and frequency of blowing; *Ruminococcaceae* (*Ruminiclostridium* and *Ruminococcaceae* UCG-005) and duration of smelling the floor; *Prevotellaceae* and latency to feed Negative correlation: Shannon index and duration of feeding; pH and frequency of startle response; *Ruminococcaceae* (*Ruminiclostridium 5*, *Ruminicoccaceae* UCG-002 and UCG-003) and latency to feed

(*Continued*)

TABLE 2 (*Continued*)

Reference	Population/animal	Diet	Length of intervention	Microbiota and metabolite changes	Cognitive/behavioral /neurochemical changes	Correlational or causal relationships
(320)	Diabetic BKS.Cg-Dock7m+/+ Leprdb/J (stock no: 000,642) Homozygous *Leprdb/db* mice (male) 3 mo old 3 sets of animals, between 10 and 13 animals per subgroup	Intermittent fasting (alternating 24-h fasting, 24-h ad libitum consumption)	28 d	↑ α-Diversity and changes in β-diversity ↑ *Lactobacillus*, *Odoribacter* ↓ *Enterococcus*, *Streptococcus* and unknown *Enterococcaceae*, *Candidatus Arthromitus*, *Rummeliibacillus*, *Leuconostocaceae* 17 zero-radius OTUs affected by intermittent fasting (5 belonged to *Lactobacillus*) 11 differentially abundant KEGG gene pathways (including bile acid biosynthesis) Changes in metabolites (e.g., ↑ 5-HT tryptophan, IPA, ↓ tyrosine, phenylacetylglycine, *p*-cresol) ↑ SCFAs ↑ Villi length and muscularis thickness and improved colonic permeability	↑ Anxiety, locomotor activity, cognitive deficits, ↑ spatial memory after intermittent fasting All measures in hippocampus: ↑ Length and width of post synaptic density; stimulated insulin signaling pathway; ↑ BDNF expression and scaffolding protein PSD-95; ↓ Neuroinflammation and microglia activation (suppression of *Nfκb* activation, *Jnk/p38*phosphorylation and *Iba*1 expression) ↑ Energy metabolism mitochondrial biogenesis	Positive correlation between *Candidatus Arthromitus* and unknown *Leucostocaceae* genera and cognition-associated blood glucose Antibiotic treatment partly abolished cognitive improvement, mitochondrial biogenesis, reduced PSD, plasma IPA ,and fecal SCFAs
(322)	Sprague–Dawley rats (female) 4–5 mo old $n = 12$ per group	Chow, cycle [3 d cafeteria (Caf) diet and 4 d chow diet] or Caf diet (continuous Caf diet)	7 wk	β-Diversity differed significantly by diet (cycle and continuous microbiome were more closely aligned) Caf diet ↓ α-diversity (lower bacterial richness and Shannon's index), but no effect on evenness Compared with chow diet, 16 OTUs ↑ in Caf and 15 OTUs in cycle diet Between cycle and Caf diets: *Porphyromonadaceae* unclassified_OTU35 ↑ in cycle and *Coprobacter*_OTU66 in Caf diet Ether lipid metabolism, flavone, and flavonol and flavonoid biosynthesis ↓ by any Caf exposure	↓ Spatial recognition (novel place recognition task) in Caf but not cycle dietBoth continuous and cycle Caf diet ↑ hippocampal cytokine expression and markers of astroglial and microglial proliferation, but only continuous Caf diet affected downstream proinflammatory signaling and blood–brain barrier integrity	Performance in novel place recognition task was significant predictor of global microbiome composition Association between overall microbiome composition and hippocampal *Il1b*, *Ikbkb*, and place exploration ratio in novel place recognition task (marginal distance-based linear modeling using Bray–Curtis similarity matrix) In chow group: correlation between *Coprobacter*_OTU66 and spatial recognition memory (this bacterium was enriched in Caf diet)
(294)	C57BL/6JOlaHsd mice Dietary intervention at postnatal day 28 (onset of adolescence) to postnatal day 49; behavior testing and microbiota analysis 3 wk after end of treatment $n = 36$	Standard diet, HFD, or Caf diet	21 d	↓ Shannon diversity in HFD mice β-Diversity identified structural changes in microbiota after diet Changes in members of families *Ruminococcaceae*, *Lachnospiraceae*, *Erysipelorichaceae*, *Coriobacteriaceae*, and *Alcaligenaceae* after HFD and Caf HFD: change in UCG-010, *Roseburia*, *Lachnoclostridium*, *Turicibacter*, *Gordonibacter*, *Enterorhabdus*, and *Parasutterella* Caf: changes in *Roseburia*, *Turicibacter*, *Enterorhabdus*, and UCG-002	Amygdala genes involved in neuroimmunity, neurotransmission, tight junctions, and SCFA signaling were analyzed; 19 were altered by HFD and 18 by Caf; Differentially affected genes: HFD ↑ in *Il1b*, glucocorticoid receptor *Nr3c1*, tight junction protein 1 (*Tjp1*), proteolipid protein 1 (*Plp1*) Caf upregulation in *Il10*, *claudin 5* No differences in behavior (anxiety, fear, sociability, and	No correlations were reported

(*Continued*)

TABLE 2 (*Continued*)

Reference	Population/animal	Diet	Length of intervention	Microbiota and metabolite changes	Cognitive/behavioral /neurochemical changes	Correlational or causal relationships
				HFD and Caf differed in *Ruminiclostridium* 9, *Anaerotruncus*, UCG-001, and *Parasutterella* More genera were affected by HFD, but Caf affected genera more strongly	memory) measures were observed	
(324)[5]	(Post hoc analysis) FRL ($n = 12$) and FSL ($n = 46$) rats (male) 5 wk of age	CD or HFD	12 wk	Shift in β-diversity ↑ Observed richness in FSL Compared with CD, HFD had ↓ *Bacteroidetes*, *Bacteroidaceae*, and *Bacteroidales*_S24–7 group, and ↑ *Fusobacteria*, *Proteobacteria*, *Alcaligenaceae*, *Clostridiaceae*, *Coriobacteriaceae*, *Desulfovibrionaceae*, *Micrococcaceae*, *Peptostreptococcaceae*, *Rikenellaceae*, and *Streptococcaceae*	↑ Depressive-like behavior (immobility time and swimming behavior) after HFD ↑ Activity in open field test after HFD ↑ CD4/CD8 ratio in brain of HFD rats Behavior results reported in (222)	Association (linear regression) between depressive-like behavior and principal component 2 (including increased taxa such as *Gemella*, S24–7, *Alistipes indistinctus*, *Butyricimonas*, *Blautia glucerasea*, *Erysipelatoclostridium ramosum*, *Holdemania filiformis*, etc.) Plasma metabolites associated with microbiota (α-ketoisovaleric acid, cholate and pipecolate) predicted depressive-like behavior

