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Psychological comorbidity in gastrointestinal diseases: Update on the brain-gut-microbiome axis

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Abstract

The high comorbidity of psychological disorders in both functional and organic gastrointestinal diseases suggests the intimate and complex link between the brain and the gut. Termed the brain-gut axis, this bidirectional communication between the central nervous system and enteric nervous system relies on immune, endocrine, neural, and metabolic pathways. There is increasing evidence that the gut microbiome is a key part of this system, and dysregulation of the brain-gut-microbiome axis (BGMA) has been implicated in disorders of brain-gut interaction, including irritable bowel syndrome, and in neuropsychiatric disorders, including depression, Alzheimer's disease, and autism spectrum disorder. Further, alterations in the gut microbiome have been implicated in the pathogenesis of organic gastrointestinal diseases, including inflammatory bowel disease. The BGMA is an attractive therapeutic target, as using prebiotics, probiotics, or postbiotics to modify the gut microbiome or mimic gut microbial signals could provide novel treatment options to address these debilitating diseases. However, despite significant advancements in our understanding of the BGMA, clinical data is lacking. In this article, we will review current understanding of the comorbidity of gastrointestinal diseases and psychological disorders. We will also review the current evidence supporting the key role of the BGMA in this pathology. Finally, we will discuss the clinical implications of the BGMA in the evaluation and management of psychological and gastrointestinal disorders.

Keywords

Functional gastrointestinal disorders; Disorder of the brain-gut axis; Brain-gut-microbiome axis; Irritable bowel syndrome; Inflammatory bowel disease; Psychological treatments

1. Introduction

While traditional dualistic models of human health separated the activities of the mind from the body, there is now an understanding of the close interconnectivity between these

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two entities (Mehta, 2011). Instead of dualism, human disease is best understood through a biopsychosocial model, which assesses the reciprocal interactions and significance of biological, environmental, and psychological factors (Engel, 1980). Gastrointestinal diseases provide a useful application for the biopsychosocial model, particularly due to our growing knowledge of the brain-gut-microbiome axis (BGMA) (Drossman, 1996). This system of bidirectional communication between the central nervous system (CNS) and enteric nervous system (ENS) is influenced by the gut microbiome and relies on immune, endocrine, neural, and metabolic pathways (Khlevner et al., 2018). The BGMA maintains gut homeostasis, and its dysregulation has been implicated in numerous gastrointestinal diseases, most notably disorders of gut-brain interaction (DGBI) (H. R. Mertz, 2003). This circular communication loop connecting the mind and the body provides a physiologic rationale for the interpretation of gastrointestinal illness within the biopsychosocial model (Martin et al., 2018).

It is a common misconception that psychological concerns in gastrointestinal diseases only relate to DGBI, including irritable bowel syndrome (IBS) and functional dyspepsia (FD), or only occur as an adjustment reaction to physical illness (Wu, 2012). Psychological symptoms are common in patients with DGBI and are believed to be part of the genesis and maintenance of these disorders (Van Oudenhove et al., 2016). However, there is a growing body of literature suggesting significant and persistent psychological comorbidity, particularly mood disorders, in organic gastrointestinal disorders, including inflammatory bowel disease (IBD), celiac disease (CeD), and eosinophilic esophagitis (EoE) (Cossu et al., 2017; Neuendorf et al., 2016; Reed et al., 2020). This underscores the importance of considering psychological factors in the evaluation and management of all gastrointestinal diseases. Having a physical illness, being symptomatic, and requiring treatment can be distressing in itself, promoting distorted thinking, maladaptive coping, and mood disturbance. The possibility of perturbations of the BGMA in these diseases altering bottom-up signaling and contributing to physiological concerns is intriguing but poorly understood.

Numerous studies have demonstrated the adverse impact of psychological comorbidity in a host of medical conditions, including IBD, diabetes, and heart disease (W. K. Davis et al., 1988; Gracie et al., 2016; Lazzarino et al., 2013). The negative consequences of psychological comorbidity can be indirect such as when a patient with diabetes and depression suffers complications after not taking their insulin due to feelings of hopelessness and amotivation. However, the BGMA demonstrates how psychological factors can also *directly* influence gastrointestinal disease through top-down signaling. There is evidence that psychological concerns directly affect both functional and organic gastrointestinal disorders, including both symptoms and inflammation in IBD (Araki et al., 2020; Gracie et al., 2018; Sexton et al., 2017; Van Oudenhove et al., 2016).

While significant advances have been made recently in our understanding of the BGMA and how it relates to psychological and gastrointestinal disease, most of this research is preclinical. Clinical studies have, at times, been conflicting, though exciting possibilities of modifying the gut microbiome to treat gastrointestinal and neuropsychiatric disease have been raised. For this reason, better understanding of this relationship is essential to expand available treatment modalities. In this article, within the context of the BGMA, we review psychological comorbidity in gastrointestinal disease. We will discuss the management

of psychological disease in gastrointestinal disorders, including the current evidence for treatments targeting the BGMA.

