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Harnessing Gut Microbes for Mental Health: Getting from Here to There

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Abstract

There has been an explosion of interest in the study of microorganisms inhabiting the gastrointestinal tract (gut microbiota) and their impact on host health and physiology. Accumulating data suggest that altered communication between gut microbiota and host systems could participate in disorders such as obesity, diabetes mellitus, and autoimmune disorders; as well as neuropsychiatric disorders including autism, anxiety, and major depressive disorders. The conceptual development of the microbiome-gut-brain axis has facilitated understanding of the complex and bidirectional networks between gastrointestinal microbiota and their host, highlighting potential mechanisms through which this environment influences central nervous system (CNS) physiology. Communication pathways between gut microbiota and the CNS could include autonomic, neuroendocrine, enteric, and immune systems; with pathology resulting in disruption to neurotransmitter balance, increases in chronic inflammation, and/or exacerbated hypothalamic-pituitary-adrenal (HPA)-axis activity. However, uncertainty remains as to the generalizability of controlled animal studies to the more multifaceted pattern of human pathophysiology, especially with regard to the therapeutic potential for neuropsychiatric health. This narrative review summarizes current understanding of gut microbial influence over physiologic function, with an emphasis on neurobehavioral and neurologic impairment based on growing understanding of the gut-brain axis. Experimental and clinical data regarding means of therapeutic manipulation of gut microbiota as a novel treatment option for mental health are described, and important knowledge gaps are identified and discussed.

Keywords

depression; gut-brain axis; gut dysbiosis; mental health; microbiota transplant; probiotics

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Introduction and historical context

Gut microbiota comprise all microorganisms inhabiting the intestinal tract and their respective genomes. Tens of trillions of microorganisms populate the human intestine; and although bacteria predominate, viruses, phages, and fungi are likewise included (1). Accumulating data implicates this dynamic population in physiologic functions including nutrition/digestion, growth, inflammation/immunity, and protection against foreign pathogens (2),(3),(4). Experimental and clinical studies suggest that disruption to gut microbiota can impair physical and mental health (3),(5),(6),(7), suggesting that intestinal microbiota could underlie host susceptibility to illness (8),(9). Links between microbiota and pathophysiology triggered an explosion of interest in this field, with 85% of the over 10,000 PubMed publications on “intestinal microbiota” arising in the last 5 years, currently averaging about 5 new publications per day. Indeed, the most recent Rome Foundation guidelines on gastrointestinal (GI) disorders emphasize disruption on the gut-brain axis in functional GI disease (10). Furthermore, the Integrative Human Microbiome Project (iHMP) was deployed in 2014 to drive continuing understanding of microbiome-based influences on health and disease following the 2013 culmination of the NIH Human Microbiome Project (http://hmpdacc.org/) (11). This substantial investment of intellectual and financial capitol reflects the hopeful expectation for new ways to drive beneficial mutualism with these symbiotic microbes to foster optimal health.

Notwithstanding recent investments in discovery-based approaches, microbiome manipulation is actually an ancient concept in human medicine. The first reported application of therapeutic fecal transplantation arises from the fourth century by Chinese physician Ge Hong, describing a “yellow soup” prescribed as an oral remedy for a patient with severe diarrhea (12). In the less distant past, Elie Metchnikoff theorized that health could be enhanced and “senility” delayed by manipulating the intestinal microbiome with host-friendly bacteria (13). These progressive theories might have remained adrift amongst the fringes of biomedical research had it not been for the development of high-throughput sequencing, which revolutionized microbiology with highly efficient and cost-effective strategies to identify and investigate microbial community structure. Historically, microbiology was almost entirely culture-dependent, with members of microbial communities identified by structural characteristics such as affinity for Gram stains. This restriction to cultivable microorganisms hindered researchers’ ability to fully assess diversity in physiological niches, especially at lower taxonomic levels. With the advent of inexpensive and culture-independent next-generation high-throughput sequencing (14), analyses of DNA isolated directly from biologic sites have enabled characterization of taxonomic diversity and functional metagenomics, driving the explosion of data on human microbiomes. In this non-systematic narrative review, we summarize current understanding of intestinal microbial influences on physiologic function with an emphasis on behavioral and neurologic impairment. We also summarize available experimental and clinical data regarding therapeutic manipulation of gut microbiota as a novel GI-based treatment option for mental health. Lastly, we identify important knowledge gaps, and include discussion of potential approaches to filling such gaps.

