The Gut-Brain Connection: How Microbiota and Diet Influence Major Depressive Disorder

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Abstract

Approximately 8% of Americans are diagnosed with Major Depressive Disorder (MDD) annually [1][2], with millions of individuals experiencing alterations in mood, cognitive function, memory, and emotional regulation [1][3]. The majority of existing literature emphasizes neurobiological mechanisms as primary contributors to MDD. However, emerging science implicates the gut-microbiota-brain (GMB) axis, which connects the digestive and nervous systems, as a significant factor in mental health [4]. Gut microbiota, the complex ecosystem of bacteria within the gastrointestinal tract, influence the brain through bidirectional communication by releasing neurotransmitters, cytokines, and microbial metabolites through the GMB axis [5][6]. Microbial dysbiosis, characterized by inflammation and immune dysfunction, has been associated with increased stress vulnerability, anxiety-like behaviors, depressive symptoms, and broader emotional dysregulation [7][8]. Toxins such as Lipopolysaccharides (LPS) are released into the bloodstream, triggering neuroinflammation and disrupting neurotransmitter systems – both processes involved in MDD symptomatology [9]. By contrast, eubiosis supports intestinal epithelium and immune function. The gut microbiota composition is primarily modulated by dietary patterns, as micro- and macronutrients present in foods can promote or suppress growth of specific bacteria phyla. Mediterranean-style diets show a significant growth of Firmicutes and Bacteroidetes through intake of fiber, complex carbohydrates, and fermented foods containing live microbes. Conversely, Western dietary patterns are associated with enrichment of Proteobacteria, associated with pro-inflammatory signaling triggered by elevated omega-6 fatty acid intake, refined sugars, and low dietary fiber [7]. Taken together, evidence from both the Mediterranean and Western diets demonstrates a clear relationship emerges between dietary choices and mental health.

Introduction

The gut-microbiota-brain (GMB) axis, is a highly complex physiological system containing the microbiota, their metabolic products; the enteric nervous system; the sympathetic and parasympathetic branches within the autonomic nervous system; and the neuroendocrine system, all of which collectively impact one's overall brain function, neuronal signaling, and mental well-being [10]. The microbiome comprises six bacterial phyla: Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia. Around 99% of the identified species in the gut belong to the two phyla Firmicutes and Bacteroidetes, which constitute about 70% of the total microbiota [11]. Gut microbes influence physiology through multiple pathways and mechanisms, including signaling along the GMB axis. One major function of the GMB axis involves the synthesis of short-chain fatty acids (SCFAs), which initiate anti-inflammatory pathways. SCFAs are produced when gut microbiota hydrolyze dietary fiber, a process that contributes to neurotransmitter synthesis [12]. However, this hydrolysis can only occur in the presence of dietary fiber and specific microbiota capable of producing metabolites such as SCFAs. In contrast, other microbiota contribute to pathology by stimulating immune cells to release cytokines and toxins [5]. Furthermore, certain strains can produce hormones

that influence body and brain functions [13]. Together, these microbial processes – both advantageous and harmful – influence serotonin production pathways, and severity of inflammation in the brain, thereby modulating the risk or severity of MDD [14, 34]. The presence of specific microbiota capable of producing the appropriate molecules to help avert MDD is critical. Proteobacteria and Fusobacteria directly contribute to dysbiosis by altering the diversity and composition of gut microbiota [15]. A primary cause of dysbiosis is intestinal permeability, which permits toxins such as lipopolysaccharide (LPS), a molecule found on the outer membrane of Gram-negative bacteria which triggers neuroinflammation and oxidative stress in the central nervous system [16]. This interaction then alters the normal microbial population and changes the production of neurotransmitters and metabolites, disrupting normal brain signaling, emotional regulation, and cognitive functions [7]. By contrast, eubiosis denotes a healthy microbiome, characterized by increased levels of the specific microbiota Firmicutes and Bacteroidetes, which produce neurotransmitters, SCFAs, and metabolites that support gut and brain health. Firmicutes and Bacteroidetes promote anti-inflammatory effects and control immune-regulatory mechanisms [15]. Implementing fiber-rich, plant-based diet fosters microbial diversity, modulates the production of cytokines, and ultimately, regulates communication between the gut-brain axis [17].

