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# Sex Differences in the Gut-Brain Axis: Implications for Mental Health

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## Abstract

**Purpose of Review—**The purpose of this article is to highlight how sex differences in the gut-brain axis may contribute to the discrepancies in incidence of neurodevelopmental, psychiatric, and neurodegenerative disorders between females and males. We focus on autism spectrum disorder, psychotic disorders, stress and anxiety disorders, depression, Alzheimer's disease, and Parkinson's disease and additionally discuss the comorbidity between inflammatory bowel disorder and mental health disorders.

**Recent Findings—**Human and animal studies show that sex may modify the relationship between the gut or immune system and brain and behavior. Sex also appears to modify the effect of microbial treatments such as probiotics and antibiotics on brain and behavior.

**Summary—**There is emerging evidence that assessing the role of sex in the gut-brain axis may help elucidate the etiology of and identify effective treatments for neurodevelopmental, psychiatric, and neurodegenerative disorders.

### Keywords

Gut-brain axis; Mental health; Sex; Brain; Microbiome; Microbiota

## Introduction

Sex and gender differences exist in the incidence and prevalence of most psychiatric [1], neurodevelopmental [2], and neurodegenerative [3] disorders, as described in this Special Issue. There is a growing consensus of the importance of the gut-brain axis, including the

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gut microbiome, for influencing health. Given the interactions between the gut-brain axis and the rest of the body, including the neuroendocrine and immune systems, which also differ by sex, and the role these systems play in maintaining health, it makes sense to consider how sex differences in the gut-brain axis may partially drive sex differences in neuropsychiatric disorders.

The concept of sex differences in the gut-brain axis has very recently been brought to the forefront, including in reviews by Jaggar et al. 2020 [4••] and Jašarević et al. 2016 [5], which provide a comprehensive overview of sex differences in the gut-brain axis over the life course, as well as evidence from animal studies. The purpose of this present review is to highlight how sex differences in the gut-brain axis may contribute to the discrepancies in incidence of neuropsychiatric disorders between females and males. We first begin with a brief overview of the gut-brain axis and then describe evidence by clinical disorders for which there is at least a moderate body of evidence regarding sex differences in the gut-brain axis: autism spectrum disorder, psychotic disorders, stress and anxiety disorders, depression, Alzheimer's disease, and Parkinson's disease. Lastly, we touch on the comorbidity between inflammatory bowel disease (IBD) and mental health symptomology, highlighting possible explanations for the increased mental health burden among women with IBD, relative to men.

Of note, in this manuscript, we use the term "sex" to refer primarily to the "assigned" or "biological" sex at birth, and we describe the biological processes typically associated with each sex. Yet, we acknowledge the heterogeneity that exists within the binary category of female versus male sex, in terms of hormones, chromosomes, and genitals, as well as the existence of other categories of sex (e.g., individuals with XY chromosomes that physically appear to be girls or were assigned to female sex at birth, individuals with ambiguous genitalia, etc.) [6]. Of course, there are also important *gender* differences in the incidence and prevalence of brain and behavioral disorders which do not necessarily overlap with "assigned" or "biological" sex. As the roles of sex and gender in the gut-brain axis are still relatively new areas of research, we have focused this review on the biological pathways linking the gut and the brain with sex assigned at birth. Future research needs to consider the complexity of sex and gender in this work.

## Overview of the Gut-Brain Axis

The gut-brain axis refers to the set of bidirectional communications and interactions between the gut and neurological systems, particularly the brain [7]. Included in this concept is the interplay between the neurological system and gut microbiota and the collection of microorganisms (bacteria, fungi, viruses, protozoa, and archaea) that reside within the gastrointestinal (GI) tract. The collective genetic material of these microbes in and on the human body is referred to as the microbiome [8].

A number of reviews have described the myriad of ways the gut and brain communicate (e.g., Wang & Wang 2016 and Kavvadia et al. 2017) [9, 10], including via the enteric nervous system ("second brain"), vagus nerve, and the production by microbes of cytokines

and chemokines, neurotransmitters, short-chain fatty acids, hormones, and other molecules and metabolites that act on the central nervous system [10].