Gut microbiota and mental health: experimental evidence

Mental illness contributes substantially to the global burden of disability, and to uncover new avenues for treatment the generally tight association of neurobehavioral and metabolic dysfunction has come under intense scrutiny (15),(16),(17). The search for underlying mechanisms common to both bowel and mental illness has revealed many humoral and neural pathways of gut-brain communication (18), and gut microbiota have emerged as a key node in this system (19),(20). Indeed, bi-directional pathways between gut and brain regulates metabolism and energy balance, and represents an ancient biological defense system to guarantee adequate energy (21). The role of gut microbiota in this system is highlighted by the well-established relationship between over-nutrition and reduced intestinal microbial diversity and disrupted pathogen/commensal balance (dysbiosis) (22),(23),(24),(25). Intestinal dysbiosis is also linked to behavioral impairment (5),(6),(7),(26),(27), stimulating extensive research into the role of gut microbiota in mental/neurologic health.

An pivotal early study on gut microbiota and neurobehavioral function revealed that that germ-free mice lacking intestinal and other microbiota display maladaptive and exaggerated responses to stress that can be normalized by probiotic-induced intestinal recolonization (28). Indeed, germ-free mice show that gut microbiota are essential for development of neuronal circuits underlying motor control, anxiety behavior, and social responses (29),(30). Fecal microbial transfer experiments likewise demonstrate the link between intestinal microbiota and behavior. For example, germ-free BALB/c mice typically display impaired sociality and exaggerated caution (31). However, microbiome transplants from NIH Swiss mice, which lack social/exploratory impairment, normalize behavior in BALB/c recipients (32). The reverse is also true, as NIH Swiss mice transplanted with BALB/c microbiota display exaggerated caution and hesitancy (33). Subsequent studies in conventionally housed mice with microbiome transplants from high-fat diet-fed donor mice revealed that high fat-shaped microbiota are sufficient to disrupt exploratory, cognitive, and stereotypical/impulsive behaviors (6). Other reports reveal that probiotics improve mood, anxiety, and cognition, as well as signaling and neural activity in animal models (34),(35),(36),(37). Finally, experimental studies have shown that probiotics prevent stress-induced decreases in hippocampal neurogenesis and enhance expression of hypothalamic genes involved in synaptic plasticity (38).

The intestinal ecosystem is thought to be established at or soon after birth, facilitated by vertical transmission and exposure/ingestion of environmental flora (39),(40),(41). Thus maternal influences on the offspring’s microbiome are significant, potentially altering the risk for mental impairment. Indeed, it has been proposed that both the development of the brain and risks of future illness can be viewed in the context of the developing microbiome (42). For example, data suggest that obesity and diabetes during pregnancy increases risk for neuropsychiatric disorders in offspring (43), and that maternal diet-induced intestinal dysbiosis can impair offspring behavior in a sex-specific manner (44). Maternal stress and immune activation can also program maladaptive offspring behavior via microbiome alterations. For example, maternal immune activation causes behavioral impairment in offspring that is prevented by probiotics (45). Furthermore, prenatal stress-induced changes

to the vaginal microbiome alter vertical transmission of microbiota, seemingly shaping an intestinal niche that increases disease risk (46),(47). These collective data suggest a significant and essential link between maternal microbiota and offspring programming, raising the possibility that maternal microbiota could link unhealthy modern diets to the increased prevalence of neurodevelopmental and childhood disorders (48),(49),(50). While currently under intensive study (reviewed in (51), (52)), the potential pathways whereby maternal microbiota affect offspring neurologic function remain unknown (Fig. 1).

Potential mechanisms whereby intestinal microbiota influence host health

Numerous pathways between the gut and brain have been delineated, and data indicate that gut-brain communication is bidirectional and mediated by neural and humoral mechanisms. Specific descending pathways include autonomic and enteric pathways and the hypothalamic-pituitary-adrenal (HPA) axis. Ascending pathways include sensory vagal and dorsal root ganglion pathways, cytokines and immune mediators, and secreted microbial/intestinal metabolites. With neural pathways acting in a rapid and somatotopic manner combined with the slower and somatically less specific humoral route, these complementary pathways facilitate the effects of gut microbiota on brain and behavior (Fig. 2).

