Exploration of Neuroscience

Open Exploration

Open Access Review

Do enteric glial cells play a role in the pathophysiology of major depression?

Ravi Philip Rajkumar*

Department of Psychiatry, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006, India

***Correspondence:** Ravi Philip Rajkumar, Department of Psychiatry, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006, India. ravi.psych@gmail.com

Academic Editor: Dirk M. Hermann, University of Duisburg-Essen, Germany

Received: February 17, 2024 **Accepted:** March 29, 2024 **Published:** April 28, 2024

Cite this article: Rajkumar RP. Do enteric glial cells play a role in the pathophysiology of major depression? Explor Neurosci. 2024;3:156–74. https://doi.org/10.37349/en.2024.00042

Abstract

Major depressive disorder (MDD) is a common mental disorder associated with significant suffering and disability. Recent evidence has highlighted the role of the gut-brain axis in the pathogenesis of MDD. Enteric glial cells are a structurally and functionally diverse population that plays a key role in regulating enteric nervous function and maintaining intestinal mucosal integrity. These cells may be implicated in the origin of several digestive and extra-digestive disorders, known as enteric neuro-gliopathies (ENG). This paper reviews the evidence that MDD may also belong to the category of ENG. Animal models suggest that environmental adversity can lead to enteric glial dysfunction and depressive-like behaviors. Conditions that are highly comorbid with MDD, both intestinal and extra-intestinal, have been linked to enteric glial alterations. Peripheral blood markers linked to glial integrity and function are altered in patients with MDD, and certain treatments for MDD may have beneficial effects on enteric glial functioning. Though much of this evidence is indirect and provisional, it suggests that MDD may belong to the group of ENG. Further investigation of enteric glial functioning in MDD may yield valuable insights into the pathophysiology and treatment of this disorder.

Keywords

Major depression, gut-brain axis, gut microbiota, inflammation, stress, enteric glial cells, enteric neuro-gliopathy

Introduction

Major depressive disorder (MDD), also known as major depression, depressive disorder, or clinical depression, is a common mental disorder characterized by pervasive low mood and associated changes in thought, behavior, and biological functions [1]. At least 350 million individuals suffer from MDD, and it is projected to become the leading contributor to the global burden of disease burden at a global level by 2030 [2]. The etiology and pathogenesis of MDD are complex and incompletely understood. Broadly, MDD

can be seen as arising from an interaction between genetic vulnerability and exposure to stressful life events [3]. However, MDD is associated with dysregulation of several biological systems, such as the immune system, the hypothalamic-pituitary-adrenal (HPA) axis, and cardiac autonomic regulation [4–6].

In the past two decades, several researchers have found an association between MDD and dysfunction of the gut-brain axis [7]. The term "gut-brain axis" refers to a complex system of two-way communication between the central nervous system (CNS) and the enteric nervous system (ENS) [8]. The ENS is made up of over 500 million neurons, arranged in thousands of ganglia, and an even larger number of glial cells. These function together as a complex system that integrates a wide range of signals and regulates various aspects of intestinal function. For this reason, the ENS has been referred to as a "second brain" [9, 10]. More recently, it has been suggested that depression is related to a three-way interaction between the CNS, ENS, and the intestinal microbial flora, collectively known as the "microbiota-gut-brain axis". Communication between these three components involves several molecules, including conventional neurotransmitters, immune-inflammatory mediators and metabolites produced by gut bacteria. These send and transmit signals via the vagus nerve and the immune system [11, 12]. External factors such as stress and diet can influence gut-microbiome-brain "cross-talk" and alter the risk of developing major depression [13, 14].

Enteric glial cells and enteric neuro-gliopathies

When considering gut-brain axis interactions, it is important to note that the ENS is composed both of enteric neurons and of a much larger number of enteric glial cells. Though sharing a common origin from the neural crest during embryonic development, enteric glia are structurally and functionally diverse. Four subtypes (types I–IV) have been characterized in mammalian species, with specific localizations in the gut wall. These subtypes can be well characterized in biopsy specimens in terms of morphology, location, and expression of specific proteins. Type I enteric glia are "protoplasmic", with shorter processes, and express the glial fibrillary acidic protein (GFAP) as a marker, while type II glia are "fibrous", with longer processes that come into contact with enteric neurons but do not envelop them. Type III glia are seen in the extra ganglionic region, and their processes have been found to cover blood vessels. Type IV glia have a "bipolar" shape and are located in the smooth muscle layers of the gut, along the length of enteric nerve fibers [15]. In living organisms, enteric glia exhibit "phenotypic plasticity", and can alter their functioning in response to stimuli such as gut peptides or mucosal injury [16]. In the past, it was thought that the main function of these cells was to provide structural and nutritional support to neurons. It is now understood that enteric glia responds to external stimuli, regulate neuronal functioning, and influence the structural integrity and functioning of epithelial cells [17]. This "bidirectional" communication between enteric glia and neurons appears to modulate gut motor functioning [18]. In addition, enteric glia have wider roles in gut homeostasis, including interactions with intestinal stem cells and immune cells such as lymphocytes and macrophages [19].

In light of these findings, it has been suggested that enteric glial cells play an important role in the pathophysiology of certain intestinal disorders, such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and chronic constipation. Bassotti et al. [20, 21] have suggested that conditions previously described as "functional" bowel disorders may in fact be related to structural or functional alterations in enteric glia and their interactions with enteric neurons. Research in patients with functional bowel disorders has provided preliminary support for this hypothesis. In IBS, there is evidence of altered expression of cellular markers on enteric glia, and of altered interactions between these cells and mast cells [22, 23]. In chronic idiopathic constipation (CIC), reduced numbers of enteric glial cells have been demonstrated in both Meissner's and Auerbach's plexuses [24, 25]. Thus, these disorders could be considered "enteric neuro-gliopathies" (ENG) [20].

Extra-digestive ENG

The concept of ENG has primarily been applied to disorders of gut functioning. However, there is evidence that enteric glia could contribute to the pathophysiology of disorders not primarily involving the gut. Such

conditions could be considered "extra-digestive" ENG [26]. Given the intimate and complex connections between the functioning of the ENS and the CNS, it is possible that some disorders with primarily neuropsychiatric manifestations could be influenced, at least in part, by the dysfunction of enteric glial cells. Enteric glia have been shown to release a number of neurotrophic factors *in vitro*, including brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and nerve growth factor (NGF) [27–29]. These molecules are essential in promoting neural survival, differentiation, and connectivity [30]. Enteric glia have been shown to exert beneficial effects in cellular or animal models of several neurological disorders, including spinal cord injury [30], Alzheimer's disease (AD) [31], and multiple sclerosis [32]. It has been suggested that signaling between enteric glia and astrocytes in the brain is implicated in the pathogenesis of some neurodegenerative disorders, such as Alzheimer's dementia and Parkinson's disease (PD), that are strongly associated with MDD [33, 34]. It is plausible that enteric glia are implicated in the pathogenesis of depression, but this hypothesis has not been extensively investigated to date [35]. The purpose of the current review is to examine and critically evaluate pre-clinical and clinical evidence for a possible role of enteric glia in the etiology and pathophysiology of MDD, including the possibility that MDD may be an "extra-digestive" ENG.

Enteric glia in animal models relevant to depression

Though no studies have examined alterations in enteric glia in human patients with MDD, there is evidence that these cells may be linked to the genesis of depressive-like behaviors in animal models. In rats, exposure to chronic experimental stress was associated with increases in the number of enteric glial cells expressing GDNF. This led to changes in the activity of specific neurons in the ENS, leading to altered intestinal barrier function and alterations in the gut microbiome that could be relevant to the pathogenesis of MDD [36]. A study of rats exposed to a similar stressor found evidence both of increased GDNF expression and of immune activation in enteric glia. This could be attenuated by pre-treatment with the neuropeptide hormone oxytocin [37]. In mice fed a high-fat diet for five months, enteric glia showed altered expression of GDNF and of the immune receptor toll-like receptor 4 (TLR-4). These changes were associated with reduced BDNF levels, reduced numbers of dendritic spines in ENS neurons, and depressive-like behaviors. All these changes could be prevented by pre-treatment with the drug fluorocitrate, which is toxic to enteric glia [38]. In a more detailed investigation carried out in mice, it was found that stress-induced release of glucocorticoids was associated with increased expression of genes related to inflammation in enteric glia. This was associated with microscopic and behavioral evidence of colonic inflammation. Such changes were not seen in mice where the glucocorticoid receptor gene nuclear receptor subfamily 3 group C member 1 (*NR3C1*) was deleted, or in transgenic mice with lower numbers of enteric glia [39]. It has also been found that exposure to more severe forms of stress causes greater functional changes in enteric glia. This was demonstrated in a study of male rats exposed to maternal separation in childhood, experimental stress in adulthood, or both. Rats exposed to both forms of stress had a two-fold increase in morphological changes in enteric glia compared to those exposed to a single stressor [40].