2. The brain-gut-microbiome-axis

2.1. A brief overview of the gut-microbiome

The gut microbiome represents a highly complex microbial community comprised of bacteria, fungi, archaea, viruses, and protozoa. Humans have evolved with these microbes, creating symbiotic ecosystems that change in response to host physiology (Lloyd-Price et al., 2016). An individual's gut microbiome is made up of 10^4 bacteria in a 1.3:1 ratio to their somatic cells (Sender et al., 2016). The vast majority of gut microbes are bacteria, with *Firmicutes, Bacteriodetes,* and *Actinobacteria* being the three major bacterial phylae and representing over 90% of intestinal microorganisms (Jandhyala et al., 2015; Tap et al., 2009). Numerous genetic, geographical, and environmental factors shape an individual's microbiome, and there is evidence the gut begins to become colonized in utero (De Filippo et al., 2010; Stinson et al., 2019; Yatsunenko et al., 2012). It continues to develop and is subject to dynamic changes until stabilizing at three years-of-age (Backhed et al., 2015; Yatsunenko et al., 2012). There is evidence that far more modest alterations to the gut microbiome can continue to occur throughout the lifespan, including with enteric infections, antibiotics, and changes in diet (Guarner and Malagelada, 2003). The gut microbiome is thought to be a crucial part of protecting the gut from pathogens and maintaining the integrity of the intestinal mucosal barrier (Ohland and Macnaughton, 2010; Zhu et al., 2020). Perturbations in the gut microbiome are believed to be part of the pathogenesis of various gastrointestinal diseases, including IBD and IBS as well as influencing metabolism and contributing to obesity (C. D. Davis, 2016; Quigley, 2018; Zuo and Ng, 2018).

2.2. Brain-gut-microbiome signaling

The BGMA represents the bidirectional communication between the CNS and ENS, which is influenced by the gut microbiome's interaction with the ENS as well as through endocrine and immune signaling pathways (Martin et al., 2018). The ENS is the intrinsic innervation of the gastrointestinal tract, and has been dubbed the "second brain," as it is the only part of the peripheral nervous system that contains extensive neural circuits that are capable of local autonomous function to control gut movement, local blood flow, and fluid exchange between the gut and its lumen (Furness et al., 2014; Gershon, 1999). It has been well established the ENS is modulated by the Autonomic Nervous System (ANS) via efferent and afferent vagal parasympathetic and prevertebral sympathetic signaling (Khlevner et al., 2018). In homeostasis, there is no conscious perception of continuous afferent gut-brain signals. However, pain and other pathology that represents a salient noxious stimulation is communicated via visceral afferents and requires a behavioral response (Mayer and Tillisch, 2011). This signaling from the vagal afferents is processed within a homeostatic-afferent network, which then integrates with neurocircuits responsible for both emotional and cognitive response and also sends descending signals to the dorsal horn of the spinal cord where pain is modulated (Urien and Wang, 2019). This modulation can either increase or decrease pain signaling, and abnormal pain inhibitory mechanisms have been observed in IBS (Wilder-Smith et al., 2004). The central integration of visceral

input with emotional and cognitive neurocircuits is important in understanding the role of psychological factors in individual visceral pain perception. For example, the presence of dysfunctional cognitions, such as catastrophizing, were shown to independently negatively influence IBS symptom severity and quality of life (Thijssen et al., 2010). Another study, again, demonstrated catastrophizing and also somatization were associated with worsening IBS severity (van Tilburg et al., 2013). These maladaptive psychological constructs are targets for psychotherapeutic interventions, as discussed later. However, it is important to note they are only present in a subset of patients with chronic gastrointestinal illness (Weinland et al., 2010).

Neuroimaging has also supported brain-gut connectivity as well as implicated the gut microbiome in this process. Early imaging studies of patients with both IBS and FD demonstrated greater activation of the homeostatic-afferent network than healthy controls with rectal or gastric distention, respectively (Oudenhove et al., 2010; Tillisch et al., 2011). Additionally, IBS patients showed increased activation of emotional-arousal networks and less activation of modulatory networks, and FD patients showed increased activation of sensory networks. These findings correlate to clinical observations in IBS of increased sympathetic arousal, anxiety, and hypervigilance. Examination of communication between areas of the brain in IBS has suggested upregulated connectivity between emotional-arousal circuitry and also implicated serotonin as a potential modulator of this circuitry (Berman et al., 2002; Labus et al., 2011; Mayer et al., 2015). Functional alterations in regions comprising the default mode network, sensorimotor processing, and salience networks have been observed (Hong et al., 2016; Icenhour et al., 2017; Longarzo et al., 2017; Weng et al., 2017). More recently, characterization of brain circuitry in DGBI has advanced to include network analysis, where large scale structural and functional networks are compared to clinical and other biological parameters (Mayer et al., 2019). This methodology was recently used to demonstrate differences in microbial subnetworks in IBS patient versus healthy controls, which were associated with structural brain alterations in sensory integration and salience networks (Labus et al., 2019). Other studies have linked the gut microbiome with both functional and structural brain changes. Functional magnetic resonance imaging of healthy women who ingested a four week course of fermented milk product demonstrated alteration of brain regions associated with central emotional processing and sensation (Tillisch et al., 2013). Interestingly, two recent studies have linked changes to the gut microbiome profile in IBS patients to both structural and functional neurologic differences (Labus et al., 2017; Tillisch et al., 2017). In one of these studies, women with IBS were grouped based on having a gut microbiome with *Bacteriodes* abundance or *Prevotella* abundance, and those with *Prevotella* abundance showed greater behavioral response to negative emotional stimuli and had less hippocampal activity (Tillisch et al., 2017).