Direct activation of neuronal pathways

Vagal primary afferents provide pervasive sensory innervation of the GI tract, with an estimated 60,000 fibers in humans and 20,000 fibers in the mouse, comprising the only set of fibers that directly connect the GI mucosa to the brain (53). Numerous studies have demonstrated activation of GI tract vagal afferents by gut hormones, cytokines, microbial signals, and mechanical stimuli (reviewed in (54)), and vagal afferents have been implicated in probiotic-induced neurobehavioral changes in the mouse (35,55). For example, the probiotic *Lactobacillus rhamnosus* can directly increase single- and multiunit firing rate of the mesenteric nerve bundle and can decrease stress-induced corticosterone and anxiety/depression in mice (35),(56). Moreover, these behavioral effects of *L. rhamnosus* are abolished by vagotomy (35). However, selective vagal deafferentation has not yet been used to conclusively prove a role for vagal afferents in microbiota-brain communication. This is important because the non-selective vagotomy technique used in these studies eliminates vagal motor innervation of the entire GI tract which is crucial for its homeostasis. For example, stimulation of vagal motor outflow attenuates macrophage activation and dampens intestinal inflammation via α-7 nicotinic cholinergic receptors (57),(58). Relatively selective (surgical) vagal deafferentation in a rat model (59) resulted in reduced innate anxiety-like behaviors, increased expression of auditory fear conditioning, and associated neurochemical changes in limbic system components (60). Therefore, this surgical model or next-generation genetic-based selective vagal deafferentation (61) should be used in future studies to tease out the exact role of vagal afferents in microbiome-brain interactions.

Besides the vagus nerve, spinal pathways also serve as high-speed links between gut and brain. On the sensory side, dorsal root ganglion (DRG) afferents relay pain and other supra-physiological stimuli from the gut to the brain (62). While a role for DRG afferents in the effects of microbiome manipulation on brain function is plausible, it has not yet been tested

likely owing to difficulties in selective ablation/stimulation of these diffuse nerve fibers. Sympathetic innervation is another avenue for the brain to influence gut function and its organization is slightly more accessible for selective manipulation. Much of the sympathetic innervation to the gut is relayed from preganglionic to postganglionic neurons within the celiac and supramesenteric ganglia and activity of postganglionic neurons can be blocked relatively selectively with noradrenergic antagonists.

Microbial metabolism of nutrients and production of circulating mediators

Intestinal microbial elements can influence host physiology with products of their own metabolism, including the neuroactive molecules 5-hydroxytryptophan (5-HT (serotonin)) and γ-aminobutyric acid (GABA) (63),(64),(65). Specific examples include generation of GABA by members of the *Lactobacilli* and *Bifidobacteria* families, dopamine and noradrenalin by members of the *Bacillus* family, and noradrenalin and 5-HT by the *Escherichia* family (66),(66,67). Furthermore, male germ-free mice have increased hippocampal 5-HT, increased plasma tryptophan, decreased hippocampal BDNF, and altered anxiety (68), suggesting that microbiota alter the development of CNS neurotransmitter systems. Overall, metabolism of plant-based carbohydrates by intestinal bacteria produces a variety of neuroactive compounds, which potentially could affect both local autonomic/enteric neurons as well as central neural elements.

Short chain fatty acids (SCFAs) including butyrate, propionate and acetate are produced by microbial metabolism of otherwise indigestible dietary fibers also significantly impact host physiology (69). SCFAs are the preferential energy source for colonocytes (70) and also provide a significant fraction of the daily caloric requirement in humans (71). Furthermore, butyrate increases mitochondrial oxidation, attenuates NFkB activation and metabolic endotoxemia, and activates gluconeogenesis (72). With regard to mental health, SCFA directly stimulate sympathetic and autonomic nervous system via activation of G protein-coupled receptors 41 and 43 (73),(74). While SCFA are blood-brain permeable, the degree to which endogenous SCFAs cross into the brain to affect neurologic function remains unclear, although they have been shown to maintain the integrity of the blood brain barrier (75),(76). Application of exogenous SCFAs at pharmacological concentrations, however, has pronounced effects on the brain. For example, application of the combined propionate-, butyrate-, and acetate-sodium salts reverses defects in microglia differentiation and function observed in germ-free mice (77). In addition, sodium butyrate can reduce disease progression in animal models of Parkinson’s and Huntington’s disease (78),(79). However, other studies suggest that SCFA increase microglial signaling and motor dysfunction in animal models of Parkinson’s disease (80), and propionic acid has specifically been implicated in autism (81), based on studies of behavioral, electrographic, neuroinflammatory function in rodents (82),(83). While it is clear that SCFA are powerful signaling molecules, further studies must link changes in their production to altered gut microbial populations and to specific disease states.

