Feeding the microbiota-gut-brain axis: diet, microbiome, and neuropsychiatry

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The microbial population residing within the human gut represents one of the most densely populated microbial niche in the human body with growing evidence showing it playing a key role in the regulation of behavior and brain function. The bidirectional communication between the gut microbiota and the brain, the microbiota-gut-brain axis, occurs through various pathways including the vagus nerve, the immune system, neuroendocrine pathways, and bacteria-derived metabolites. This axis has been shown to influence neurotransmission and the behavior that are often associated with neuropsychiatric conditions. Therefore, research targeting the modulation of this gut microbiota as a novel therapy for the treatment of various neuropsychiatric conditions is gaining interest. Numerous factors have been highlighted to influence gut microbiota composition, including genetics, health status, mode of birth, and environment. However, it is diet composition and nutritional status that has repeatedly been shown to be one of the most critical modifiable factors regulating the gut microbiota at different time points across the lifespan and under various health conditions. Thus the microbiota is poised to play a key role in nutritional interventions for maintaining brain health. (Translational Research 2017;179:223–244)

Abbreviations: ASD = Autism spectrum disorder; ADHD = Attention-deficit hyperactive disorder; AMPK = AMP-activated protein kinase; ANS = Autonomic nervous system; BDNF = Brain-derived neurotrophic factor; BMI = Body mass index; BCFA = Branched chain fatty acid; CCK = Cholecystokinin; CNS = Central nervous system; CREB = cAMP response element-binding protein; DA = Dopamine; EECs = Enteroendocrine cells; ENS = Enteric nervous system; FOS = Fructo-oligosaccharides; FXR = Farnesoid X receptor; GOS = Galacto-oligosaccharides; GF = Germ-free; GLP1 = Glycogen-like protein 1; GABA = Gama-aminobutyric acid; GI = Gastrointestinal tract; HPA = Hypothalamus-Pituitary Axis; IBS = Irritable bowel syndrome; IL = Interleukin; LPS = Lipopolysaccharide; LTP = Long-term potentiation; MAMP = Microbes-associated molecular patterns; NOD = Nucleotide-binding-oligomerization domain containing peptide; PYY = Peptide YY; PUFA = Polyunsaturated fatty acid; Reg3γ = Regenerating family member 3 gamma; SCFA = Short chain fatty acid; sp = Species; SPF = Specific-pathogen-free; TMAO = Trimethylamine oxide; TNF = Tumor necrosis factor; T-regs = regulatory T cells; WHO = World Health Organization; ZO = Zonula occludens

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INTRODUCTION

"Let food be thy medicine and medicine be thy food."

—Hippocrates

This oft-quoted adage from Hippocrates from over two thousand years ago may still be as relevant today where there is a growing renaissance in our appreciation of the importance of diet in maintaining health, including brain health.[1] In parallel, the importance of diet in regulating the composition of the human gut microbiota has gained much attention of late.[2] Accumulating evidence continues to highlight the importance of the gut microbiota in maintaining homeostasis and contributing to a variety of different physiological processes including protection from pathogens,[3] food metabolism,[4,5] host fat storage,[6] and even regulation of brain physiology and behavior.[7-9] More recently researchers have started to address the role of the gut microbiota within multiple different neuropsychiatric conditions, including autism,[10] depression,[11,12] stroke,[13] and schizophrenia.[14] The gut microbiota is influenced by various factors such as host genetics, health status, lifestyle, mode of delivery at birth, antibiotic usage, and dietary pattern based on different cultural practices.[15-18]

Given that diet is a key contributor in shaping the composition of the gut microbiota and that changes in dietary patterns show a direct effect on the composition of the gut bacteria.[18-22] It is important to contextualize diet and nutrition effects on the microbiota-gut-brain axis. Therefore, in this review, we discuss recent advances in the understanding of the critical role diet plays in establishing a link between the gut microbiota and host health. Furthermore, the role of the microbiota in the gut-brain axis in relation to its association with various neuropsychiatric disorders will be explored.

BIDIRECTIONAL CROSS-TALK BETWEEN GUT MICROBIOTA AND THE CNS

The gut-brain axis acts as an integrative physiological system amalgamating endocrine, immunologic, nutritional, efferent, and afferent neuronal signals between the gastrointestinal (GI) system and the brain.[23] The microbiota is now seen as a key component of this gut-brain axis, and disturbances in the homeostasis or dysregulation of the gut-microbiota-brain axis have been implicated in various immunologic, neurologic, and psychiatric conditions.[23-25] The complex network of communication between the gut microbiota and central nervous system (CNS) is mediated through the autonomic nervous system (ANS), the enteric nervous system (ENS), the immune system, and the bacterial metabolites.

Neuronal pathways. After ingestion of a meal, the presence of nutrients in the GI tract initiates complex neural and hormonal responses informing the brain of the ongoing change in the nutritional status. The gut is innervated with primary visceral afferent nerve fibers from both sympathetic and parasympathetic branches of the ANS.[26] The afferent fibers project information from the gut to the subcortical and cortical centers of the brain including the cerebral cortex, cingulate, and insular regions, whereas effector fibers project to the smooth muscles of the gut.[27] In addition, the gut also informs the brain about the current nutritional status by secreting a host of gut peptides from intestinal cells including enteroendocrine cells (EECs). Some of these hormones communicate with CNS primarily via effects on nearby afferent nerve fibers supplying the gut, whereas others are secreted from the gut into the circulatory system and whereupon they enter the brain to mediate their central effects.[28]

This bidirectional communication helps in maintaining a proper GI homeostasis and cognitive function.[23] The vagus nerve is the major nerve of the parasympathetic system of the ANS and crucial for mediating the effects of gut microbiota on different neurophysiological function[29] (Fig 1). For example, vagotomized mice failed to show any improvement in anxiety or depressive-like behaviors following treatment with a potential probiotic *Lactobacillus rhamnosus* indicating that behavioral properties of this bacterial strain are dependent upon gut-brain signaling via the vagus nerve.[32] Similarly, a potential probiotic *Bifidobacterium longum* failed to produce an anxiolytic effect in a vagotomized colitis mouse model.[33]

The vagus nerve terminating near the mucosa conveys information from the intestine to the brainstem through nuclei such as the nucleus tractus solitaries and the nodos ganglion, which represent an intermediate relay in brain-gut axis bidirectional communication.[34] (Fig 1). The vagus nerve does not project directly into the lumen, and its activation is partly dependent on the secretion of chemical signals such as peptide hormones (peptide YY [PYY], glucagon-like peptide 1 [GLP-1], cholecystokinin [CCK]) by EECs, specialized endocrine cell in intestinal tract[35] (Fig 1). For instance, $PYY_{3–36}$, the major circulating PYY, binds to the hypothalamic neuropeptide YY_2 receptors and is associated with reduction in food intake in rodents and humans[36] and vagotomy blocks $PYY_{3–36}$-induced hypophagia and associated activation of neurons in the hypothalamic arcuate nucleus.[37]