Although we are in the early stages of understanding the complex ways in which the gut microbiome influences health, dysbiosis (microbial imbalance) has been associated with many diseases or disorders, including cancer, irritable bowel syndrome, obesity [11•], as well as neurodevelopmental disorders, mental illness, and neurodegeneration [12•].

In early life, the gut microbiome is relatively simple, in terms of composition and diversity, unstable, and highly susceptible to environmental exposures (e.g., diet, stress, medications) [13]. The complexity and stability of the gut microbiome increase into adulthood but remain malleable and dynamic across the life course [13]. This plasticity is what makes the microbiome an exciting potential therapeutic target. While dysbiosis has been linked to suboptimal mental health, numerous studies have found that populating the gut with beneficial bacteria (“probiotics” or “psychobiotics”) can create positive changes in the composition and diversity of the gut microbiome as well as corresponding improvements in the brain and mental health [14•, 15], as well as physical health [16].

## Autism Spectrum Disorder

Autism spectrum disorder, or ASD, is characterized by impairments in social communication and interaction and repetitive and restricted behaviors [17]. The cumulative incidence of ASD in the USA is 10.2 per 1000 children at age 4 and 8.3 per 1000 at age 8. The incidence rate for girls appears to plateau around 3 years while it continues to climb among boys, resulting in a higher prevalence of ASD in males relative to females [18]; 1 in 54 school-aged children have ASD, with a male to female ratio of about 4 to 1 [19].

It has been well established that individuals with ASD are more likely to have GI symptoms compared to typically developing children [20, 21]. Despite the many studies exploring the gut microbiome in ASD, no consistent ASD signature has been identified, and findings have been inconsistent, though differences have been identified in *Prevotella*, Firmicutes at the phylum level, and Clostridiales clusters including *Clostridium perfringens* and *Bifidobacterium* species [22].

A 2019 study by Wang et al. sought to identify differences in gut microbiome-associated epitopes (a term which refers to the part of an antigen where an antibody attaches) between children with ASD and typical development (TD), as well as other correlates of those epitopes. In addition to identifying differences in gut-associated epitopes and stool IgA between children with ASD and TD, the authors found that sex was also associated with specific epitopes. Further, while diversity of the epitopes differed between males with ASD versus TD, the diversity was not different between females in the two groups. This suggests that sex may affect the immune function of the gut microbiota and could help explain sex differences in autism [23••].

Animal models of ASD have also implicated sex-gut-brain differences. Coretti et al. (2017) used BTBR T + tf/J (BTBR) inbred mice, a frequently used animal model of ASD, to examine the gut microbiota, behavior, intestinal barrier integrity, and immune profiles of

tissues from the colon. The BTBR mouse had increased intestinal dysbiosis, permeability, immune abnormalities, and behavioral differences, compared to the control mouse (C57BL/6j strain), as expected. The BTBR behavioral phenotype consists of decreased social interaction (measured using the three-chamber social interaction test) and increased marble burying and spontaneous self-grooming. Though these are crude phenotypes relative to the complexity of autism in a person, these are typically considered "autism-like" symptoms because they represent social, stereotyped, and repetitive behavior, which are the core symptoms of ASD. Coretti et al. also found that sex of the BTBR (i.e., ASD) mouse was associated with differential relative abundance of the *Bacteroides*, *Parabacteroides*, *Sutterella*, *Dehalobacterium*, and *Oscillospira* genera. Among female BTBR mice, increases in *Parabacteroides* and *Sutterella* and decreases in *Dehalobacterium*, *Oscillospira*, and a member of TM7 (unclassified) were associated with altered behavior as well as expression of TNF-alpha in the colonic tissue. Among male BTBR mice, members of *Helicobacteraceae* were associated with altered behavior and decreased expression of IL-10, while lower levels of *Dehalobacterium*, *Ruminococcus*, and *Desulfovibrio* corresponded to increased intestinal permeability [24••].

