An Update on the Relationship Between the Gut Microbiome and Obsessive-Compulsive Disorder

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ABSTRACT

The gut microbiome, the collection of microbes and their genetic material in the human gastrointestinal tract, has recently become a topic of interest in psychiatry. To date, animal studies have repeatedly shown behavior to be affected by alterations in the gut microbiota. Furthermore, studies in clinical psychiatric populations have also illustrated that microbial dysbiosis may play a role in these conditions, but results have been inconsistent. Given the existing animal and human literature providing evidence for a role of the microbiome in anxiety and depressive disorders, this review explores and develops similar lines of evidence in obsessive-compulsive disorder. Theoretical treatment options targeting the gut microbiome are also discussed.


Obsessive-compulsive disorder (OCD) is a psychiatric condition marked by recurrent intrusive thoughts and ritualistic behaviors aimed at reducing the associated distress. The etiology of OCD is complex and involves multiple pathways, with imbalances in central serotonin, glutamate, and dopamine systems thought to play a causative role. This etiological basis remains largely theoretical and has received mixed scientific support. The current theories are premised on the observed benefit of pharmacological interventions such as serotonin reuptake inhibitors (SRIs). Given that 40% to 60% of patients with OCD do not respond to first-line treatments such as SRIs or cognitive-behavioral therapy (CBT), it is important that...
researchers examine alternative putative pathophysiological mechanisms that may be involved in OCD. The connection between the gut microbiome and brain is a novel pathway, and its role in mental health is currently being explored. There is some evidence to suggest that it may play a role in the neurobiological underpinnings of OCD.

**WHAT IS THE GUT MICROBIOME?**

The human gut microbiome refers to the collection of microbes and their genetic material in the human gastrointestinal (GI) tract. These microorganisms populate the human distal gut and outnumber all remaining human cells by more than 10-fold. They serve numerous structural, metabolic, and protective functions, and it is believed that a delicate balance of these bacteria may contribute to overall health.

The composition of the core bacteria is established in early life and begins to resemble the fully formed adult gut microbiome by age 3 years. The adult gut microbiome is predominantly stable and dominated by the Firmicutes (species such as *Lactobacillus*, *Clostridium*, and *Enterococcus*) and Bacteroidetes (species like *Bacteroides*) phyla. Other phyla such as Actinobacteria (*Bifidobacterium*), Proteobacteria (*Escherichia coli*), Fusobacteria, Verrucomicrobia, and Cyanobacteria are also present. Many factors affect the relative proportions of the bacteria comprising the microbiome. For instance, whether a person was born vaginally or via cesarean delivery, whether they were breast-fed or bottle-fed, his or her diet, medications, and stress have all been shown to alter the presenting gut microbial profile.

**HOW DOES THE GUT MICROBIOME RELATE TO MENTAL HEALTH?**

Research has shown that the gut and brain are connected through a system termed the “gut-brain axis,” and the microbiota are thought to modulate this bi-directional pathway. Because of the ability of the gut microbiota to alter behavior, researchers have begun exploring its involvement in neuropsychiatric conditions. The existing scientific literature strongly supports the theory that the behavioral influence of the gut microbiota may be regulated by the immune system via cytokine release, leading to an inflammatory response. Other proposed mechanisms of action include release of gut hormones activating the enteric nervous system and signaling the brain via ascending neural pathways (ie, vagus nerve). The final proposed mechanism involves the inherent ability of these bacteria to produce neurotransmitters such as serotonin, dopamine, gamma-aminobutyric acid, norepinephrine, and acetycholine, as dysregulation of many of these neurotransmitter systems has been implicated in numerous psychiatric conditions.

**Animal Studies**

To date, animal studies have repeatedly shown that rodent behavioral responses change when the gut microbiome is modified. For example, germ-free (GF) mice (those with no commensal intestinal bacteria) exhibit altered anxiety behaviors compared to conventionally reared mice. This theory has been furthered by exploiting the inherent behavioral differences in BALB/c (generally more anxious) and National Institutes of Health (NIH) Swiss mice (generally more exploratory). When GF mice of both breeds are colonized with the microbiomes of each respective breed, the recipient’s exploratory behaviors become representative of the donor. Furthermore, re-establishment of the gut microbiota in GF mice during the early part of life also alters their behavior such that they begin to act similarly to non-GF mice. This normalization, however, does not apply if the microbiota are reconstituted in adulthood, suggesting that the anxiety response may be programmed during a critical period early in life. Studies using probiotic treatments have also shown reduced anxiety and depression-like symptoms in healthy mice, effects that are lost when part of the vagus nerve is removed, suggesting a role for vagal response in the gut-brain axis. Similarly, top-down modulation of the gut-brain axis has also been observed with external stressors (eg, maternal separation, prolonged stressors) affecting the composition of the gut microbiome. This indicates a role for the hypothalamic-pituitary-adrenal (HPA) axis in the gut microbiome, which is enhanced in GF mice.Taken together, these findings suggest a role of the gut microbiome in mental health.

**Human Studies**

The existing dogma surrounding microbiome research suggests that “dysbiosis” is associated with a diseased state. The extant literature has linked alterations in the gut microbiota to several physical conditions, including celiac disease, obesity, inflammatory bowel disease (IBD; ie, ulcerative colitis and Crohn’s disease), and irritable bowel syndrome (IBS). Interestingly, high levels of comorbid psychiatric symptoms, particularly depression and anxiety, have also been documented in these populations. As such, the attention of microbiome research has shifted to psychiatric populations.

Presently, the gut microbiome has only been evaluated in clinical populations of patients with autism spectrum...
WHY OBSESSIVE-COMPULSIVE DISORDER?

