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Gut Microbiota, Bacterial Translocation, and Interactions with Diet: Pathophysiological Links between Major Depressive Disorder and Non-Communicable Medical Comorbidities

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Key Words

Mood disorders · Obesity · Depression · Diabetes · Microbiota · Chronic fatigue syndrome · Inflammation · Psychiatry · Irritable bowel syndrome · Oxidative stress

Abstract

Background: Persistent low-grade immune-inflammatory processes, oxidative and nitrosative stress (O&NS), and hypothalamic-pituitary-adrenal axis activation are integral to the pathophysiology of major depressive disorder (MDD). The microbiome, intestinal compositional changes, and resultant bacterial translocation add a new element to the bi-directional interactions of the gut-brain axis; new evidence implicates these pathways in the patho-aetiology of MDD. In addition, abnormalities in the gut-brain axis are associated with several chronic non-communicable disorders, which frequently co-occur in individuals with MDD, including but not limited to irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), obesity, and type 2 diabetes mellitus (T2DM). ***Methods:*** We searched the PubMed/MEDLINE database up until May 1, 2016 for studies which investigated intestinal dysbiosis and bacterial translocation (the 'leaky gut') in the pathophysiology of MDD and co-occurring somatic

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comorbidities with an emphasis on IBS, CFS, obesity, and T2DM. ***Results:*** The composition of the gut microbiota is influenced by several genetic and environmental factors (e.g. diet). Several lines of evidence indicate that gut-microbiota-diet interactions play a significant pathophysiological role in MDD and related medical comorbidities. Gut dysbiosis and the leaky gut may influence several pathways implicated in the biology of MDD, including but not limited to immune activation, O&NS, and neuroplasticity cascades. However, methodological inconsistencies and limitations limit comparisons across studies. ***Conclusions:*** Intestinal dysbiosis and the leaky gut may constitute a key pathophysiological link between MDD and its medical comorbidities. This emerging literature opens relevant preventative and therapeutic perspectives.

Introduction

Persistent low-grade immune-inflammatory processes are an integral part of the pathophysiology of a substantial subset of patients with major depressive disorder (MDD) [1, 2]. Among various immune-inflammatory marker elevations in MDD, meta-analytic evidence indicates that peripheral levels of interleukin (IL)-1β, IL-6, C-reactive protein (CRP), and soluble IL-2 receptor (sIL-2R) are higher in individuals with MDD compared to healthy controls [3, 4]. Integrative theoretical frameworks for MDD propose that environmental triggers such as psychosocial stress, sleep disruption, poor diet, physical inactivity, and smoking, together with medical factors such as autoimmune disorders and inflammatory medical conditions, activate neuroprogressive, low-grade inflammatory, oxidative and nitrosative stress (O&NS) pathways [5–8]. The role of these systems in structural brain changes, cognitive deterioration, and treatment refractoriness in a subset of individuals has been thoroughly reviewed [5, 9]. A recent addition to this literature is the emerging role of the microbiome and the possibility of microbiota-brain interactions being active in depression [10, 11]. The microbiota-gut-brain axis, which includes both commensal and pathogenic bacteria in the gut, may influence behaviour in several ways, including but not limited to putative interactions with the vagus nerve, changes in central nervous system functioning, the enteric nervous system, brain plasticity [12], and the immune system [13, 14]. In addition, experimental data indicate that the gut microbiota regulates blood-brain barrier permeability throughout life [15].The composition of microbiota in the intestine influences barrier integrity and an increase in gut permeability (also referred to as the 'leaky gut') and its role in the translocation of bacteria (and their products) into tissue [16]; this process has been implicated in the pathophysiology of MDD. Furthermore, this bacterial translocation is associated with several conditions that are frequently comorbid with MDD and are characterized by their psychosomatic symptoms, including irritable bowel syndrome (IBS) [17, 18], chronic fatigue syndrome (CFS) [19, 20], obesity, and type 2 diabetes mellitus (T2DM) [21–23].

Here, we review extant literature on the role of intestinal dysbiosis and the leaky gut in the pathophysiology of MDD and its medical comorbidities. In addition, resultant preventative and therapeutic perspectives are critically discussed.

Search Strategy

For this narrative review we searched the PubMed/MEDLINE database up until May 1, 2016 for studies with the following search terms: 'gut dysbiosis', 'microbiota', 'leaky gut', 'probiotics', 'prebiotics' cross-referenced with 'depression', 'irritable bowel syndrome', 'chronic fatigue syndrome', 'type 2 diabetes' and 'obesity'. We included peer-reviewed original articles written in English that investigated microbiota dysbiosis and the leaky gut in MDD and related somatic comorbidities, namely CFS, IBS, obesity, and T2DM. In addition, clinical trials that investigated dietary interventions as well as prebiotics and probiotics as a treatment for MDD and these aforementioned comorbidities were considered.