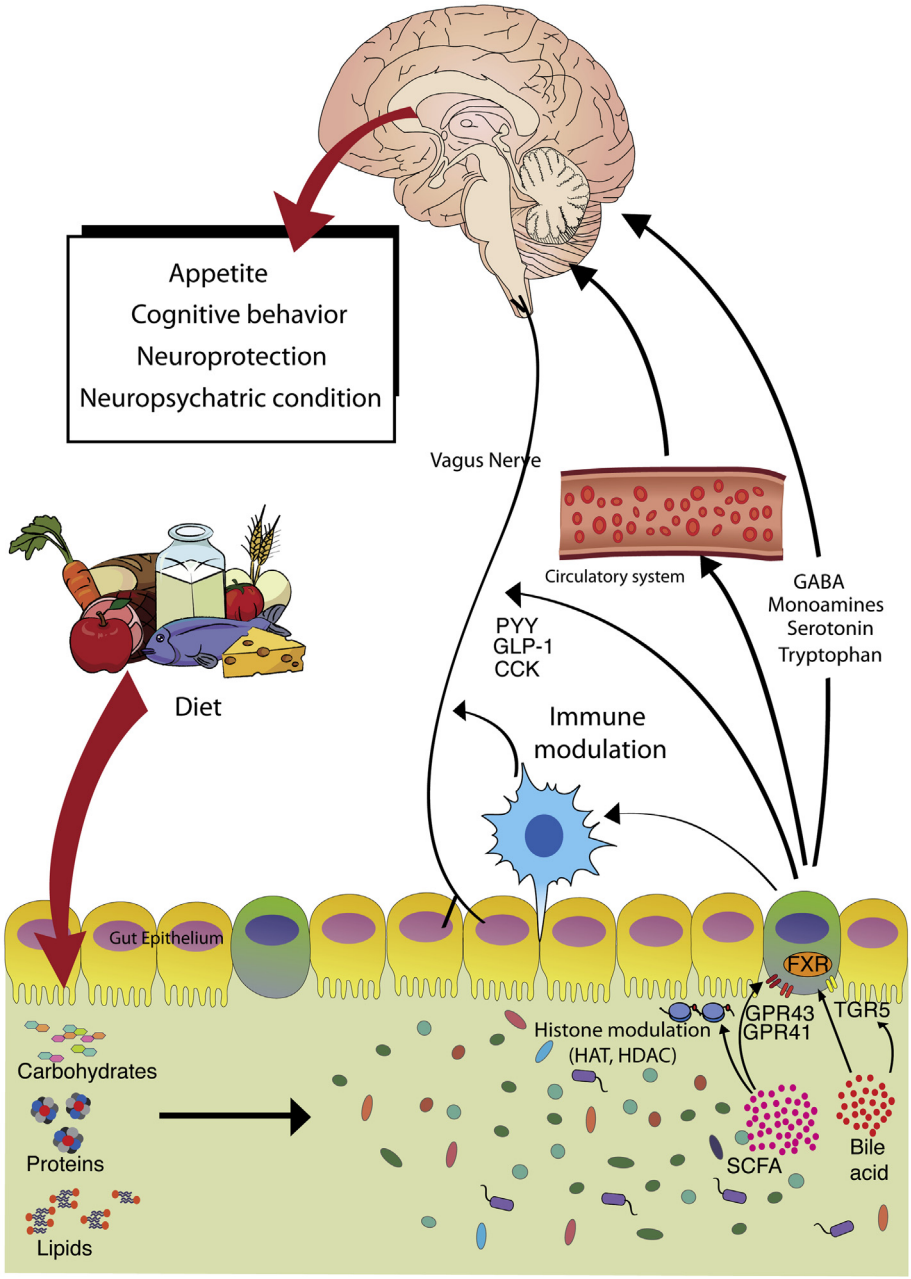

Fig 1. Cross talk between diet-derived macro- and micronutrients, the microbiota and its metabolites, and the brain: The food in our diet is broken down into carbohydrates, protein and lipids, which can be further metabolized by the gut microbiota. The by-products from carbohydrate fermentation can result in the synthesis of SCFA, which have the possibility to induce epigenetic modulation of the intestinal epithelial cell in addition to direct effects on GPCRs (GPR43/41) on EECs.[30] Bile acids derived from fatty acid metabolism can also have multiple effects including interacting with GPCR TGR5 (also known as G protein-coupled bile acid receptor 1 [GPBAR1]) and the nuclear receptor farnesoid X receptor (FXR) on the (EECs).[31] Both SCFA and bile acids can thus stimulate the modulation of gut hormones secretion, including PYY, GLP-1 and CCK as well as having immunomodulatory responses. The satiety hormones can modulate CNS function and regulate appetite and food intake. Finally, a myriad of neurotransmitters and neuroactive substances produced by the gut microbiota can regulate a host of peripheral and central functions via indirect and direct mechanisms. In addition, some metabolites can pass into the blood and through the circulatory system, indirectly via receptors on cells or directly through the blood brain barrier, modulate brain function. CCK, Cholecystokinin; EECs, Enteroendocrine cells; FXR, Farnesoid X receptor; GABA, Gamma-aminobutyric acid; GLR-1, Glycogen like protein; GPCR, G protein-coupled receptor; HAT, Histone acetyltransferase; HDAC, Histone deacetylases; PYY, Peptide YY; SCFA, Short chain fatty acid.

Enteroendocrine cells. EECs are a set of specialized endocrine cells forming 1% epithelial cells of the GI tract and are capable of sensing luminal content and producing and releasing signaling molecules or hormones.[34] As referred to in the previous section, EECs release peptides and these peptides act on the receptors located along the vagal afferent fibers. The information generated by EECs is passed to the brain by the vagal nerve and therefore EEC is critical for the bidirectional gut-brain communication.[38] CCK, a satiety peptide hormone, transmits sensory signals from the gut lumen through direct EEC-nerve communication or via paracrine mechanisms, that is, activation of the vagal pathway.[34,39] Exogenous administration of CCK activates CCK1 receptor and induces reduction of meal size and satiety. However, CCK1 receptor null mice fail to show reduction of meal size or satiation.[40]

EECs are located along the GI tract in direct contact to the lumen and also in close proximity with the gut microbiota, which allows for the bacterial commensal to interact with EECs with metabolites and regulate the secretion of various gut peptides.[26,34] For instance, short chain fatty acids (SCFAs; metabolic products of polysaccharide fermentation) interact with G-protein–coupled receptor 41 (GPR41) expressed upon EECs in the gut epithelium, which causes a reduction in the expression of PYY thereby inhibiting gut motility, increasing intestinal transit rate, and reducing nutrient contact time.[41,42] Consistent with this finding, *Ffar2*-and *Ffar3*-knockout mice display impaired oral glucose tolerance and increased intestinal transit time.[42,43] However, further research is required to clarify the mechanisms of different metabolites on the EECs or intestinal gut cells and their corresponding role in gut-microbiota-brain cross talk.

Circulatory system. Microbial-derived metabolites present in the intestinal lumen are absorbed into the circulatory system by passive or active mechanisms, whereas metabolites structurally similar to amino acids, sugars, and vitamins are actively transported via specific transporters. For instance, SCFAs are transported either by monocarboxylate transporters or via diffusion.[44] Conversely, microbial metabolites may cross the barrier via paracellular (between cells) transport when the epithelial barrier is breached ("leaky gut") which may often result in altered microbiota composition and induction of an inflammatory response.[45] Thus, blood circulation not only mediates the flow of metabolites throughout the host system but also regulates gut microbiota message to the brain.

Immune system. The bacterial commensals present in the GI tract are often found at sites enriched with immune cells including epithelial cells, mucus, immunoglobulin A (IgA), and antimicrobial peptides.[46] These immune cells have an important role to play as they keep a check on the homeostatic relationship between the microbiota and the host. In addition, the mucus produced by goblet cells offer the first line of protection by limiting the contact between the microbiota and host tissue, thus preventing microbial translocation.[46,47] Further production of the antimicrobial peptides by the intestinal epithelial cells helps to limit the commensal microbiota to the gut. For instance, regenerating family member 3 gamma (Reg3γ), a mucosal antimicrobial peptide secreted by intestinal epithelial cells has been shown to directly kill gram-positive bacteria and thus regulating the microbiota composition.[48] Germ-free (GF) mice known to have immunologic deficits[49] were found to express diminished levels of Reg3γ, suggesting a potential role of gut microbiota in immunity regulation. However, colonization of GF mice with the gram-negative bacteria *Bacteroides thetaiotaomicron* induced expression of Reg3γ. Conversely, when GF mice were colonized with the gram-positive bacteria, *B. longum,* Reg3γ expression was reduced.[50-52] Such results highlight an important regulatory interaction between the gut microbiota and the immune system. Immunoglobulin A is an immune regulator that is associated with the compartmentalization of intestinal bacteria. Intestinal dendritic cells together with T and B cells in the Peyer's patches mediate the production of IgA specific for commensal-derived antigens and regulate microbial translocation.[52]

The immune system is not only involved in maintaining homeostasis between the gut microbiota and the gut, it may also act as an intermediary between the gut microbiota and the brain.[53] The gut microbiota may mediate an immune response by releasing certain molecules, which are potent promoters of the innate immune system; for example, lipopolysaccharide (LPS) or peptidoglycan. When the integrity of the intestinal mucosal barrier is compromised, gram-negative bacteria expressing LPS can be translocated from the gut into the circulatory system leading to peripheral immune activation. Preclinical and clinical studies have both shown that peripheral immune activation following LPS administration can lead to depressive-like behaviors.[54,55] This highlights how the bacterial commensals can modulate behavior via the immune system. A recent study in GF mice showed a link between the brain's resident immune cells, microglia, and the gut microbiota.[56] The GF mice display defects in microglia with altered cell proportions and immature phenotype.[56] Moreover, microglial activation was diminished in GF mice following LPS administration

further suggesting that the absence of a microbiota leads to an attenuated neuroimmune response. This was further supported by Erny et al when they depleted the microbiota of animals with antibiotics to find a similar aberrant microglial phenotype and activation.[56] Thus, the microbiota is fundamental for maintaining a proper neuroimmune response.