There is also increasing evidence as to the importance of the endocrine system in the BGMA, and dysbiosis can lead to the release of pro-inflammatory cytokines, bioactive molecules, and microbial antigens that can activate or attenuate the hypothalamic-pituitary axis (HPA) (Malagelada, 2020; van de Wouw et al., 2018). The HPA, in turn, releases hormones, such as corticotropin releasing factor, adrenocorticotropic hormone, and cortisol, in response to these signals and also stress, and there is some evidence these hormones can further alter gut microbial composition and increase intestinal permeability (A. J. Park et al.,

2013). While dysregulation of the HPA axis has been implicated in numerous psychiatric disorders, perturbations in the gut microbiome have also been associated with depression, anxiety, and cognitive changes (Barandouzi et al., 2020; Keller et al., 2017; M. Sun et al., 2020b; Tafet and Nemeroff, 2020).

Gut microbiota can interact with the CNS through the bioactive compounds they produce, and the best understood compounds are short chain fatty acids, secondary bile acids, and tryptophan metabolites (Silva et al., 2020; van de Wouw et al., 2018; Yano et al., 2015). These intermediates can interact with enterochromaffin and enteroendocrine cells directly, and in this way are able to participate in bottom-up signaling through stimulating the release of neurotransmitters and hormones (Kidd et al., 2009; Palazzo et al., 2007; Yano et al., 2015). There is also evidence these intermediates can cross the blood brain barrier, though it is not understood whether they reach any specific brain target. The CNS can signal the gut through the release of endocrine mediators that interact with microbes or directly signal via the ANS. This direct signaling can alter gut physiology, including intestinal transit time, fluid secretion, nutrient availability, and intestinal permeability, all affecting bacterial clearance rates (Houlden et al., 2016; Mayer, 2011; Roager et al., 2016).

Taken together, there is currently strong preclinical and some clinical evidence to support the crucial role of the BGMA, and this axis provides an interesting circuit to conceptualize the frequent comorbidity of psychological and gastrointestinal illness.

2.3. The biopsychosocial model and the gut microbiome axis

Emerging preclinical and clinical evidence about the role of the BMGA in cognition, behavior, and personality has interesting implications in the interpretation of gastrointestinal illness within the biopsychosocial model. The biopsychosocial model of illness examines the reciprocal and complex interactions between biological, psychological, and environmental contributors to disease. In this model, gastrointestinal disease can be seen as more than just an isolated pathophysiologic process, but in the context of psychosocial factors that may be key to the genesis and maintenance of the illness. For example, it is well known that early adverse life events (EALs) increase the risk of developing IBS, and the number of EALs experienced and the perceived severity of these EALs further increase this risk (Bradford et al., 2012; Ju et al., 2020; S. H. Park et al., 2016). Stressful life events are also associated with the exacerbation of IBS symptoms and have even been implicated in causing flaring in IBD (Araki et al., 2020; Bennett et al., 1998; Sexton et al., 2017; Whitehead et al., 1992). Further, DGBI have been associated with patterns of distorted thinking, symptom hypervigilance, and health anxiety, independent of psychiatric comorbidity, and these cognitive-affective processes can worsen symptom severity and are targets for psychotherapeutic treatment (Lackner et al., 2018; Van Oudenhove et al., 2016).

The BGMA’s interaction with the HPA axis and emerging data regarding its influence in neurodevelopment, mood, and cognition provide an interesting context through which to interpret psychopathology in gastrointestinal disease. Several studies have suggested the importance of the gut microbiome in early brain development, including one clinical study where gut microbiome composition at 1 year-of-age was associated with cognition at 2 years-of-age (Carlson et al., 2018; Hoban et al., 2016). Mostly preclinical data suggests that

throughout the lifespan metabolites produced by the microbiome can influence microglia, the macrophage cells of the CNS that mediate immune response, and this signaling has been implicated in neurodegenerative diseases (M. Sun et al., 2020a; Y. Wang et al., 2018; Zhu et al., 2020). Stress, particularly early life stress has been shown to cause alterations to the HPA axis, and alterations to the HPA axis have been seen in IBS, even in the absence of EALs (S. H. Park et al., 2018; Videlock et al., 2009). As discussed previously, there is evidence to support signaling between the HPA axis and the microbiome, and both dysbiosis and HPA axis dysregulation have been implicated in psychiatric diseases (Misiak et al., 2020).

While much of the research surrounding the role of the gut microbiome and mood, behavior, and cognitions has been done in animal models, clinical data has associated the gut microbiome with both temperament in early childhood and adult personality traits (Davidson et al., 2018; K. V. Johnson and Foster, 2018; K. V. A. Johnson, 2020; Sarkar et al., 2020). While clinical data is lacking and direct causality has not been shown between the microbiome and these neurocognitive outcomes, the BGMA provides a compelling justification for the biopsychosocial model and potential explanation for psychological findings in gastrointestinal diseases.

3. Psychological comorbidity in gastrointestinal diseases

3.1. Disorders of gut-brain interaction

Formerly referred to as functional gastrointestinal disorders, DGBI are being reclassified to better represent their pathophysiology, which is related to dysbiosis, altered immune function, visceral hypersensitivity, and CNS dysregulation of visceral afferent, descending inhibitory modulation, and gut motility (Drossman and Hasler, 2016). They represent a diverse group of esophageal, gastroduodenal, bowel, centrally mediated, and anorectal disorders, and in a large-scale multinational study more than 40% of respondents to internet and household surveys met criteria for a DGBI (Sperber et al., 2020). DGBI are associated with lower quality of life, more frequent doctor's visits, and disability (Cunningham et al., 2017; Koloski et al., 2000; Williams et al., 2006). As discussed previously, psychological concerns are believed to be part of the genesis and maintenance of these disorders as part of the biopsychosocial model. Here we will review the current evidence for psychological comorbidity in specific DGBI as well as the existing data regarding implications for the BGMA.