The Gut Microbiota

In human adults, the intestinal microbiota consists of approximately 100 trillion organisms in a dynamic, symbiotic, mutualistic relationship with the host. This microbial community is very diverse, developing from the nearly sterile gut of a newborn to an adult composition, 90% of which is comprised of the phyla *Bacteroidetes* and *Firmicutes* [24]. Over 3.3 million genes are jointly encoded by the intestinal microbiota, with over 1,000 bacterial species identified as part of this ecosystem [24]. Advances in understanding the microbiome have in large been attributable to new methodologies in metagenomics, metatranscriptomics, proteomics, and metabolomics, each of which have been able to elucidate a portion of

host-microbiota interactions. However, in spite of large-scale studies (e.g. the National Institutes of Health Human Microbiome Project, MyNewGut, the Canadian Microbiome Initiative, and the European MetaHIT initiative), much remains to be elucidated in characterizing a 'normal' microbiome in humans, its immune and biochemical functions, and the changes that occur in pathogenesis.

In addition, it is worthy to note that several limitations still hamper the comparability of findings across studies, which have been investigating changes in microbiota composition across disease states. These methodological inconsistencies include differences in methodology, variations in sample source, significant inter-individual differences, comorbidities, previous exposure to antibiotics, and potential confounders (e.g. differences in dietary habits), as well as differences in sample selection. Considering the heterogeneity in the clinical population with MDD and several of its co-morbid disorders, it is important to better understand how microbiota composition, diversity, and function might aid the stratification of individuals into different clinical subtypes.

A multitude of factors influence the composition of the microbiome. For instance, compelling data have indicated differences in the gut microbiota composition between babies born via Caesarean section versus natural birth [25, 26], while the microbiome of breast-fed infants differs from that of formula-fed babies [27, 28]. Diet shapes the composition of the gut microbiome throughout life [for review, see 29]. For example, in mice, a high-fat diet was associated with a decrease in *Bacteroidetes* and an increase in both *Firmicutes* and *Protebacteria* [30, 31], although results have been conflicting [32]. In addition, a recent seminal study illustrates the influence of diet and exercise on microbiota diversity. In this study, protein consumption was associated with elevated microbial diversity (across 22 phyla), and athletes with a lower BMI had higher levels of *Akkermansia*, which has been inversely correlated with obesity in both mice [33] and humans [34]. Finally, a recent animal study has found, using a novel approach (multi-taxon insertion sequencing method), that the host genotype may influence diet-microbiome interactions [35].

Insights into the role of the microbiome and its interactions with the host immune system have provided some details into its numerous functions in the human gut and at distant organs. Healthy gut microbiota contribute to normal intestinal homeostasis through immune signalling, for example, commensals can activate toll-like receptors (TLRs) in a manner that triggers heat shock protein (member of a family of protective factors) – production by the host, thereby responding to disruptions in epithelial homeostasis and injury [36]. Importantly, certain gut microbiota produce short-chain fatty acids (ScFAs) like acetate, propionate, and butyrate, which are derived from the fermentation of undigested and unabsorbed carbohydrates. Butyrate modulates intestinal epithelial proliferation, apoptosis, and cell differentiation in the bowel, and also inhibits NF-κB, thus supporting mucosal barrier integrity [37, 38]. ScFAs have neuroactive properties, while several classical neurotransmitters like GABA (γ-aminobutyric acid) are also produced by the microbiota [39]. Microbiota also produce gasses such as hydrogen and ammonia, which are potentially neuroactive [40, 41]. Whether or not these neuroactive chemicals are produced in sufficient quantity to extend beyond the local intestinal environment and influence the central nervous system is not yet clear. In the sections below, we overview evidence that gut compositional changes and intestinal inflammation related to a leaky gut may contribute to the pathophysiology of MDD and also to common non-communicable medical comorbidities. Here, we consider IBS, CFS, obesity, and T2DM as exemplars, although other non-communicable disorders such as cardiovascular disease and osteoporosis would probably be similarly impacted.

Microbiota and Gut-Derived Inflammation in MDD

The pathophysiology of MDD is typified by complex interactions with the following events in subsets of individuals: (1) increased low-grade inflammatory response, including raised peripheral levels of pro-inflammatory cytokines namely tumour necrosis factor-α (TNF-α), IL-1β, IL-6, sIL-2R, and CRP, an acute phase protein and inflammatory marker [3, 4]; (2) hypothalamic-pituitary-adrenal (HPA) axis dysregulation [42, 43]; (3) O&NS, marked by an imbalance between systemic antioxidants and harmful reactive oxygen species (ROS) and reactive nitrogen species (RNS), which damage lipids, proteins, and nucleic acids [5], and (4) aberrations in cell-mediated immunity [9]. This cascade can have downstream detrimental effects on mitochondrial bioenergetics, which is of relevance to mood disorders as well as disorders such as CFS and diabetes [44]. These pathophysiological events appear to be influenced by perturbations in the equilibrium of the gut microbiota and by disruptions in the gut barrier.

A recent study has found that the microbiota of patients with MDD is significantly different compared to

healthy controls and is characterized by a relative abundance of *Firmicutes*, *Actinobacteria*, and *Bacteroidetes* [10]. In addition, this study found that faecal transplantation of germ-free mice with microbiota from MDD patients but not from healthy controls led to depressive-like behavioural alterations, which appeared to be driven by disturbances of microbial genes and host metabolites involved in carbohydrate and amino acid metabolism [10]. Previous investigations have consistently observed microbiota compositional changes in patients with MDD compared to healthy controls, notwithstanding the fact that specific differences in microbial composition have varied across studies [10, 11, 45]. Online supplementary table S1 (see www.karger.com/doi/10.1159/000448957), which accompanies the online version of this article, presents differences in gut microbial composition observed in clinical studies of MDD compared to healthy controls. Linking specific bacterial to clinical phenotypes is a necessary step in order to better understand how to target microbiota in treatment and in drug development.