Overall, these studies suggest that chronic stress or unhealthy diets can lead to morphological and pro-inflammatory changes in enteric glia, leading to intestinal inflammation, gut dysbiosis, and reduced structural and functional integrity of the ENS. In turn, this can cause alterations in CNS functioning leading to depressive-like symptoms. Moreover, the effect of stress appears to be dose-dependent and can be reversed by pharmacological manipulation. In animals not exposed to stress, enteric glia do not exhibit pro-inflammatory activity; instead, they protect enteric neurons against oxidative stress [41, 42]. Though the results of these studies require replication and extension to human subjects, they provide a plausible physiological pathway through which enteric glia act as "stress transducers" and induce depression via alterations in gut-to-brain signaling. This process is illustrated graphically in Figure 1 below.

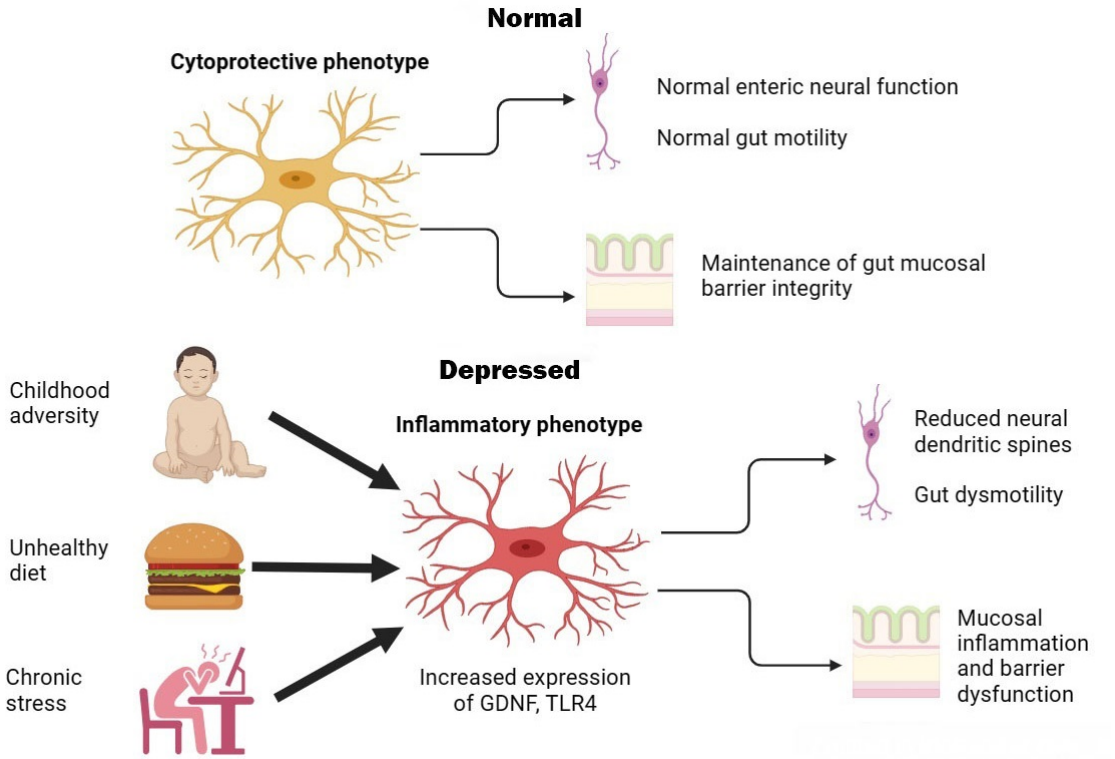

Figure 1. Graphical illustration of putative enteric glial changes in MDD. In health, enteric glia exerts regulatory effects on enteric neurons and protects neurons and epithelial cells against oxidative stress. Exposure to environmental factors can shift enteric glia to an activated or inflammatory phenotype, leading to gut dysmotility, inflammation, and barrier dysfunction that are associated with symptoms of MDD

Enteric glial dysfunction in disorders commonly associated with depression

There is evidence to suggest that enteric glial structure and functioning are altered in several clinical disorders that are highly comorbid with depression. These associations have been demonstrated in both intestinal and extra-intestinal disorders, and are considered in detail in this section.

Intestinal disorders

IBS

IBS is a functional gastrointestinal disorder that is highly comorbid with MDD. About 23% to 29% of patients with IBS have symptoms of MDD, and the risk of MDD is increased 3–7 fold in patients with IBS when compared to the general population [43, 44]. This relationship is bidirectional: patients with MDD are 2–2.5 times more likely to have IBS, and this association is specific to MDD and not to other mood disorders, such as bipolar disorder [45]. As noted in the introductory section, there is some evidence of altered enteric glial physiology in patients with IBS [22, 23]. In a rat model of IBS, exposure to multiple stressors was associated with increased overlap between enteric glia and neurons, and this was associated with greater IBS-like symptoms. These changes are similar to those noted in rodents where IBS was not the focus of the investigation, and could be partially blocked by administration of fluorocitrate [46]. Similarly, exposure to stress in male rats was associated with a decrease in enteric glia positive for S100 calcium-binding protein B (S100B), a neurotrophic factor; this was associated both with symptoms of IBS and with reductions in specific groups of submucous and myenteric neurons [47].

A study of colonic biopsy specimens in human patients with IBS yielded results very similar to those seen in animal models: immunoreactivity for S100B in enteric glia was markedly reduced, and this was correlated with symptom severity. It is noteworthy that 40% of IBS patients in this sample suffered from MDD [48]. In a study of human patients reporting IBS after exposure to the anti-platelet drug clopidogrel, drug-induced IBS was associated with higher levels of pain symptoms considered to be related to psychological factors such as stress, depression, or anxiety. Female patients with these symptoms showed a

higher level of expression of the clopidogrel receptor platelet adenosine diphosphate (purinergic) receptor ($P2Y_{12}R$) in enteric glia than in enteric neurons on biopsy. This suggests that altered enteric glial function may be related both to IBS and to its psychological concomitants in women [49].

Though much of this evidence is at a preliminary level, it suggests that both IBS and its association with MDD could be linked to dysfunction of enteric glial cells. This could be due to reductions in specific glial cell populations, or to altered enteric glial physiology caused by stress- or depression-induced inflammation [50].

IBD

MDD is specifically associated with an increased risk of IBD and often predates the onset of IBD by up to five years [45]. Given the role played by enteric glial cells in gut functioning, structural integrity, and inflammation, it is plausible that they are relevant to the pathophysiology of IBD. In a mouse model, experimental ablation or immune-mediated damage to enteric glia was associated with extensive small bowel inflammation, similar to that seen in Crohn's disease [51, 52]. Mice with experimentally-induced depressive behaviors were susceptible to IBD-like colonic inflammation following vagotomy, and these changes were reversed following treatment with a tricyclic antidepressant [53]. This effect was found to be mediated by intestinal macrophages, whose functioning is regulated by enteric glia [54, 55].

Direct evidence linking enteric glia to depression in IBD in humans is not yet available. However, markers of inflammation have been associated with elevated depressive symptoms in patients with IBD. This link was observed only in patients with a prior history of MDD [56]. Intestinal biopsies of patients with IBD have shown evidence of impaired enteric glial functioning, resulting in reduced intestinal barrier integrity [57, 58]. Recent research in patients with MDD has found evidence of intestinal barrier damage [59, 60].

Overall, these findings suggest that both IBD and depression are associated with impaired intestinal barrier integrity and that this may be related to impairments in enteric glial regulation of immune-inflammatory responses. Enteric glial dysfunction could explain the bidirectional link between these disorders.

Chronic constipation

About 6–14% of the general population suffers from chronic constipation for which no clear cause can be found. This condition is termed CIC [61, 62]. Like IBS, CIC is considered to be a "functional" gastrointestinal disorder related to stress or lifestyle factors. CIC is one of the first conditions to be considered an ENG, in view of preliminary evidence of glial dysfunction in biopsy specimens [20, 24, 25]. CIC is strongly associated with MDD [63]. The presence of severe depressive symptoms is associated with a 2.5-fold increase in the prevalence of CIC [64], while prior CIC is associated with a 2-fold increase in the risk of MDD [65]. Around 30–40% of patients with CIC have significant symptoms of MDD [66, 67]. In patients with MDD and no formal diagnosis of CIC, 8–25% have chronic constipation [68–70], and an association between severe ("psychotic" or "melancholic") MDD and constipation is well-documented in the psychiatric literature [71].