Diet and The Gut Microbiota

The Mediterranean diet is characterized by whole foods (fruits, vegetables, nuts, seeds, and whole grains), healthy fats (olive oil and omega-3 fatty acids), and probiotic-rich foods such as yogurt, kefir, and other fermented dairy products. Notably, foods from the Mediterranean diet are fiber-rich. Soluble fiber is indigestible by humans and can only be digested by specific microbiota. In the anaerobic gut environment, microbiota ferment dietary fiber instead of using aerobic respiration [18] These fibers are then fermented into short-chain fatty acids (SCFAs) such as acetate and butyrate, helping maintain gut stability. SCFAs promote gut homeostasis and stability and lower the colon's pH, protecting against harmful toxins and bacteria such as Enterobacteriaceae [19]. While all dietary fiber is beneficial, specific types of fiber can change levels of fiber-fermenting microbiota and produce different types of SCFAs [10]. For example, more butyrate (a type of SCFA) causes an increase in phyla Firmicutes, and more acetate (another type of SCFA) increases levels of phyla Bacteroidetes and Actinobacteria [15]. SCFAs have been known to help control hunger, reduce inflammation, and improve overall brain health. An increase in fiber increases the amount of fiber-fermenting microbiota, creating a cycle of healthy bacteria when eating a high-fiber diet.

The diet includes probiotics (live microorganisms) and prebiotics (substrates supporting microbial growth), contained in fruits, vegetables, and whole grains are commonly seen in the Mediterranean Diet. Individuals with deficient gut health may take fiber supplements, such as Benefiber, to support a stronger gastrointestinal system and promote the growth of beneficial probiotic species [20,35]. Benefiber contains wheat dextrin, a type of prebiotic supporting the growth of many microbiota, including phyla Actinobacteria, Verrucomicrobia, and Firmicutes. This supplement mimics the impact of plant-based foods on gut microbiota composition.

The Western Diet is known to be high in sugar, saturated fats, omega 6 fatty acids, red meat, salt and processed foods overall [21]. This dietary pattern promotes pro-inflammatory pathways, and exacerbates chronic disorders, such as type 2 diabetes, cardiovascular disease, and irritable bowel syndrome. Most western foods exacerbate inflammatory pathways and

responses, but a diet high in sugar/ fructose is one of the main factors to gut dysbiosis. Fructose causes high levels of the Proteobacteria phyla, a gram-negative bacterium that has LPS as the major component of its outer membrane. Through growth of the Proteobacteria culture in the gut, LPS get released through cell death, overgrowth of cells, and from inflammation in the gut. This ultimately causes the “leaky gut”, where other toxins such as LPS can easily enter the digestive system. The release of LPS impairs anti-inflammatory pathways, activating the immune system through TLR4, a pro-inflammatory sensory receptor which sends “alerts” to trigger the NF-kB pathway, a protein complex in cells used to turn on inflammatory genes [22] This process continues to attract immune cells and cause worsening of the inflammation, and further “shedding” of LPS from the Proteobacteria into the gut. This establishes a vicious cycle: LPS toxin release worsens inflammatory signaling, causing pro-inflammatory genes to become functional, perpetuating intestinal damage and further inflammation [7].

Although the Western Diet has health-supportive components (e.g., higher protein intake, vitamin rich foods, and artificially added fiber and probiotics), daily consumption disrupts gastrointestinal health [23]. Foods of the Western diet are prepared differently- with much more oil (includes fats, omega-6), and commonly fried. Despite having some nutritional value, the foods are unhealthy due to preparation. Although the Mediterranean diet is widely recognized for its benefits, certain limitations have been found. Foods from the Mediterranean diet are low in protein and iron – two nutrients necessary for energy and muscle growth. The emphasis on plant-based foods makes it healthy and safe for the gut. The Mediterranean diet may not be ideal for those working to build muscle, but when it comes to gut health, the high-fiber, plant-based approach is one of the most beneficial diets.