Bile acids have been coined “the new gut hormones” as understanding of their function has expanded from simple emulsifiers to inter-organ communicators (84). Synthesized in the liver, conjugated primary and secondary bile acids are de-conjugated by gut microbiota, and

activate bile acid receptors such as the nuclear receptor farnesoid receptor and the G protein-coupled bile acid receptor-1 (85). While frequently tied to weight regulation (86), altered bile acid profiles are associated with a range of systemic diseases (reviewed in (87). For example, tauroursodeoxycholic acid (TUDCA) the taurine conjugate of ursodeoxycholic acid, has neuroprotective and anti-inflammatory properties and protects against both Alzheimer's and Parkinson's pathology in animal models (88),(89). Further, circulating bile acids are linked to circadian rhythmicity (90), while brain levels are altered in animal and human models of Alzheimer's disease (91). While these reports are compelling, experimental studies that directly link bile acids to neurologic or physiologic disease are needed to confirm any potential roles of these signaling moieties in CNS disease. Importantly, whether and when bile acids enter the general circulation in sufficient amounts to affect CNS function and/or enter the brain needs to be very clearly addressed.

Immune activation and circulating inflammatory mediators

Inflammation typifies both intestinal dysbiosis and neurologic/psychiatric disorders (92), (93), (94), highlighting the potential role of inflammatory mediators linking gut to brain. Intestinal microbiota influence the generation, maturation, and function of numerous immune cells; which in turn modify the balance and metabolic activity of intestinal microbes (95). This important reciprocal relationship likely participates in inflammation and autoimmunity (reviewed in (96) (97)). For example, intestinal microbiota modify autoimmune processes driven by myelin-specific $CD4^+$ T cells in mice (98). With regard to diet-induced intestinal inflammation, dietary fats, particularly trans and saturated fats, have been shown to transiently increase intestinal inflammation even in healthy subjects (99), (100), which in turn alters gut microbial populations by decreasing commensal (i.e., Bacteroidetes) and increasing pathogenic (i.e, Proteobacteria, Enterobacteriaceae) taxa (101),(102),(103). Importantly, hexacylated endotoxin produced by pathogenic gram-negative strains is a more powerful agonist of toll receptors and more effectively degrades mucosal barriers relative to pentacylated endotoxin produced by commensals like Bacteroidetes (104),(105),(106),(107). Indeed, increases in intestinal Proteobacteria are associated with intestinal permeability and circulating endotoxin (24),(108),(109),(110), (111), which are in turn linked to brain inflammation and neurobehavioral dysfunction (6). Gut dysbiosis and intestinal permeability are also seen in genetic mouse models of autism (45), though cause and effect relationships are unknown. Indeed, the effect of host genetics on gut microbiota is not fully understood (112), although available data strongly support innate immune effects on diet-independent variations in gut microbiota (113),(114),(115). Collectively, these data indicate that intestinal dysbiosis and increased intestinal inflammation can synergistically drive a cascade of local-to-systemic inflammation.

Therapeutic manipulation of gut microbiota

Diet quality

Studies show that the effects of diet on the human gut microbiome are rapid (116),(117), (118) and driven by quality and quantity of dietary fat and carbohydrates (119). Interestingly, the diversity of gut microbiota is increased in rural/indigenous populations that consume high fiber plant-based diets compared to industrialized urban populations with

highly processed/low fiber foods (120),(121),(122) and indeed, high fat/low fiber diets are known to reduce intestinal microbial diversity (reviewed in (123)). More importantly, recent experimental data indicate that chronic consumption of high fat/low fiber diets across generations in mice progressively decreases intestinal microbiome diversity, and that this pattern becomes irreversible even when high fiber is reintroduced (124). The typical Western diet may thus permanently reduce the capacity of the gut to support diversity, a serious concern given the association of reduced microbial diversity with disease (125),(126). For example, highly processed, lower quality foods that decrease intestinal microbial diversity and disrupt pathogen/commensal balance are linked to increased risk for mental disorders (127), and clinical studies show significant inverse relationships between symptoms of mental illness and metrics of diet quality (128),(129),(130),(131). However, the data on this association are mixed (132),(133), indicating the need for more controlled trials. Nonetheless, a diet rich in diverse and seasonal plant-based products is in keeping with most general dietary guidelines and would likely foster a more diverse and resilient microbiome. Finally, while the components of a healthy diet are generally well known, it is important to note that numerous societal factors - poverty, crime, food deserts, and irregular work schedules - can undercut an individual's ability to maintain a healthy diet.