Short chain fatty acids (SCFAs). SCFAs (eg, acetate, propionate, and butyrate) are one of the dominant metabolites produced in the colon and small intestine through bacterial fermentation.[57] Bacteria from the Bacteroidetes phyla mainly produce acetate and propionate, whereas butyrate is predominately synthesized by Firmicutes. SCFAs regulate physiological processes. For instance, acetate has been shown to influence the availability of histone acetyltransferase substrate, critical for epigenetic modulation by inducing histone acetylation.[58] Whereas butyrate produced by the microbiota supplies the majority of energy to colonic epithelial cells.[59] A growing body of evidence indicates that the gut microbiota regulates host gut physiology and immune function via epigenetic mechanisms through the production of SCFAs.[60,61] For instance, butyrate regulates the function of regulatory T cells (T-regs) by mediating their induction within the colon. This modulatory role on T-regs cells is believed to be mediated by the ability of SCFAs (notably butyrate) to inhibit histone deacetylases.[62-65] This epigenetic property of butyrate is being looked into as a potential treatment for colon cancer and various other conditions.

Among the various functions of SCFAs, they are also known to affect lipid, glucose, and cholesterol metabolism in various tissues.[66-68] Acetate and propionate are shown to strongly reduce adipose tissue lipolysis. This is mediated by acetate and propionate activating Ffar2.[69,70] In human studies, a mixture of SCFAs, including acetate and propionate, reduced lipolysis along with reducing plasma fatty acid and glycerol levels.[71,72] Moreover, oral administration of acetate and propionate reduced glycemia in the hyperglycemic diabetic mouse model and in normal rats.[68,73] This reduction in gluconeogenesis has been suggested to occur via the liver through the activation of the hepatic AMP-activated protein kinase (AMPK) pathway.[73]

SCFAs also control the release of satiety hormones such as PYY, GLP-1, and CCK. SCFAs interact with G-protein–coupled receptors (GPR43 and GPR41) upon gut epithelial cells to modulate the secretion of satiety peptides.[74] A study in which mice were treated with labeled acetate (^{11}C-acetate) showed that this particular SCFA has a direct role in the central control of appetite by regulating brain regions associated with appetite regulation including the hypothalamus. Acetate mediates this function by activating acetyl-CoA carboxylase which leads to changes in the expression profile of GLP-1 and PYY that favor appetite suppression.[75] A clinical study showed acute intake of inulin-propionate ester which selectively increases propionate production resulting in the increase of GLP-1 and PYY in the plasma, thus suggesting an important role of propionate with appetite regulation.[76] Moreover, increasing colonic propionate production reduced BOLD signal in the caudate and nucleus accumbens during fMRI food evaluation paradigm.[77] In the caudate, there was significant reduction in BOLD signal to high-energy food. Subjects with high colonic propionate showed reduction in subjective appeal of high-energy food picture and low energy intake during an ad libitum meal, thus suggesting the critical role of SCFAs especially propionate in the regulation of brain regions associated with reward-based eating behavior.[77] This data suggests a critical role of SCFAs in the regulation of the gut-microbiota-brain cross talk.

Neurotransmitters. The gut microbiota has been associated with the synthesis of not only metabolites but also different neuroactive molecules including serotonin, melatonin, gamma-aminobutyric acid (GABA), catecholamine, acetylcholine, and histamine.[78-80] More work is required to determine whether these microbial-derived neurotransmitters influence their corresponding central levels. However, there is some evidence to suggest that the microbiota influences central neurotransmitter. GF mice have increased plasma levels of tryptophan and serotonin compared with conventional mice.[81,82] However, postweaning colonization of the GF mice results in the normalization of the tryptophan levels in the blood plasma. Interestingly, the change in tryptophan level with colonization might be temporary because in another study, GF mice showed changes in tryptophan levels in plasma 4 days following gut microbiota colonization but not at day 30.[83]

INFLUENCE OF AGE ON THE GUT MICROBIOTA

The composition of the gut microbiota has been observed to change substantially across the lifespan.[84,85] It is important to realize that the impact of diet on the microbiota-gut-brain axis will also vary across the different epochs of life.

From birth to weaning. The bacterial composition of the gut during the early stages of development has a significant effect on the immune programming and physiology of the individual.[86] Maternal and neonatal diet is critical for shaping the gut microbiota.[85-87] Breast milk,

an initial food source for infants is rich in a wide variety of important prebiotics (carbohydrates in the form of ~200 isomers of human milk oligosaccharides [HMO]), nucleotides, immunoglobulins, cytokines, and SCFAs.[88,89] It is considered to be an optimal diet for infants and recommended by the World Health Organization (WHO) for newborns until the age of 6 months followed by supplemental breast-feeding until 2 years of age.[90] A recent study has shown that Malawian infants fed on breast milk deficient in a specific HMO (ie, sialylated HMO) for 6 months showed severely stunted growth.[91] Similar growth deficits were also replicated in GF mice colonized with microbiota from these infants. However, when the GF mice colonized with microbiota from malnourished infants were fed with sialylated bovine milk oligosaccharide (S-BMO), they gained more weight and improved lean and body mass.[91]

Human milk is abundant in oligosaccharides which are the preferred metabolic substrates for *Bifidobacteria*, the most prevalent bacterial species in infants gut.[88] *Bifidobacteria* are important for the production of SCFAs (acetate and butyrate) in infants' gut.[92] Moreover, *Bifidobacteria* provide low environmental pH thus inhibiting pathogen invasion, helping in the maintenance of GI homeostasis.[93]

Infants fed on breast milk have a microbiota dominated by *Bifidobacteria* and lactic acid bacteria.[88] Whereas infants on a formula-fed diet typically show a higher microbial diversity including *Bacteroidetes*, *Clostridia*, and *Bifidobacteria*, with an overall increase in facultative anaerobic bacteria such as Staphylococci, Enterobacteriaceae, and Streptococci.[94-96] Moreover, breast-fed infants have fewer bacterial species associated with pathogenesis such as *Escherchia coli*, *Bacteroides fragilis*, and *Clostridium difficile* compared with the formula-fed infants.[97,98] Formula-fed infants also show higher amounts of fecal SCFAs compared with breast-fed infants, with elevated levels of propionate and, to a lesser extent, butyrate.[76] Interestingly, when infants are fed a formula diet containing prebiotics, the number of *Bifidobacteria* and *Lactobacillus sp*. are increased along with a reduction in *Clostridium*, *Enterococcus*, and *E. coli*.[99-101]

Postweaning. A shift from breast milk/formula diet to a solid diet results in an increase in the Bacteroidetes to Firmicutes ratio in the gut, with a reduction in *Proteobacteria* and *Bifidobacteria* and an overall increase in different functional genes that are characteristic of an adult microbiota.[102,103] A recent study showed the critical role of diet during the early stages of life for the growth of an individual and for shaping the microbiota.[104] When the microbiota from malnourished children was transplated into GF mice, the animals displayed impaired growth, an altered bone morphology, and dysregulated brain metabolism. However, administration of an adult microbiota, which included *Ruminococcus gnavus* and *Clostridium symbiosum*, ameliorated the effects of the malnourished-microbiota transplant.[104] Such findings suggest that despite the detrimental physiological effects caused by diet or microbiota deficits, the effect can be rescued. However, a recent study showed that despite the importance of early life perturbations of the microbiota, they have limited consequences on adult microbiota composition.[105] Therefore, further studies need to be done to fully understand the complex role of diet and microbiota at different time points during the life of an individual.