3.2. Irritable bowel syndrome

IBS is a common DGBI with a prevalence of 4–5% of the general population (O. S. Palsson et al., 2020; Sperber et al., 2020). It is marked by abdominal pain, sometimes related to defecation. It is associated with changes in bowel habits, which may include constipation (IBS-C), diarrhea (IBS-D), or alternating constipation and diarrhea (IBS-M). On evaluation there is an absence of biochemical or structural abnormalities to explain these symptoms (Mearin et al., 2016). Numerous studies have shown the frequent comorbidity of psychological concerns and disorders in IBS, most notably depression and anxiety (Fond et al., 2014; Whitehead et al., 2002). A recent multivariate analysis of 769 IBS patients

meeting Rome III criteria, demonstrated 44.9% reported significant anxiety and 25.7% reported significant depression (Midenfjord et al., 2019). Their analysis further suggested other factors including non-gastrointestinal symptoms, fatigue, gastrointestinal-specific anxiety, and visceral hypersensitivity separated IBS patients with and without psychological distress, emphasizing the interconnectedness of these factors in determining psychological status. Panic disorder has also been identified in IBS, with some studies suggesting 25–44% of patients with IBS meet criteria for panic disorder (Kaplan et al., 1996; Kumano et al., 2004). A recent systemic review with meta-analysis confirmed that post-traumatic stress disorder is a significant risk factor for IBS, though this analysis was limited by significant study heterogeneity (Ng et al., 2019). There is little evidence for an association between bipolar disorder and IBS (Karling et al., 2016). There is some literature suggesting an increased prevalence of IBS in schizophrenia, with one study finding 19% of patients with schizophrenia assessed in an outpatient primary care setting meeting criteria (Gupta et al., 1997). With regards to substance use disorders, multiple studies have suggested concerning patterns of opiate prescribing to manage gastrointestinal pain, including for DGBIs (Dorn et al., 2011; Kanuri et al., 2015; Sayuk et al., 2018). This is particularly concerning in functional bowel disorders, as chronic opiate use can result in narcotic bowel syndrome. In this condition, hyperalgesia occurs, and pain can result from escalating opiate dosages (Farmer et al., 2017). Some studies have also suggested an association between IBS and cannabis use disorder, though this should be considered within the context that cannabis is being actively explored as a therapeutic for this disease (Adejumo et al., 2019; R. S. Patel et al., 2020).

Beyond formally meeting criteria for a psychological disorder, psychological concerns are often identified in patients with IBS, including distorted thinking patterns (i.e. catastrophizing), illness anxiety, and hypervigilance (Hunt et al., 2009; Van Oudenhove et al., 2016). GI-specific anxiety has been shown to be a significant mediator between general anxiety symptoms and IBS symptom severity (Labus et al., 2007). The psychological concerns serve as key contributors to the affective-cognitive aspects of DGBI. For example, a patient who suffers from IBS-D might fixate on the normal sensation of abdominal distention after eating (hypervigilance and worry) and succumb to GI-specific anxiety, having thoughts that their day will be ruined if they develop diarrhea (catastrophizing). They may then decide to stay home and not go to a social event, potentially reinforcing avoidance behaviors and causing other life dysfunction. These behaviors are often the targets of GI specific psychotherapies, like cognitive behavioral therapy (CBT), discussed later (Kinsinger, 2017). Somatization, the psychological experience and communication of a somatic symptom, has also been associated with IBS, particularly IBS-M (P. Patel et al., 2015). Somatization may also explain the frequent overlap of IBS with other functional somatic syndromes, like pelvic pain, headaches, and fibromyalgia (Riedl et al., 2008).

Both preclinical and clinical studies have begun to uncover the relationship between IBS, psychological comorbidity, and the microbiome. Two recent rodent studies involving fecal microbiota transplant (FMT) have shown an association between depression and anxiety behaviors, gut microbiome, and GI symptoms. One study transferred stool from 34 patients with major depression and 33 healthy controls to a microbiota-deficient rat model (Kelly et al., 2016). They noted behavioral changes in the rats consistent with depression and

anxiety after FMT, alterations in tryptophan metabolism, and a reduction of richness and alpha diversity of the gut microbiome. In another study, germ-free mice were colonized with fecal microbiota from patients with IBS-D and developed faster gastrointestinal transit, intestinal barrier dysfunction, innate immune activation, and anxiety like behaviors (De Palma et al., 2017). In clinical studies, Liu *et al.* demonstrated similar fecal microbiota signatures in patients with IBS-D and depression, characterizing three groups by high proportions of *Bacteroides* (type I), *Prevotella* (type II), or nondominant microbiota (type III) (Liu et al., 2016). Patients with depression or IBS-D had 85% and 80% type I or type II, respectively, and colon tissue from patients with types I and II demonstrated higher levels of inflammatory markers than type III.

3.3. Functional dyspepsia

Patients with FD experience combinations of post-prandial fullness, early satiety, epigastric pain, and epigastric pain that interfere with usual activities and have no structural or biochemical abnormalities (Enck et al., 2017). Studies have suggested varying population prevalence in different areas of the world, with a recent multinational internet and household survey suggesting 7.2% prevalence (Sperber et al., 2020). While FD was the most common gastroduodenal DGBI, there was a wide variability between countries ranging from 2.2% prevalence in Japan to 12.3% in Egypt in internet surveys. FD is believed to occur through similar mechanisms as IBS, and visceral hypersensitivity causes discomfort with distention of the gastric fundus in the resting or fed states (H. Mertz et al., 1998).