Evidence of increased bacterial translocation has now surfaced in the pathophysiology of depression, wherein bacterial translocation, marked by the serum presence of lipopolysaccharide (LPS)-respondent IgM and IgA has been observed [14]. LPS is a component of cell walls of Gram-negative bacteria. Cells of the gut mucosa are bound by tight junctions, which in homeostatic, healthy conditions provide a barrier between luminal bacteria from the interstitium. The disruption of tight junctions and barrier integrity may thus cause normally non-invasive bacteria to translocate to the mesenteric lymph nodes, the lamina propria, and the peripheral blood. In mesenteric lymph nodes and peripheral blood, the translocated Gram-negative bacteria and related bacterial products such as LPS may cause immune activation, binding to TLR-2/4 complexes and causing increased production of pro-inflammatory cytokines and ROS/RNS [46, 47].

Heightened IgA and IgM-mediated immune responses to LPS from *Hafnia alvei*, *Pseudomonas aeruginosa*, *Morganella morganii*, *Pseudomonas putida*, *Citrobacter koseri*, and *Klebsiella pneumoniae* in MDD are consistent with increased bacterial translocation of gut microbiota due to a leaky gut [14]. Furthermore, disruptions in the gastrointestinal mucosa could then contribute to immune activation and O&NS in the pathophysiology of MDD [48]. The administration of LPS to humans may affect mood and elevate anxiety, while increasing peripheral levels of several cytokines [49]. Indeed, the infusion of inflammatory cytokines is arguably good evidence that cytokines contribute to depression as depressive symptoms are observed clinically with the therapeutic administration of interferon [50, 51].

Changes in gut barrier function can occur as an effect of dysbiosis and immune-inflammatory responses, whereby permeability of the intestinal mucosa may be amplified, and bacteria, along with toxic compounds, translocate into the nearby capillaries [14]. The movement of Gram-negative bacteria into mesenteric lymph nodes and the bloodstream is particularly important to these pathogenic processes because this pathway may cause amplified immune-inflammatory responses. Further, Gram-negative bacteria translocation is linked to inflammatory mechanisms by a pathway induced by LPS (and other pathogen-associated molecular patterns) via the activation of TLR-2/4, which leads to the induction of immune mechanisms, ROS/RNS, and subsequent low-grade inflammation and activated O&NS processes [52]. The latter in turn may produce redox-derived DAMPs (damage-associated molecular patterns), which further activate TLR-2/4 complexes, leading to a vicious cycle referred to as the TLR-2/4 radical cycle [52], which has been proposed to be a major driver of chronic immune activation and O&NS processes in several neuro-immune disorders. Immune activation can include the synthesis of TNF-α [53] and the activation of NF-κB and MAPK, which trigger the production of pro-inflammatory cytokines and result in gut-derived systemic inflammation [54]. Immune-inflammatory responses also include the production of inflammatory mediators such as antibacterial lysozyme, an inflammatory mediator secreted by monocytes [55, 56]. Inflammation may contribute to the translocation of commensal bacteria via transcytotic pathways. The translocation of Gram-negative bacteria from the gut has been linked to rising levels of O&NS and autoimmune responses secondary to O&NS, including peroxides and antibodies against oxidized LDL and IgM-mediated autoimmune responses to malondialdehyde, azelaic acid, phophatidyl inositol, nitro-tryptophan, and nitro-tyrosine in individuals with MDD [57]. Pro-inflammatory cytokines can also disrupt tight junctions, aiding these translocating processes [58]. In addition, LPS can enhance the expression of inducible nitric oxide (NO) synthase, which triggers the formation of NO by macrophages through a process involving IFN-γ activation [53, 59]. LPS also stimulates nicotinamide adenine dinucleotide phosphate-oxidase, which generates ROS and inflammatory markers, including superoxide, peroxide, cyclooxygenase-2 expression, and NF-κB activation [55, 60–62]. Mi-