From adulthood into elderly. The composition of the intestinal microbiota varies drastically from young healthy adults to elderly individuals due to age-related factors such as nutritional behavior, deterioration in digestion, dentition, and intestinal transit time, stress, and lifestyle.[106,107] Elderly individuals show changes in gut physiology and morphology, along with reductions in microbiota diversity and composition. The level of bacterial species such as *Bifidobacteria*, *Bacteroides sp.* reduces with age along with a concomitant increase in the abundance of *Ruminococcus*, *Clostridium*, *Enterobacteria,* and *Lactobacilli sp*.[107-109] However, future studies are required to better understand the functional consequences of age-mediated change in the gut microbiota on brain health and its corresponding role in the onset of different neuropsychiatric and neurodegenerative disorders.

ROLE OF DIET IN SHAPING THE GUT MICROBIOTA

Extreme and rapid changes in diet composition have a direct influence on the gut microbiota because it significantly impacts the microbial beta diversity (a measure of the turnover of the microbiota species) in individuals.[110-112] Changes in diet even within a short duration can drastically alter the gut microbiota composition. For instance, when individuals fed with either plant- or animal-based diets are switched to another diet, even over a short duration of 24 hours, demonstrated a drastic change in gut microbiota composition.[2] Diet composition also has a dramatic impact on the gut microbiota composition. For example, diet rich in fat or protein (ie, a typical Western diet) show significant reductions in *Bifidobacteria* and butyrate-producing bacteria.[113-115] On the other hand, supplementation of high-fat diet with fermentable fibers/prebiotics have shown to restore the depleted levels of these *Bifidobacteria* and butyrate-producing

bacteria,[116] which further emphasize the strong impact of diet in shaping the gut microbiota.

The recent global shift in diet has been suggested as one of the contributing factors in the growing epidemic of chronic illnesses in the developed world, including obesity, inflammatory bowel disease (IBD), allergies, diabetes, autoimmune disorders, depression, and other neuropsychiatric disorders.[117-119]

The Mediterranean vs the Western diet. Different types of diets show different effects on the composition of the gut microbiota and the overall physiology of an individual. Herein, we will discuss 2 diets: the Western diet rich in fats, salt, and sugar vs the Mediterranean diet. Both diets exert distinct effects upon the composition of the gut microbiota of the individual consuming the diet. The Western diet has garnered a lot of media attention for its association with the prevalence of diet-induced obesity, and it is suggested to be the main culprit in this epidemic[19,120] (Fig 2, *A*). Consumption of Western diet showed a change in Bacteroides to Firmicutes ratio of similar levels as observed in the gut microbiota of obese individuals.[121-124]

This clear association in changing microbial diversity with high-fat diet is further highlighted in preclinical studies where administration of high-fat diet for one day to mice colonized with human microbiota showed a drastic shift in gut microbiota with a significant increase in Firmicutes and reduction in Bacteroides phyla[122,125] (Fig 2, *A*). In addition, elevation of the relative abundance of *Collinsella*, a bacteria associated with obesity, has been observed in humans with Western diet,[123] clearly showing a strong association between diet, gut microbiota composition, and host health (Fig 2, *A*).

On the other hand, the Mediterranean diet has long been touted as a healthy dietary habit.[126] Mediterranean diet consists mainly of cereals (whole grains), legumes, nuts, vegetables, and fruits, with moderate consumption of fish and poultry and low consumption of meat (Fig 2, *A*). Data from different individual groups consuming Mediterranean diet show a significant reduction in the mortality and incidence of major chronic diseases such as cancer, neurodegenerative, and autoimmune diseases.[127] Moreover, consumption

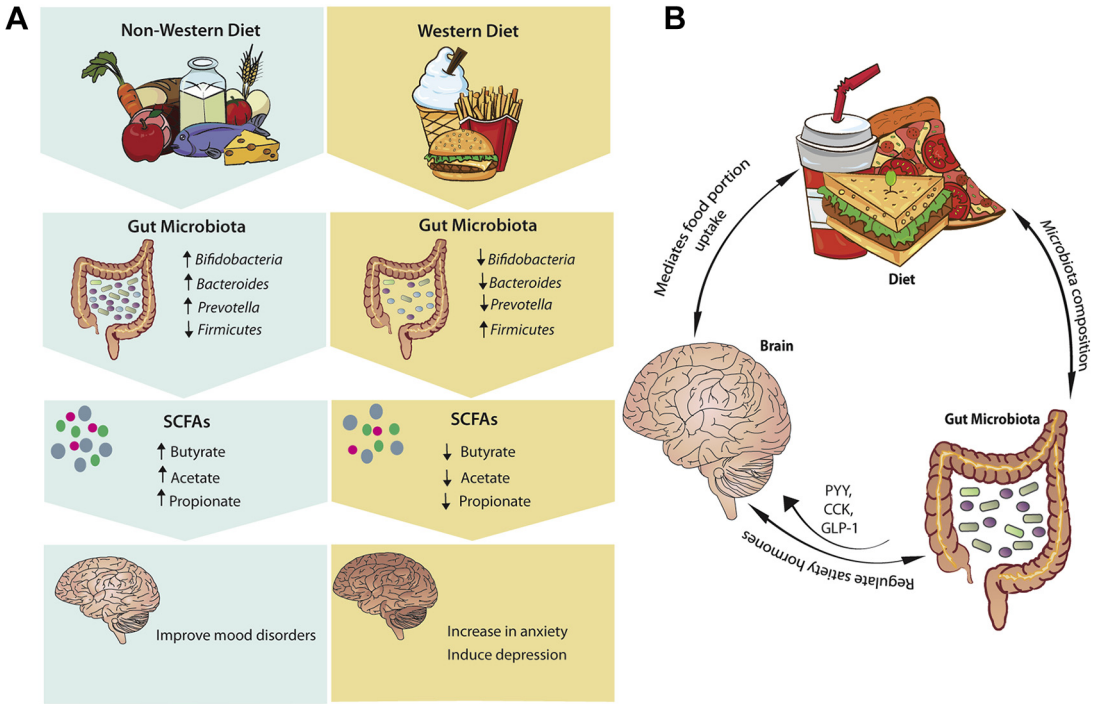

Fig 2. Triad relationship: interaction between the diet, gut microbiota, and the brain. (**A**) A nonwestern vs a Western diet shows alterations in the gut microbiota composition with subsequent changes in short chain fatty acids (SCFA). Strong alterations in the behavior profile (ie, anxiety and depressive phenotypes) are hypothesized to ensue from diet-induced alterations within the microbiota-gut-brain axis. (**B**) The triad relationship between the diet–gut microbiota and the brain is depicted. Diet provides the substrate for the gut microbiota, whereas the gut microbiota controls the diet uptake through its impact on the release of satiety hormone. Finally food intake is orchestrated by the brain, following integration of peripheral signals derived from the interaction of microbiota-derived metabolites from diet fermentation and the gut intestinal cells.

of Mediterranean diet has been shown to improve the health of patients with Crohn's disease. This has been credited to its anti-inflammatory effects which are often linked with changes in the gut microbiota composition with an increase in Bacteroides and Clostridium phyla and decrease in Proteobacteria and Bacillaceae phyla[128] (Fig 2, *A*). Human intervention studies have shown significant increase in SCFAs in individual on Mediterranean diet and interestingly the SCFAs levels correlated with high intake of fruits, vegetables, legumes, and cereals, a core component of Mediterranean diet. SCFAs are known to increase AMPK activity in liver and muscle tissues.[66,68,129] This activation of AMPK stimulates peroxisome proliferation-activated receptor co-activator-1α which is known to control the transcriptional activity of several transcriptional factors such as liver X receptor, farnesoid X receptor (FXR), and peroxisome proliferator-activator receptor (PPAR) α; these factors are critical for the regulation of cholesterol, lipid, and glucose metabolisms.[130,131] Moreover, individuals on Mediterranean diet showed a significant reduction in trimethylamine oxide—a compound that was linked to cardiovascular disease, in urine especially of vegetarian and vegans. However, the analysis showed that more omnivores on Mediterranean diet showed lower levels of trimethylamine oxide.[132] This correlates the ability of Mediterranean diet to reduce the incidence of metabolic, cardiovascular, and inflammatory disease through the regulation of SCFAs levels.[132]

Olive oil, one of the main components of the Mediterranean diet, is gaining support for its health benefits. Olive oil polyphenols have been claimed to play a protective role in cancer and other inflammatory diseases.[133] Polyphenol of olive oil induces its protective effect by modulating different signaling cascades including nuclear factor- kappaB (NF-κB), inflammatory response, and oxidative stress response.[133,134] However, clinical trials are required to substantiate the effect of olive oil in cancer and inflammatory diseases and its role in brain health.