Alterations in enteric glial cells in relation to constipation have been documented by several researchers. Enteric glia plays a key role in animal models of chronic constipation induced by opioids. At the cellular level, this effect appears to be mediated through increased purinergic receptor activity, connexin-43 expression, and increased release of pro-inflammatory cytokines; at the tissue level, this is associated with low-grade colonic inflammation [72, 73]. Mice with chronic constipation induced in this way exhibit depressive-like behaviors, which improve when constipation is treated [74].

In human subjects, reduced numbers of S100B-positive enteric glia in the myenteric plexus have been associated with age-related idiopathic constipation [75]; these changes are similar to those documented in IBS associated with depression [48]. In patients with CIC, evidence of chromosomal anomalies in enteric glia, and of increased proximity between glia and degranulated mast cells, has been obtained [76, 77].

The available evidence on enteric glia and their relationship to depression in CIC does not lend itself to a straightforward synthesis. However, it is still possible that the enteric glial dysfunction seen in CIC may lead both to colonic inflammation and reduced intestinal motility. Both these alterations can increase the risk of MDD.

Extra-intestinal disorders

PD

PD is a neurodegenerative disorder characterized by symptoms of resting tremor, bradykinesia, rigidity, and postural instability, with associated cognitive, behavioral, and somatic changes. Classically, PD has been considered to arise from the abnormal accumulation of alpha-synuclein in Lewy bodies, with associated inflammation and degeneration of nigrostriatal dopaminergic pathways [78]. However, recent evidence has implicated the gut-brain axis in the pathophysiology of PD [79, 80].

There are significant epidemiological and pathophysiological links between PD and MDD. Patients with MDD have a 2-fold increase in the risk of subsequent PD [81], and 30–38% of patients with PD have symptoms of MDD [82, 83]. Gastrointestinal symptoms, particularly constipation, are frequently seen as "non-motor" symptoms of PD, and the presence of constipation in patients with MDD may predict subsequent PD [84, 85]. Gastrointestinal and depressive symptoms are reciprocally and positively correlated in patients with PD [86].

Most research on gut-brain axis dysfunction in PD has focused on alterations in gut microbial flora. Over the past decade, researchers have also identified evidence of alterations in enteric glial functioning. In a mouse model of toxin-induced PD, enteric glial changes included shortening and thickening of cell processes and increased immunoreactivity, which appeared to be correlated with increases in inflammatory markers [87]. In a primate model of PD using the same toxin, increased glial cell density in the small bowel was noted, and this was associated with impaired intestinal contractility [88]. Rodent models using a different toxin to induce PD-like phenomena also exhibited enteric glial changes in the form of reduced immunoreactivity to GFAP and S100B, mitochondrial dysfunction, and production of pro-inflammatory mediators [89, 90]. Administration of aggregates of alpha-synuclein was found to cause enteric glial activation both *in vitro* and in mouse models, and this was associated with intestinal inflammation and behavioral changes. In mice genetically predisposed to alpha-synuclein accumulation, colonic administration of these aggregates caused both gut inflammation and degeneration of nigrostriatal dopaminergic neurons, with more severe behavioral changes [91]. In a transgenic mouse model of PD, alpha-synuclein deposition in the gut was associated with glial cell activation, increased levels of interleukin-1β and tumor necrosis factor-α, impaired intestinal barrier functioning, and both motor and non-motor manifestations of PD [92]. Exposure to experimental stress exacerbated both enteric glial cell inflammation and CNS changes in a toxin-induced mouse model of PD [93].

In human patients, PD is associated with elevation and hypo-phosphorylation of GFAP in enteric glia [94]. In more advanced stages of PD, these cells are increased in number and density, a histological picture suggestive of reactive gliosis [95]. Serum levels of GDNF, which is produced by enteric glia and has protective effects on both the ENS and the mucosal barrier, are reduced in patients with PD who have constipation as a prominent symptom [96]. Constipation in PD is associated with more severe motor symptoms and depression [97].

On the basis of animal and human evidence, enteric glia seems to be significantly involved in the pathogenesis of PD, particularly its non-motor symptoms. There is an apparent bidirectional link between neuropathological changes and alterations in enteric glia. Though it is not yet clear whether depression in PD is related to enteric gliopathy, or whether enteric glial changes associated with MDD predispose to subsequent PD, both possibilities are consistent with the available data.

Other neurodegenerative disorders

Apart from PD, MDD is also associated with an increase in the subsequent risk of dementia, particularly AD and vascular dementia (VaD) [98]. Recent evidence has implicated gut-brain axis dysfunction in the

pathogenesis of both these disorders [34, 99, 100]. There is as yet no human evidence linking depression, enteric glial dysfunction, and these conditions. Enteric glial cells treated *in vitro* with β-amyloid showed increased release of interleukin-1β and TLR4, and increased glial activation has been seen in a mouse model of AD [101]. These findings suggest a link between enteric glial dysfunction, intestinal inflammation, and neurodegeneration that may be directly or indirectly related to MDD, but this possibility requires further testing.

Other evidence implicating enteric glia in gut-brain axis dysfunction relevant to depression

Similarity between toxin-induced and stress-induced changes in enteric glial function

In a study of human enteric glial cells, exposure to the bacterial toxin lipopolysaccharide (LPS) or to the pro-inflammatory cytokine interferon-gamma (IFNγ) led to these cells shifting to a "reactive" phenotype, characterized by up-regulation of pro-inflammatory genes [102]. These changes are akin to those induced by stress in a murine model [39]. Early life adversity, which is also strongly linked to subsequent MDD, has been shown to alter enteric glial responsiveness to mast cell signals, increase GFAP expression, and reduce the length of glial cell processes in mice [103]. The implications of these findings are two-fold. First, intestinal inflammation may itself shift enteric glia to a pro-inflammatory phenotype, causing a vicious cycle of increased inflammation, barrier dysfunction, and dysbiosis which can lead to depression. Second, early life stress may lead to subtle enteric glial dysfunction, which may predispose both to MDD and to associated digestive and extra-digestive disorders. Stress may act synergistically on enteric glial cells with other factors, such as diet and infection, in the pathogenesis of ENGs, including depression.

Treatment effects

Vagal nerve stimulation

The vagus nerve acts as a key neural link between the gut and the brain [104]. Vagal nerve stimulation (VNS), which is an effective treatment for MDD, has been shown to increase the expression of GFAP in enteric glia, which was associated with protective effects on gut mucosa in a mouse model [105]. In contrast, vagal ablation increased susceptibility to intestinal inflammation in a mouse model of depression, and this was reversed by antidepressant treatment [53]. This suggests that at least some effective treatments for MDD may act through vagal-mediated stimulation of enteric glia and reduction in intestinal inflammation.

Probiotics

The intestinal microbiome plays a key role in regulating the integrity and functioning of enteric glial cells [106, 107]. Patients with MDD have evidence of altered gut microbial flora in the form of altered beta diversity, and treatment with adjunctive probiotics has been shown to reduce depressive symptoms in MDD [108, 109]. Treatment with probiotics in patients with PD is associated with improvements in depression, motor symptoms, and gastrointestinal motility [110]. Though none of the trials of probiotics in these disorders have evaluated enteric glial functioning either directly or indirectly, it is possible that these treatments may exert their beneficial effects at least partly through restoration of enteric glial functioning.

Links between MDD and peripheral biomarkers related to enteric glia

Certain compounds that are measurable in peripheral blood may reflect enteric glial integrity or functioning. For example, serum S100B is significantly reduced in patients with ulcerative colitis (UC), which may reflect enteric glial inflammatory activation [111], while serum GDNF has been associated with constipation in patients with PD and may reflect impaired enteric glial functioning [96]. GFAP has also been proposed as a putative marker of enteric glial activation, though it is not detectable in the serum of patients with UC [111].

There is evidence of altered serum S100B levels in MDD, though the direction of findings has varied across studies. Some researchers have found elevated levels of S100B that correlate with the number and severity of depressive episodes [112, 113]; however, serum S100B may be reduced in youth with initial

episodes of MDD, in adult patients with multiple episodes of MDD, or in those on antidepressant treatment [114–116]. There are fewer studies evaluating serum GFAP in depression, but there is some evidence that this biomarker may be reduced in untreated patients with MDD [117]. These findings have been interpreted in terms of brain neuronal integrity or plasticity, but they could also reflect changes in enteric glial number, integrity, or functioning and associated comorbidities over the course of MDD.

No significant alterations in serum GDNF have been identified in patients with MDD, suggesting that this neurotrophin may not be a reliable marker of either depressive symptoms or enteric glial function [118].