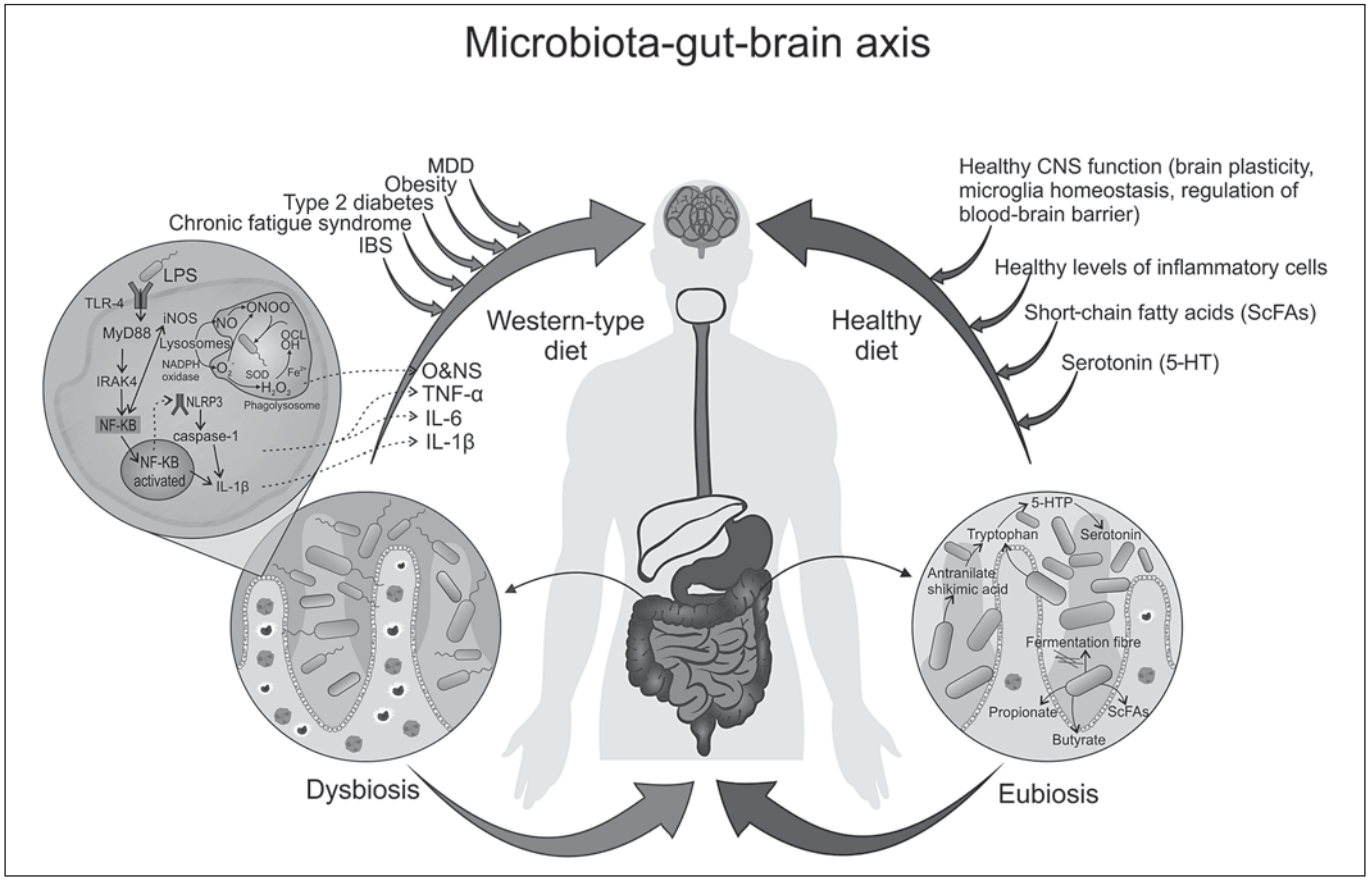

Fig. 1. Gut dysbiosis disrupts tight junctions of the gut epithelia, leading to bacterial translocation. LPS from the wall of Gram-negative bacteria is recognized by pattern recognition receptors (e.g. TLR-4); this activates a signalling pathway relayed by myeloid differentiation protein 88 (MyD88), which recruits the IL-1 receptor-associated kinase (IRAK-1), which is activated via phosphorylation and associated with TNF receptor-associated factor 6 (TRAF-6), driving the activation of NF-κB and the production of inflammatory cytokines by macrophages and other immune cells (e.g. TNF-α, IL-1β, and IL-6). In addition, LPS activates inducible NO synthase and NADPH oxidase, leading to O&NS. LPS also activates the microglia and disrupts the blood-brain barrier. These pathophysiological events are shared to some extent between MDD and related somatic comorbidities such as IBS, CFS, obesity, and T2DM. Conversely, a healthy microbiota produces several neuroactive mediators, including serotonin (5-HT) and ScFAs such as butyrate, which may aid in the maintenance of an intact gut barrier.

croglia, when activated by LPS, synthesize ROS, which initiate oxidative processes to proteins and may lead to proteolysis [63].

LPS injections in experimental animals led to increased levels of malondialdehyde, nitrite, and nitrate and reduced levels of glutathione within the brain – the latter finding evident across many psychiatric disorders [64, 65]. Furthermore, the administration of antioxidants such as quercetin reduce LPS-induced O&NS [66], indicating the reversible nature of these processes. O&NS processes exacerbate disruptions in tight junction integrity in the gut, further driving gut-derived inflammation in a vicious cycle [67]. Thus, bacterial translocation from the gut may play a role in O&NS among individuals with MDD. In addition, bacterial translocation may trigger the generation of neo-antigenic determinants in patients with MDD, thereby contributing to the propensity towards autoimmunity observed in this illness [57, 68].

Gut Dysbiosis and Bacterial Translocation as a Link between MDD and Its Medical Comorbidities

Many of the aforementioned pathways appear to be involved in the pathophysiology of somatic diseases that frequently co-occur in patients with MDD. Further, some

medical comorbidities of MDD exhibit disruptions in intestinal barrier integrity and microbiota composition and express O&NS and immune-inflammatory aberrations. Figure 1 provides a wide-angle lens view of these pathoetiological interactions.