Numerous studies have suggested higher rates of anxiety and depression in FD, though estimates of comorbidity vary significantly (Hartono et al., 2012; Li et al., 2002; Oudenhove et al., 2010). In one study in Sweden, 10 year follow up of 887 participants demonstrated anxiety at baseline was associated with new-onset FD, but not depression (Aro et al., 2015). Interestingly, when Fluorine-18-deoxyglucose positron emission tomography-computed tomography was performed on 40 patients with FD, increased glucose metabolism abnormalities were noted within the insula, anterior cingulate cortex, middle cingulate cortex, and middle frontal cortex (Nan et al., 2015). These abnormalities were positively correlated with subject anxiety and depression scores, implicating psychopathology may affect glucose metabolism in these homeostatic afferent and sensory areas, not simply visceral afferent signaling. Early research has supported the role of dysbiosis in the pathophysiology of FD and suggests through analysis of both stool and gastric aspirates that intestinal dysbiosis may be associated with symptom occurrence (Tziatzios et al., 2020). More investigation is not only needed to understand the role of the gut microbiome in FD, but also its implication for psychological comorbidity.

3.4. Functional constipation

FC is marked by persistent, difficult, infrequent, or seemingly incomplete defecation (Bharucha et al., 2013). It differs from IBS in that any resulting abdominal discomfort dissipates with resolution of the constipation, while IBS patients continue to suffer from abdominal pain even with normal bowel movements. Anxiety and depression have been found to be more prevalent in several studies of patients with FC (Cheng et al., 2003; Hosseinzadeh et al., 2011). A recent preclinical study implicated serotonin production in

the pathogenesis of both constipation and depression (Israelyan et al., 2019). TPH2-R439H mice were used, which lack the gene encoding the rate-limiting enzyme responsible for serotonin production and have a depression phenotype. They were fed either chow with or without 5HTP slow release, which restores serotonin levels in the CNS and reduces depressive behaviors. Mice fed chow without 5HTP slow release retained their depression phenotype and also had abnormalities in ENS development and ENS-mediated GI function, including reduced motility and intestinal epithelial growth. Meanwhile, mice fed 5HTP slow release reversed these findings. The gut microbiome has also been implicated in the pathogenesis of functional constipation, though this has not been related to psychologic comorbidity (Shin et al., 2019).

3.5. Other disorders of brain-gut interaction

Other DGBI, including esophageal disorders (functional heartburn, globus, reflux hypersensitivity), gastroduodenal disorders (belching disorder, rumination disorder), centrally mediated abdominal pain syndrome, anorectal disorders (fecal incontinence, functional defecation disorders), and childhood disorders (functional abdominal pain, aerophagia), have similarly been found to increase psychological comorbidity with less data available regarding the role of the BGMA in this process (Absah et al., 2017; Galmiche et al., 2006; Meyer and Richter, 2015).

Inflammatory Bowel Disease.—IBD is an organic and immune-mediated inflammatory disorder with a relapsing and remitting course. In the case of ulcerative colitis (UC), inflammation occurs in the colon and is confined to the colonic mucosa. Crohn's disease (CD) can involve any area of the digestive tract and the inflammation can be transmural. While the prevalence of inflammatory bowel disease is often quoted as being around 1% of the general population, numerous studies have suggested the incidence is rising, including in very young children (Benchimol et al., 2014; GBD 2017 Inflammatory Bowel Disease Collaborators, 2020; Dahlhamer et al., 2016). The overall rate of anxiety symptoms in patients with IBD is 19–35% and depressive symptoms is 27% (Neuendorf et al., 2016; Walker et al., 2008). There is some suggestion rates of depression and anxiety are higher in CD versus UC both in disease remission and during flares (Neuendorf et al., 2016). Further, there is increasing evidence to suggest the presence of anxiety and depression can increase the risk of disease recurrence in IBD (Mikocka-Walus et al., 2016). Whether comorbid psychological conditions in IBD are the end result of disease burden or a manifestation of a systemic inflammatory process is a subject of active inquiry (Moulton et al., 2019). Post-traumatic stress disorder has also been associated with CD (Camara, Gander, Begre, von Kanel, and Swiss Inflammatory Bowel Disease Cohort Study, G, 2011; T. H. Taft et al., 2019a). Again, more study is needed to explore this association, as inflammation has been directly implicated in the pathogenesis of PTSD and it is not clear if trauma related to CD, systemic inflammation, or both could lead to PTSD (Speer et al., 2018).