Possible serotonergic links between enteric glial functioning and depression

Serotonin plays a key role in the pathophysiology of depression, as well as in the actions of most antidepressant medications [119–122]. This neurotransmitter also plays a key role in the regulation of gastrointestinal functioning: it is estimated that over 90% of plasma serotonin originates from enterochromaffin (EC) cells in the gut [123]. Though serotonin is synthesized independently in the CNS and in the gut, there is evidence of a moderate correlation between central (cerebrospinal fluid) and peripheral (plasma) levels of serotonin [124]. Given that most plasma serotonin is synthesized by EC cells, this suggests a degree of functional coordination between brain and gut serotonergic systems [125]. Alterations in gut serotonergic functioning have been hypothesized to play a role in many of the disorders putatively linked to enteric glial dysfunction, including IBS [126], IBD [127], AD [128], and multiple sclerosis [129]. It has also been suggested that alterations in gut serotonergic transmission may be related to the changes in mood seen in MDD [130, 131]. Like enteric glial cells, the serotonergic division of the ENS shows functional alterations in relation to the composition of the gut microbiome, and may show meaningful responses to probiotic treatments [132–134]. It has been suggested that intestinal serotonin may act as a "continuous regulatory signal" for various organs, particularly for the brain [135].

Evidence linking serotonin to enteric glial function or dysfunction is still preliminary. Enteric serotonergic neurons have extensive contact with glial cells [136]. A subset of enteric glia shows increased intracellular signaling and expression of GFAP when treated with serotonin [137–139]. This activation of enteric glia by serotonin has been shown to occur in response to acute infection or inflammation, where it may represent an attempt to restore homeostasis [139–141]. In addition, activation of the serotonin type 1A (5HT1A) receptor has been shown to protect enteric glia from apoptosis *in vitro* and animal models of intestinal inflammation [142]. This receptor is of particular interest because functional variations in the gene encoding it have been associated with susceptibility to MDD [143, 144].

Overall, though there is no direct evidence linking serotonergic transmission to enteric glial cell functioning in depression, various lines of evidence suggest that this pathway merits further investigation.

Summary and limitations of the available evidence

The evidence reviewed in this paper is summarized in Table 1 and Figure 2. It provides preliminary support for the concept that enteric glial dysfunction is involved in the pathogenesis of MDD—in other words, MDD may represent, at some level, an extra-digestive ENG.

Table 1. Evidence of possible enteric glial dysfunction associated with MDD

Source of evidence	Findings
Animal models of environmental adversity	Increased expression of GDNF, TLR-4, inflammatory mediators in enteric glia;
	Associated reduction in neuronal dendritic spines and mucosal inflammation.
IBS-animal models	Increased overlap between enteric glia and neurons;
	Reduced S100B positivity;
	Reductions in neuronal subpopulations.
IBS-human studies	Reduced enteric glial S100B immunoreactivity in IBS with comorbid MDD;
	Increased $P2Y_{12}R$ expression in enteric glia in women with clopidogrel-induced IBS and associated psychogenic pain.

Table 1. Evidence of possible enteric glial dysfunction associated with MDD (*continued*)

Source of evidence	Findings
IBD-animal models	Enteric glial ablation or damage associated with small bowel inflammation;
	Mice with experimentally induced depression sensitive to colonic inflammation after vagotomy;
	Reversible with tricyclic antidepressant.
IBD-human studies	Elevated intestinal inflammatory markers associated with depressive symptoms in IBD with prior MDD;
	Impaired enteric glial functioning in biopsies;
	Linked to mucosal barrier impairment similar to that seen in MDD.
CIC-animal models	Drug-induced chronic constipation associated with altered protein expression and inflammatory mediator release by enteric glia;
	Associated with depressive-like behaviors.
CIC-human studies	Reduced numbers of S100B-positive enteric glia;
	Chromosomal anomalies in enteric glia;
	Increased proximity between enteric glia and degranulated mast cells.
PD-animal models	Increased glial cell density;
	Reduced positivity for GFAP and S100B;
	Increased release of inflammatory mediators;
	Associated with gut dysmotility, mucosal barrier impairment, and PD symptoms;
	Glial changes exacerbated by exposure to stress.
PD-human studies	Elevated levels and hypo-phosphorylation of GFAP in enteric glia;
	Reactive gliosis;
	Reduced serum GDNF;
	Associated with constipation is linked to depression in PD.
Effects of VNS	Increased GFAP expression by enteric glia;
	Associated with mucosal barrier integrity in a mouse model.
MDD	Elevated serum S100B in adult patients with MDD;
	Reduced S100B in adolescents with MDD and after antidepressant treatment;
	Reduced serum GFAP in drug-naïve patients with MDD.

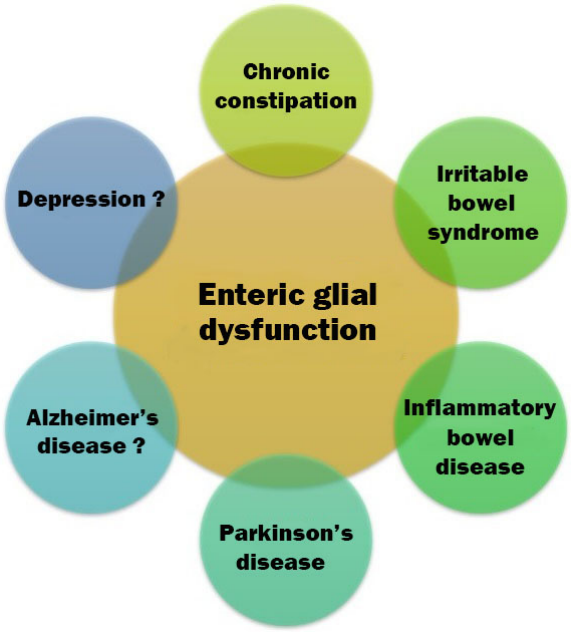

Figure 2. Graphical illustration of disorders that may be ENG. Firm associations have been established with gastrointestinal disorders. As one moves clockwise, toward the neuropsychiatric disorders, associations are more tentative but still plausible

However, certain limitations should also be acknowledged. First, much of this evidence is indirect in nature. There are no human studies that have directly evaluated enteric glial function in MDD, and studies of peripheral blood markers such as GFAP and S100B may not necessarily reflect enteric glial dysfunction. Second, even though there is evidence of enteric glial changes in animal models related to depression, it is not known if these changes are causal or merely correlated with behavioral changes. Third, it is not certain to what extent findings in rodent models can be applied to human subjects. Fourth, in spite of enteric glial dysfunction occurring in many disorders linked to depression, none of the human research on these disorders has specifically linked enteric glial dysfunction to depressive symptoms in these patients. Fifth, it is still not known if these findings apply to enteric glial cells in general, or to only some of the subtypes of enteric glia. Finally, it is possible that even if enteric glial dysfunction is demonstrated in depression, this may be epiphenomenal in nature and the result of more fundamental alterations in gut microbiota or immune-inflammatory functioning. Despite these limitations, the available evidence suggests that enteric glia could act as a link between gut and brain dysfunction in MDD, and this hypothesis needs to be investigated further.

Implications for practice and research

From a clinical point of view, there is no established treatment for depression that is known to affect enteric glial dysfunction. However, evidence from animal models and human subjects with other disorders suggests that four treatment approaches may be of value. First, stress reduction or stress management techniques may reduce the synergistic interaction between inflammation due to stress and other causes that result from enteric glial dysfunction. This approach may be useful in patients with mild MDD occurring in response to life events. Second, probiotics with evidence of beneficial effects on enteric glial structure and function could be used as adjuncts to standard antidepressant therapy or psychotherapy [145]. Third, treatments that directly or indirectly stimulate vagal function (e.g., VNS, some antidepressants) may have a positive effect on enteric glia, shifting them from an “inflammatory” to a “cytoprotective” phenotype. Finally, immune-based therapies could reduce the intestinal inflammation and barrier dysfunction that are putatively linked to “activated” enteric glia, leading to reduced peripheral and central inflammation and alleviating depressive symptoms [146].

From a research perspective, the results summarized in this review highlight the need for specific investigations of enteric glial function in patients with MDD. This could involve either direct examination of intestinal tissue using small bowel or colonic biopsies, or the use of fecal or peripheral blood markers that may reflect enteric gliopathy. If evidence of enteric glial dysfunction is demonstrated and replicated in MDD, it should be studied in association with the onset and course of depression, the presence of comorbid diagnoses or symptoms, and its response to various forms of treatment. Finally, studying the molecular mechanisms associated with enteric gliopathy in MDD-for example, using studies of gene or protein expression could yield new clues about the pathophysiology of this disorder, and could aid the development of novel gut-based therapies in patients who do not respond to conventional treatment.