Vignette

The following anonymized patient narrative, shared with consent, illustrates her personal experience of being diagnosed with Irritable Bowel Syndrome (IBS). This narrative illustrates the lived experience of chronic gastrointestinal dysfunction. A 25-year-old woman was diagnosed with Irritable Bowel Syndrome (IBS) in May 2025 following a dietary switch from a Mediterranean diet to the Southern-style Western diet. She reported symptoms such as: pain in the abdomen, nausea, cramping, and general indigestion/discomfort. These symptoms worsened her IBS, demonstrating that dietary changes can directly impact microbiota composition, gastrointestinal function and overall health. Her personal experience underscores the beneficial effects of the Mediterranean diet, which she followed before her diagnosis of IBS, versus the adverse effect of the Western Diet, which contributed to her diagnosis of IBS. Her experience clearly states the association between the Western diet and dysbiosis, when opposed to the positive, eubiotic effects of the Mediterranean dietary patterns.

The Gut Microbiome and Major Depressive Disorder

Major Depressive Disorder (MDD) is linked to reduced microbial diversity and heightened intestinal inflammation [24]. Altering normal amounts of microbiota, such as reductions in Bifidobacterium and Lactobacillus contribute to increased intestinal permeability (“leaky gut”), allowing toxins such as LPS and cytokines through the gut barrier and initiate cascades of neuroinflammatory pathways [25]. Proinflammatory cytokines, including IL-1β, IL-6, TNF-α all are elevated during immune responses. Whether cytokines are leaked in the gut or found in the bloodstream through another inflammatory process, they end up reaching the brain through

indirect signaling, or crossing the blood-brain barrier (BBB) [9]. Cytokines signaling activates indoleamine 2,3-dioxygenase (IDO), an enzyme with immunomodulatory effects [26]. However, in the brain, IDO's activation by inflammation has an adverse, double effect. IDO converts tryptophan, an amino acid and precursor for serotonin, into kynurenine. Kynurenic acid is a metabolite derived from the breakdown of tryptophan, causing both neuroprotective molecules and neurotoxic compounds [27]. During chronic inflammation, Kynurenine breaks down into Quinolinic acid, and causes excitotoxicity [9]. Bifidobacterium and Lactobacillus have a direct relationship with the production of tryptophan - supporting serotonin production by diverting tryptophan from the kynurenine pathway. Bifidobacterium has been found to reduce conversion of tryptophan to kynurenine, when similarly, Lactobacillus can metabolize tryptophan themselves, producing metabolites that balance serotonin levels [25] Reduced serotonin via the Kynurenic pathway is a contributing factor to MDD, exacerbating cognitive impairments and depressive symptoms.

Cytokines can activate the Hypothalamic-Pituitary-Adrenal (HPA) Axis, the body's primary stress system, causing elevated cortisol and corticotropin-releasing hormone (CRH) levels, both central to stress regulation. IL-1β, IL-6, and TNF-α are all types of cytokines, which are often known to trigger stress and inflammation responses. CRH signals the anterior pituitary to secrete the adrenocorticotropic hormone (ACTH), a hormone which stimulates the adrenal glands to release cortisol. This cortisol binds to glucocorticoid receptors (GRs) in the hippocampus, activating the HPA axis without any regulation, resulting in hypercortisolemia due to HPA axis overactivity [9]. However, persistent chronic inflammatory response and production of cytokines can induce glucocorticoid receptor (GR) resistance, impeding the brain's ability to properly detect cortisol, therefore disrupting the healthy negative feedback loop [28]. This causes the HPA axis to be overactive. Hypersecretion of cortisol damages the brain, specifically reducing hippocampal volume, and impairing functions of memory, focus, emotion, and more [29].