Probiotics and prebiotics

A potential tactic to counterbalance the effects of Western diets is via probiotics and/or prebiotics. The term "psychobiotic" was originally coined to describe probiotics (134), but has been extended to include prebiotics (135) that share the potential to relieve neuropsychiatric symptoms. Probiotics are living microorganisms, generally gram-positive taxa from the *Lactobacillus* and/or *Bifidobacterium* genus(135),(136,137,138), and are frequently prescribed for GI conditions like constipation and irritable bowel syndrome (IBS). Interestingly, gut dysbiosis in IBS correlates not just with GI symptoms but and also with regional brain volumes and early life trauma (139), and *B. longum* reduces depression and increases quality of life in IBS patients (140). Other randomized trials confirm beneficial effects of probiotics on mood (138),(137),(112); and a recent placebo-controlled trial showed that *L. casei* reduces physiologic responses to stress while increasing intestinal microbial diversity (141). However, other studies report no benefit of probiotic over placebo on mood, anxiety, stress or sleep quality in healthy volunteers (142). Finally, while the Generally Recognized as Safe (GRAS) designation has been applied to many probiotics (143), systematic studies are needed to define the prevalence/severity of adverse events, particularly in vulnerable populations (144). Overall, while evidence supporting probiotics in mental health is compelling, additional trials in diverse populations are needed to define efficacy and address key limitations in the field, including questions on beneficial strains, dosing and administration, and duration of treatment and benefits (145).

Prebiotics are nondigestible plant-based carbohydrates (oligosaccharides and resistant starches) that cultivate beneficial microbiota. Prebiotics can attenuate stress behaviors in rodents (146),(147), and a randomized human trial revealed decreased stress responses and improved emotional affect following galactooligosaccharide supplementation in healthy volunteers (148). While the exact mechanisms of the beneficial effects of prebiotics are not fully understood, fermentation of prebiotics affects both the mass and diversity of cecal and

colonic microbiota, and also produces the SCFA butyrate. In summary, while regular consumption of probiotics and/or prebiotics may improve mental health and quality of life by supporting gut microbial diversity and composition, additional well-controlled and well-powered studies are needed.

Fecal microbiota transplantation

Although not as widely used as probiotics, fecal microbiota transplantation (FMT) is a procedure in which healthy donor fecal microbiota are introduced orally or through enemas or colonoscopy into recipient patients. FMT has been progressively refined over the past several years, and has shown success in treating refractory *Clostridium difficile* infection (149), even in profoundly ill patients or those with *C. difficile* in the context of Inflammatory Bowel Disease (150). Other applications for FMT may include diseases associated with dysbiosis such as inflammatory bowel syndromes (151), although the efficacy of FMT in treatment of ulcerative colitis and Crohn's disease is inconsistent (152). A double-blind clinical trail of FMT for obesity/metabolic syndrome compared auto-transplants (patient's own feces) to transplants from thin donors (experimental group), showing significant improvements in insulin sensitivity in the experimental group (153). Regarding neuropsychiatric disorders, Parkinson's disease, depression, and autism are all frequently comorbid with GI dysfunction (154),(155), and fecal transplants from affected humans to mice can impair behavioral and motor function (156),(80). Nonetheless, the clinical efficacy of FMT for neurobehavioral disorders remains generally untested with the exception of a recent open-label trial of FMT in children with autism (157), showing improved GI and behavioral function following FMT. There was also a significant negative correlation between metrics of GI distress and parent-reported behavioral improvement (157). However, this trial was not placebo-controlled, blinded, nor randomized; and further trials are needed to confirm the therapeutic benefit and long-term safety of FMT for autism. The relative contribution of FMT-adjunctive medications (e.g., antibiotics, proton pump inhibitors), as well as practical issues related to donor selection/screening, sample handling and storage, and transplant administration also require resolution before this approach could be widely deployed.

Open Questions and Future Directions

These provocative data strongly suggest that intestinal microbiota could be harnessed to fight disease, and this prospect has garnered significant attention. New companies offer personalized analyses of fecal microbial content, promising consumers inroads into personalized health, while untested and potentially risky DIY instructions for microbiome "cleansing" are proliferating online. Headlines such as 'We Are Our Bacteria', from the *The New York Times* and the *@microbiome* Twitter handle also attest to the growing enthusiasm for this field. And logically so, as gut microbiota can be manipulated directly and efficiently, as opposed to traditional neurologic therapies that must unfortunately expose the entire body to the high drug levels needed to breach the blood-brain barrier. Overall, while this topic has raised considerable hope (and hype) in popular literature, key data are needed to confirm legitimacy of the microbiome as a valid therapeutic target for mental illness (see Table 1).