[1]Unless otherwise specified, human populations studied were healthy volunteers; only behavioral/cognitive outcomes measures and associations between microbiota/metabolites and behavior outcome measures are reported. AD, Alzheimer's disease; AHAD, American Heart Association Diet; BD, lean beef-supplemented diet; BDNF, brain-derived neurotrophic factor; Caf, cafeteria diet; CD, control diet; *C-Jun*, AP-1 transcription factor subunit; CN, cognitive normal; *Comt*, catechol-O-methyltransferase; CREB, cAMP response element-binding protein; FRL, Flinders resistant line; FSL, Flinders sensitive line; GABA, γ-aminobutyrate; GFAP, glial fibrillary acidic protein; *Glun*, ionotropic glutamate receptor; *Glut3*, glucose transporter 3; HA-7, high-amylose corn starch; HB, high starch; HF, high fiber; HFD, high-fat diet; HFHS, high fat high sucrose; *Homer1*, Homer protein homolog 1; Iba1, ionized calcium binding adaptor molecule 1; IBD, inflammatory bowel disease; *Igf1*, insulin-like growth factor 1; *Ikbkb*, inhibitor of nuclear factor κB kinase subunit β; IPA, indolepropionic acid; ITF, inulin-type fructans; *Jak2*, Janus kinase 2; *Jnk/p38*, Jun N-terminal kinases and p38 mitogen-activated protein kinases; KD, ketogenic diet; KEGG, Kyoto Encyclopedia of Genes and Genomes; LEfSe, Linear discriminant analysis Effect Size; *Maoa*, monoamine oxidase A; *Mapk*, mitogen-activated protein kinase; MCI, mild cognitive impairment; *mGlur5*, metabotropic glutamate receptor subtype 5; MMKD, modified Mediterranean ketogenic diet; *mTOR*, mammalian target of rapamycin; NCS, normal corn starch; NeuN, neuronal nuclei; *Nfκbia*, nuclear factor κBia; NMDA, *N*-methyl-D-aspartate; *Nod2*, nucleotide binding oligomerization domain containing 2; *Npy*, neuropeptide Y; *Nr3c1*, nuclear receptor subfamily 3 group C member 1; NU-AGE, European Project on Nutrition in Elderly People; OSHA-7, high-amylose corn starch modified with 10% octenyl succinic anhydride; OTU, operational taxonomic unit; PFC, prefrontal cortex; PICRUSt, Phylogenetic Investigation of Communities by Reconstruction of Unobserved States; *Pomc*, pro-opiomelanocortin; PP, pellet powder chow mixture; PSD-95, scaffolding protein in the excitatory postsynaptic density; RS, resistant starch; SPF, specific pathogen-free; 5-HT, serotonin; *5-ht1a*, serotonin 1A receptor; *5-ht2c*, serotonin 2C receptor.

[2]According to Japanese guidelines BMI $\geq$ 25kg/m^2 is considered obese.

[3]VSL#3 includes 3 strains of bifidobacteria (*B. longum* DSM 24,736, *B. infantis* DSM 24,737, *B. breve* DSM 24,732), 4 strains of lactobacilli (*L. acidophilus* DSM 24,735, *L. paracasei* DSM 24,733, *L. bulgaricus* Df1SM 24,734, *L. plantarum* DSM 24,730), and 1 strain of *Streptococcus salivarius* subsp. *thermophilus* DSM 24,731; only results of cafeteria diet treatment are shown.

[4]The second part of the experiment also investigated the impact of medication (sitagliptin or imipramine), which is not included here.

[5]The study also included probiotic treatment; however, only results of HFD treatment are outlined here.

could have similar beneficial effects on the gut–brain axis. In a pilot study with 47 healthy young medical students, consumption of a fermented milk drink containing *L. casei* strain Shirota was able to reduce physical symptoms of stress such as abdominal pain or cold symptoms, prevented the increase in salivary cortisol observed in the placebo group, and could potentially normalize stress-induced aberration in tryptophan metabolism and improve 5-HT biosynthesis (344). In another small-scale study in healthy female volunteers, consumption for 4 wk of a fermented milk product containing 5 probiotic strains (*Bifidobacterium animalis* subsp. *lactis*, *Streptococcus thermophilus*, two strains of *Lactobacillus bulgaricus*, and *Lactococcus lactis* subsp. *lactis*) altered the activity of extensive brain networks (i.e., primary interoceptive and somatosensory regions, a cluster in the midbrain region centered on the periaqueductal gray) (345).

Among the interventional studies using whole-dietary approaches published to date, only one included healthy adults as volunteers, and reported improved nutritional behaviors and intrapersonal emotional competence following a diet rich in inulin-type fructans (331). In an obese population, a nutrition education program focusing on the gut microbiota (increase in fiber-containing and fermented foods) resulted in a decrease in the depression score and an increase in self-rated health, as well as an increase in α-diversity and abundance of beneficial bacteria such as *B. bifidum* and *S. thermophilus* (332). Other biological outcomes associated with depression, such as inflammatory status (346), tryptophan–kynurenine metabolism (347), and HPA axis activity (348), were not reported. Thus, it is difficult to decipher whether the reduction in depression scores observed in this study was due to overall subjective positive changes and body satisfaction or had underlying biological or microbial mechanisms. In a population of older adults at risk of developing Alzheimer's disease, microbial changes after consumption of a modified Mediterranean diet correlated with improved biomarkers of Alzheimer's disease in the cerebrospinal fluid (333), suggesting that a dietary intervention could lead to bacterial changes with potential protective properties. In the NU-AGE cohort, Mediterranean diet-induced increases in microbial taxa were associated with improved cognition and reduced risk of frailty and inflammation in elderly individuals who followed a customized Mediterranean diet for 12 mo (300). Although convincing evidence from human studies is emerging, the limited number of research studies available makes it difficult to provide evidence-based recommendations for the use of specific diets in improving mental health or to treat some symptoms of disease (7). Thus, future high-quality and large-cohort studies are imperative to further our understanding of this promising field.

Proposed Mechanisms Underlying Dietary Manipulation of Gut–Brain Communication

Multiple mechanisms of the microbiota–brain communication have been proposed (2). Some of these mechanisms are prone to dietary modulation and have been suggested to underlie the effect of diet on the brain in some investigations. An overview of these mechanisms is outlined in **Figure 2**.

Microbial metabolites

SCFAs.

Due to the ability of microbes to metabolize undigested food, the metabolites produced are key mediators of the diet–microbiota–brain triangle. Various mechanisms whereby metabolites can affect host brain function and behavior have been described. Recently, the administration of microbial metabolites that were found to be differentially increased after intermittent fasting resulted in improved cognitive function, partially supporting a causal role for microbial metabolites in improving cognition in animals (320). Perhaps the best studied metabolites are the products of microbial fermentation of fiber, SCFAs. Importantly, SCFA receptors, mainly free fatty acid receptors (349) and monocarboxylate transporters (350, 351), have been discovered in the central nervous system (CNS) and peripheral nervous system, indicating direct signaling potential. Additionally, SCFAs can stimulate neurotrophic factors [nerve growth factor, BDNF, and glial cell line-derived neurotrophic factor (352)] or neurotransmitter synthesis [glutamate, glutamine, and GABA (353)], thus regulating the growth, survival, differentiation, and excitability of neurons and synapses in the CNS (352) and playing an important part in learning, memory, stress, and mood. In an animal model, administration of SCFAs reduced behavioral deficits (depressive-like behavior), stress responsiveness and intestinal permeability associated with psychosocial stress (354), indicating that SCFAs can directly influence brain homeostasis and behavior. In addition, SCFAs, specifically butyrate, were also shown to enhance BBB integrity by increasing occludin expression (355, 356), thereby protecting the brain from potential neurotoxic factors. Lastly, butyrate and, to a lesser extent, other SCFAs can also act as a potent inhibitor of histone deacetylases (HDACs) (357). HDACs have been implicated in a range of neuropsychiatric disorders [e.g., depression and schizophrenia (358)] and HDAC inhibitors could be potential cognitive enhancers in anxiety- and fear-related disorders (359).