An earlier study by Foley at al. (2014) found sex-specific social behavioral changes in the adolescent rat offspring of pregnant dams injected with prenatal propionic acid (PPA) or lipopolysaccharide (LPS). PPA is a microbial-produced short-chain fatty acid, while LPS is a large molecule found in the outer membrane of Gram-negative bacteria, also produced by enteric bacteria, that results in immune activation when administered to mammalian cells [25]. Foley et al. based their experiments on the knowledge that PPA and LPS are both microbial products, which in previous research have been shown to activate the immune system. Specifically, PPA induces activation of microglia and reactive astrogliosis [26, 27] in adult rats, while prenatal LPS leads to increases in proinflammatory cytokines and subsequent alterations in gene expression [28, 29]. Foley et al. found that both the male and female PPA-treated pups demonstrated delayed olfactory-mediated nest-seeking behavior but no changes in terms of social interactions. LPS did not influence social behavior in the neonatal or adolescent rats, but the adult male and female rates did have a decrease in defensive behavior, which the authors hypothesized could reflect decrease responsiveness to the social partner. Relative to females, adolescent males born to PPA-treated dams had an increased approach to a novel object as well as increased locomotor activity in a novel open-field activity. This was not accompanied by differences in social interactions, however. These findings raise the possibility that brief prenatal exposure to these microbial products (PPA and LPS) can subtly influence behavior, in sexually dimorphic ways, at various points in the lifespan. While the behavioral outcomes measured in this study are far reflecting autism-like symptoms, the authors framed the paper in terms of implications for autism and other neurodevelopmental conditions, given the impairments in social communication and interaction in autism, as well as the extant literature showing associations between PPA, LPS, and other immune-activating exposures on autism and neurodevelopment more broadly [27, 30, 31]. This paper suggests that microbial-related exposures during pregnancy can have potentially sex-specific effects on development and behavior of the offspring.

## Schizophrenia Spectrum and Other Psychotic Disorders

Disorders of psychosis include schizophrenia, schizotypal, and other psychotic disorders that are characterized by delusions, hallucinations, distortions in thinking, perceptions and emotions, disorganized or catatonic behavior, and negative symptoms such as lack of emotional expression [32]. A recent meta-analysis of all psychotic disorders estimated a pooled incidence of 26.6 per 100,000 person years, with incidence rates slightly higher in men compared to women prior to age 40 but higher in women after age 40 [33].

Multiple studies have found that patients with schizophrenia differ in the amount of *Lactobacillus* found in their microbiome compared to controls and that abundance of these bacteria correlate with severity of schizophrenia symptoms [34–36]. Recent research has also found that adults with schizophrenia or schizoaffective disorder have elevated levels of antigliadin immunoglobulin G (AGA-IgG), representing a heightened generalized immune response to the ingestion of gluten, compared to healthy controls [37, 38]. In a double-blind randomized clinical trial of adults with diagnoses of schizophrenia or schizoaffective disorder who had elevated AGA-IgG, patients randomized to the gluten-free diet (versus those on a diet containing gluten) showed an improvement in negative symptoms, particularly avolition and affective blunting and improvements in attention and verbal learning. The gluten-free group also showed significant improvements in GI distress [39].

At least some of the sex differences in psychotic disorders may be due to a gut component. A case-control study stratified by sex found elevated IgG antibodies to *Candida albicans*—an opportunistic pathogen yeast living in the GI, genitourinary, and respiratory tracts—to be associated with 2–9.5 times the risk of schizophrenia in males compared to male controls. Seropositivity was also associated with lower scores on cognition in females with schizophrenia compared to female controls as measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). By also examining a subset of medication naïve patients, the authors showed that seropositivity was not affected by antipsychotic medications. GI disturbances were associated with elevated *C. albicans* in males with schizophrenia, though not females [40]. This same research group showed that male patients with schizophrenia treated with probiotics had reductions in GI discomfort, decreased *C. albicans* antibodies, and improvements in positive symptoms. However, these changes were not found in females treated with probiotics versus placebo [41••].