Conclusions

The concept of extra-digestive ENG is relatively new. Though much of the evidence available is at a preliminary stage, there are several indications that MDD may be related to structural or functional alterations in different populations of enteric glia. While it may be premature to label MDD an ENG, it is highly likely that enteric glia may be a key “player” in the gut-brain interactions that underlie this disorder. Further clinical and translational investigations of enteric glial dysfunction in MDD, and its relationship to the gut and brain changes seen in this disorder, could shed new light on novel molecular and cellular processes linking gut dysfunction to mental health. This, in turn, could lead to the development of safer and more efficacious treatments for MDD.

Abbreviations

AD: Alzheimer's disease

CIC: chronic idiopathic constipation

CNS: central nervous system

ENG: enteric neuro-gliopathies

ENS: enteric nervous system

GDNF: glial cell line-derived neurotrophic factor

GFAP: glial fibrillary acidic protein

IBD: inflammatory bowel disease

IBS: irritable bowel syndrome

MDD: major depressive disorder

PD: Parkinson's disease

S100B: S100 calcium-binding protein B

TLR-4: toll-like receptor 4

VNS: vagal nerve stimulation

Declarations

Author contributions

RPR: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing.

Conflicts of interest

The author declares that he has no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

References

1. Kendler KS. The phenomenology of major depression and the representativeness and nature of DSM criteria. Am J Psychiatry. 2016;173:771–80.

2. Yang F, Lodder P, Huang N, Liu X, Fu M, Guo J. Thirty-year trends of depressive disorders in 204 countries and territories from 1990 to 2019: an age-period-cohort analysis. Psychiatry Res. 2023; 328:115433.
3. Fang Y, Scott L, Song P, Burmeister M, Sen S. Genomic prediction of depression risk and resilience under stress. Nat Hum Behav. 2020;4:111–8.
4. Křenek P, Hořínková J, Bartečků E. Peripheral inflammatory markers in subtypes and core features of depression: a systematized review. Psychopathology. 2023;56:403–16.
5. Sahu MK, Dubey RK, Chandrakar A, Kumar M, Kumar M. A systematic review and meta-analysis of serum and plasma cortisol levels in depressed patients *versus* control. Indian J Psychiatry. 2022;64: 440–8.
6. Wu Q, Miao X, Cao Y, Chi A, Xiao T. Heart rate variability status at rest in adult depressed patients: a systematic review and meta-analysis. Front Public Health. 2023;11:1243213.
7. Fetissov SO, Déchelotte P. The new link between gut-brain axis and neuropsychiatric disorders. Curr Opin Clin Nutr Metab Care. 2011;14:477–82.
8. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol. 2015;28:203–9.
9. Gershon MD. The enteric nervous system: a second brain. Hosp Pract. 1999;34:31–52.
10. Spencer NJ, Hu H. Enteric nervous system: sensory transduction, neural circuits and gastrointestinal motility. Nat Rev Gastroenterol Hepatol. 2020;17:338–51.
11. Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, et al. The microbiota-gut-brain axis. Physiol Rev. 2019;99:1877–2013.
12. Grau-Del Valle C, Fernández J, Solá E, Montoya-Castilla I, Morillas C, Bañuls C. Association between gut microbiota and psychiatric disorders: a systematic review. Front Psychol. 2023;14:1215674.
13. Medina-Rodriguez EM, Cruz AA, De Abreu JC, Beurel E. Stress, inflammation, microbiome and depression. Pharmacol Biochem Behav. 2023;227–8:173561.
14. Nasab MG, Heidari A, Sedighi M, Shakerian N, Mirbeyk M, Saghazadeh A, et al. Dietary inflammatory index and neuropsychiatric disorders. Rev Neurosci. 2023;35:21–33.
15. Boesmans W, Lasrado R, Vanden Berghe P, Pachnis V. Heterogeneity and phenotypic plasticity of glial cells in the mammalian enteric nervous system. Glia. 2015;63:229–41.
16. Valès S, Touvron M, Van Landeghem L. Enteric glia: diversity or plasticity? Brain Res. 2018;1693: 140–5.
17. Thomasi B, Gulbransen B. Mini-review: intercellular communication between enteric glia and neurons. Neurosci Lett. 2023;806:137263.
18. Baghdadi MB, Kim TH. The multiple roles of enteric glial cells in intestinal homeostasis and regeneration. Semin Cell Dev Biol. 2023;150–1:43–9.
19. Sanchini G, Vaes N, Boesmans W. Mini-review: enteric glial cell heterogeneity: is it all about the niche? Neurosci Lett. 2023;812:137396.
20. Bassotti G, Villanacci V, Fisogni S, Rossi E, Baronio P, Clerici C, et al. Enteric glial cells and their role in gastrointestinal motor abnormalities: introducing the neuro-gliopathies. World J Gastroenterol. 2007;13:4035–41.
21. Bassotti G, Villanacci V. Can "functional" constipation be considered as a form of enteric neuro-gliopathy? Glia. 2011;59:345–50.
22. Lilli NL, Quénéhervé L, Haddara S, Brochard C, Aubert P, Rolli-Derkinderen M, et al. Glioplasticity in irritable bowel syndrome. Neurogastroenterol Motil. 2018;30:e13232.
23. Meira de-Faria F, Casado-Bedmar M, Mårten Lindqvist C, Jones MP, Walter SA, Keita ÅV. Altered interaction between enteric glial cells and mast cells in the colon of women with irritable bowel syndrome. Neurogastroenterol Motil. 2021;33:e14130.

24. Iantorno G, Bassotti G, Kogan Z, Lumi CM, Cabanne AM, Fisogni S, et al. The enteric nervous system in chagasic and idiopathic megacolon. Am J Surg Pathol. 2007;31:460–8.
25. Bassotti G, Villanacci V, Nascimbeni R, Asteria CR, Fisogni S, Nesi G, et al. Colonic neuropathological aspects in patients with intractable constipation due to obstructed defecation. Mod Pathol. 2007;20: 367–74.
26. Neunlist M, Rolli-Derkinderen M, Latorre R, Van Landeghem L, Coron E, Derkinderen P, et al. Enteric glial cells: recent developments and future directions. Gastroenterology. 2014;147:1230–7.
27. von Boyen GBT, Steinkamp M, Reinshagen M, Schafer KH, Adler G, Kirsch J. Nerve growth factor secretion in cultured enteric glia cells is modulated by proinflammatory cytokines. J Neuroendocrinol. 2006;18:820–5.
28. Xiao W, Wang W, Chen W, Sun L, Li X, Zhang C, et al. GDNF is involved in the barrier-inducing effect of enteric glial cells on intestinal epithelial cells under acute ischemia reperfusion stimulation. Mol Neurobiol. 2014;50:274–89.
29. Sugiyama T, Shiotani A. The cutting edge research of functional gastrointestinal disorders in Japan: review on JGA Core Symposium 2018–2020. Digestion. 2021;102:6–11.
30. Hansebout CR, Su C, Reddy K, Zhang D, Jiang C, Rathbone MP, et al. Enteric glia mediate neuronal outgrowth through release of neurotrophic factors. Neural Regen Res. 2012;7:2165–75.
31. Esposito G, Sarnelli G, Capoccia E, Cirillo C, Pesce M, Lu J, et al. Autologous transplantation of intestine-isolated glia cells improves neuropathology and restores cognitive deficits in β amyloid-induced neurodegeneration. Sci Rep. 2016;6:22605.
32. Subhramanian S, Ariyath A, Sabhi R, Xavier T, Anandakuttan A, Kannoth S, et al. Translational significance of GMF-β inhibition by indazole-4-yl-methanol in enteric glial cells for treating multiple sclerosis. ACS Chem Neurosci. 2023;14:72–86.
33. D'Antongiovanni V, Pellegrini C, Antonioli L, Ippolito C, Segnani C, Benvenuti L, et al. Enteric glia and brain astroglia: complex communication in health and disease along the gut-brain axis. Neuroscientist. 2023;0:10738584231163460.
34. Denman CR, Park SM, Jo J. Gut-brain axis: gut dysbiosis and psychiatric disorders in Alzheimer's and Parkinson's disease. Front Neurosci. 2023;17:1268419.
35. Rudzki L, Maes M. The microbiota-gut-immune-glia (MGIG) axis in major depression. Mol Neurobiol. 2020;57:4269–95.
36. Lu T, Huang C, Weng R, Wang Z, Sun H, Ma X. Enteric glial cells contribute to chronic stress-induced alterations in the intestinal microbiota and barrier in rats. Heliyon. 2024;10:e24899.
37. Xu S, Qin B, Shi A, Zhao J, Guo X, Dong L. Oxytocin inhibited stress induced visceral hypersensitivity, enteric glial cells activation, and release of proinflammatory cytokines in maternal separated rats. Eur J Pharmacol. 2018;818:578–84.
38. Seguella L, Pesce M, Capuano R, Casano F, Pesce M, Corpetti C, et al. High-fat diet impairs duodenal barrier function and elicits glia-dependent changes along the gut-brain axis that are required for anxiogenic and depressive-like behaviors. J Neuroinflammation. 2021;18:115.
39. Schneider KM, Blank N, Alvarez Y, Thum K, Lundgren P, Litichevskiy L, et al. The enteric nervous system relays psychological stress to intestinal inflammation. Cell. 2023;186:2823–8.e20.
40. Tominaga K, Fujikawa Y, Tanaka F, Kamata N, Yamagami H, Tanigawa T, et al. Structural changes in gastric glial cells and delayed gastric emptying as responses to early life stress and acute adulthood stress in rats. Life Sci. 2016;148:254–9.
41. Abdo H, Derkinderen P, Gomes P, Chevalier J, Aubert P, Masson D, et al. Enteric glial cells protect neurons from oxidative stress in part *via* reduced glutathione. FASEB J. 2010;24:1082–94.
42. Abdo H, Mahé MM, Derkinderen P, Bach-Ngohou K, Neunlist M, Lardeux B. The omega-6 fatty acid derivative 15-deoxy-$\Delta^{12,14}$-prostaglandin J2 is involved in neuroprotection by enteric glial cells against oxidative stress. J Physiol. 2012;590:2739–50.