The HPA Axis and Treatment Resistant Depression

Treatment resistant depression (TRD) occurs when SSRIs or other antidepressants lose efficacy, a condition associated with neuroinflammation, and HPA axis hyperactivity, causing GR resistance and cortisol hypersecretion [30]. However, a clear consensus of TRD is lacking in the psychiatry community [31]. In normal patients with depression, serotonin levels are low, and signaling is off. However, with treatment that elevates serotonin supply, levels can slowly recover, allowing the system to respond. In TRD, serotonin levels may be adequate or even elevated, but excess cortisol disrupts serotonergic signaling, preventing any normal function. Serotonin receptors (such as 5-HT1A) become less sensitive to serotonin, blocking normal function of serotonin signaling [32].

The prednisolone suppression test (PST) is a commonly used test to measure GR receptor dysfunction. In those without depression, Prednisolone acts as cortisol, binding to the GR receptor to signal the HPA axis to shut down, reducing cortisol production. In patients with severe TRD, prednisolone signaling fails – either from impaired receptor binding, or successful binding, without resulting in gene activation [33].

Juruena and colleagues (2009) conducted a study on 45 in-patients with major depression (24 responding to treatment, 21 with TRD) and 46 healthy individuals. Participants both received one placebo, and 5 mg of prednisolone on two different nights.

	$AUC_{PLACEBO}$ Mean (s.e.m.)	AUC_{PRED} Mean (s.e.m.)	Suppression,[a] % Mean (s.e.m.)	Plasma prednisolone levels, ng/ml Mean (s.e.m.)
Group				
Controls (*n*=46)	33.8 (2.5)	16.1 (1.6)	−49.6 (4.0)	66.5 (10.9)
Depression (*n*=45)	55.1 (5.1)	32.1 (4.4)	−42.2 (4.8)	56.1 (5.1)
P	<0.001	<0.001	0.24	0.40
Patients with depression				
Responding to subsequent treatment (*n*=24)	53.1 (8.2)	23.5 (4.2)	−52.5 (4.7)	74.9 (17.3)
Not responding to subsequent treatment (*n*=21)	57.2 (5.7)	41.9 (7.7)	−30.6 (8.2)	54.8 (10.1)
P	0.69	0.046	0.022	0.34

Prednisolone suppression test in depression: Prospective study of the role of HPA axis dysfunction in treatment resistance [31].

This study demonstrated a pronounced reduction in cortisol suppression from the TRD patients compared to controls. The controls with normal GR function and prednisolone binding had a large drop in cortisol (-49.6% suppression), while those with depression had some GR resistance, and less cortisol suppression (-42.2% suppression). Those without TRD had functional GR receptors and proper suppression – providing proof of the treatment's success. (-52.5% suppression) However, those with TRD had severe GR resistance, and weak suppression (-30.6% suppression).

The results (Table 3) showed a clear decreasing linear relationship between HPA axis dysfunction and cortisol suppression [31]. As depression severity increased across groups, cortisol suppression declined.

Conclusion

The gut microbiota exerts a profound impact on mental health by mediating a complex pathway that links the gastrointestinal and nervous systems. Although evidence supporting the impact of the gut-microbiota-brain (GMB) axis continues to grow, current research remains limited in specificity and scope. The GMB axis represents one of the body's crucial systems, regulating cognition, emotions, and stress responses through the release of neurotransmitters and immune signaling. Chronic inflammation is a central feature of Major Depressive Disorder (MDD), linking dysbiosis to MDD onset and treatment resistance through the Hypothalamic-Pituitary-Adrenal (HPA) axis. Diet-induced alterations can initiate chronic inflammation cascades – releasing cytokines, disrupting serotonin regulation, and ultimately leading to HPA axis dysregulation and further chronic neuroinflammation. This intricate molecular pathway significantly influences not only mental health but broader physiological functions and overall health. Accordingly, dietary strategies that enhance gut health may be a promising approach for the treatment and management of MDD, reinforcing the need for continued investigation into these pathways and mechanisms.

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