The BGMA provides a viable link between psychological concerns and IBD, and may suggest that anxiety and depression seen in IBD is not just the result of disease-related burden. Numerous studies of the composition of the gut microbiome, its functional activity, and its metabolome in IBD have suggested aberrations that promote a pro-inflammatory

state (Glassner et al., 2020). Preclinical evidence has implicated dysbiosis in disease development, and there is even evidence that the gut microbiome can predict response to IBD therapy (Ananthakrishnan et al., 2017; Franzosa et al., 2019; Glassner et al., 2020). Manipulation of the gut microbiome is used to manage IBD, and antibiotics are used as well as fecal diversion. Inflammation has been a target for the management of depression, including the use anti-tumor necrosis factor agents, which are also used to manage IBD (McIntyre et al., 2019; Raison et al., 2013). Unfortunately, use of these agents has only shown limited success, working in a portion of patients with treatment-resistant depression and baseline elevation of c-reactive protein. Vedolizumab, an α4β7 integrin inhibitor which blocks the trafficking of activated lymphocytes to the gut and is used to treat IBD, was shown to reduce depression and anxiety scores and improve sleep quality in a cohort of moderate-to-severe IBD patients (Stevens et al., 2017). Inflammation related to dysbiosis could result in depression through various pathways including the HPA axis (Iob et al., 2020). Further it has been shown that inflammatory cytokines reduce serotonin through activation of indoleamine-2,3-dioxygenase, which metabolizes tryptophan to neurotoxic kynurenine metabolites (Dantzer, 2017). Lastly, studies of depression and the BGMA have suggested potentially direct and indirect signaling from the gut microbiome to the CNS, which could become dysregulated in an inflammatory state (Barandouzi et al., 2020; Lach et al., 2018). Taken together, the BGMA provides an interesting mechanism and therapeutic target for depression observed in IBD.

3.6. Celiac disease

CeD is an autoimmune illness where intolerance to gluten leads to both gut and systemic inflammation and a variety of intestinal and extra intestinal manifestations. CeD has a prevalence of 1% in the general population and has a variable clinical presentation that sometimes includes abdominal pain, diarrhea, bloating, and weight loss (Caio et al., 2019; Rubio-Tapia et al., 2012). It is believed to have a multifactorial pathogenesis, including environmental and genetic factors. Microbiome research has suggested possible differences in early life gut microbiome composition between infants at genetic risk for CeD who go on to develop this disease and those who do not (Valitutti et al., 2019). There are known neurologic manifestations of celiac disease, which include ataxia, encephalopathy, and seizures (Jackson et al., 2012). Studies in CeD have suggested elevated reports of depression (14%−68.7%) and anxiety (62.5%−71.4%), though there is significant variability between studies (Slim et al., 2018). It is also believed that in CeD, undigested gluten may directly interact with the CNS or cause CNS changes via neuroimmune pathways, providing a mechanism outside of the BGMA for psychopathology (Fasano, 2017). While the BGMA and its role in CeD remains an interesting area of inquiry, more investigation is needed to understand the role of the gut microbiome in the pathogenesis of CeD and comorbid psychological concerns seen in this disease.

3.7. Eosinophilic esophagitis

EoE is a chronic allergic inflammatory condition of the esophagus in response to trigger foods. Recent studies of both the esophageal and gut microbiome have suggested possible alterations associated in EoE, and a recent study demonstrated the a relative abundance of *Haemophilus* in the esophageal microbiome predicted disease severity in a pediatric

population (Hiremath et al., 2019; Kashyap et al., 2019). There is a lack of literature on psychological comorbidity in this population, though a recent review of the available adult data suggests 12% of patients report depression and 9.3 % report anxiety (Taft et al., 2019b). A recent retrospective review of 883 patients showed 23% of patients with anxiety and 17% with depression (Reed et al., 2020). More investigation is needed to both understand the extent of psychological comorbidity in this disease and any potential role of the BGMA.

3.8. Gastroparesis

Gastroparesis is a condition where there is delayed gastric emptying in the absence of mechanical obstruction of the stomach. It can occur as a result of injury to the vagus nerve, in hypothyroidism, from diabetes, and after infections. A recent systematic review demonstrated anxiety and depression being present in 24% of an adult cohort, with severe anxiety reported in 12.4%, and depression in 21.8–23% (Woodhouse et al., 2017). The role of the BGMA and this increased psychological comorbidity has not been explored.

3.9. Gastroesophageal reflux disease

GERD is a condition where acid from the stomach rises into the esophagus sometimes causing esophageal erosion, marked by symptoms of heartburn, sore throat, and nausea. GERD is associated with higher rates of anxiety and depression than healthy controls (Javadi and Shafikhani, 2017). A Norwegian population based study showed anxiety increased the risk of reflux three-fold, depression increased the risk 1.7 fold, and having both increased the risk of reflux 2.8-fold (Jansson et al., 2007). While microbiome has been investigated related to GERD-related esophageal complications, it has not been studied related to psychological concerns (Yang et al., 2014).

4. Implications for treatment

Numerous treatments to address dysregulation of the BGA have been investigated, including medications, psychotherapies, antibiotics, psychobiotics, dietary interventions, and FMT. While they are most often studied in the treatment of DGBI and psychological disorders, they may have role in treating organic gastrointestinal disorders as well.

Central neuromodulators (tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, atypical antidepressants, and atypical antipsychotics) are believed to help relieve pain in conditions like IBS through their effect on serotonin, norepinephrine, and dopamine to centrally regulate incoming visceral signals from the gut (Dekel et al., 2013; Drossman et al., 2018). They may also treat comorbid anxiety and depression. While rigorous investigation of many of these agents is lacking in DGBI, there has been evidence to support the use of tricyclic antidepressants to manage pain in both IBS and FD (Ford et al., 2014; Talley et al., 2015).