Cause and effect relationships need to be established, as many studies do not meet this criterion. Even if gut dysbiois is capable of facilitating disease, the reciprocal effects of impaired host physiology on intestinal populations remain unclear. For example, a recent report documented decreased microbial diversity in elderly subjects in residential facilities compared to community dwellers, and a correlation between frailty metrics and distinct microbiome signatures in elderly subjects (158). While a causal relationship of diet/residence in long-term care facilities on microbiome diversity is reasonable; the reverse relationship - i.e., does frailty/poor health disrupt the gut microbiome - was not explored. Another example relates to obesity, as a recent study sought to assess causality in this system by transplanting microbiota from discordant twins (one obese, one not) into mice. Mice previously colonized with an 'obese' microbiome lost weight when supplied with a 'lean microbiome', but only when *also* fed a low-fat diet as neither transplant nor diet were effective alone (159). This well-controlled and thorough experiment underscores the myriad of factors that complicate delineation of gut microbiota-induced pathophysiology. Understanding when dysbiosis *causes* disease rather than accompanying it would advance this important field.

In a related note, identification of the specific bacterial populations that drive maladaptive physiology would be valuable. For example, even if distinct microbiome signatures are causally linked to disease, whether this effect is mediated collectively by groups of microbes or by individual microbes with other taxa acting as mere passengers of the particular phenotype remains unknown. Indeed, the exact changes in microbiota that reflect pathology are unknown even in animal systems, and this limits the diagnostic utility of microbiome analyses and contributes to the unacceptable signal/noise ratio in this field. An unbiased systemic approach to identify the specific taxa where enrichment or depletion is linked to loss of homeostasis could resolve this issue, particularly if adequately powered and validated across multiple models. Modern technology can now also allow for finer distinctions and the study of multiple genes in parallel, an ability that may enable the identification of 'metabolic networks' revealing the biochemical reactions that a microbiome can perform. This kind of analysis could identify gene combinations, potentially from multiple species across a microbial community that affect health for good or ill.

An additional issue relates to the validity of *fecal* sampling as a reliable tool to assess intestinal health along both vertical and horizontal axes. Much of the work on gut microbiota is based on stool samples using 16S metagenomics analyses (161). However, intestinal bacteria affect specific and discrete gut segments and niches of the luminal/mucous layers (162),(163),(164). While some experimental studies have investigated site-specific microbiota-host interactions (165),(166),(167),(168), understanding of these discrete regional interactions between microbiota, diet components, bile acids, digestive enzymes, and the host mucosa are likely necessary to yield the promise of microbiome-based therapeutics. While longitudinal biopsy samples from throughout the GI tract are understandably contraindicated in human studies, animal studies could be designed to test if specific fecal signatures can be identified that reflect health/disease in more proximal GI locations.

Once a direct relationship between gut dysbiosis and a pathophysiological phenotype is established, microbiome-based therapeutic strategies could be generated. However, it is possible that realization of microbiome-based benefits may require elucidation of mechanisms. Indeed, determining if dysbiosis triggers disease via activation of vagal afferents, impaired regulation of serum tryptophan, and/or intestinal transfer of endotoxin could direct which therapeutic avenue to pursue. However, still remaining to be resolved are the numerous limitations of current microbiome based therapies (discussed individually above) across different cohorts. These limitations are likely based in part on the remarkable degree of inter-personal variability in human microbiota (160). Thus, it seems clear that collective resolution of cause and effect, mechanisms, participating taxa, and fidelity of fecal samples to overall intestinal and systemic physiology will be necessary before the full potential of personalized medicine offered by microbiome-based therapeutics can be realized.