Irritable Bowel Syndrome

IBS is the paradigmatic disorder of the brain-gut axis, presenting with abdominal pain and discomfort as well as alterations in bowel habits [69, 70]. IBS is associated with significant deficits in psychosocial function and impaired quality of life [71]. While its specific pathophysiology is currently unknown, gut-brain axis dysfunction has been implicated [72]. IBS is highly comorbid with MDD, with up to 30% of IBS patients presenting a diagnosis of MDD, while psychosocial variables appear to predispose individuals to IBS [73]. Patients with comorbid IBS and MDD are less likely to respond to treatment with either psychotherapy or antidepressants [74, 75].

Similarly to MDD, increased gut permeability has been noted in IBS [76, 77]. Histological changes in IBS include upregulation of intraepithelial lymphocytes, lamina propria CD3+ and CD25+ cells, and neutrophils and mast cells [78]. In addition to immune cell activation in the distal bowel, peripheral low-grade inflammation appears to play a major role in the pathophysiology of IBS. Furthermore, evidence of chronic gut dysbiosis in IBS is substantial, which may lead to changes in gut motility and nociception [79]. Microbiota composition is distinctively different between those with IBS and healthy controls, characterized by a 2:1 ratio of *Firmicutes* to *Bacteroidetes*, an increase in *Dorea* sp., *Ruminococcus* sp., and *Clostridium* spp., and a decrease of *Bifidobacterium* sp. and *Faecalibacterium* sp. [80], consistent with findings of composition studies in MDD (suppl. table S1). Mast cells that are upregulated in IBS appear to have a higher expression of inducible NO synthase, an enzyme that produces large amounts of NO. Further, levels of IL-1β are upregulated in IBS, where NO may also drive the production of numerous cytokines, including IL-1β, IL-1, IL-13, TNF-α, and monocyte chemotactic protein-1, sustaining the inflammation observed in IBS [81]. Increased peripheral levels of cytokines in IBS, including IL-6, TNF-α, and IL-1β [82], overlap with the cytokine profile seen in MDD. Moreover, exaggerated HPA axis activity in both IBS and MDD add to the overlapping pathophysiology of these disorders [83–85].

Evidence of bacterial translocation in IBS is also provided by higher peripheral levels of LPS as well as higher concentrations of anti-flagellin antibodies [86]. Moreover, *Escherichia coli* LPS-induced IL-6 secretion is elevated in IBS, indicating an enhanced response against Gram-negative bacteria in this disorder [82]. Changes in cell-mediated immunity may additionally contribute to the pathophysiology of IBS. For instance, Th1, Th2, Treg, and B cells are key elements in the progression of IBS [87, 88]. Critically, the probiotic administration in IBS reduces levels of pro-inflammatory cytokines and T-cell function and preserves the integrity of the gut mucosa [89–91]. This reconciliation of intestinal dysbiosis by probiotic treatment, which is associated with improved gut integrity, immune function, and IBS symptoms, suggests that the underlying cause of this disorder may be rooted in intestinal dysbiosis and its consequences, including the leaky gut. Bacterial products interact with TLRs and nucleotide oligomerization domain receptors, further driving mucosal immune activation [92].

Chronic Fatigue Syndrome

CFS is a disorder characterized by persistent and unexplained fatigue that is worsened by physical and mental exertion. Psychosocial factors play a role in CFS, which is frequently diagnostically comorbid with and difficult to disentangle from MDD [93, 94]. MDD is thus highly prevalent among those with CFS and involves overlapping symptomatology [95].

Several shared pathophysiological mechanisms can explain the associations between CFS and MDD. There is a growing body of literature describing immune dysfunction in CFS [96, 97]. 'Flu-like' symptoms and virus and bacterial infections frequently precede CFS [98]. In addition, higher peripheral levels of IL-1, IL-6, and TNF-α are also observed in CFS patients compared to healthy controls [20, 98]. Finally, CFS (like depression) is accompanied by mitochondrial dysfunction [99] and increased O&NS [100, 101], which play a key role in CFS.

Evidence of changes in gut permeability and resultant bacterial translocation as a source of shared pathophysiology of CFS and MDD comes from observed IgA and IgM responses against LPS from enteric bacteria, including *H. alvei*, *P. aeruginosa*, *M. morganii*, *P. mirabilis*, *P. putida*, *C. koseri*, and *K. pneumoniae* [102]. In addition, IgA responses to LPS are linked to increased levels of IL-1, TNF-α, and neopterin [103]. Furthermore, changes in microbiota composition have been noted in CFS; for instance, levels of *Dialister* appear to be decreased in CFS [104], similarly to findings observed in samples with MDD [11], whereas levels of *Alistipes* are increased in both diseases, though less consistently so in MDD [11, 45, 105]. It is noteworthy that CFS frequently co-occurs with IBS, and gut inflammation and endotoxemia may play a

patho-etiological role in both diseases [100, 106, 107]. Similarly to MDD, CFS is characterized by a propensity towards O&NS-induced autoimmune responses [108].

Furthermore, CFS is accompanied by inducible NO synthase activation and peripheral markers of O&NS like thiobarbituric acid reactive substances (indicative of lipid peroxidation) and oxidized LDL [100, 109]. As in MDD, antioxidant levels are diminished in CFS, including zinc and dehydroepiendrosterone sulphate [110, 111]. Immune reactivity indexed by IgM antibodies against fatty acids, including oleic, palmitic, and myristic acid, malondialdehyde, and phosphatidyl-inositol, is also observed in CFS; these are by-products of oxidative damage to lipids [110]. Antibodies against nitrogen monoxide derivatives, including nitro-tyrosine, nitro-phenyl-alanine, nitro-tryptophan, and other nitrosative stress markers are also seen [110]. Finally, LPS induces an exaggerated production of TNF-α and IL-6 in CFS patients, further strengthening the evidence for an association of CFS with disruptions in the intestinal mucosa and resultant bacterial translocation [112].