## Anxiety and Trauma- and Stressor-Related Disorders

Anxiety disorders are conditions characterized by excessive fear and anxiety that lead to behavioral disturbances that may impair performance in school or work and/or negatively impact personal relationships. These include generalized anxiety disorder (GAD), panic disorder, post-traumatic stress disorder, social phobia, and specific phobia. The lifetime morbid risk of anxiety disorders ranges from 2 to 18%, depending on the specific disorder [42].

In a comparison of adults with GAD to healthy controls, those with GAD were found to have reductions in microbial diversity, short-chain fatty acid producing bacteria, and

increases in *Escherichia-Shigella*, *Fusobacterium*, and *Ruminococcus gnavus* [43]. Further, in a double-blind randomized control study of healthy college students, those taking a 28-day daily probiotic, relative to placebo, showed greater improvements in panic anxiety, neurophysiological anxiety, negative affect, worry, and negative mood regulation [44].

Sex differences in the microbiome have been associated with childhood temperament in toddlers. In both boys and girls, greater degree of surgency or extraversion was associated with higher phylogenetic diversity. Among boys only, this phenotype was also associated with Shannon Diversity Index (another measure of microbial diversity) as well as microbiome composition, specifically differences in the relative abundance of *Dialister*, *Rikenellaceae*, *Ruminococcaceae*, and *Parabacteroides*. Among girls, but not boys, greater effortful control was associated with lower alpha diversity, and fear was associated with increased relative abundance of *Rikenellaceae* [45].

Animal studies have provided some of the most pertinent information on sex differences in stress and anxiety to date. As Audet et al. describe, some of the increased risk of anxiety (and depressive disorders) associated with being female might partially be due to the remodeling of the gut microbial community and subsequent immune alterations that accompany hormonal changes associated with pregnancy, postpartum, and menopause [46••]. For example, ovariectomized mice who were subsequently administered progesterone experienced an increase in *Lactobacillus* species, decreased intestinal expression of IL-6, and improvement in depression- and anxiety-like behaviors [47]. Animal studies have also shown that rats who lack estrogen, whether due to having ovaries removed or lacking an estrogen receptor, had increased permeability in the large intestine, offering a pathway for metabolites to cross into the bloodstream [48].

The gut also seems to be involved in sex-specific effects of exposures or treatments on depression and anxiety in animal studies. For example, in a study using rats, early life maternal separation stress was associated with earlier pubertal onset in females but later maturity in males. Probiotic treatment restored pubertal timing in both sexes, however [49•]. In a study investigating the effects of docosahexaenoic acid (DHA), an omega-3 fatty acid, on the behavior of mice that had been socially isolated for 28 days, male mice who were given any supplementation of DHA showed reductions in both anxious and depressive behaviors. Further analysis showed levels of *Allobaculum* and *Ruminococcus* to be correlated with these behavioral changes [50]. Female mice, however, who also underwent social isolation and were given DHA did not show any behavioral changes. This suggests that behavioral treatments that influence the gut may have differential effects depending on sex.

However, we note that these experiments were performed in animals, not humans, and the phenomenology of anxiety and depressive symptoms and disorders among humans is likely much more complex than the simple behaviors measured in animal experiments. Further, the etiology of anxiety and depression is highly complex and multifactorial, and we do not expect these microbial changes to be the dominant or only one exposure responsible for this sex and gender discrepancy.

## Major Depressive Disorder

Major depressive disorder (MDD) is characterized by depressed mood and anhedonia, in combination with marked cognitive and behavioral changes [17]. Globally, the annual incidence of MDD in adults is 3.4% in females and 2.7% males [51], though prevalence estimates are much higher; the prevalence of MDD in the USA in 2017 was 8.7% among females and 5.3% among males [52].