Other pathways through which SCFAs can influence gut–brain communication and brain function include immune, endocrine, neuronal, vagal, and other humoral pathways (360). The effect of SCFAs on inflammation can be mediated by improvement of the intestinal barrier (361), thereby potentially preventing immune molecules and bacterial LPS translocating into the periphery and thus reducing systemic inflammation and ultimately neuroinflammation (362). Likewise, SCFAs can mediate the differentiation and activation of immune cells such as cytokines, dendritic cells, macrophages, and T cells (363). SCFAs also activate vagal afferents in the gastrointestinal tract (364), transducing electric signals to modulate neurotransmitter levels in the brain and brain function. Lastly, SCFAs can also indirectly affect brain circuits through stimulating the secretion of

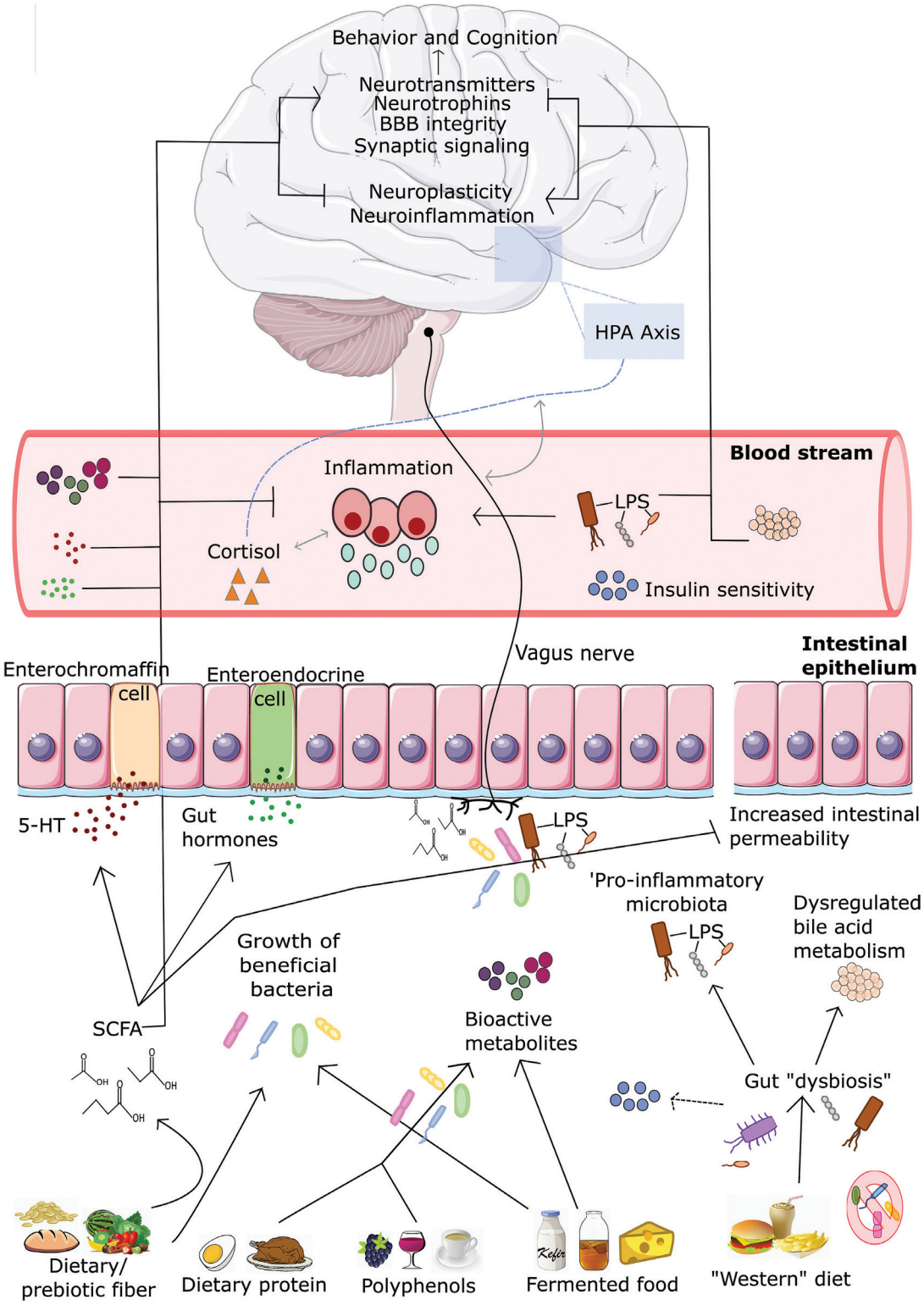

FIGURE 2 Mechanism of the gut–brain communication prone to dietary modulation. Multiple mechanisms exist whereby diet could modulate the gut-to-brain communication, including microbial-derived metabolites, hormonal, immune, metabolic, and neuronal pathways. Healthy dietary intake (e.g., dietary fiber, polyphenols, or fermented foods) can promote the growth of beneficial microbes. These microbes can stimulate production of bioactive metabolites, neurotransmitters [e.g., serotonin (5-HT)], and gut hormones, which can affect brain and behavior through direct or indirect signaling pathways. Another important avenue of communication is stimulation of the vagus nerve through microbial metabolites from food degradation or microbes. Unhealthy dietary habits (e.g., Western diets) can lead to the proliferation of harmful bacteria. This gut "dysbiosis" could result in dysfunctional brain processes and neuroinflammation through alterations in bile acid metabolism, intestinal permeability, inflammation, and metabolic pathways. BBB, blood–brain barrier; HPA, hypothalamic–pituitary–adrenal.

various other gut hormones, including glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), by G-protein-coupled receptor (GPCR) activation. Although these hormones have neuroactive potential, how the changes in PYY and GLP-1 levels induced by SCFAs relate to brain function remains to be determined (360). Interestingly, recently it was shown that SCFAs can attenuate signaling through the ghrelin receptor, a key GPCR at the interface of mood and food intake (365). This further highlights the emerging therapeutic potential of SCFAs and other microbiota metabolites for their potential to target key GPCRs, expressed in the gut–brain axis, with a wide array of functionalities that span both the periphery and the CNS.

It should be noted that potential detrimental effects of SCFAs on brain function have been reported that could contribute to the symptomology of certain neurological diseases. In animal models, for example, propionate (although directly administered to the brain intracerebroventricularly or in high concentrations) can induce autism-like behaviors (366, 367) and elevated levels of fecal SCFAs have been reported in humans with ASD (221, 368). Likewise, in GF mice the administration of an SCFA mixture resulted in microglia activation and motor deficits (369), hallmark symptoms of Parkinson's disease, potentially indicating a role of SCFAs in Parkinson's disease symptomology. However, the results are inconclusive (370–372), warranting additional research to understand the mechanisms of SCFAs in brain health in specific disease states.