Obesity and Type 2 Diabetes

There is a vast pathophysiological overlap between obesity, T2DM, and depression, with bidirectional relationships being consistently reported [113, 114]. These disorders also share common risk factors such as poor diet and physical inactivity [115, 116]. In addition, these epidemiological associations are further illustrated by the recent proposal of a distinct metabolic-mood syndrome, characterized by changes in mood and metabolism after chronic stress exposure, and possibly cognitive dysfunction [117]. These conditions have been consistently related to immune activation and aberrations in HPA axis function [118–120].

Obesity, T2DM, and MDD share increased peripheral levels of cytokines like IL-6, TNF-α, and IL-1β [1, 121, 122]. Type 2 diabetes and obesity are also marked by higher concentrations of acute-phase proteins such as CRP, plasminogen activator inhibitor, and serum amyloid A [123–126]. Furthermore, increased peripheral levels of CRP, IL-6, and IL-1β levels may predispose individuals to T2DM [127, 128]. Obesity predispose immune cells towards a Th17 cell profile [126], and T2DM patients also have a skewed balance of Treg to Th17 cells and Treg to Th1 cells [129], a finding that has also been observed in MDD [130]. It is worth noting that the infiltration of abdominal adipose tissue by macrophages and other immune cells may play a significant role in the patho-aetiology of T2DM and obesity, driving the production of adipokines [131, 132].

A number of O&NS pathways are activated in both T2DM and obesity. For instance, in T2DM the activation of NADPH oxidase, NO synthase, and oxidative phosphorylation may contribute to the production of ROS and RNS [133]. Hence, several oxidative stress markers appear elevated in T2DM, including but not limited to an increased ratio of GSH to glutathione levels, nitrotyrosine, S-glutathionylated proteins, advanced glycoxidation end products, and F2-isoprostane levels [134]. In obesity, elevated F2-isoprostane, malondialdhyde, and thiobarbituric acid reactive substance (a marker of lipid peroxidation) are observed [135]. Antioxidant levels, including vitamins E and C, are reduced in T2DM [136], while in obesity, the total antioxidant capacity is decreased [135].

Intestinal dysbiosis also appears to be involved in the patho-aetiology of obesity and T2DM [32]. In addition, increased peripheral levels of LPS are observed in individuals with T2DM, and this endotoxemia may contribute to adipose tissue inflammation via the activation of TLRs [137, 138]. Furthermore, the role of inflammation induced by Gram-negative bacteria in T2DM is evidenced by the fact that human abdominal adipocyte induction with LPS leads to enhanced IL-6 and TNF-α production [137]. The precise alterations in microbiota composition in T2DM have varied across studies [32], although a large Scandinavian cohort has found a higher frequency of butyrate-producing bacteria (*Roseburia intestinalis* and *Faecalibacterium prausnitzii*) among postmenopausal women with T2DM compared to women with impaired glucose tolerance [139] (suppl. table S1). Butyrate contributes to the homeostasis and survival of colonocytes (see above), and thus these alterations may contribute to abnormalities in the gut barrier.

Higher peripheral levels of LPS in obese compared to lean individuals have also been demonstrated [140]. In addition, 4 h after the ingestion of a high-fat diet, obese individuals displayed higher peripheral increments in LPS compared to healthy controls [141]. Evidence from both animal and human research has consistently demonstrated that obesity is associated with microbiota dysbiosis [141].

A recent fascinating study illustrated the role of the microbiota in the patho-aetiology of obesity. In a cohort of female twins discordant for obesity, the transplantation of germ-free mice with an 'obese microbiota' transmitted an increase in total body and fat mass. Furthermore, co-housing humanized mice with the 'obese microbiota' with mice transplanted with a 'lean microbiota' prevented the development of obesity; the invasion of

specific members of the *Bacteriodetes* phylum derived from the 'lean microbiota' prevented the development of obesity in co-housed mice transplanted with the 'obese microbiota' [142]. In addition, microbiota invasion and phenotypic change in mice transplanted with an obesogenic microbiota was dependent on dietary fibre and fat content [142]. Thus, diet and environment may interact with the gut microbiota to drive the progression of different metabolic phenotypes.

Mechanistic Insights into Microbiota Changes in MDD and Its Comorbidities

Recent studies have started to elucidate putative mechanisms underlying changes in the composition of microbiota as a pathophysiological aspect of MDD and related comorbidities. For instance, changes in phylum-level composition or the presence of particular species such as a decrease in *Bacteroidetes* (observed in MDD) [10, 143], IBS [80], obesity [144], impaired glucose tolerance [145], and CFS [105] could represent a consistent finding across these disorders. Nevertheless, another study found an increase in *Bacteroidetes* MDD patients [11], rendering these findings not entirely consistent.