43. Zamani M, Alizadeh-Tabari S, Zamani V. Systematic review with meta-analysis: the prevalence of anxiety and depression in patients with irritable bowel syndrome. Aliment Pharmacol Ther. 2019; 50:132–43.
44. Ghoshal U, Biswas SN, Dixit VK, Yadav JS. Anxiety and depression in Indian patients with irritable bowel syndrome: a meta-analysis. Indian J Gastroenterol. 2023;42:32–9.
45. Nikolova VL, Pelton L, Moulton CD, Zorzato D, Cleare AJ, Young AH, et al. The prevalence and incidence of irritable bowel syndrome and inflammatory bowel disease in depression and bipolar disorder: a systematic review and meta-analysis. Psychosom Med. 2022;84:313–24.
46. Fujikawa Y, Tominaga K, Tanaka F, Tanigawa T, Watanabe T, Fujiwara Y, et al. Enteric glial cells are associated with stress-induced colonic hyper-contraction in maternally separated rats. Neurogastroenterol Motil. 2015;27:1010–23. Erratum in: Neurogastroenterol Motil. 2016;28:306.
47. Traini C, Evangelista S, Girod V, Faussone-Pellegrini MS, Vannucchi MG. Changes of excitatory and inhibitory neurotransmitters in the colon of rats underwent to the wrap partial restraint stress. Neurogastroenterol Motil. 2016;28:1172–85.
48. Rosenberg HJ, Rao M. Enteric glia in homeostasis and disease: from fundamental biology to human pathology. iScience. 2021;24:102863.
49. Soghomonyan S, Abdel-Rasoul M, Zuleta-Alarcon A, Grants I, Davila V, Yu J, et al. Clopidogrel IBS patients have higher incidence of gastrointestinal symptoms influenced by age and gender. Dig Dis Sci. 2017;62:2728–43.
50. Fukumoto M, Takeuchi T, Koubayashi E, Harada S, Ota K, Kojima Y, et al. Induction of brain-derived neurotrophic factor in enteric glial cells stimulated by interleukin-1β via a c-Jun N-terminal kinase pathway. J Clin Biochem Nutr. 2020;66:103–9.
51. Bush TG, Savidge TC, Freeman TC, Cox HJ, Campbell EA, Mucke L, et al. Fulminant jejuno-ileitis following ablation of enteric glia in adult transgenic mice. Cell. 1998;93:189–201.
52. Cornet A, Savidge TC, Cabarrocas J, Deng WL, Colombel JF, Lassmann H, et al. Enterocolitis induced by autoimmune targeting of enteric glial cells: a possible mechanism in Crohn's disease? Proc Natl Acad Sci U S A. 2001;98:13306–11.
53. Ghia JE, Blennerhassett P, Collins SM. Impaired parasympathetic function increases susceptibility to inflammatory bowel disease in a mouse model of depression. J Clin Invest. 2008;118:2209–18.
54. Hupa KJ, Stein K, Schneider R, Lysson M, Schneiker B, Hornung V, et al. AIM2 inflammasome-derived IL-1β induces postoperative ileus in mice. Sci Rep. 2019;9:10602. Erratum in: Sci Rep. 2020;10:3457.
55. Progatzky F, Shapiro M, Chng SH, Garcia-Cassani B, Classon CH, Sevgi S, et al. Regulation of intestinal immunity and tissue repair by enteric glia. Nature. 2021;599:125–30.
56. Ballesio A, Micheli F, Baccini F, Zagaria A, Del Forno A, Fiori V, et al. Inflammation as an aetiological trigger for depressive symptoms in a prospective cohort of patients with inflammatory bowel disease. J Psychosom Res. 2024;177:111592.
57. Pochard C, Coquenlorge S, Jaulin J, Cenac N, Vergnolle N, Meurette G, et al. Defects in 15-HETE production and control of epithelial permeability by human enteric glial cells from patients with Crohn's disease. Gastroenterology. 2016;150:168–80.
58. von Boyen GB, Schulte N, Pflüger C, Spaniol U, Hartmann C, Steinkamp M. Distribution of enteric glia and GDNF during gut inflammation. BMC Gastroenterol. 2011;11:3.
59. Wu H, Wang J, Teng T, Yin B, He Y, Jiang Y, et al. Biomarkers of intestinal permeability and blood-brain barrier permeability in adolescents with major depressive disorder. J Affect Disord. 2023;323: 659–66.
60. Stevens BR, Goel R, Seungbum K, Richards EM, Holbert RC, Pepine CJ, et al. Increased human intestinal barrier permeability plasma biomarkers zonulin and FABP2 correlated with plasma LPS and altered gut microbiome in anxiety or depression. Gut. 2018;67:1555–7.

61. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. Am J Gastroenterol. 2011;106:1582–91.
62. Liang J, Almario CV, Chey WD, Higgins CS, Spiegel BMR. Prevalence and burden of illness of Rome IV chronic idiopathic constipation, opioid-induced constipation, and opioid-exacerbated constipation in the United States. Am J Gastroenterol. 2023;118:2033–40.
63. Nellesen D, Chawla A, Oh DL, Weissman T, Lavins BJ, Murray CW. Comorbidities in patients with irritable bowel syndrome with constipation or chronic idiopathic constipation: a review of the literature from the past decade. Postgrad Med. 2013;125:40–50.
64. Vu NTH, Quach DT, Miyauchi S, Luu MN, Yoshida M, Nguyen DTN, et al. Prevalence and associated factors of chronic constipation among Japanese university students. Front Public Health. 2024;12: 1258020.
65. Yun Q, Wang S, Chen S, Luo H, Li B, Yip P, et al. Constipation preceding depression: a population-based cohort study. EClinicalMedicine. 2024;67:102371.
66. Hosseinzadeh ST, Poorsaadati S, Radkani B, Forootan M. Psychological disorders in patients with chronic constipation. Gastroenterol Hepatol Bed Bench. 2011;4:159–63.
67. Lv CL, Song GQ, Liu J, Wang W, Huang YZ, Wang B, et al. Colorectal motility patterns and psychiatric traits in functional constipation and constipation-predominant irritable bowel syndrome: a study from China. World J Gastroenterol. 2023;29:5657–67.
68. Garvey M, Noyes R Jr, Yates W. Frequency of constipation in major depression: relationship to other clinical variables. Psychosomatics. 1990;31:204–6.
69. Ballou S, Katon J, Singh P, Rangan V, Lee HN, McMahon C, et al. Chronic diarrhea and constipation are more common in depressed individuals. Clin Gastroenterol Hepatol. 2019;17:2696–703.
70. Wang P, Shen X, Wang Y, Jia X. Association between constipation and major depression in adult Americans: evidence from NHANES 2005–2010. Front Psychiatry. 2023;14:1152435.
71. Parker G, Roussos J, Mitchell P, Wilhelm K, Austin MP, Hadzi-Pavlovic D. Distinguishing psychotic depression from melancholia. J Affect Disord. 1997;42:155–67. Erratum in: J Affect Disord. 1997;46: 309.
72. Bhave S, Gade A, Kang M, Hauser KF, Dewey WL, Akbarali HI. Connexin-purinergic signaling in enteric glia mediates the prolonged effect of morphine on constipation. FASEB J. 2017;31:2649–60.
73. Gao H, Zhang Y, Li Y, Chang H, Cheng B, Li N, et al. μ-Opioid receptor-mediated enteric glial activation is involved in morphine-induced constipation. Mol Neurobiol. 2021;58:3061–70. Erratum in: Mol Neurobiol. 2021;58:6714–5.
74. Li B, Li M, Luo Y, Li R, Li W, Liu Z. Engineered 5-HT producing gut probiotic improves gastrointestinal motility and behavior disorder. Front Cell Infect Microbiol. 2022;12:1013952.
75. Baidoo N, Sanger GJ, Belai A. Effect of old age on the subpopulations of enteric glial cells in human descending colon. Glia. 2023;71:305–16.
76. Rossi E, Villanacci V, Fisogni S, Morelli A, Salerni B, Grigolato P, et al. Chromosomal study of enteric glial cells and neurons by fluorescence *in situ* hybridization in slow transit constipation. Neurogastroenterol Motil. 2007;19:578–84.
77. Bassotti G, Villanacci V, Nascimbeni R, Cadei M, Manenti S, Antonelli E, et al. Increase of colonic mast cells in obstructed defecation and their relationship with enteric glia. Dig Dis Sci. 2012;57:65–71.
78. Murphy J, McKernan DP. The effect of aggregated alpha synuclein on synaptic and axonal proteins in Parkinson's disease—a systematic review. Biomolecules. 2022;12:1199.
79. Shen T, Yue Y, He T, Huang C, Qu B, Lv W, et al. The association between the gut microbiota and Parkinson's disease, a meta-analysis. Front Aging Neurosci. 2021;13:636545.
80. Nielsen SD, Pearson NM, Seidler K. The link between the gut microbiota and Parkinson's disease: a systematic mechanism review with focus on α-synuclein transport. Brain Res. 2021;1769:147609.