Metabolites from protein degradation.

Besides metabolites from carbohydrate digestion, metabolites from microbial digestion of other nutrients might be involved in the diet–gut–brain connection. Some taxa within the intestinal microbiota possess the enzymatic capacity (i.e., proteases) to degrade dietary protein (e.g., *Bacteroides*, *Clostridium*, *Fusobacterium*, *Streptococcus*), which could play especially important roles in protein-rich, low-fiber diets, in which microbial energy harvest shifts from carbohydrate to protein sources (373, 374). Microbial proteolytic activity not only influences the availability of amino acids to the host (375), but also results in the production of bioactive metabolites [e.g., neurotransmitters, BCFAs, amines, phenols, and indoles (376)].

Several microbes have the capability of producing neurotransmitters from dietary protein, including GABA, norepinephrine, dopamine, and 5-HT (377). While the exact mechanisms of how these microbially derived neurotransmitters influence host brain function are still being uncovered, the vagus nerve, the immune system, and the regulation of peripheral availability of precursors for the synthesis of neurotransmitters have been proposed as candidate pathways (2). Thus, it is likely that the reach of these neurotransmitters can go beyond the local effects and could have important implications for CNS functioning (378). For example, it was recently reported that microbial metabolism of the aromatic amino acids tryptophan (precursor of 5-HT), tyrosine, and phenylalanine (both precursors of dopamine) and their catabolites was associated with impaired short-term and working memory in mice that received a microbial transplant from obese human subjects (379). BCFAs could be especially important microbial messengers in scenarios of high-protein, low-complex carbohydrate (i.e., dietary fiber) consumption, as studies have shown that consumption of these diets can increase the microbial production of BCFAs (121, 380, 381). Microbial-derived BCFAs, isovalerate, and isobutyrate have been linked to epithelial physiology and the mucosal immune system (380, 382, 383). High levels of isovalerate have been correlated with depressive mood and cortisol levels in human studies (384). In patients with irritable bowel syndrome, concentrations of isovalerate and valerate were positively associated with abdominal pain and hypersensitivity (385). Lastly, a large research focus has also been placed on the microbial production of trimethylamine (TMA) from dietary choline. Once absorbed, TMA is converted to TMAO, which has been implicated in various chronic diseases, especially those related to the circulatory system [e.g., stroke (386)].

Tryptophan metabolites.

Tryptophan metabolism, specifically the main pathways leading to the production of 5-HT, kynurenine, and indole derivatives, appears to be closely regulated by the gut microbiota (378, 387). These metabolites serve as important bioactive messengers in the microbiota–brain communication and can be modulated by dietary intake, specifically protein. The majority (95%) of 5-HT in the body is produced by intestinal enterochromaffin cells from dietary tryptophan. While a direct effect of intestinally produced 5-HT on the brain is unlikely as it cannot penetrate the BBB, stimulation of vagal afferents and regulation of the immune responses could be potential signaling pathways (388, 389). Additionally, the production of 5-HT can affect peripheral tryptophan availability and, thus, indirectly affect brain 5-HT levels, suggesting that peripheral alterations in 5-HT can affect the central 5-HT signaling system (390, 391).

Other metabolites of tryptophan metabolism, kynurenines, have also been implicated in a range of neurobiological functions (392). Kynurenine can cross the BBB and be further metabolized to neuroactive glutamatergic products, such as kynurenic and quinolinic acid. As an antagonist to the *N*-methyl-D-aspartate (NMDA) receptor, kynurenic acid is usually neuroprotective, whereas quinolinic acid acts as an agonist to the NMDA receptor and exerts neurotoxic effects (393). However, at high concentrations both metabolites can disrupt neurotransmission and induce cognitive impairment (394). Dysregulation of the kynurenine pathway has been linked to several brain disorders, including depression (395), schizophrenia (396, 397), and ASD (398). Indeed, several preliminary clinical intervention studies have reported that probiotic and prebiotic interventions can modulate tryptophan–kynurenine metabolites. For example, two randomized controlled trials in people with clinical depression reported an altered kynurenine:tryptophan ratio and kynurenine concentrations after receiving a probiotic intervention compared with placebo (399, 400). Similar

results were reported in a randomized controlled trial of resistant dextrin in a sample of women with type-2 diabetes mellitus (401). Other prebiotic dietary components, such as polyphenols, may also modulate kynurenine metabolism (402, 403).

Although many important beneficial functions (e.g., antioxidative effect) have been linked to indoles, overproduction of these metabolites resulted in anxiety- and depression-like behavior in animals (404). Additionally, indoles increase the expression of inflammation-associated genes by binding to certain receptors (e.g., aryl hydrocarbon receptor) and can bind to 5-HT receptors to impact behavior and gut motility (405). A direct effect of diet on tryptophan metabolites in humans was demonstrated in a recent pilot study, in which consumption of a Mediterranean and fast-food diet differentially affected tryptophan metabolites (205). An increase in indole-3-lactic acid and indole-3-propionic acid, which have been shown to confer beneficial effects on neuronal cells, was observed after the Mediterranean diet, but these metabolites were decreased after the fast-food diet.

Bile acids.

Bile acids, which are generated by hepatic and bacterial enzymes to aid in lipid digestion, may be involved in the fat–microbiota interaction effect on brain function (406). Microbially derived secondary bile acids are hypothesized to be interkingdom signaling molecules due to their ability to influence the composition and function of the gut microbiota as well as host physiology (407, 408). Recently, abnormal bile acid metabolism was described in neurological diseases, suggesting a role for the transformation of bile acids by gut microbiota as a factor in Alzheimer's disease development/progression and cognitive decline (409, 410). Different CNS pathways through which bile acids can signal have been proposed. Some reports suggest that bile acids can cross the BBB, whereas other bile acid conjugates have been shown to signal directly to the brain as neuroactive ligands, either by binding to farnesoid X receptor and Takeda G protein-coupled receptor 5 (TGR5) present in the CNS or indirectly by binding these receptors in the gastrointestinal tract and initiating a signaling cascade (411). In rats, bile acids were also demonstrated to increase permeability of the BBB (412), which could increase the flow of other neuroactive metabolites or neurotoxins into the brain and affect brain function and behavior. While there is only preliminary evidence suggesting that bile acids could be an important pathway for the microbiota to influence certain brain processes, recent experimental data suggested that shifts in the gut microbiota induced by a Western diet resulted in neuroinflammation and reduced synaptic plasticity via dysregulation of bile acid synthesis, and disruption of TGR5 signaling (406).

Other metabolites.