Specific pathogenetic mechanisms of members of different genera of intestinal microbes have recently emerged. For example, an increased abundance of the *Clostridium* XIVB cluster is associated with decreases in serum levels of BDNF [11], a plasticity-associated neurotrophic factor whose peripheral levels appear to be decreased in MDD [146], and has also been implicated in the pathophysiology of IBS [147], CFS [148], and obesity [149].

Furthermore, *Faecalibacterium* – a genus of the Ruminococcaeceae family and an abundant commensal (approx. 5% in humans) – was found to be decreased in the faecal microbiota of MDD patients compared to healthy controls [11], while *Faecalibacterium* spp. are lowered by 1.5 in faecal samples of individuals with IBS in comparison to controls [80]. the presence of *Faecalibacterium* bacteria within the gastrointestinal tract is linked to anti-inflammatory activities. For instance, *F. prausnitzii* downregulates the synthesis of the pro-inflammatory cytokines IL-12 and IFN-γ and increases production of IL-10 by mononuclear cells. The effects of *F. prausnitzii* can be in part attributable to the termination of NF-κB signalling and IL-8 synthesis [150]. *F. prausnitzii* is additionally associated with the fermentation of digestion-resistant carbohydrates into ScFAs, including butyrate, formate, and lactate [151]. Numerous taxa (e.g. *Roseburia* spp., *Bacteroides* spp. [152, 153]) are associated with the production of butyrate, which may have beneficial functions, including but not limited to an increment in mucin synthesis, a decrease of bacterial translocation across the intestinal barrier, and the maintenance of the integrity of tight junctions within the intestinal epithelium in addition to the intrinsic signalling properties of ScFAs [154, 155]. ScFAs may additionally contribute to endocrine signalling through their effects on hormones such as glucagon-like peptide-1 (GLP-1), which are closely linked to metabolic disorders [156]. A number of taxa, disruptions of which are common in MDD, IBS, CFS, and metabolic disorders, are also linked to bile acid metabolism [157]. Bile acids can induce ONS and damage [158], which can disrupt the intestinal barrier [159–161].

A higher abundance of *Alistipes* in MDD [11, 143] may lead to changes in tryptophan levels, as *Alistipes* species are able to convert tryptophan to indole [162] and subsequently serotonin availability within the intestine, as tryptophan is its precursor. Such increases in *Alistipes* taxa have been additionally linked to gut inflammation and to abdominal pain in IBS [163], and have additionally been found to be elevated in patients with CFS [105]. Dietary changes, particularly animal-based diets, can further elevate *Alistipes* bacteria in the gastrointestinal tract [164]. Differences in the abundance of several bacterial taxa have been observed in MDD, including but not limited to *Enterobacteriaceae, Erysipelotrichaceae* spp., and *Prevotellaceae*. These bacteria may promote both mucosal and systemic immune activation [46, 57, 165–169] through mechanisms including an increase in intestinal permeability and the presence of inflammogenic flagellin components in particular.

Notwithstanding that several microbiota-mediated pathophysiological mechanisms could be involved in MDD, many of these have yet to be thoroughly investigated. Online supplementary table S1 outlines overlaps in microbiota composition at the level of phyla, family, and genera, which have been reported across studies in individuals with MDD, IBS, CFS, obesity, and T2DM, as well as putative pathophysiological mechanisms related to specific bacteria.

Clinical Implications

Probiotics

The term probiotics refers to 'live microorganisms that, when administered to adequate amounts, confer a health benefit to the host' [170]. The idea of treating psy-

chiatric disorders with probiotics is not new; in 1910 Dr. George Porter Phillips reported that although *Lactobacillus* tablets and powder were ineffective, a gelatin-whey formula comprised of lactic-acid-producing bacteria improved depressive symptoms in melancholic adults [171]. Preclinical studies and clinical trials have increasingly investigated a role for probiotics in the treatment of depressive-like behaviours [for an extensive review, see 172]. Several studies have demonstrated effects of probiotics in healthy volunteers; however, the benefit of these changes is not yet clear. For example, orally consumed *Lactobacillus casei* milk had no significant mood-elevating effects in healthy volunteers, while also impacting two measures of memory [173]. A recent randomized controlled trial (RCT) found that a multispecies probiotic composed of *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *L. casei* W56, *Lactobacillus salivarius* W24, and *Lactococcus lactis* (W19 and W58) reduced cognitive reactivity to sad mood via a reduction in rumination and aggressive thoughts in healthy individuals [174]. This small RCT provided a proof of concept for probiotic supplementation as a potential preventative strategy for MDD.

A recent systematic review and meta-analysis of 15 RCTs on the use of probiotics for IBS [175] found that although probiotics varied in strain composition, these compounds reduced abdominal pain after 8 and 10 weeks of treatment. Furthermore, probiotics improved the severity of IBS symptoms, although not significantly compared to placebo [175], providing preface to probiotics as a conjunctive treatment for both disorders.

The treatment of individuals meeting formal criteria for CFS with the *L. casei* strain Shirota resulted in significant improvements in anxiety symptoms; these beneficial effects on anxiety correlated with an increase in *Lactobacillus* and *Bifidobacteria* in those taking the *L. casei* strain Shirota [176]. The finding of a rise in *Bifidobacteria* was significant considering that levels of this microorganism could be low in CFS [106]. In addition, preclinical data suggest that *Bifidobacteria* may contribute to the maintenance of gut barrier integrity (thus preventing endotoxemia) [177].