81. Wang S, Mao S, Xiang D, Fang C. Association between depression and the subsequent risk of Parkinson's disease: a meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2018;86:186–92.
82. Chendo I, Silva C, Duarte GS, Prada L, Vian J, Quintão A, et al. Frequency of depressive disorders in Parkinson's disease: a systematic review and meta-analysis. J Parkinsons Dis. 2022;12:1409–18.
83. Cong S, Xiang C, Zhang S, Zhang T, Wang H, Cong S. Prevalence and clinical aspects of depression in Parkinson's disease: a systematic review and meta-analysis of 129 studies. Neurosci Biobehav Rev. 2022;141:104749.
84. Yao L, Liang W, Chen J, Wang Q, Huang X. Constipation in Parkinson's disease: a systematic review and meta-analysis. Eur Neurol. 2023;86:34–44.
85. Walter U, Heilmann R, Kaulitz L, Just T, Krause BJ, Benecke R, et al. Prediction of Parkinson's disease subsequent to severe depression: a ten-year follow-up study. J Neural Transm. 2015;122:789–97.
86. Jones JD, Dominguez B, Bunch J, Uribe C, Valenzuela Y, Jacobs JP. A bidirectional relationship between anxiety, depression and gastrointestinal symptoms in Parkinson's disease. Clin Park Relat Disord. 2021;5:100104.
87. Ellett LJ, Hung LW, Munckton R, Sherratt NA, Culvenor J, Grubman A, et al. Restoration of intestinal function in an MPTP model of Parkinson's disease. Sci Rep. 2016;6:30269.
88. Coletto E, Dolan JS, Pritchard S, Gant A, Hikima A, Jackson MJ, et al. Contractile dysfunction and nitrergic dysregulation in small intestine of a primate model of Parkinson's disease. NPJ Parkinsons Dis. 2019;5:10.
89. Dos Santos JCC, Rebouças CDSM, Oliveira LF, Cardoso FDS, Nascimento TS, Oliveira AV, et al. The role of gut-brain axis in a rotenone-induced rat model of Parkinson's disease. Neurobiol Aging. 2023;132: 185–97.
90. Palanisamy BN, Sarkar S, Malovic E, Samidurai M, Charli A, Zenitsky G, et al. Environmental neurotoxic pesticide exposure induces gut inflammation and enteric neuronal degeneration by impairing enteric glial mitochondrial function in pesticide models of Parkinson's disease: potential relevance to gut-brain axis inflammation in Parkinson's disease pathogenesis. Int J Biochem Cell Biol. 2022;147:106225.
91. Yang ZX, Zhang Y, Wang Q, Zhang L, Liu YF, Zhang Y, et al. Addition of α-synuclein aggregates to the intestinal environment recapitulates Parkinsonian symptoms in model systems. Acta Pharmacol Sin. 2024;45:36–51.
92. Pellegrini C, D'Antongiovanni V, Miraglia F, Rota L, Benvenuti L, Di Salvo C, et al. Enteric α-synuclein impairs intestinal epithelial barrier through caspase-1-inflammasome signaling in Parkinson's disease before brain pathology. NPJ Parkinsons Dis. 2022;8:9. Erratum in: NPJ Parkinsons Dis. 2023; 9:83.
93. Dodiya HB, Forsyth CB, Voigt RM, Engen PA, Patel J, Shaikh M, et al. Chronic stress-induced gut dysfunction exacerbates Parkinson's disease phenotype and pathology in a rotenone-induced mouse model of Parkinson's disease. Neurobiol Dis. 2020;135:104352.
94. Clairembault T, Kamphuis W, Leclair-Visonneau L, Rolli-Derkinderen M, Coron E, Neunlist M, et al. Enteric GFAP expression and phosphorylation in Parkinson's disease. J Neurochem. 2014;130: 805–15.
95. Emmi A, Sandre M, Russo FP, Tombesi G, Garrì F, Campagnolo M, et al. Duodenal alpha-synuclein pathology and enteric gliosis in advanced Parkinson's disease. Mov Disord. 2023;38:885–94.
96. Chen G, Du Y, Li X, Kambey PA, Wang L, Xia Y, et al. Lower GDNF serum level is a possible risk factor for constipation in patients with parkinson disease: a case-control study. Front Neurol. 2022;12: 777591.
97. Guan X, Wang Y, Li Q, Wei M, Chen L, Cheng O. Analysis of the clinical features of early Parkinson's disease with comparatively integrated intestinal function. Neurol Sci. 2018;39:1847–56.

98. Stafford J, Chung WT, Sommerlad A, Kirkbride JB, Howard R. Psychiatric disorders and risk of subsequent dementia: systematic review and meta-analysis of longitudinal studies. Int J Geriatr Psychiatry. 2022;37:10.1002/gps.5711.
99. Villavicencio-Tejo F, Olesen MA, Navarro L, Calisto N, Iribarren C, García K, et al. Gut-brain axis deregulation and its possible contribution to neurodegenerative disorders. Neurotox Res. 2023;42:4.
100. Cuartero MI, García-Culebras A, Nieto-Vaquero C, Fraga E, Torres-López C, Pradillo J, et al. The role of gut microbiota in cerebrovascular disease and related dementia. Br J Pharmacol. 2024;181:816–39.
101. D'Antongiovanni V, Pellegrini C, Antonioli L, Benvenuti L, Di Salvo C, Flori L, et al. Palmitoylethanolamide counteracts enteric inflammation and bowel motor dysfunctions in a mouse model of Alzheimer's disease. Front Pharmacol. 2021;12:748021.
102. Liñán-Rico A, Turco F, Ochoa-Cortes F, Harzman A, Needleman BJ, Arsenescu R, et al. Molecular signaling and dysfunction of the human reactive enteric glial cell phenotype: implications for GI infection, IBD, POI, neurological, motility, and GI disorders. Inflamm Bowel Dis. 2016;22:1812–34.
103. McClain JL, Mazzotta EA, Maradiaga N, Duque-Wilckens N, Grants I, Robison AJ, et al. Histamine-dependent interactions between mast cells, glia, and neurons are altered following early-life adversity in mice and humans. Am J Physiol Gastrointest Liver Physiol. 2020;319:G655–68.
104. Cao Y, Li R, Bai L. Vagal sensory pathway for the gut-brain communication. Semin Cell Dev Biol. 2024;156:228–43.
105. Costantini TW, Bansal V, Krzyzaniak M, Putnam JG, Peterson CY, Loomis WH, et al. Vagal nerve stimulation protects against burn-induced intestinal injury through activation of enteric glia cells. Am J Physiol Gastrointest Liver Physiol. 2010;299:G1308–18.
106. Seguella L, Palenca I, Franzin SB, Zilli A, Esposito G. Mini-review: interaction between intestinal microbes and enteric glia in health and disease. Neurosci Lett. 2023;806:137221.
107. Vicentini FA, Keenan CM, Wallace LE, Woods C, Cavin JB, Flockton AR, et al. Intestinal microbiota shapes gut physiology and regulates enteric neurons and glia. Microbiome. 2021;9:210.
108. Alli SR, Gorbovskaya I, Liu JCW, Kolla NJ, Brown L, Müller DJ. The gut microbiome in depression and potential benefit of prebiotics, probiotics and synbiotics: a systematic review of clinical trials and observational studies. Int J Mol Sci. 2022;23:4494.
109. Forth E, Buehner B, Storer A, Sgarbossa C, Milev R, Chinna Meyyappan A. Systematic review of probiotics as an adjuvant treatment for psychiatric disorders. Front Behav Neurosci. 2023;17: 1111349.
110. Park JM, Lee SC, Ham C, Kim YW. Effect of probiotic supplementation on gastrointestinal motility, inflammation, motor, non-motor symptoms and mental health in Parkinson's disease: a meta-analysis of randomized controlled trials. Gut Pathog. 2023;15:9.
111. Celikbilek A, Celikbilek M, Sabah S, Tanık N, Borekci E, Dogan S, et al. The serum S100B level as a biomarker of enteroglial activation in patients with ulcerative colitis. Int J Inflam. 2014;2014: 986525.
112. Yang K, Xie GR, Hu YQ, Mao FQ, Su LY. The effects of gender and numbers of depressive episodes on serum S100B levels in patients with major depression. J Neural Transm. 2008;115:1687–94.
113. Tural U, Irvin MK, Iosifescu DV. Correlation between S100B and severity of depression in MDD: a meta-analysis. World J Biol Psychiatry. 2022;23:456–63.
114. Bilginer Ç, Yaman H, Karadeniz S, Hızarcı Bulut S, Yaman SÖ, Aydoğdu S. Oxidative stress and serum S100B levels in adolescents with first-episode drug-naive unipolar depression. Psychiatr Danub. 2021;33:158–64.
115. Levchuk LA, Roschina OV, Mikhalitskaya EV, Epimakhova EV, Simutkin GG, Bokhan NA, et al. Serum levels of S100B protein and myelin basic protein as a potential biomarkers of recurrent depressive disorders. J Pers Med. 2023;13:1423.