Other microbial metabolites are being discovered to mediate the gut–brain communication, including bioactive molecules produced from the metabolism of polyphenols and phenolic compounds as well as phytates (413). For example, ferulic acid, a phenolic compound found in plant stems and various herbs, is broken down by the esterase activity of *Lactobacillus* spp. into 4-vinylguaiacol and hydroferulic acid (414) and further converted into caffeic and vanillic acids. These compounds have potent therapeutic effects for neurodegenerative diseases such as Alzheimer's disease (415), and can reduce oxidative stress and cognitive impairment in mice (416) and attenuate BBB disruption and anxiety-like behavior (417). Furthermore, several studies demonstrated that multiple biologically available microbiota-derived phenolic acids were able to modulate mechanisms associated with inflammation and synaptic plasticity (418, 419). Likewise, some of the beneficial effects of dietary polyphenols that are often found in the Mediterranean diet (i.e., isoflavones and lignans) could be attributed to the metabolites of microbial polyphenol degradation, which exhibit higher BBB permeability and exert more protective effects against neuroinflammatory stress than intact polyphenols themselves, suggesting that microbial metabolism of polyphenols is a mechanism to protect brain integrity and mental health (420). Lastly, inositol phosphate, a metabolite produced from the microbial degradation of phytates, which are enriched in nuts, beans, and grains, was shown to be a potent regulator of HDAC3 (421). Given the potential role of HDACs in neuropsychiatric disorders, this could be another potential microbial metabolite at the interface of the diet–brain connection.

Immune signaling

A balanced microbiome is necessary for the development and maintenance of a healthy immune system and disruptions in this equilibrium can have long-lasting health consequences (422). Because inflammation has been identified as an underlying cause in various psychiatric diseases, including depression (423, 424), the immune system has emerged as a key link between the gut microbiota and mental health. Nutrition could mark a pivotal regulator of this interrelationship (425, 426). Animal studies have illustrated that the consumption of a high-fat diet increases colonic, peripheral, and neuroinflammation potentially through promoting a "proinflammatory" microbial profile that can result in cognitive impairment (427, 428). Likewise, the gut microbial profile (decreased bacterial diversity, compositional changes) elicited by diets high in processed food was recognized as a trigger factor for low-grade systemic inflammatory and oxidative changes, favoring the development of neurodegenerative and inflammation-related diseases (429, 430). Different types of mechanisms describing the diet–microbiota–immune interaction have been proposed, including diet-derived metabolites, modulation of the fitness of immunomodulatory microbes, and alteration in microbial composition and activity, as well as changes in host or microbe metabolism of immunomodulatory dietary factors (431). As an example, the following scenario could be proposed: unhealthy dietary habits result in increased proinflammatory signaling through the microbiota and intestinal permeability, promoting a so-called leaky gut (362).

Consequently, immune cells and bacterial components (e.g., LPS) can escape the inflamed intestinal tract and translocate into the circulation. The resulting systemic low-grade inflammation can ultimately elicit a neuroinflammatory response through various pathways, such as binding of bacterial LPS to Toll-like receptors on brain endothelial cells, activating proinflammatory transcription factor NFκB (nuclear factor κ-light chain enhancer of activated B cells) signaling or MAP (mitogen-activated protein) kinase pathways (432). Some reports also suggest that systemic inflammation can impair BBB integrity, allowing the passage of brain-foreign molecules into the brain, triggering cytokine release and activating microglia and the proinflammatory potential of astrocytes, and initiating neuroinflammation and the destruction of neurons and nerve and brain processes (426, 433, 434). It was also recently demonstrated in an animal model that the microbiota influences the presence of immune cells (specifically IgA) in the meninges (membrane coverings of the brain and spinal cord), which in turn can prevent the infiltration of pathogens into the brain (435). Thus, it could be suggested that a diet-altered microbiota could reduce the amount of protective immune cells and allow the entry of neuroinflammation-causing bacteria. Microbiota-induced inflammation associated with poor dietary habits (i.e., high-calorie/fat diets) could also lead to detrimental effects on behavior and cognition through vagus nerve remodeling (436, 437) or alterations in neurotransmitter synthesis and secretion (438). It has also been suggested that food fragments that molecularly mimic BBB proteins can translocate through the leaky gut and elicit an immune response, producing antibodies that then attack and impair BBB integrity (439). Lastly, inflammation could also result in dysregulation of the kynurenine pathway. With increased peripheral inflammation, cytokines can stimulate the kynurenine pathway and increase the supply of kynurenine to the brain, promoting the production of downstream metabolites such as kynurenic and quinolinic acid and disrupting cholinergic, glutamatergic, and dopaminergic neurotransmission (392, 394). In depression, the kynurenine pathway has been proposed as the link between inflammation and depressive symptoms (395, 440).

Due to the accumulating knowledge regarding the impact of inflammation on host health, the anti-inflammatory diet has been proposed as a treatment approach in clinical practice (441). Central to the anti-inflammatory diet is the consumption of vegetables and fruit high in polyphenols, plant-based protein sources and fish, whole grains, and olive oil, while also incorporating herbs, spices, and supplements. This diet has been suggested as a potentially effective treatment for reducing depressive symptoms, with observational studies demonstrating a reduced risk of depression with greater adherence to an anti-inflammatory dietary pattern (442). Mounting evidence also suggests that dietary modulation of the microbiota could drive (in the case of high-fat diets) or improve (in association with high fiber intake) inflammatory status, an association that was suggested as having potential to develop treatments for neuroimmune or neuroinflammatory diseases, such as Parkinson's and Alzheimer's diseases (443). Indeed, some studies have started to highlight reduced inflammation as a mechanism underlying the benefits of healthy diets for mental health. Recently, kefir was demonstrated to direct the microbiota toward distinct immunological and behavioral effects, suggesting a signaling cascade through the microbiota–gut–immune–brain axis (58). These anti-inflammatory properties of fermented food were proposed previously and could in part be attributed to an increase in beneficial microbes or bioactive compounds (444). Likewise, the cognitive and mental health benefits of consuming high-fiber foods could be attributed to the modulatory role of nutrition on the microbiota–immune interaction. For example, SCFAs are immunomodulatory, stimulate GPCRs, promote innate immune responses, and induce regulatory T cells (445). Supplementation with SCFAs protected against high-fructose diet-associated neuroinflammation and neuronal loss by alleviating intestinal barrier impairment (342). Another study showed that MACs prevented microbial alterations, enhanced intestinal tight junctions, reduced colonic, systemic, and neuroinflammation, and improved synaptic signaling molecules and cognitive impairments in animals fed a high-fat, fiber-deficient diet (446). These positive effects were not observed after antibiotic treatment, suggesting that the microbiota was the key modulator in the interplay between diet, inflammation, and cognitive dysfunction. Similarly, resistant starch supplementation reverted microbial changes, improved systemic inflammation, and prevented remodeling of vagal afferent fibers in high-fat-fed rats (447), and a prebiotic (10% oligofructose-enriched inulin) reversed stress-induced microbial changes as well as immune priming and microglia activation in middle-aged mice (299). Other microbial metabolites of dietary components, i.e., tryptophan derivatives, could reduce neuroinflammation by modulating microglia and astrocyte activity (448, 449).

Vagus nerve and neuronal function

Landmark animal studies demonstrating that certain behavioral effects of microbes are abolished after vagotomy have established the vagus nerve as another key player in transmitting microbiota-originating signals to the brain, making it the most direct route of communication (450–452). Briefly, vagal afferents located beneath the enteric epithelium can be stimulated by the gut microbes or microbial metabolites. Microbes shown to use vagal signaling include the pathogen *C. jejuni* (453) or the symbionts *L. rhamnosus* and *B. longum* (450, 451). Among microbial metabolites with vagal-stimulating activity are SCFAs, specifically butyrate, which can activate intestinal vagal terminals (454), and neurotransmitters, e.g., GABA, which can bind the receptors present on vagal afferent neurons (455). Likewise, vagal stimulation by bacterial LPS was shown to result in neuroinflammation, altering brain function and inducing depressive-like or anxious behaviors in animal models (456).