Individuals with MDD have increased bacterial translocation with subsequent immune activation, which are associated with and may contribute to the somatic symptoms associated with depression (e.g., fatigue, malaise, autonomic and gastrointestinal symptoms) [53]. Bacterial translocation refers to the passage of bacteria and bacterial products from inside the intestinal tract into extraintestinal sites, such as the bloodstream, liver, spleen, kidney, and mesenteric lymph node complex. This process can occur via dysbiosis of the gut microbiome and intestinal bacterial overgrowth, increased permeability of the mucosal barrier in the intestine (“leaky gut”), or impairments in host immune defenses, or a combination of the above [54].

Dysbiosis of the gut microbiome has also been implicated in MDD, including differences in relative abundance of Bacteroidetes, Proteobacteria, Actinobacteria, Firmicutes, and Faecalibacterium, which are implicated in gut dysbiosis and disease outcomes [53, 55, 56]. Experimental studies in both rats and humans have shown that probiotics are associated with a decrease in depressive-like behaviors [57, 58]. Compelling rodent studies have also demonstrated that induced gastric inflammation [59] or irritation [60, 61] can lead to symptoms of anxiety and depression.

There is evidence that the association between gut microbiome composition and MDD may be differential by sex. One small study found that females with MDD showed increased levels of Actinobacteria compared to healthy controls, while males with MDD had decreased levels of Bacteroidetes compared to healthy controls [62••].

Although we have focused here on MDD, it is worth noting that sex differences in the gut-brain axis are also evident in other mood disorders. For example, individuals with bipolar disorder (BD) also suffer from chronic GI issues and dysbiosis of the gut microbiome, which have been shown to be associated with increased BD symptoms [63, 64]. Limited research on sex differences in BD has shown that compared to males, females have increased levels of *Flavonifractor* and *Candida albicans*, decreased microbial diversity, and increased GI symptoms [40, 65–67].

## Alzheimer’s Disease

Alzheimer’s disease (AD) is a progressive neurodegeneration disorder characterized by cognitive decline as well as changes in personality and behavior [68]. The hallmark pathologies of AD are accumulation of beta-amyloid protein (plaques) outside neurons in the brain and twisted strands of tau protein (tangles) inside the neurons, concomitant with damage to and death of neurons [68]. At age 45, the estimated overall lifetime risk for AD is about 20% for woman and 10% for men [69].

AD has been associated with decreased diversity of the microbiome [70]. An analysis of the microbiome composition of AD patients found decreased abundance of 13 genera in patients compared with controls. Notably, the *Bifidobacterium* genus was diminished in AD patients. *Bifidobacterium* are protective against intestinal permeability and inflammation, suggesting that when depreciated, a patient's risk of disease increases. It is still unclear what triggers the decline of these bacteria, though it has been hypothesized to precede neurodegeneration [70, 71].

The sex differences in AD presentation for men and women may stem in part from sex steroids, which protect from the development and symptomology of AD [72, 73]. A recent study collected imaging data from cognitively healthy older adults and discovered that while women had increased AD pathology, they did not exhibit increased AD symptomology compared to men [74•]. This suggests that although women have increased risk of AD pathology, sex-specific factors may protect women from experiencing early symptomology [75••]. Although estrogens have been implicated as one of the potential explicatory factors in sex-related differences in AD prevalence and clinical presentation, research is still underway to elaborate on this relationship [76]. A small post-mortem study assessing the hippocampus of AD patients and controls identified that estrogen receptor α (ERα) co-localizes with neurofibrillary tangles and therefore increases interaction between ERα and tau proteins. Increased tau-ERα interactions are hypothesized to inhibit ERα signaling and hinder the neuroprotective effect of estrogen [77]. The gut is relevant to this body of work because it plays a critical role in influencing the level of estrogen throughout the body. In brief, the gut secretes β-glucuronidase, an enzyme responsible for de-conjugating estrogen, making it biologically active and able to bind to receptors and carry out downstream functional changes in the body [78, 79].