There is also considerable evidence to suggest that a Mediterranean diet may serve as a potential therapeutic intervention in the treatment of neuropsychiatric conditions, for example, administration of Mediterranean diet specifically has been shown to reduce incidence of clinical depression and usage of antidepressant medication in young adult populations.[126,135-137] One potential mechanism through which a Mediterranean diet may have antidepressant properties is through its high vitamin B content which is a major nutrient that has been linked to the synthesis of neurotransmitters like serotonin, noradrenaline, and dopamine.[136] Given the strong association of these monoamine neurotransmitters with major depression, a Mediterranean diet may regulate mood and depressive behaviors by boosting monoamine neurotransmitter turnover.[138] A study in Italian subjects on the Mediterranean diet revealed a high abundance of *Prevotella* and SCFAs in the fecal samples[136] (Fig 2, *A*). SCFAs are critical for the maintenance of intestinal barrier; for instance, butyrate has been shown to influence the expression of tight junction protein including claudin-2, occludin, and zonula occludens protein (ZO-2, ZO2).[139,140] Butyrate has been found to facilitate the association between the transcription factors and the claudin-1 promoter, increase AMPK kinase activity, and thus reduce bacterial translocation.[139-142]

Oxidative stress is often suggested to play a role in the pathology of psychiatric disorders.[143] This oxidative stress is defined as a disturbance in the balance between the production of free radicals and reactive oxygen species/reactive nitrogen species, which leads to oxidative damage to lipids, protein, and DNA and followed by damaged to cell and organ. Components of Mediterranean diet including red wine, olive oil, and fruits are rich source of polyphenols with antioxidant properties. Evidence shows that polyphenols mediate their neuroprotective effect by modulating specific signaling pathways involved in cognitive processes and synaptic plasticity.[144] Moreover, polyphenols can increase brain-derived neurotrophic factor (BDNF) expression through the induction of the cAMP response element binding (CREB) signaling.[145] This is very critical because BDNF levels are often altered in various neuropsychiatric conditions including depression[146] and schizophrenia.[147]

Further research needs to be carried out to understand the relative contribution of various exact components of the Mediterranean diet, and their interaction with the microbiota, to its potential beneficial effects in various neuropsychiatric states.

The influence of dietary components upon the microbiota.

Carbohydrates. Carbohydrates constitute a major part of the human diet and are metabolized by the gut microbiota and are further absorbed in the intestine as simple sugars. Carbohydrate fermentation produces highly efficient energy from undigested food through the production of metabolites.[148] Its fermentation results in multiple groups of metabolites and SCFAs, which constituent a major group of metabolites.[149] Here, we will discuss different dietary source of carbohydrate and their respective functions.

Resistant carbohydrates are indigestible carbohydrates and they are often metabolized in the distal part

of the colon. Cellulose and hemicellulose are 2 such resistant carbohydrates that are found in plants. Degradation of cellulose is mediated by *Bacteroides sp*. or *Ruminococcus sp.* and results in the production of SCFAs. *Bacteroides*, a major constituent of gut microbiota, is primarily associated with plant polysaccharide degradation.[148] Abundance in the *Bacteroides sp.* has been reported in the population studies with subjects on the rural diet compared with the Western diet.[15] The change in the diet composition with high plant polysaccharide results in high SCFAs levels, whereas the Western diet has been associated with the reduction in *Bacteroides* levels[15]

Recent studies demonstrated that 6 week of resistant starch diet treatment in mice was able to alter the gut microbiota composition with an increase in Proteobacteria in mice on high-resistant starch diet (~36%). Furthermore, mice on resistant starch diet showed reduced exploration and low rearing in open field.[150] This data clearly shows that the role of different dietary components should be looked into to better understand their corresponding role in the host physiology and pathologic state.

Fibers belong to a group of carbohydrates or carbohydrate-containing compounds which are not easily digested or absorbed in the small intestine and have an important role in human nutrition. Fiber diet has been shown to be critical for the maintenance of a healthy microbiota because of long-term study on low-fiber diet intake, result in depletion of a complex microbial ecosystem in the mammalian gut with irreversible loss of diversity of the microbiota that may extend to 3–4 generations.[151] Therefore, growing evidence suggests that a fiber-rich diet is one of the critical factors that allow for an individual's overall health and maintenance of a diverse healthy gut microbiota.

In addition, fiber-rich diets have been associated with a variety of positive benefits including reduced body mass index levels and ameliorate obesity-induced inflammation.[138,152] They have been shown to indirectly affect the immune system by shaping the intestinal microbiota[15]; for example, high-fiber diet has been associated with the enrichment of *Bifidobacterium* in the human intestine.[153] Moreover, fiber intake is also associated with the regulation of circulatory estrogen levels; for example, individuals on high fiber show 7.5% reduction in the estradiol levels.[154]

Fructo-oligosaccharide, an oligosaccharide that occurs in plants such as asparagus, artichoke, banana, garlic, and onions are extensively studied dietary fibers for their bifidogenic activity.[155] Studies have indicated their ability to induce numerous beneficial physiological effects such as reduction of carcinogenicity, improvement of mineral absorption, and decrease in levels of serum cholesterol.[156] One key study has shown a significant reduction in both inflammatory cytokine and body weight when fructo-oligosaccharide was administered to genetically obese mice.[157]

However, galacto-oligosaccharides (GOS), another oligosaccharide present in human milk, are being used as a prebiotic in infant-formula diet.[158,159] Evidence suggest infants on formula diet supplemented with Bimuno-galactooligosaccharide (B-GOS) show a significant increase in *Bifidobacteria* and *Lactobacilli* levels, and these microbiota levels are of similar value as observed in breast-fed infant.[160,161] This clearly highlights the positive effect of GOS during early life. However, GOS is also being looked into as a potential prebiotic during later life. A recent study showed administration of B-GOS in elderly population to induce a significant increase in *Bifidobacteria* and *Bacteroides sp*. with an increase in lactic acid in fecal water. This was associated with the induction of an immunomodulatory effect, with a reduction in proinflammatory cytokines, and an increase in the anti-inflammatory cytokines IL-10 and IL-8.[162] Although these studies are exciting, more work is needed to dissect the mechanism of action and understand the role of GOS both in gut-brain axis signaling and on the immune response.

A small human study has shown that 3 weeks of B-GOS administration results in a significant reduction in waking salivary cortisol levels, a key stress-related hormone.[163] Moreover, B-GOS treated subjects showed altered behavioral outcomes through decreased vigilance to negative vs positive information in a dot-probe task.[163] This opens up the concept of prebiotic such as GOS being a potential treatment of stress-related disorders.