The role of the vagus nerve in regulating food intake has been appreciated for quite some time (457). More recently, preclinical studies provided some evidence that a diet-induced shift in the gut microbiota can disrupt vagal gut–brain communication (436, 437, 458). For example, high-fat/high-sugar diets induced microbial shifts that resulted in intestinal inflammation and increased intestinal permeability, leading to increased microglia activation and vagal remodeling (436, 437). Interestingly, vagal remodeling was suppressed after antibiotic treatment (436), suggesting that the microbiota mediates the detrimental effect of a high-fat diet on vagal signaling. Similarly, inflammation of the hypothalamus induced by a high-fat diet was reduced by vagotomy (459), again indicating that the vagus nerve is a key connector between diet-induced and microbiota-associated neuroinflammation.

To date, investigations into other neuronal functions as a pathway of the diet–microbiota–brain triangle are lacking and thus further investigation is warranted. However, studies illustrating that probiotic strains (*B. longum* and *L. rhamnosus*) modified neuronal excitability and firing potential (460, 461) suggest that the health benefits of foods containing probiotic strains, i.e., fermented foods, could be partially mediated through neuronal alterations. Recently, the underlying link between neuropsychiatric disorders, the microbiota, and regulation of multiple aspects of neuronal activity has been proposed as a promising future therapy for some diseases (462).

Hormonal pathways

While hormones have long been established in the regulation of nutrient digestion and absorption as well as food intake, the notion that the gut microbiota can regulate levels of these intestinal peptides has only recently emerged. Various mechanisms by which the gut microbiota can influence host hormones, including cholecystokinin, PYY, GLP-1, and ghrelin, have been proposed, including direct production by several microbes as well as indirect mechanisms through the modulation of enteroendocrine cells via metabolites or microbial components (463, 464). Receptors for these hormones have been identified on various areas of the brain (465, 466) or vagal afferent terminals (467) and some were shown to cross the BBB to directly bind to receptors (468). Thus, their function can be extended beyond the local regulation of gut motility to the central control of appetite, mood, anxiety, and depression (464).

Studies directly investigating the role of gut hormones in the diet–microbiota–brain triangle are missing, but an indirect pathway through microbial metabolites could be proposed. Highly fermentable prebiotics influenced the microbiota-elicited changes in GLP-1 and PYY and resulted in increased satiety, reduced hunger and changes in appetite in both animal (469) and human (470) studies, providing some initial evidence for the involvement of gut endocrine function in the diet–microbiota–brain interaction. More studies investigating whether hormonal changes associated with dietary manipulation of the gut microbiota translate to behavioral outcomes are warranted.

Metabolic pathways

Traditionally, insulin is most known for its function in maintaining blood glucose homeostasis. Now, an increasing body of literature also suggests that the availability of insulin and insulin receptors is pertinent for normal brain function, not just for providing the necessary energy source but also for ensuring proper neuronal activity and signaling circuits [e.g., dopaminergic and serotonergic systems (471)]. Thus, unsurprisingly, insulin resistance has been implicated in neurological health and cognitive impairment (472) and an association between reduced insulin signaling and the pathogenesis of neurodegenerative diseases has been proposed (471). Due to the established direct link between microbiota composition and peripheral and central insulin sensitivity (473), and animal studies demonstrating that high-fat diets alter microbiota composition and contribute to metabolic changes (including insulin resistance and glucose homeostasis) as well as depression- and anxiety-like behavior (474), an underlying mechanism between microbial alterations associated with high-fat diets, metabolic dysfunction, and psychological problems could be proposed (475). Two animal dietary interventions have successfully targeted the microbiota and improved metabolic and, consequently, cognitive function. Supplementation with MACs (446) and intermittent fasting (320) improved brain parameters, which was attributed to improved insulin resistance markers and signaling. In both studies, administration of antibiotics abolished the dietary effects observed on metabolic and cognitive parameters, suggesting that the microbiota is required for the diet-associated improvements. Microbial metabolites could also be of interest in the insulin–neuronal health interplay, as some (e.g., inositol) have been shown to have insulin-sensitizing effects, thereby potentially contributing to the functioning of the CNS (476).

HPA axis

The HPA axis is the main neuroendocrine regulator of stress responses in mammals. Dysregulation of the HPA axis has long been implicated in a variety of stress-related neuropsychiatric disorders, such as depression (477, 478). Evidence for the pivotal role of the gut microbiota in regulating the HPA axis comes from studies demonstrating a hyperresponsiveness of the HPA axis in the absence of a gut microbiota (218), as well as from preclinical and clinical studies observing reduced levels of corticosterone (479) or cortisol (329) after probiotic or prebiotic supplementation.

Nutrition interventions have been shown to normalize HPA axis activity. Supplementation with vitamin C (480), fish oil (481), or polyphenol-rich dark chocolate (482) resulted in reduction of the cortisol level and subjective stress measures in human cohort studies. A whole-foods diet, specifically the increase in dietary carbohydrate, improved salivary cortisol levels in overweight or obese women (483). Although detailed information on the specific type of carbohydrate

was not provided, other studies demonstrating that SCFAs modulate HPA axis activity and attenuate cortisol responses to an acute stressor (484) could suggest that microbial metabolism of dietary fiber is involved in the regulation of the HPA axis. Because the gut microbiota composition was not characterized (483) or the SCFAs were directly administered to the colon, thus bypassing microbial action (484), it remains to be determined whether these positive effects of nutrition on the HPA axis and mental health are mediated by the microbiota. However, targeting HPA-axis activity through microbiota-directed dietary interventions has been suggested (485) and some studies have shown that the gut microbiota might be involved in the nutritional modulation of stress responses. For example, in a preclinical study, HPA-axis dysregulation and cognitive dysfunction induced by maternal separation in early life was attenuated by supplementation with milk fat-globule membrane and prebiotics while also impacting microbiota composition (486). In another animal model of chronic unpredictable social stress, prebiotic administration normalized stress-induced microbiota alterations and elevations in corticosterone levels (487).

While we are beginning to understand the role of diet in mediating the mechanism underlying the microbiota–brain crosstalk, additional studies are required to fully elucidate the relation. Certainly, due to the combination of food components humans ingest daily and the complex mechanisms of the diet–microbiota–brain signaling, a multitude of intertwined pathways will most likely underlie the diet–microbiota–brain interaction. For example, SCFAs stimulate the production and release of neurotransmitters and gut hormones in the gastrointestinal tract (353, 360), and the HPA axis interacts closely with the vagus nerve (488) and the immune system (489). Thus, it is likely that whole-dietary approaches will initiate a variety of mechanisms through which the diet-induced microbial profile will influence brain function and mental health. A comprehensive new review covers the most recent knowledge regarding the mechanisms by which diet may influence depression, including via the gut microbiota (490).