The therapeutic potential of probiotics for the management of obesity and T2DM has been extensively reviewed elsewhere [32, 178]. A recent meta-analysis found that treatment with probiotics (especially when composed by multiple strains) led to a reduction in several cardiovascular risk factors, including total cholesterol, LDL cholesterol, BMI, waist circumference, and inflammatory markers, compared to placebo [179]. ScFAs (e.g. butyrate) appear to be a promising target for the probiotic treatment of T2DM; SCFAs bind to G-protein-coupled receptors, namely GPR41 and GPR43 [180, 181], to influence the host enteroendocrine system, driving the synthesis of proglucagon, GLP-1, peptide YY, and leptin [32]. Interestingly, GLP-1 analogues are effective approved treatments for T2DM [182], and preclinical data indicate that these drugs could be novel targets for cognitive improvement in MDD [183].

In conclusion, promising mechanistic experimental data indicate that manipulation of the gut microbiota with probiotics may open a new avenue for the prevention and treatment of MDD and associated comorbidities. These beneficial effects could attenuate metabolic endotoxemia. However, clinical trials have methodological inconsistencies and variations in protocol. Therefore, the field awaits the design of large-scale and well-designed clinical trials.

Prebiotics

The Food and Agricultural Organization (FAO) of the United Nations define prebiotics as 'a nonviable food component that confers a health benefit on the host modulated by the microbiota' [184]. These 'functional foods' escape absorption in the small bowel and enter the colon, providing nutrients to specific bacteria, including *Bifidobacteria* and *Lactobacilli*. Several prebiotics are non-digestible carbohydrates: monosaccharides (e.g. fructose), disaccharides (e.g. lactose), oligosaccharides (e.g. fructo-oligosaccharides and galacto-oligosaccharides), and polyols, and the fermentable oligo- di- and monosaccharides and polyols or FODMAPs (e.g. inulin) [185]. A recent systematic review found that no RCT to date has evaluated prebiotics as a treatment strategy for MDD [186]. In addition, clinical trial data have been inconsistent for IBS [92]. Some positive signals have been observed for metabolic disorders, although clinical findings remain inconclusive [187].

The Potential of Dietary Change to Benefit Gut Permeability and Disease Status

Diet quality profoundly influences immune function, systemic inflammation, and antioxidant capacity [for review, see 7 and 5]. Moreover, both short- and long-term diet is a key driver of microbiome composition and gut health. Individual gut microbiome enterotypes are linked to long-term dietary patterns [188], while in a key intervention study, only 2 weeks of dietary change had a profound impact on gut microbiota composition and markers of mucosal inflammation [189]. There are also exten-

sive data from animal models to show that high-fat diets induce intestinal permeability and inflammation [for review, see 190]. Specifically, high-fat diets can alter the intestinal barrier structure and increase inflammation via a reduction of tight junction proteins [191]. However, key issues in the field relate to the lack of clarity regarding the potential differential impact of differing dietary fats as well as carbohydrate intake on gut health, immune and metabolic outcomes, and whether the impact of high-fat diets and similar paradigms is the same in humans as it is in animals. These issues are currently subject to intense investigation due to their likely relevance to public health and clinical approaches.

While it is well established that diet is of critical importance to the development of cardiovascular diseases, T2DM and obesity, it is increasingly clear that diet is also of substantial relevance to depression [192]. Indeed, two recent meta-analyses report that diet quality is inversely related to the likelihood of or risk for MDD [193], while emerging intervention data suggest a beneficial impact of dietary improvement on depression risk [194] and symptoms of depression [195]. In addition, preliminary prospective data indicate that the consumption of certain nutrients like red meat [196] and even milk [197] may confer a higher risk of developing depression. The recognition that diet is a key driver of gut health, as well as inflammation and oxidative stress, highlights the likely importance of the gut in mediating the association between diet and MDD [198] and points to the utility of targeting dietary quality to improve gut health and resulting disease states, including MDD [199, 200], IBS [201], and metabolic disorders [202, 203]. For instance, alterations in the abundance of *Roseburia*, which has been noted in MDD, IBS, CFS, and obesity [10, 105, 204, 205], can be decreased by low-fat, high-complex carbohydrate diets [206].

Conclusions

The influence of commensal microbiota in the pathophysiology of MDD and its associated medical comorbidities is only beginning to be uncovered. Here we describe evidence that microbiota composition changes, bacterial translocation from a disrupted gut barrier, and metabolic endotoxemia may play a significant shared pathophysiological role in MDD and somatic comorbidities. The leaky gut (and resulting metabolic endotoxemia) in particular may contribute to immune activation, HPA axis imbalances, and O&NS. This cascade of interacting events could be attenuated by several promising strategies targeting gut-related inflammation, including but not limited to dietary interventions and treatment with probiotics. However, large-scale, well-designed RCTs are awaited. An inherent limitation of these research efforts relies on the phenotypic heterogeneity of MDD and co-morbid diseases, and thus these mechanisms may distinctively contribute to the pathophysiology of different subsets of patients, who otherwise seem deceptively similar as they may share the same categorical diagnoses [207]. There is an unmet need in the field to translate these fascinating findings into preventative and therapeutic advances for MDD and related medical comorbidities.

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