Inulins, plant storage polysaccharides, are among the most-studied and well-established prebiotics. They are predominant and found in wheat and a variety of fruits and vegetables including onions, bananas, asparagus, and artichokes.[155] Fermentation of inulin is limited to the colon with an increase in the *Bifidobacteria sp.* especially *Bifidobacteria adolescentis*, *longum*, and *Faecalibacterium prausnitzii* being observed.[164,165] This was further shown when subjects on a Western diet followed by a low-fat diet supplemented with inulin showed a significant increase in *Bifidobacteria* in fecal flora compared with control subjects with no inulin supplementation.[166] Moreover, dietary intake of inulin by dextran sulfate sodium–induced colitis mice model showed a significant increase in *Lactobacilli* in the colon with improvement in colitis symptoms.[167] More recently, a study showed inulin/GOS prebiotic supplementation during pregnancy and lactation to induce protection against food allergies with the reduction in

histamine levels and stronger intestinal permeability in the offspring.[168]

Another polysaccharide getting popular are beta-glucans that are widely present in seeds and cereals (barley and oats) and they are reported to reduce hyperglycemia, hyperlipidemia, and hypertension.[169] Beta-glucans act on different immune cells and trigger immune response and therefore are being studied as a potential treatment in cancer biology.[170] Moreover, due to their antioxidant capacity, they are suggested as a potential treatment for diabetes, cancer, and associated neurologic diseases.[171]

Proteins and bile acids. The increase in protein food intake results in an increase in protein fermentation with branched chain fatty acid, SCFAs and other potential toxic metabolites (ammonia, amine, indolic, phenolic, and sulfur-containing compounds) produced mostly in the distal colon. *Bacteroides sp*. is associated with the initial proteolysis of the protein to amino acid; therefore, increase in protein-rich diet is often associated with an increase in *Bacteroides* levels in the gut.[172] *Atopodium*, *Clostridium*, *Prevotella*, and *Veillonella sp.* are additional gut bacteria associated with protein fermentation and metabolite synthesis.[148] In addition, increase in protein consumption results in an abundance of bile-tolerant microbiota including *Alistipes* and *Bilophila* with a reduction in Firmicutes.[173] However, consumption of protein-rich animal-based diet shows a significant increase in *Bilophila wadsworthia*, a gut-specific bacterium associated with colitis and a variety of IBD in mice.[174]

Bile acids (BA) are biosynthesized in hepatocytes and are critical for the emulsification and solubilization of fats. Intestinal bacteria is important for bile acids synthesis; for example, a study using GF mice showed the role of intestinal *Bacteroides sp.* in bile acid deconjugation[175] This metabolic transformation of the bile acid by the microbiota is of critical importance because it helps to protect the colonic epithelium cells from genotoxic agents.[176] Similar, IBD patients show a significant reduction in both deconjugated and secondary bile acid levels because of the disrupted microbiota composition.[177] Studies indicate that intestinal microbiota contribute to the transformation of primary bile acids into a more bioactive secondary bile acid and results in bile acid composition which further activates/inhibits FXR and subsequently alters bile acid pool via an FXR-dependent feedback loop.[178] However, intestinal microbiota not only mediates the expression of bile acids but bile acids also regulate the expression of intestinal microbiota. Bile acid as such glycodeoxycholic acid induces an antimicrobial effect either directly or indirectly to regulate intestinal microbiota expression.[174,179] For instance, fecal microbiota transplantation (FMT) helps to restore intestinal microbiota and also bile acid composition in patients with recurrent *C. difficile* infection.[180] The primary bile composition helps to stimulate the spore germination of *C. difficile*, whereas secondary bile acid composition inhibits the bacterial strain.[181] FMT helps to restore the intestinal microbiota and further facilitate the conversion of bile acid from primary to secondary form and thus inhibit the spore germination of *C. difficile*.[182] Interestingly, a recent study in GF mice has shown that bacterial bile salt hydrolase, an enzyme critical for the generation of primary bile acid, is responsible for the mediation of a microbe-host cross-talk that regulates host lipid metabolism, weight gain, and cholesterol metabolism.[183] Future studies are needed to unravel the crosstalk between bile acids and host's gut microbiota and how it may be critical for host metabolism and brain-gut signaling.

Omega 3 and omega 6 polyunsaturated fatty acids. Omega 3 and omega 6 polyunsaturated fatty acids (PUFAs) are biosynthetic derivative of alfa-linoleic acid (ALA) and linoleic acid (LA) and are found mainly in fish and in some plant oils.

Omega 3 is among the widely studied PUFA because of its effects on brain function including neuroprotection,[184-186] restoration of energy metabolism,[187] regulation of neurotransmitter levels,[188,189] and maintenance of membrane structure and composition.[190]

PUFAs especially omega 3 are being investigated for their role in regulating microbial metabolism by being protective to the microbial composition especially during early life stress state.[191] For instance, most of the beneficial anaerobic bacteria including *Roseburia*, *Bifidobacteria*, and *Lactobacillus sp.* are widely found in the distal end of the gut, a site for PUFA metabolism from linoleic acid.[192] Interestingly, a recent study showed that early-life omega 3 exposure helped to prevent gut microbiota alterations, the onset of metabolic disorder, and chronic inflammation associated with early-life exposure to antibiotics.[193] This is in line with our findings that long-term exposure to omega 3 (in utero and early life) results in an increase of both *Bifidobacterium* and *Lactobacillus sp.* with higher *Bifidobacteria* to *Enterobacteria* ratio in adult mice exposed to omega 3 diet.[194] However, human studies are required to further support the effect of omega 3 interacting with the microbiota as playing a role in stress-related disorders. Nonetheless, the growing body of literature suggests that PUFAs may have a beneficial effect as adjunctive therapies in a variety of psychiatric disorders.[195]

Vitamins. The intestinal microbiota are known to be associated with the synthesis of a variety of vitamins such as vitamin B12 (cobalamin), B6 (pyridoxal phosphate), B5 (pantothenic acid), B3 (niacin), vitamin D, and vitamin K. Microbiota helps in the conversion of the nonabsorbed dietary vitamin B12 to corrinoids, heterocyclic compounds similar to porphyrins.[57] Most of the dietary vitamins are absorbed in the proximal tract of the small intestine; however, predominant of the microbial produced vitamins are absorbed in the colon.[196]

Vitamin deficiency has been known to affect appropriate immune responses and one suggestive pathway is through the interaction of microbiota with vitamins and correspondingly with the immune system.[57] For instance, vitamin A deficiency causes a complete loss of TH12 cells in the small intestine of specific pathogen-free mice with a significant reduction in a gut bacteria belonging to Clostridiaceae, a phyla known to be associated with the regulation of TH17 response in mice.[197,198] Similarly, administration of vitamin D3 supplementation results in the reduction in gamma *Proteobacteria* in the upper GI tract. Dietary supplementation of vitamin D3 results in an increase of $CD8^+$ T cells which further affects the microbiota composition in the gut. In the same study, they even showed a significant reduction in the *Helicobacter sp.* in healthy subjects with 8 weeks of vitamin D3 supplementation.[199] Interestingly, vitamin D is being investigated for its positive benefit on the host.[200,201] Human studies have shown deficits in vitamin D to be associated with various neuropsychiatric,[202] inflammatory,[203] and metabolic disorders.[204]

In addition, the microbiota also plays a role in vitamin synthesis including biotin and folate which are closely involved in the epigenetic regulation of colonic epithelial proliferation.[205,206] Biotin is a vitamin that mammalian cells cannot produce and they depend on a constant supply of biotin from the intestinal microbiota to maintain normal levels of protein biotinylation. Biotinylation is an important epigenetic process that involves the attachment of biotin to histone proteins resulting in gene regression, and it also plays a role in DNA repair and chromatin structure.[207]

Similarly, folate is another vitamin with an epigenetic function and associated with various metabolic pathways, such as methyl group biogenesis and synthesis of nucleotides, vitamins, and some amino acids.[208] Folate availability affects the efficiency of DNA replication, repair, and methylation and intestinal bacteria being one source of this vitamin.[209] Interestingly, folate deficiency has been associated with treatment resistant depression.[210] Moreover, methylfolate is one of the only medical foods licensed for treating major depression.[211,212] The relationship between microbiota composition, folate metabolism, and mood disorders warrants further investigation. Therefore, vitamins are a critical component of the diet and microbiota have a critical role to play in mediating a constant supply of vitamins to the host.