Several psychotherapies have been shown to be useful in DGBI, most notably CBT, hypnotherapy (HT), and mindfulness-based therapy (MBT) (Ballou and Keefer, 2017; Black et al., 2020; E. L. Garland et al., 2012a; Kinsinger, 2017; Rutten et al., 2013). CBT was first developed to treat depression, but has since been adapted for a variety of disorders, including chronic medical illnesses (Beck, 1997; White, 2001). In this therapy, patients learn

how external events, cognitions, behaviors, and symptoms interact (Kinsinger, 2017). They also learn that how they interpret a situation can be biased and lead to an exaggerated response, including worsening anxiety and worsening gastrointestinal symptoms. Cognitive restructuring is used to challenge and replace self-defeating and irrational beliefs to promote a more adaptive response. Problem-solving and relaxation techniques are also emphasized, and patients receive psychoeducation about their condition, including the BGA. CBT has been shown to provide a sustained benefit in IBS (H. A. Everitt et al., 2019; Lackner et al., 2018). There are also numerous studies supporting the use of different modes of delivery of CBT, including telephone sessions and internet platforms (Bonnert et al., 2017; H. Everitt et al., 2015). The role of CBT has also been explored in IBD, with a suggestion it can improve quality of life measures and mood symptoms (Paulides et al., 2020; Szigethy et al., 2014).

In HT, patients are induced into a hypnotic state, where they experience heightened receptivity (Olafur S. Palsson and Ballou, 2020). This receptive state is enhanced by the therapist through deepening techniques, and post-hypnotic suggestions are then delivered to facilitate changes in cognitions, emotions, or physical symptoms. This can be particularly useful in gastrointestinal disorders, as post-hypnotic suggestions can work to normalize gastrointestinal function and reduce the connections between emotions and symptoms. Patients can then practice self-hypnosis exercises at home. HT has shown benefit in reducing symptom severity in IBS, functional abdominal pain, and FD, and this benefit sustains at least one year after treatment (Calvert et al., 2002; Flik et al., 2019; Vlieger et al., 2012). HT is understudied in IBD, though there is evidence to support it can improve quality of life measures, and one study suggesting it may reduce the rate of disease relapse in patients with UC in remission (Keefer et al., 2013; Lee et al., 2020; Szigethy, 2015).

In MBT, patients are taught through relaxation and meditative action to develop a complete and non-judgmental awareness of the present, including their cognitions, emotions, and sensations (Vago and Silbersweig, 2012). As this practice can be applied to a variety of situations and disease states, including depression, stress, and chronic pain, it has broad applications (Khoury et al., 2013; Majeed et al., 2018). Various models have been proposed as to how mindfulness might exert its therapeutic effects, and it is believed to work by modifying attentional control and body awareness (Cebolla et al., 2018). In gastrointestinal disorders, MBT can reduce attention to certain cognitions, emotions, and sensation to reduce visceral hypersensitivity and reduce catastrophizing (Eric L. Garland et al., 2012b). Several studies have suggested the efficacy of MBT in reducing symptoms and improving quality of life in IBS (Naliboff et al., 2020; Zernicke et al., 2013). MBT has also been shown to be helpful in reducing anxiety and depression and improving quality of life in patients with IBD (Ewais et al., 2019; Neilson et al., 2015). Interestingly, a recent two-armed randomized control trial showed that IBD patients undergoing a mindfulness intervention had significantly lower inflammatory biomarkers at six month follow-up compared to patients receiving standard medical care (González-Moret et al., 2020). This supports the importance of the BMGA, and that interventions targeting the CNS could have an impact on the gut.

Antibiotic exposure has been associated with microbiome depletion and increased risk for depression and other cognitive changes in mainly preclinical studies (Hao et al., 2020).

Broad spectrum antibiotic exposure in adult rodents was shown to cause depletion of the gut microbiome and changes in behavior, including reduced anxiety and cognitive deficits (Desbonnet et al., 2015). Likely contributing to cognitive changes, they were found to have decreases in concentrations of serum tryptophan, brain serotonin metabolites, and hypothalamic vasopressin and oxytocin. In a clinical study, Lurie *et al.* showed in a nested case-control analysis of a large population-based medical record database in the United Kingdom that treatment with a single course of antibiotics mildly increased the risk of depression (Lurie et al., 2015). This risk increased further with recurrent antibiotic exposure.

Prebiotics and probiotics, sometimes called psychobiotics when used to address cognition or mood, have been studied in both preclinical and clinical settings to address stress, depression, and anxiety with mixed results as to efficacy (Lachance and Ramsey, 2015; Sarkar et al., 2016; Vaghef-Mehrabany et al., 2020). While this remains an exciting potential therapeutic option for neuropsychiatric disorders, studies with larger sample sizes and longer durations may be useful in fully elucidating the role of psychobiotics in the management of neuropsychiatric disorders. In gastrointestinal diseases, probiotics have been shown to be useful in children with functional abdominal pain (Ding et al., 2019). They have shown promise in the management of both IBS and FD (Igarashi et al., 2017; J. R. Sun et al., 2020b). Interestingly, probiotics may exert their beneficial effects both on the gut and CNS. Treatment with *Bifidobacterium lactis* was shown in one study to accelerate whole-gut transit and improve symptoms in patients with IBS-C (Agrawal et al., 2009). Neuroimaging has also suggested probiotics may modulate CNS function, and one study showed changes in brain areas controlling emotional processing and sensation in healthy volunteers receiving a probiotic (Tillisch et al., 2013). A recent RCT where participants were subjected to social stress via a virtual game, showed that subjects treated with four weeks of *Bifidobacterium longum* 1714 reported greater vitality with magnetoencephalography data suggesting possible corresponding neurophysiologic changes (H. Wang et al., 2019). The role of prebiotics and probiotics is less clear in organic gastrointestinal disease, and studies in inflammatory disease have not supported their routine use (Abraham and Quigley, 2020).