Responders and Nonresponders to Dietary Interventions

With the increase in studies targeting the microbiota to improve human health, interindividual variability in metabolic response to these interventions is increasingly being described (e.g., 491–493), with some studies reporting that <30% of participants reach the desired outcome (494). Identifying which diet an individual could benefit from is an important consideration for the development of dietary therapies for certain diseases, but also for designing personalized nutrition approaches. Various factors could determine an individual's microbial and systemic responses, including, but not limited to, age, gender, genetics, exercise, baseline microbiota composition, and habitual dietary patterns (495–498).

Regarding the baseline microbiota composition, the ratio of bacterial groups and the presence of specific microbes have been described as constituting an important determinant of diet intervention success. Due to the specialized ability of microbial taxa to metabolize food components, the make-up of a responsive microbial community will depend on the dietary intervention of interest. The use of so-called enterotypes has been proposed as a way to determine an individual's response to a dietary intervention and as an approach for personalized nutrition (499). Enterotypes were first described in 2011 as clusters of microbiota that were dominated by *Prevotella*, *Bacteroides*, or *Ruminococcus* (88). Since then, studies have shown that stratifying participants based on these enterotypes predicted responses to dietary interventions (specifically fiber), especially regarding metabolic improvements and weight loss (70, 500). The success of calorie restriction diets, on the other hand, depended on baseline abundance of *A. muciniphila* (68), some clostridial species [*Eubacterium ruminantium*, *Clostridium felsineum*, and *C. sphenoides* (501)] or abundances of *Lactobacillus*, *Leuconostoc*, and *Pediococcus* (502). Since microbes in the human gastrointestinal system are part of a community and often do not function in isolation but rely on a complex interaction with other microbes for survival and growth, success of a dietary intervention was also shown to be contingent on the presence of a group of microbes and microbe–microbe interactions. Using linear discriminant analysis, Zhang et al. (503) identified 43 operational taxonomic units (OTUs) that discriminated between rats that were susceptible and those that were resistant to a fermented milk product intervention. In a human intervention study, network complexity analysis revealed that in nonresponders the negative interactions between microbial species increased after the intervention, meaning that more species competed for the same substrate, whereas in responders the positive interactions between species and the complexity of interactions increased after the intervention (70).

Baseline bacterial richness and diversity might be another important predictor of the success of a dietary intervention (66, 504). Thus, an individual response to fiber could depend on the initial target bacterial levels and those individuals with the lowest fiber intakes and a limited microbial richness at baseline potentially might have the most to gain from increasing fiber intake and exhibit greater microbiota changes (505). It has also been suggested that microbial stability could determine the responsiveness to a dietary intervention. Thus, a relatively stable microbiota might benefit from a stable diet, whereas an unstable microbiota could mean a flexible response to dietary intervention and constant re-evaluation of the optimal diet (506). Lastly, microbial gene richness, harboring microbes with the enzymatic activity to metabolize food components, and the concentration of microbial metabolites were described as decisive factors in the diet intervention response. In fact, the extent of the beneficial systemic effect of certain nutrients (e.g., polyphenols) depends on the ability of an individual's microbiota phenotype to convert the nutrients into bioavailable compounds (507).

For example, there is substantial interindividual variability in the rate and concentration of the bioactive metabolite urolithin A following consumption of the pomegranate-derived polyphenols ellagic acid, punicalagin, and ellagitannin (508). A further example is the isoflavone metabolite equol, which has considerable estrogenic properties, but upwards of half of the population lack the microbiota composition to produce it (509). Which microbial enzymatic repertoire is required for a dietary intervention to be successful depends on the nutrients present in the study diet (70, 494, 510).

Due to the pronounced effect of diet on microbiota composition, habitual dietary habits prior to the intervention could also be an important determinant of the microbiota responsiveness. Studies have shown that poor dietary habits over a long period of time could lead to the potential extinction of some microbes (13, 511). Therefore, the microbial enzymatic capacity to respond to healthy diets (i.e., high-fiber diets) could be missing. Thus, in order for an individual to respond to a dietary intervention, administration of the missing microbes may be necessary. Indeed, a combined dietary–probiotic approach led to a greater reduction in anxiety symptoms, as measured by the Hamilton Anxiety Rating Scale, than each intervention alone in a small-scale study (512). In a prebiotic supplementation study, participants with high fiber intake at baseline showed a greater microbial response in response to an inulin-type fructan prebiotic than those with low habitual fiber intake (513). Several other studies have reported that the baseline diet of an individual predicted the systemic and microbial responses to the diet intervention (70, 514). These studies indicate that thorough dietary assessment of participants is crucial in microbiota-targeted interventions. However, many studies do not adequately capture information on habitual dietary intakes prior to commencement of interventions (515).

While advances in predicting an individual's response to a diet intervention have been made, there is a lack of research studies investigating factors that predict the effect on cognitive outcomes. Additional larger, well-powered clinical trials with defined confounders known to impact the microbiota composition (e.g., ethnicity, age, gender, and habitual dietary pattern), consistent sample collection, and sequencing techniques as well as the use of other "omics" approaches (transcriptomics, proteomics, and metabolomics) to discover microbial biomarkers are needed to further distinguish between responders and nonresponders to diet interventions and for this approach to become applicable in clinical care (495, 516). Extensive characterization of baseline dietary habits will also be crucial, as there is no clear consensus yet as to how dietary patterns direct host responses. For example, it has been proposed that low dietary fiber intake at baseline can lead either to greater responsiveness to a prebiotic supplement, because the increase in available substrate will allow low-abundance bacteria that are able to use it to flourish and result in a stronger host response, or to lower responsiveness due to the absence of bacterial enzymatic capacity to use complex carbohydrates (516).

Is Microbiota Modulating the Effect of Diet on Brain and Behavior?

Whether the beneficial effects of dietary interventions are microbiota-mediated, caused by the direct effect of dietary components on the host or a combination of the two, is a current topic of debate. It has been suggested that the microbiota could be a mediator or moderator of the effect of the diet on host responses (517). As a mediator, diet directly changes the microbiota composition and function, which in turn impacts the host, whereas, as a moderator, the effect of the diet on the host response is not dependent on the microbiota, but the microbiota could strengthen the relation (**Figure 3**). One example of a mediating effect could be the intake of dietary fiber and brain endpoints. Inaccessible to the host, dietary fiber is fermented by the gut microbiota, supporting the growth and activity of SCFA-producing bacteria and increasing the production of SCFAs. In turn, SCFAs can directly or indirectly signal to the brain, influencing brain physiology and behavior. On the other hand, a moderating effect could be observed in the impact of ω-3 fatty acids or polyphenols. On its own, these nutrients are potent modulators of brain physiology and can be neuroprotective. However, bioavailability and some biological activity might also be dependent on conversion by the gut microbiota (413), which is the case in the interaction between polyphenols, microbiota, and associated beneficial effects (507).