Polyphenols. Polyphenols are heterogeneous group of compounds characterized by hydroxylated phenyl moieties, found in grapes, apple, pear, cherries, berries, tea, coffee, red wine, dry legumes, cereals, and chocolate.[213]

A small portion of polyphenols are absorbed in the small intestine but the majority are fermented by the gut microbiota (including *Bifidobacterium sp., Lactobacillus sp.*, *Bacteroidetes sp.*, *Eubacterium sp.* and *E. coli*) in the large intestine. Henceforth, microbiota are important for bioavailability of polyphenol in the host system.

Polyphenols are known to induce numerous beneficial effects associated with inflammation, neuroprotection, antioxidant, cardiovascular diseases, cerebral ischemia, and metabolic disorders.[214-218] Moreover, they also regulate learning and memory, prevent neuroinflammation, and modulate neurotransmitter levels.[219] For instance, *Curcuma longa* containing curcumin, a widely consumed polyphenol, has been shown to modulate the expression of brain serotonergic and dopaminergic neurotransmission.[219]

In addition, resveratrol, another naturally occurring polyphenol present in peanuts, red grape and wine[220] has been found to induce an increase in monoamine neurotransmission,[221] increase hippocampal BDNF levels,[222] and exert antidepressant activity in animal models.[222]

Fisetin is another polyphenol found in abundance in strawberries known to induce anti-inflammatory effects by suppression of various inflammatory markers such as tumor necrosis factor-alpha (TNF-α) and prostaglandin E2 in microglia cells.[223] Fisetin administration resulted in antidepressant-like behavior in mice[224] concomitant with changes in monoamine neurotransmission. On the other hand, blueberry extract rich in proanthocyanidin, a natural polyphenol when administered to aged but not young animals markedly increased neuronal plasticity.[225,226]

Green tea polyphenols are popular and widely consumed natural polyphenols, with some evidence suggesting a role in prevention of both cancer and cardiovascular diseases, in addition to enhancing brain function as they can penetrate the blood-brain barrier.[227-229] Indeed, oral green tea polyphenols administration (7 days) induced antidepressant-like

effects in mice concomitant with effects at the level of the hypothalamus-pituitary axis (HPA).[230] It is also worth noting that tea polyphenols modulate monoamine oxidase enzyme activity thus increasing monoamine concentrations.[231]

A growing body of evidence suggests that the microbiota may be responsible for some of the beneficial effects of polyphenols. Indeed, data from in vitro, animal, and human studies have shown that polyphenols may enhance the gut microbiota composition diversity, whereas others might inhibit certain bacterial populations.[219] One such example is catechin, found in green tea, which significantly inhibits the growth of *Clostridium sp.*, whereas the growth of *Bifidobacterium sp.* and *Lactobacillus sp.* remained unaffected.[232] Another study showed a significant shift from predominant phyla of Bacteroidetes, *Clostridium*, and *Propionibacterium sp.* to Bacteroidetes, *Lactobacillus sp.*, and *Bifidobacterium sp.* in rats supplemented for 16 weeks with proanthocyanidin, a red wine extract.[233] In addition, 2 weeks of proanthocyanidin intake through grape seed extract increased *Bifidobacteria* levels in the gut microbiota.[234] A dietary intervention of a cocoa in a rodent model showed significant decreases in the proportion of *Bacteroides*, *Clostridium*, and *Staphylococcus* genera in the fecal samples of the diet-treated group.[235] Resveratrol commonly found in grape promotes fecal numbers of *Bifidobacterium sp.* and *Lactobacillus* in a rodent model.[236] Similarly, consumption of red wine showed significant increases in cell count of *Enterococcus*, *Prevotella*, *Bacteroides*, *Bifidobacterium*, *Bacteroides uniformis*, *Blautia coccoides*, and *Eggerthella lenta*, whereas *Lactobacillus* numbers remained unaffected.[237] Recent in vitro study showed catechin inhibited the growth of Bacteroidetes and Firmicutes, downregulated Bacteroidetes to Firmicutes ratio, and modulated the rate of oligosaccharide metabolism by the bacteria.[238] This clearly shows a strong association between the polyphenols and gut microbiota composition.

CONNECTING THE DOTS: THE ROLE OF DIET AND MICROBIOTA IN NEUROPSYCHIATRIC DISORDERS

There is a growing interest in the role of diet in microbiota function and its corresponding effect on behavior because it is tempting to speculate that designer diets could be developed that specifically target the microbiota in order to improve brain health of an individual. Epidemiological studies have shown impairment in cognitive function in individuals that have diets high in saturated fat, whereas consumption of the diet rich in PUFA induced beneficial effects on cognition.[239,240] Moreover, there is growing evidence to suggest that the microbiota is affected in neuropsychiatric conditions such as autism, anxiety, and depression, and this may be a contributing factor in their pathology. Diet may represent a means to target a dysregulated gut microbiota in these conditions to improve behavior.

Autism spectrum disorder. Autism spectrum disorder (ASD) is a complex heterogenous neurodevelopmental disorder which has a strong genetic basis. It has 3 core symptoms: social behavior deficit, impaired communication, and repetitive behaviors but is often associated with GI co-morbidities.[241] Recent studies have shown altered levels of Bacteroidetes and Firmicutes phyla with abundance in Clostridium phyla, highlighting the dysregulation of the gut-microbiota in autistic children and therefore establishing a strong link between gut microbiota and ASD.[242-245] An increase in microbiota diversity has been reported in autistic children with Bacteroidetes was found to be in abundance in severe autistic cases and with a significant difference in the Actinobacteria and Proteobacteria phyla.[243] Other gut commensals altered in autism are *Bifidobacterium*, *Lactobacillus*, *Prevotella*, and *Ruminococcus* genus.[240,246]

Preclinical studies have provided some insight into the role of the microbiota-gut-brain axis in ASD. For instance, disruption in the composition of the gut microbiota has been identified in animal models of autism, which can be ameliorated following treatment with candidate probiotic strains (ie, *B. fragilis* and *Lactobacillus reuteri*).[247-249] Moreover, antibiotic treatment in autistic children alleviated anxiety with short-term benefits to regressive behavior[250] and onset possible mechanism via LPS concentration regulation, central cytokine expression, and increasing the BDNF levels in the brain,[251,252] thus further emphasizing the role of gut microbiota composition and autism.

In addition, autistic children have been reported to show a significant increase in SCFAs in fecal samples providing a further indication for an altered microbiota in this neurodevelopmental disorder.[140] However, the role of SCFAs in ASD is not fully understood. For instance, administration of butyrate has been shown to improve repetitive symptoms in a murine model of ASD, whereas intracerebroventricular infusions of propionic acid were shown to induce autistic-like behaviors in rats,[253,254] thus suggesting SCFAs play differential roles in mediating ASD behavior. Further research is warranted to dissect the role of SCFAs in autism.

Diet may influence autistic behavior through changes in food patterns and nutritional uptake.[248,255] For instance, analysis of fecal samples from children with ASD showed significant increases in cyanobacteria/chloroplast phyla compared with normal children. This increase in the phyla has been

suggested due to the consumption of diet rich in chia seeds as opposed to the disorder per se[256] and thus more research into diet intervention may offer a potential therapy for ASD.[257] To further support the role of diet with ASD, studies show that the removal of food products containing gluten and casein helps to ameliorate symptoms of ASD because both these proteins are metabolized into opioid peptides such as exorphins. However, administration of opioid blockers such as naltrexone helps to improve the symptoms in ASD patients.[258] This may be due to dietary components to induce analgesics like effect, which is been often reported in some cases of ASD.[259] The relative contribution of the microbiota to such effects is unclear and more research is required to better understand the impact of dietary components on the microbiota and its relationship with ASD symptomology.

Diet and its components have been associated with proinflammatory response in some cases of ASD.[260,261] Moreover, children with ASD display an elevation in IL-6 and TNF levels in the serum and this has been linked with deficits in sociability[262-264] However, there is some evidence to suggest that altering the diet may be able to curtail this aberrant immune response in ASD. As previously discussed, elevated levels of IL-6 are associated with social deficits in ASD children. However, treatment with luteolin, a natural flavonoid helps to normalize IL-6 by inhibiting its release from mast cells.[260] Therefore, luteolin could be a potential treatment for ASD children with social deficits. However, information about the role of different diet component in ASD is still limited and therefore more clinical and preclinical research is required.