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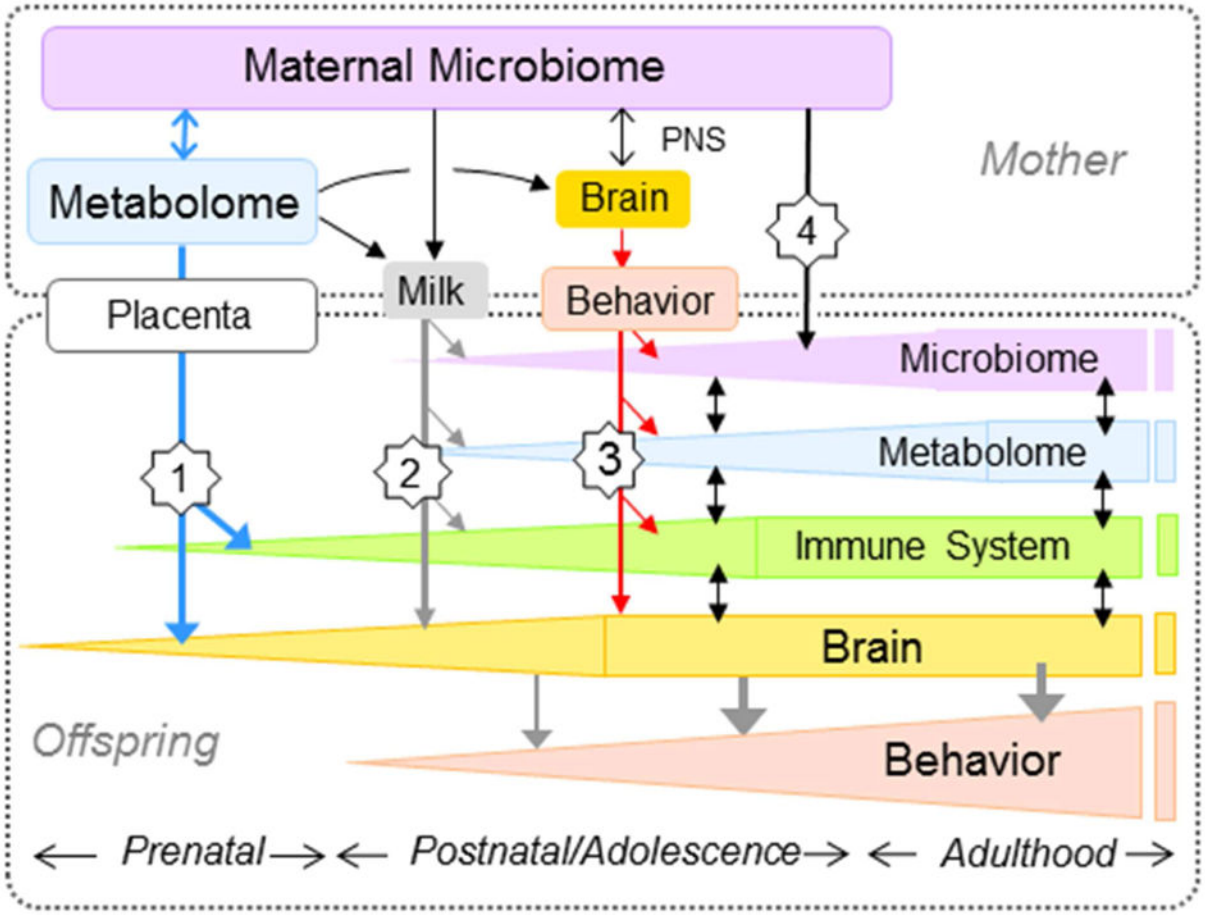

Figure 1. Schematic diagram showing the four major pathways of potential information transfer from the maternal gut microbiome to the brain and behavior of offspring

(1) Metabolites shaped by the maternal microbiome may enter the fetal circulation and affect early neurodevelopment of the fetus during gestation. (2) Metabolites shaped by the maternal microbiome contained in the milk may be ingested by offspring during lactation. (3) Maternal microbiota could affect mothering behavior via the mother's brain during the early neonatal period. (4) Maternal microbiota could be directly vertically transferred to offspring at birth, and reinforced through coprophagia during the neonatal period. In addition, there are complex interactions between the microbiome, metabolome, immune system, brain, and behavior within offspring as shown in Fig. 2.