As presented in Table 2, studies investigating the impact of whole-diet approaches on the gut microbiota and behavioral or cognitive outcomes have started to provide evidence to decipher potential correlational or causal relations between the diet–microbiota–brain crosstalk. Correlation analysis revealed that diet-induced changes in the microbiota were associated with biochemical and behavioral outcomes and gene expression changes (314, 316). The most convincing evidence, however, for the potential mediating effect of the microbiota on the diet–brain relation comes from animal studies using GF mice or antibiotic treatment. In a recent study, it was revealed that the microbiota is required for the antiseizure effect of the ketogenic diet (341). The authors not only showed that GF status or antibiotic treatment abolished the antiseizure effect of the ketogenic diet, but fecal transplant of a microbiota induced by the ketogenic diet also elicited seizure protection. Likewise, the beneficial effect of intermittent fasting on cognitive impairment in a diabetic mouse model was partially abrogated after administration of an antibiotic cocktail (320). Additionally, transferring microbiota from mice fed a high-fat diet to conventional mice resulted in altered behavior and increased neuroinflammation even when the recipient mice were fed a normal chow diet (518). Similarly, hippocampal neuroinflammation induced by a high-fructose diet was suppressed by administration of a broad-spectrum antibiotic in mice (342). Lastly, results from

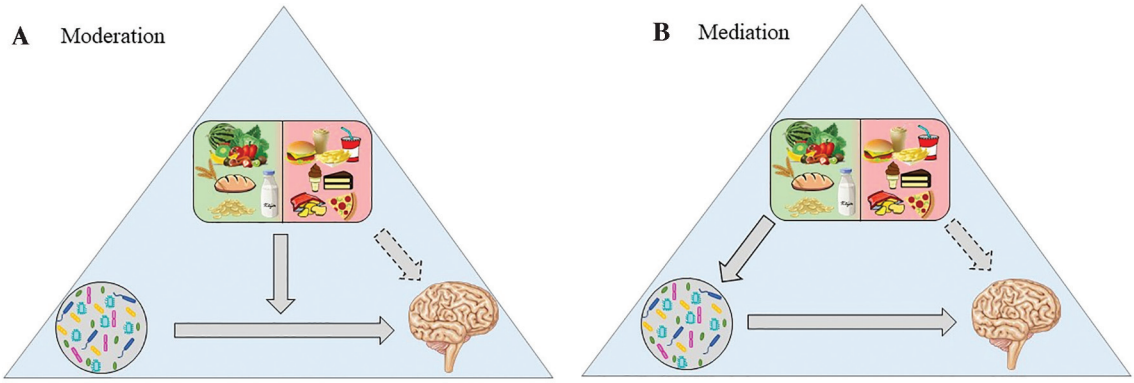

FIGURE 3 Mediating compared with moderating interactions between diet, microbiota, and the brain. Both a moderating and a mediating relation between diet, microbiota, and the brain could be proposed. (A) In the moderating relation, diet could strengthen or weaken the microbiota–brain interaction, whereas in a (B) mediating relation diet directly changes the microbiota composition and function to influence brain processes. The potential direct effect of the diet on brain processes is depicted by dashed lines.

an in vitro follow-up study using fecal lysate from high-fat-diet-fed mice suggest that the LPS components from Gram-negative bacteria induced by the high-fat diet contributed to the disturbance of neuronal cell function in vivo (318).

While animal models allow the study of the necessity of the microbiota in diet effects, these interactions are more difficult to decipher in clinical studies. Nevertheless, the fact that the success of a dietary intervention in human cohorts can in part be dependent on the baseline microbiota composition hints at the importance of the microbiota in mediating diet benefits even in human populations. Likewise, it has previously been suggested that some of the anti-inflammatory properties of the Mediterranean diet may be mediated by modulation of the microbiota (519). Other reports indicating that the microbiota is mediating the beneficial effect of diet on health outcomes (300, 501, 520) and diet intervention studies specifically targeting the microbiota (e.g., through increased dietary fiber and fermented foods) demonstrating improvements in some aspects of mental health (332) give reason to hypothesize that similar relations might be observed in the diet–microbiota–brain triangle in human cohorts.

Conclusions and Future Directions

Mounting evidence for the effect of diet on the microbiota and the crucial role of the microbiota in brain function and behavior is presented in the literature. While preclinical studies have begun to elucidate the diet–microbiota–brain interaction, there has been little human research investigating this intricate relation thus far. As outlined above, most research has focused on the detrimental effect of high-fat, high-sugar or high-calorie diets on the microbiota–brain interface using animal models, and we are just starting to understand the potential mechanisms underlying the diet–microbiota–gut–brain axis. The fact that many different dietary patterns have been linked to improved mental well-being reinforces the fact that individual components of the diet may be less important to mental health than overall dietary patterns high in plant foods and low in ultraprocessed foods. However, although the benefit of increasing plant and reducing ultraprocessed foods applies to all, studies continue to highlight variability in individual metabolic responses to particular foods, influenced by individual microbiota variations. Thus, understanding how particular components of diets influence the gut microbiota and thus health outcomes, including mental health, is a continuing imperative. Although evidence regarding the role of the microbiota in the interface between diet and brain processes is emerging and compelling results are available, especially from animal studies, this area of research is still in its infancy and one should be cautious and not overinterpret the results. Likewise, dietary studies in animal models may not always be translatable to human populations as animal diet formulations used in the studies often provide doses that are outside of the daily intake in human populations, so that the translational capacity of these studies should be considered. Many unanswered questions regarding the use of healthy dietary patterns in restoring the microbiota–brain communication and its efficacy for human interventions remain and direct effects of dietary components on the brain cannot be ignored.

To drive the development of microbiota-targeted human interventions, it will also be important for the field to further understand the determining factors that predict the individual's response to a given intervention. Given the increasing knowledge that microbial extinction is partly attributed to unhealthy eating patterns, such as increased consumption of processed and fried food and low fiber intake, it may be that future nutritional interventions will combine dietary approaches with specifically designed probiotics in order for the dietary intervention to be effective. Some research has already suggested that loss of microbial diversity over generations following a low-MAC diet was only recoverable when also administering the missing microbes. Thereby, the

missing microbes do not necessarily have to be supplied by probiotic supplements, but could be consumed through food products containing beneficial bacteria, such as fermented foods.

While the evidence from intervention studies in humans is limited, the existing data consistently support increasing the intake and variety of plant foods and reducing or eliminating ultraprocessed foods. In this sense, dietary recommendations for both mental and gut health are concordant with those for most other health states. Thus, the MyNewGut consortium has recommended that patients with depression should be encouraged to consume a plant-based diet with a high content of grains/fibers, fermented foods, and fish (521). Moreover, although there is some evidence for the use of probiotics as supplements, manipulating the microbiota through diet might be more feasible in the longer term and an economically cheaper solution than probiotic supplementation. An added benefit of adopting dietary improvement as a treatment strategy for mental health is its cost-effectiveness, given the compelling economic evaluations of 2 landmark trials investigating the efficacy of a Mediterranean-style dietary intervention on reducing depression symptoms (522, 523). This likely relates to the positive benefit of dietary improvement for overall health and functioning, including the chronic conditions that are so commonly comorbid with mental disorders. Given the average 20-y mortality gap in those with mental disorders compared with the general population, interventions that improve physical health as well as mental health are likely to yield significant benefits in both health and mental health outcomes in the many people affected by mental illness (138, 524).

Although many opportunities for improving our health apparently lie in our microbiota, more research needs to be done to establish causality, clearly define a "healthy microbiota," understand the potential and limitations of personalized nutrition approaches, and decipher mechanistic relations. It will also be crucial to go beyond characterizing the members of the microbiota and integrate multiomics approaches to better understand the overall functionality of the microbial community.

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