The role of the gut microbiome in influencing sex differences in AD pathology has more directly been probed by Minter and colleagues. Minter et al. (2016) demonstrated that in the $APP_{SWE}/PS1_{\Delta E9}$ mouse model of AD, long-term treatment with a broad-spectrum antibiotic leads to lasting shifts in the composition and diversity of the gut microbiome in both female and male mice. In males, but not females, these microbial changes were accompanied by increasing levels of soluble Aβ, altered levels of circulating cytokines and chemokines, decreased in Aβ plaque deposition, reduced plaque-localized glial reactivity, and altered morphology of microglia [80], suggesting a sex-specific immune and accompanying neuropathological response to an antibiotic-induced microbial change. Subsequent work by this group carried out only among male mice also found microbial and immune changes following early *post-natal* antibiotic treatment and accompanying reductions in Aβ plaque deposition and plaque-localized microglia and astrocytes [81••]. To our knowledge, there have been no human studies looking at the gut-brain axis in AD by sex.

## Parkinson's Disease

One of the most common movement disorders, Parkinson's disease (PD) is characterized by tremors, dementia, and bradykinesia [82]. The overall incidence rate of PD among females age 40 and older is 37.55 per 100,000 person years (95% CI 26.20–53.83) and 61.21 (95% CI 43.57–85.99) among males 40 years and older [83]. PD pathology is associated with

striatal uptake, dopaminergic neuronal loss in the substantia nigra, and Lewy body pathogens spreading to cortical and neocortical brain areas [84].

GI symptomology frequently precedes the development of motor and cognitive dysfunction in patients with PD [85]. Although the exact role of the GI system in PD remains to be elucidated, a meta-analysis of 13 human studies found that gut permeability and colonic inflammation, instigated by changes in the gut-brain axis, contributed to PD symptomology [86]. Braak's seminal theory regarding PD development also implicates the gut-brain axis. Braak suggested that an unknown neurotropic pathogen enters the gut and gives rise to Lewy pathology. He asserted that after the entrance of the Lewy Pathogens into the brain through the vagus nerve, it is only upon reaching the substantia nigra that classic PD symptoms arise [87]. While Braak's hypothesis is unproven, a growing number of animal and human models support the assertion that PD initiates in the gut (see Lionett et al. 2018 [88]). Despite the continued debate on the potential role of the gut in PD pathogenesis, it has been repeatedly demonstrated that patients with PD do have altered microbiome compositions compared to controls [89–91].

Similar to Alzheimer's disease, many sex differences in PD are thought to stem from the protective nature of estrogens [75••]. Estrogens are thought to protect healthy cells against oxidative stress [92•] and support dopaminergic function [93]. Although estrogens are known to be strongly impacted by the gut-brain axis and are explicitly driven by sex, no studies among humans have directly investigated whether sex moderates the associations between the gut-brain axis and PD pathology. Murine studies are beginning to examine the specific influences of estrogen in PD models. Siani and colleagues (2017) investigated the impact of an ovariectomy (and therefore decreased estrogen) on dopaminergic cell bodies in mice [94•]. After an ovariectomy, female mice exhibited greater dopaminergic loss in the substantia nigra pars compacta compared to controls. However, upon receiving estrogen treatments, the dopaminergic loss was reversed. This suggests that not only is estrogen protective against nigrostriatal deterioration but that it may also be a future treatment option to modulate PD degeneration [94•]. Researchers hypothesize that the protective nature of estrogens, combined with the role of the gut-brain axis in controlling the availability of levodopa [95] (a primary PD treatment), drives sex differences in PD presentation and suggests that PD treatments may require sex-specific targets that leverage the gut-brain axis.

## GI Disorders

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic diseases of the GI tract that follow a cyclic pattern of relapse and remittance over the life course. The pathogenesis of these complex diseases is still largely unknown, yet multiple factors have been implicated, including an inappropriate immune response, genetic predisposition, and environmental influences [96, 97]. Global incidence rates for CD range from 5.0 to 20.2 cases per 100,000 person years, with an estimated annual incidence of 10.7 cases per 100,000 person years in the USA [98, 99]. Global incidence rates for UC range from 6.3 to 24.3 cases per 100,000 person years, with an estimated 12.2 cases per 100,000 person years in the USA [99]. There are sex-specific differences in CD incidence, with females having lower rates of CD in childhood but

increased rates of up to 1.2 times that of males after age 20. In contrast, there are no sex-specific differences of UC until age 45 when males begin to have a higher incidence compared to females [100].