116. Rajewska-Rager A, Dmitrzak-Weglarz M, Kapelski P, Lepczynska N, Pawlak J, Twarowska-Hauser J, et al. Longitudinal assessment of S100B serum levels and clinical factors in youth patients with mood disorders. Sci Rep. 2021;11:11973.
117. Hviid CVB, Benros ME, Krogh J, Nordentoft M, Christensen SH. Serum glial fibrillary acidic protein and neurofilament light chain in treatment-naïve patients with unipolar depression. J Affect Disord. 2023;338:341–8.
118. Shi Y, Luan D, Song R, Zhang Z. Value of peripheral neurotrophin levels for the diagnosis of depression and response to treatment: a systematic review and meta-analysis. Eur Neuropsychopharmacol. 2020;41:40–51.
119. Bremshey S, Gross J, Renken K, Masseck OA. The role of serotonin in depression–a historical roundup and future directions. J Neurochem. 2024;[Epub ahead of print].
120. Fakhoury M. Revisiting the serotonin hypothesis: implications for major depressive disorders. Mol Neurobiol. 2016;53:2778–86.
121. Pannu A, Goyal RK. Serotonin and depression: scrutiny of new targets for future anti-depressant drug development. Curr Drug Targets. 2023;24:816–37.
122. Jauhar S, Cowen PJ, Browning M. Fifty years on: serotonin and depression. J Psychopharmacol. 2023; 37:237–41.
123. Jones LA, Sun EW, Martin AM, Keating DJ. The ever-changing roles of serotonin. Int J Biochem Cell Biol. 2020;125:105776.
124. Audhya T, Adams JB, Johansen L. Correlation of serotonin levels in CSF, platelets, plasma, and urine. Biochim Biophys Acta. 2012;1820:1496–501.
125. Banskota S, Khan WI. Gut-derived serotonin and its emerging roles in immune function, inflammation, metabolism and the gut-brain axis. Curr Opin Endocrinol Diabetes Obes. 2022;29: 177–82.
126. Gros M, Gros B, Mesonero JE, Latorre E. Neurotransmitter dysfunction in irritable bowel syndrome: emerging approaches for management. J Clin Med. 2021;10:3429.
127. Gonzalez Delgado S, Garza-Veloz I, Trejo-Vazquez F, Martinez-Fierro ML. Interplay between serotonin, immune response, and intestinal dysbiosis in inflammatory bowel disease. Int J Mol Sci. 2022;23:15632.
128. Aaldijk E, Vermeiren Y. The role of serotonin within the microbiota-gut-brain axis in the development of Alzheimer's disease: a narrative review. Ageing Res Rev. 2022;75:101556.
129. Melnikov M, Sviridova A, Rogovskii V, Oleskin A, Boziki M, Bakirtzis C, et al. Serotoninergic system targeting in multiple sclerosis: the prospective for pathogenetic therapy. Mult Scler Relat Disord. 2021;51:102888.
130. Jenkins TA, Nguyen JCD, Polglaze KE, Bertrand PP. Influence of tryptophan and serotonin on mood and cognition with a possible role of the gut-brain axis. Nutrients. 2016;8:56.
131. Margolis KG, Cryan JF, Mayer EA. The microbiota-gut-brain axis: from motility to mood. Gastroenterology. 2021;160:1486–501.
132. Layunta E, Buey B, Mesonero JE, Latorre E. Crosstalk between intestinal serotonergic system and pattern recognition receptors on the microbiota-gut-brain axis. Front Endocrinol. 2021;12:748254.
133. Stasi C, Sadalla S, Milani S. The relationship between the serotonin metabolism, gut-microbiota and the gut-brain axis. Curr Drug Metab. 2019;20:646–55.
134. Everett BA, Tran P, Prindle A. Toward manipulating serotonin signaling via the microbiota-gut-brain axis. Curr Opin Biotechnol. 2022;78:102826.
135. Szoke H, Kovacs Z, Bokkon I, Vagedes J, Szabo AE, Hegyi G, et al. Gut dysbiosis and serotonin: intestinal 5-HT as a ubiquitous membrane permeability regulator in host tissues, organs, and the brain. Rev Neurosci. 2020;31:415–25.

136. Okamoto T, Barton MJ, Hennig GW, Birch GC, Grainger N, Corrigan RD, et al. Extensive projections of myenteric serotonergic neurons suggest they comprise the central processing unit in the colon. Neurogastroenterol Motil. 2014;26:556–70.
137. Kimball BC, Mulholland MW. Enteric glia exhibit P_{2U} receptors that increase cytosolic calcium by a phospholipase C-dependent mechanism. J Neurochem. 1996;66:604–12.
138. Boesmans W, Cirillo C, Van den Abbeel V, Van den Haute C, Depoortere I, Tack J, et al. Neurotransmitters involved in fast excitatory neurotransmission directly activate enteric glial cells. Neurogastroenterol Motil. 2013;25:e151–60.
139. Hagbom M, De Faria FM, Winberg ME, Westerberg S, Nordgren J, Sharma S, et al. Neurotrophic factors protect the intestinal barrier from rotavirus insult in mice. mBio. 2020;11:e02834-19.
140. Westerberg S, Hagbom M, Rajan A, Loitto V, Persson BD, Allard A, et al. Interaction of human enterochromaffin cells with human enteric adenovirus 41 leads to serotonin release and subsequent activation of enteric glia cells. J Virol. 2018;92:e00026-18.
141. Spear ET, Mawe GM. Enteric neuroplasticity and dysmotility in inflammatory disease: key players and possible therapeutic targets. Am J Physiol Gastrointest Liver Physiol. 2019;317:G853–61.
142. Walldorf J, Porzner M, Neumann M, Joodi G, Niess JH, von Boyen G, et al. The selective 5-HT1A agonist SR57746A protects intestinal epithelial cells and enteric glia cells and promotes mucosal recovery in experimental colitis. Inflamm Bowel Dis. 2022;28:423–33.
143. Kishi T, Yoshimura R, Fukuo Y, Okochi T, Mastunaga S, Umene-Nakano W, et al. The serotonin 1A receptor gene confer susceptibility to mood disorders: results from an extended meta-analysis of patients with major depression and bipolar disorder. Eur Arch Psychiatry Clin Neurosci. 2013;263: 105–18.
144. Lacerda-Pinheiro SF, Pinheiro RFF, Pereira de Lima MA, Lima da Silva CG, Vieira dos Santos MD, Teixeira AG, et al. Are there depression and anxiety genetic markers and mutations? A systematic review. J Affect Disord. 2014;168:387–98.
145. Potter K, Gayle EJ, Deb S. Effect of gut microbiome on serotonin metabolism: a personalized treatment approach. Naunyn Schmiedebergs Arch Pharmacol. 2023;[Epub ahead of print].
146. Chanpong A, Borrelli O, Thapar N. Recent advances in understanding the roles of the enteric nervous system. Fac Rev. 2022;11:7.