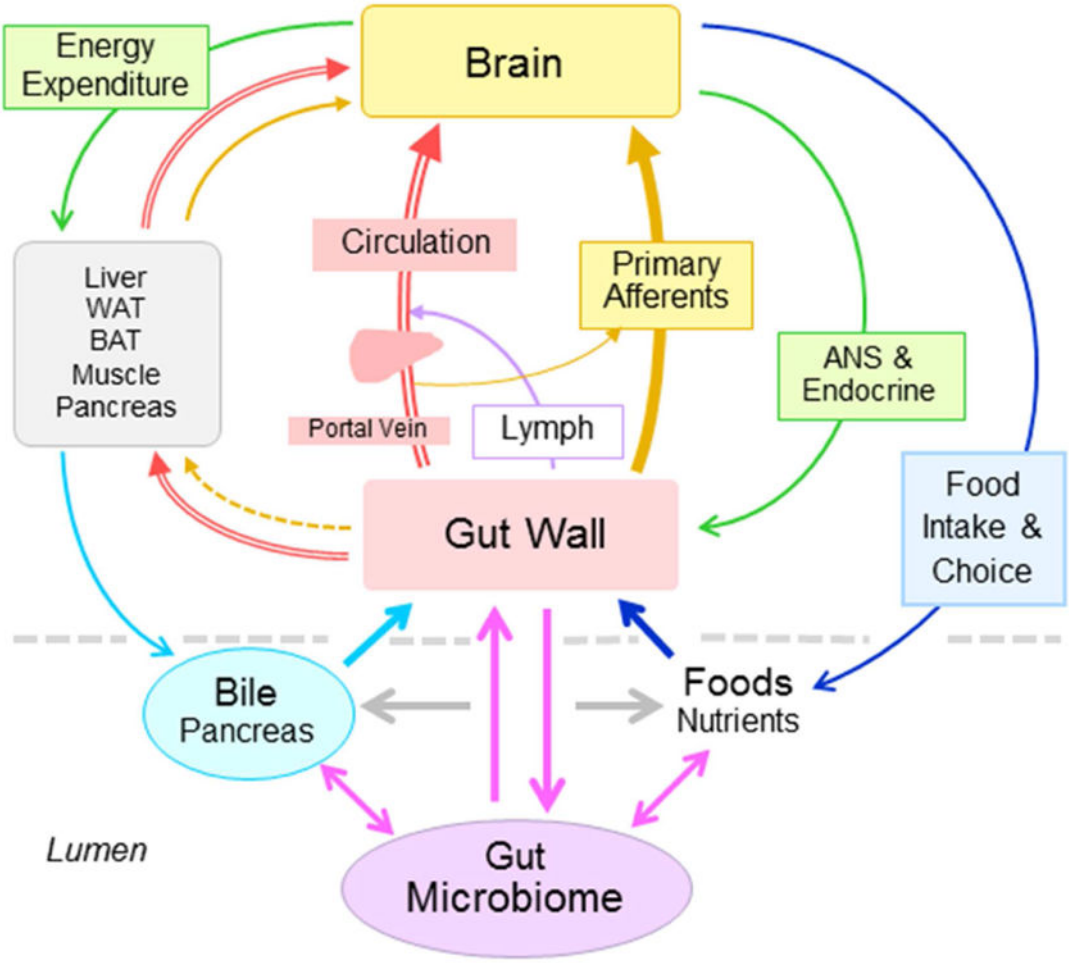

Figure 2. Signaling pathways between maternal gut microbiota and behavior

Schematic diagram showing potential signaling pathways through which the gut microbiome can affect metabolic and mental health. In the intestinal lumen, microbiota, food, bile acids, and mucosal factors interact with each other. The intestinal mucosa then propagates information to other organs including the brain through the blood circulation and sensory nerves. In turn, the brain can affect the mucosa and eventually gut microbiota directly or indirectly (via other organs) through changes in autonomic nervous system (ANS) and endocrine outflow and through changes in food intake quantity and choice.

Table 1

Conceptual and technical knowledge gaps, and potential experimental resolution, in the development of microbiome-based therapies for mental health.

Key Open Questions	Promising Experimental Approaches
1. Does intestinal dysbiosis impair mental health, and/or do mental health conditions disrupt intestinal microbiota?	*Animal Studies:* rigorously designed studies (following NIH guidelines with regard to controls, statistical power, and biological variables) in which microbiota are transplanted from diseased mice to healthy mice to determine if the phenotype is reproduced and from healthy mice to diseased mice to determine if phenotype is reversed. *Human Studies:* RCT of microbiome-based therapies in affected patients to test for efficacy (see Question 5).
2. Which microbes have the capacity to drive disease, and which are merely ancillary?	*Animal and Human Studies:* Systematic, unbiased approach to identify taxa in which enrichment/depletion is associated with a specific phenotype *across* models (depends in part on resolution of Question #4).
3. What are the mechanisms whereby altered microbiota disrupt brain function?	*Animal Studies:* rigorously designed studies using genetic, surgical, and/or pharmacologic means to interrupt key signaling pathways (eg, selective vagotomy, bile acid receptors, toll-like receptors) between gut and brain (depends on resolution of Question #1).
4. Can fecal samples adequately reflect intestinal microbiota across proximal-distal and luminal-mucosal axes?	*Animal Studies:* systematic sampling of luminal and mucosal microbiota along GI tract under both control and disease conditions to determine fidelity of fecal sampling.
5. Under what conditions are microbiome-based therapeutics (FMT, probiotics, and/or prebiotics) beneficial for mental health?	*Animal Studies:* rigorously designed studies to inform human trials – important issues include identification of the most beneficial therapy (transplant versus probiotic (strain?) versus prebiotic (type?)), dose-response relationships, duration of benefits, and adverse effects. *Animal Studies:* RCT of microbiome-based therapies for specific conditions (eg, anxiety, depression, autism).