IBD has a serious impact on overall quality of life and often co-occurs with mental health conditions, especially depression and anxiety. Pooled prevalence estimates of anxiety and IBD are around 20%, with an increase to 75% when individuals are in an active episode of IBD. Similarly, pooled prevalence estimates for depression are around 15%, with a jump to 21% during active disease [101, 102]. The incidence of MDD in people with IBD is 15 per 100 person years [103].

A bidirectional relationship exists between IBD and depression/anxiety [104]. First, IBD may be a risk factor for poor mental health. Intuitively, the abdominal pain, sleep dysfunction, and negative illness perceptions associated with IBD can lead to psychological morbidity [105], though there are biological explanations for this link as well. Rodent studies have found that induced gastric inflammation [59] or gastric irritation (a model of functional dyspepsia) can lead to symptoms of anxiety and depression [60, 61]. The biological pathways that raise the risk of IBD in individuals with depression or anxiety are not fully elucidated, though psychological distress has certainly been implicated as a risk factor for the exacerbation of IBD symptoms (increased smoking and poorer diet, sleep hygiene, and treatment maintenance are examples) [106].

Women with IBD tend to experience higher levels of depression, anxiety, and worse quality of life compared to men [102, 103, 107–109]. Given the interacting roles that genetics and the environment play in the pathogenesis of both IBD and mental illness, it is highly likely that sex-specific or sex-modified effects of genetics and environment influence the skewed mental health burden among females with IBD. In addition, factors associated with gender may be at play. Recent research has explored the role of gender-specific factors, including the influence of symptoms on body image, self-confidence, and social functioning, as potential mechanisms for the increase in psychological distress among women [107], i.e., the perceived and societal burden of GI symptoms may be more impairing for women [110].

## Conclusions

In this paper, we have highlighted recent literature showing how sex interacts with the gut-brain axis to influence brain and mental health. While this is a relatively new area of study, both human and animal studies demonstrate the bidirectional influence of sex-specific factors on the gut-brain axis, which may help to explain observed sex-differences in the incidence of psychopathology.

The mechanisms described in this paper fall broadly into two categories, as depicted in Fig. 1. First, sex may modify the relationship between the gut microbiome or immune system and brain, mental health, or behavior (Fig. 1a). This was observed in studies such as Christian et al. (2015) which showed that surgency/extroversion was associated with particular gut microbes among boys but not girls [45]. Importantly, sex may also influence the gut microbiome/immune system and brain/mental health, aside from modifying the

relationship between those domains. Second, sex may modify the effect that an experimental microbial treatment or product has on the brain, mental health, or behavior (Fig. 1b). This was observed by Minter and colleagues, where the effect of a broad-spectrum antibiotic on neuropathology (as well as circulating cytokines and chemokines) was observed in males but not females [80, 81••].

Because this field is in its nascency, we highlight some areas for future research: First, we note that human studies exploring sex differences in the gut-brain axis are relatively limited but can draw inspiration from the growing body of animal studies that are beginning to show the compelling connection between sex and the gut-brain axis. Clinical studies need to include representative samples of participants across different sexes and across the gender spectrum to be able to understand how biological, social, and environmental factors interact with the gut-brain axis. Epidemiologic studies that sample biospecimens are becoming increasingly valuable, as our ability to derive meaning from stored samples increases. Longitudinal designs and studies across the life course will be critical in helping us understand the temporal relationship between sex-related factors, such as hormones, and subsequent changes to the gut microbiome, immune system, brain, and behavior. In conclusion, it is increasingly apparent that the gut-brain axis plays a critical role in brain and mental health. Interrogating the role of sex may lead to better understanding of the etiology and treatment of brain and mental disorders.