Attention deficit hyperactive disorder. Attention deficit hyperactive disorder (ADHD) is a neuropsychiatric disorder first presenting in childhood with core symptoms of hyperactivity, impulsivity, and inappropriate attention.[265] Pharmacologic treatments are efficacious and are being widely used to ameliorate ADHD; however, they are often been associated with long- and short-term risk including loss of growth velocity and hypertension.[266-268] Henceforth, a variety of nonpharmacologic interventions are being investigated to treat ADHD and diet is being one of the modes to ameliorate ADHD symptoms.[268,269] For example, free fatty acid supplementation has shown promising effects with significant reductions in ADHD symptoms.[270,271] Children with ADHD are often reported to develop hypersensitivity reactions to foods and individually constructed diet restriction for respective hypoallergic food is being suggested as a potential treatment for ADHD.[269,272] Moreover, as dietary interventions have been shown to ameliorate ADHD symptoms, future studies are needed to explore whether the microbiota can modulate such responses.

Depression. Depression is a stress-related mood disorder often associated with a disrupted HPA axis and immune system.[54] Intriguingly, a growing body of evidence suggests that the gut microbiota has a key role to play in the modulation of depression.[273] Patients with major depression have significant change in gut microbiota with relative abundance of Firmicutes, Actinobacteria, and Bacteroidetes.[273] An increase in alpha diversity (a measure of the richness/diversity of the species) of the gut microbiota has been reported in individuals with depression compared with the healthy control group.[12] Furthermore, patients with depression show significantly lower numbers of *Bifidobacterium* and *Lactobacillus* compared with control subjects.[274] Recent work from our lab has showed that patients with major depression have altered microbiota compared with normal subjects with significant increases in genus *Eggerthella*, *Holdemania*, *Gelria, Turicibacter, Paraprevotella*, and *Anaerofilm*, whereas reductions in *Prevotella* and *Dialister* genus were observed. Interestingly, when the microbiota from patients with major depression was transferred to microbiota-deficient rats, the corresponding behavioral and physiological phenotype was also transferred, further corroborating a link between a dysregulated microbiota and depression. Moreover, depression-like changes in tryptophan such as kynurenine and kynurenine/tryptophan turnover were also altered in the rats that received the transplant.[11] Activation of the kynurenine pathway has been shown in patients with major depression[275,276] and accumulating evidence suggests that the microbiota plays an important role in tryptophan catabolism, which is critical for regulating kynurenine production[276,277] and immune system (in particular T cell response),[278,279] found to be affected in patients with depression.[280]

Different diets can have both positive and negative effects on depression. For example, Western diet consumption increases the risk for depression, whereas Mediterranean diet reduces the onset of depression.[138] Furthermore, the global shift toward a Western diet is causing an overall alteration of dietary fatty acid composition and this is resulting in an overall increase in saturated fatty acid and a reduction in omega 3 fatty acid intake.[281] One must consider that 20% of the brain is made of PUFA and 1 out of every 3 fatty acids in the CNS is PUFA.[282] Studies both in human and animal

models have shown a strong association between depletion of omega-3 PUFA and onset of major depression, depressed mood, or postpartum depression,[188,283,284] thus suggesting the role of diet in the onset of depression.

Researchers are interested in the role of diet as a potential intervention for major depression. Studies have shown reduction in omega 3 consumption with an increased risk of depression.[1,285] Therefore, administration of omega 3 through diet may confer a protective effect against depression.[286,287] In addition, alteration in omega 3 levels has been documented in postpartum depression.[282] This has been suggested due to a significant transfer of (2.2 g/d) eicosanoyl ethanolamines (EEAs) to the developing fetus during pregnancy.[288] In addition, slower normalization of DHA levels after pregnancy has been suggested as a possible cause for postpartum depression.[289] The relative contribution of the microbiota to such effects is unclear but warrants further investigations.

Apart from omega-3 consumption, probiotic treatment has displayed efficacy in the reduction of depressive-like behaviors in animal models.[290,291] Species from the *Lactobacillus* phyla are being widely used as a therapeutic intervention to suppress depressive-like behaviors in animal models. For instance, administration of a probiotic cocktail comprising of *L. rhamnosus* and *Lactobacillus helveticus* strains have shown to ameliorate depressive-like behavior and normalize corticosterone levels in the maternal separation animal model.[292] Moreover, administration of *L. rhamnosus* (JB-1) reduced depression and anxiety-related behavior and altered stress-induced corticosterone levels in plasma and GABA receptors in various brain regions.[32] Given that alteration in GABAergic neurotransmission and overactivation of the HPA axis have been reported in depression, the ability of a probiotic strain to modulate both of these systems is rather promising.

Other strains are being looked into for their beneficial effects in mood disorder patients including *Bifidobacterium*.[293] *Bifidobacterium* is another potent gut bacterial genus associated with potential antidepressant-like behavior in animals.[291] Treatment with *Bifidobacterium infantis* attenuated depression-related behavior by normalizing aberrant peripheral immune response and increasing mobile episodes during the forced swim test in maternally separated rats[290] and a similar effect was also observed with *B. longum* and *Bifidobacterium breve* on depression and anxiety-related behavior in rodents.[294] Moreover, metabolites such as SCFAs are being investigated as a potential intervention for depression given their neuroactive and immunomodulatory functions.[295] The present data shows a strong link between microbiota and depression with diet being a potential cause and cure of the pathologic state.

Anxiety. Anxiety disorders include generalized anxiety disorder, phobias, panic disorder, post-traumatic stress disorders, and obsessive-compulsive disorder.[296] They are often associated with an activation of the HPA axis through external stressors like chemical exposure, biological, and environment factors that further cause disturbances of endocrine, immune, and nervous systems.[297]

The role of the gut microbiota in anxiety disorders is also increasingly being recognized in animal studies. For example, GI inflammation has been shown to be associated with anxiety-related behavior.[233] Two days after infection with *Campylobacter jejuni*, mice showed increased anxiety-like behavior in the elevated plus maze[232] and a similar effect was observed 8 hours after infection with *Citrobacter rodentium* and *C. jejuni* in the animal model.[232] Moreover, mice infected with *Trichuris muris*, which is often associated with GI inflammation, show an increase in anxiety-like behavior.[23] Such results suggest that absence of a microbiota or induction of GI inflammation are capable of facilitating an anxiety-like phenotype. However, treatment with *B. longum* helped to ameliorate anxiety-like behavior in *Trichuris muris*–infected animals.[33] A similar reduction in anxiety, along with an enhancement in cognition, was also observed in BALB/c mice, an innate anxious strain following *Bifidobacterium* administration.[234,235]

Modulating the diet composition may represent a means to improve anxiety. For example, patients with anxiety disorder often show a strong correlation between the type of anxiety disorder and peripheral BDNF protein levels.[298] Omega 3 PUFAs found mainly in fish or plant oil have been shown to modulate not only BDNF levels but also to induce an anti-inflammatory response and is being looked into as a potential treatment for the prevention of anxiety disorders.[299] Numerous studies, both in humans and animals, show the potential role of omega 3 to ameliorate or induce a protective effect for anxiety disorder.[300,301]

CONCLUSION

Numerous studies show that the gut microbiota is critical for the normal physiological and metabolic function of the host. The gut microbiota, through the immune and endocrine system and bacterial metabolites, regulate neurophysiological function which further regulate neurotransmission, cognition, and behavior. Diet has an important role in the regulation of the gut microbiota composition. Changes in the diet pattern even for a short duration of time induce drastic effects on the gut microbiota composition, which may further contribute to

psychiatric conditions. Preclinical studies have shown that administration of prebiotics and probiotics can ameliorate different psychiatric condition such as depression and anxiety. Therefore, the use of probiotics and psychobiotics is being widely explored as a potential treatment for GI disorders, obesity and eating disorders, age-associated cognitive decline, and neuropsychiatric conditions. Clinical translation of these findings is now needed for diet as a potential therapy for different neuropsychiatry conditions.[302]

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