Postbiotics are the bioactive products of bacterial metabolism and have been implicated in preventing gastrointestinal infection, correcting dysbiosis, and preventing cancer (Malagon-Rojas et al., 2020; Rad et al., 2020; Zolkiewicz et al., 2020). They have potential advantages, including the fact they have a longer shelf-life and better safety profile, as they are not comprised or living organisms (Tsilingiri and Rescigno, 2013; Zolkiewicz et al., 2020). While they are an active topic on inquiry, there is currently limited evidence for their role in psychological disorders. There is also limited evidence for their role in gastrointestinal disorders, though in one study administration of *Lactobacillus caei* DG attenuated the inflammatory mucosal response in an *ex vivo* organ culture model of post-infectious IBS-D (Compare et al., 2017).

Nutritional interventions have shown promise in both the management of gastrointestinal diseases and in psychological conditions. The emerging field of nutritional psychiatry has explored how diet can serve as a risk factor for mental illness, and observational studies have suggested having a healthier diet and avoiding a pro-inflammatory diet may confer some protection against depression (F. N. Jacka, 2017; Lassale et al., 2019). Diet is also

emerging as a new therapeutic option, and two randomized control trials have reported significant reductions in in depressive symptoms in adults adhering to a Mediterranean-style diet (Felice N. Jacka et al., 2017; Parletta et al., 2019). While the supporting data is largely pre-clinic, the microbiome may be shaped by diet and subsequently play at important role in mood, cognition, and behavior (Marx et al., 2020). Dietary strategies are also used in the management of CD, and exclusive enteral nutrition, a formula based diet, has been used to induce disease remission in pediatric patients and alters their microbiome (Ashton et al., 2019; Gatti et al., 2017). The low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) diet has been shown to reduce symptoms in some patients with IBS (Dionne et al., 2018; H. M. Staudacher et al., 2017). While this diet is believed to eliminate carbohydrates that increase small intestinal water and colonic gas, research has also demonstrated potential modifications of the microbiome by this diet and that microbiome could be a predictor of treatment response (Chumpitazi, 2020; Halmos et al., 2015; Heidi M. Staudacher et al., 2014).

FMT has been used in the management of both UC and CD, where microbiota from healthy donors are inoculated into affected patients with the goal of reversing dysbyosis (Levy and Allegretti, 2019). More robust support for FMT exists in UC, and a recent meta-analysis pooling data between four randomized control trials and 20 uncontrolled cohort studies reported a 33% disease remission rate with a 52% clinical response (Paramsothy et al., 2017). There is less high quality evidence for FMT in CD, though the first small RTC was published in 2020 looking at preventing disease relapse after a course of corticosteroids for acute flare (Claytor and El-Nachef, 2020; Sokol et al., 2020). This showed a non-significant trend towards clinical remission. There is increasing evidence for FMT in the management of irritable bowel syndrome, and a recent RCT of 165 patients showed significant reduction in IBD symptoms scores after FMT also with significant changes intestinal bacterial profiles (El-Salhy et al., 2020). There is also some evidence of improvement in comorbid anxiety and depression in IBS patients undergoing FMT (Kurokawa et al., 2018).

5. Summary and future directions

There is growing evidence to support the role of the BGMA in the pathogenesis of both psychological and gastrointestinal diseases, providing a basis for the long-standing clinical observation of their frequent comorbidity. This also supports the application of the biopsychosocial model to the conceptualization of these diseases, as evidence for top-down and bottom-up communication between the brain and the gut, as influenced by the gut microbiome, exists.

Clinically, the presence of comorbid psychological concerns should be explored in patients being managed for DGBI or organic gastrointestinal diseases. This exploration should extend beyond screening for a frank psychological disorder, as subclinical symptoms may be present that are still impairing. Further, the presence of distorted cognitions (i.e. catastrophizing), maladaptive coping, low resilience, and low self-efficacy may impair successful medical treatment as well as contribute to individual dysfunction. Finally, given frequent occurrence of EALs in DGBA, this area should be explored carefully. Patients being managed for psychiatric disorders should be asked about gastrointestinal symptoms

as well. Appropriate referral to a gastroenterologist should be performed as indicated, and psychotropics should be modified to address either potential gastrointestinal side-effects or to take advantage of their benefits as neuromodulators.

While treatment options are being investigated for both psychological and gastrointestinal concerns separately, patient care should be comprehensive and ideally integrated between medical and behavioral health. Potential barriers to this integrated treatment include logistical barriers and lack of access to behavioral healthcare practitioners with psychogastroenterology expertise. There is some evidence for the use of prebiotics, probiotics, and FMT in the management of DGBI, though more investigation will be needed to understand which organisms benefit which individuals as well as their mechanism of action. Postbiotics offer an exciting future therapeutic option that require more evaluation in psychiatric and gastrointestinal contexts.

Understanding surrounding the BGMA and psychological and gastrointestinal disease is hampered by the lack of large-scale, controlled, and longitudinal human studies. Through these clinical investigations, it is hoped a deeper understanding of individual gut microbiome signatures and their role in susceptibility to BGMA-related diseases will be possible. Additionally, better understanding the pathogenesis of BGMA-related diseases may reveal more specific targets for therapies and even allow individually tailored interventions.

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