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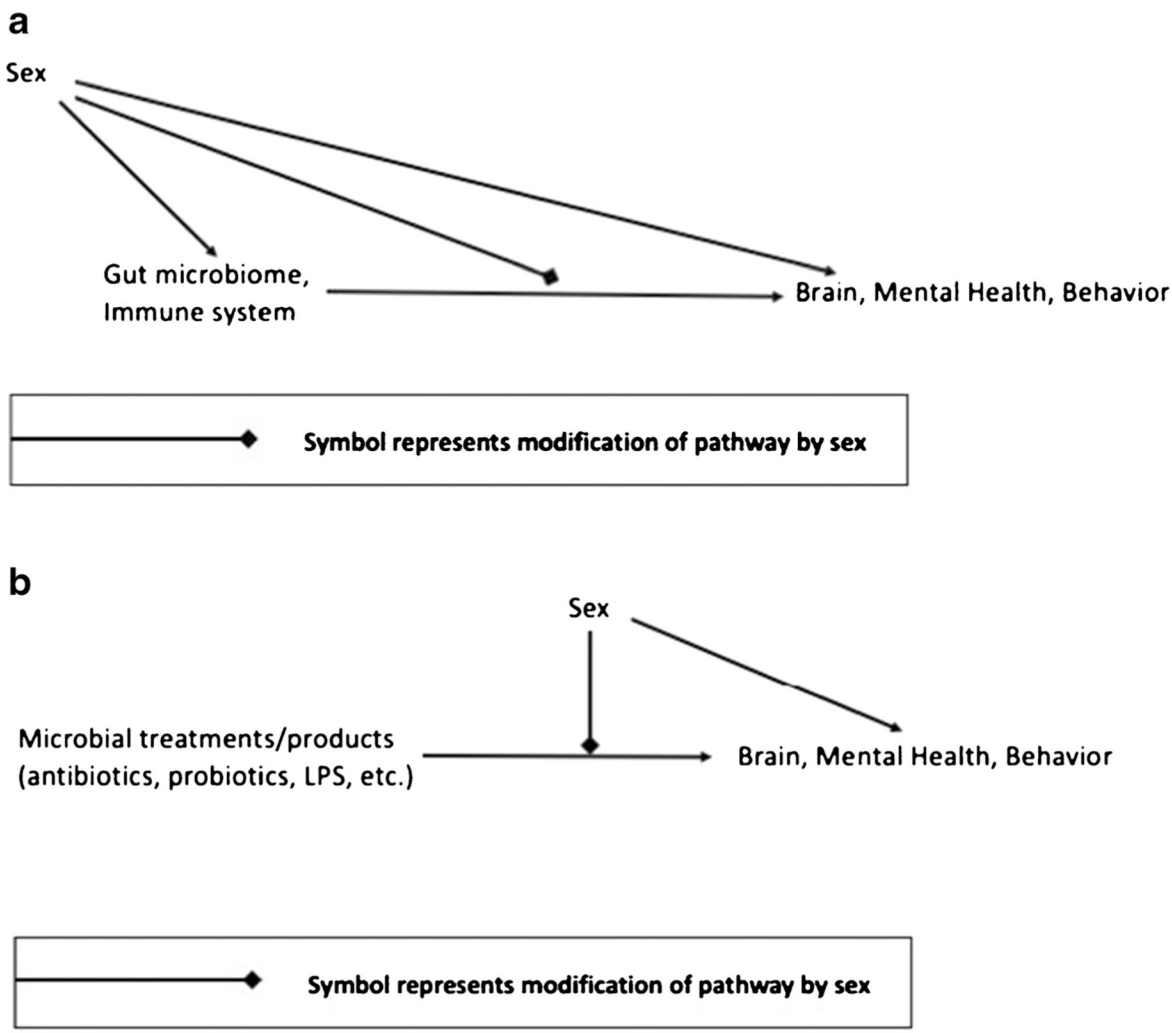


**Fig. 1.**

Conceptual diagrams highlighting key pathways by which sex influences the gut-brain axis. **a** Sex modifies relationship between gut microbiome/immune system and brain, mental health, or behavior. **b** Sex modifies effect of microbial treatment on brain, mental health, or behavior