Although no longer classified as an anxiety disorder, anxiety remains a predominant feature of OCD. As a result, much of the aforementioned animal literature regarding anxiety and the gut microbiome may also be applicable to OCD. For instance, our early neurobiological understanding of OCD posited that balancing certain neurotransmitters (ie, serotonin, dopamine, and glutamate) accounts for the treatment effects of traditional therapies (ie, SRIs and augmentation antipsychotic agents). The gut bacteria may be able to alter levels of neurotransmitters, as they are known to produce them. There is also extensive evidence linking the HPA axis and gut microbiome. Interestingly, elevated basal activity of the HPA axis has also been noted in OCD, as demonstrated by increased urinary free cortisol, and cerebrospinal fluid levels of corticotropin-releasing hormone and adrenocorticotropic hormone, suggesting a role in OCD. Although preclinical data suggest a role for the gut microbiome in anxiety disorders, the literature specific to OCD is limited. One study revealed that 2 and 4 weeks of pretreatment with a probiotic (Lactobacillus rhamnosus GG) attenuated OCD symptoms to the same degree as fluoxetine in an RU24969 (also known as 5-HT1A/1B receptor agonist) mouse model of OCD. In healthy people, 30 days of daily intake of a probiotic formulation containing Lactobacillus helveticus and Bifidobacterium longum has been shown reduce a variety of subscores on the Hopkins Symptom Checklist (HSLC-90), including “obsessive-compulsive” (P < .05) and global Hospital Anxiety and Depression Scale score (P < .05) compared to placebo. Additional lines of evidence that have typically been used to link anxiety and mood disorders and the gut microbiome may also be relevant to OCD. This includes comorbidity with GI conditions and inflammation.

Overlap with Gastrointestinal Illness

As mentioned previously, gut microbial dysregulation has been demonstrated in numerous GI conditions. These illnesses are also often paired with high rates of comorbid anxiety and mood disorders. However, the prevalence of OCD in these populations may also be significant. Whereas one study reported the lifetime prevalence of OCD was no different in their IBS proband versus controls or in relatives of these people, another indicated that 74.2% of their IBS sample had an anxiety or depressive disorder, including OCD. A more recent study examining psychiatric disorders in patients with functional bowel disorders reported that 85% of the sample was diagnosed with a psychiatric disorder, the most prevalent being dysthymia (25%) and OCD (20%). Some literature also suggests that IBS and other functional bowel disorders may also be more prevalent in OCD populations. For instance, one study reported increased prevalence of IBS in their OCD sample (n = 37) compared to age- and sex-matched nonpsychiatric controls (n = 40, P = .00002). Similar rates have also been reported in a sample from India in which 26.2% of patients with OCD and 3.5% of the control group had IBS; however, rates of IBS in OCD populations may be similar to that of community samples. In a sample of children with ASD, children with mixed bowel issues (constipation and diarrhea) were more likely to have parent reports of repetitive or compulsive behaviors and a previous OCD diagnosis as per parental report.

There may also be overlap between symptoms of OCD and GI conditions, further promoting the involvement of the gut-brain axis in OCD. Patients with IBD have been frequently described as obsessive, rigid, and compulsive. “Bowel obsession syndrome” (BOS) has also been used to describe people with an overwhelming fear of bowel incontinence when in public, paired with ritualistic behaviors surrounding prevention of such occurrences. Although not considered a functional gastrointestinal disorder, the clinical characteristics of BOS significantly overlap with the diagnostic criteria of OCD. Interestingly, these symptoms have also been successfully treated with imipramine or doxepin, clomipramine, and psychotherapy in a number of case reports. A single
case report also revealed abrupt onset of OCD in a child with Crohn’s disease without a familial or personal history of OCD.\textsuperscript{55} No previous exposure to group A beta-hemolytic streptococcal infection was noted, reducing the probability of pediatric autoimmune neuropsychiatric disorder associated with streptococcal (PANDAS) infection. The only determined temporal association to the onset of OCD symptoms was a change in medication from infliximab to adalimumab (two immunomodulating medications) after exacerbation of IBD symptoms. Although the OCD symptoms resolved after 10 days without any intervention,\textsuperscript{55} this highlights the overlap between OCD and GI illness while furthering the suggestion of OCD potentially being immunomodulated. Overall, the data suggest that there may be a more substantial link between OCD and GI conditions than previously thought, promoting the link between OCD and the gut microbiome.

**Immune Dysregulation**

There is much support for the role of inflammation in neuropsychiatric conditions, including OCD. Some evidence draws from PANDAS, a condition where antibodies produced against the streptococcal proteins find targets in the brain leading to inflammation of the basal ganglia and bilateral lentiform nuclei.\textsuperscript{61} Given the sudden onset, it is thought that the repetitive behaviors may be a result of this neuroinflammation. Increased levels of systemic pro-inflammatory markers (tumor necrosis factor [TNF]-alpha and eotaxin-3, $P < .05$) and decreased anti-inflammatory (interleukin [IL]-8, interferon gamma-induced protein-10, IL-17a, interferon-gamma, IL-10, and IL-12; $P < .05$) markers have been reported in patients with PANDAS when compared to children who experienced a group A streptococcal infection but did not subsequently develop PANDAS.\textsuperscript{62} Human leukocyte antigen analysis has also revealed positive association in patients with a diagnosis of pediatric acute-onset neuropsychiatric syndrome (PANS) versus controls, and prevalence rates for arthritis and autoimmune disease (ie, Hashimoto’s thyroiditis, celiac disease, and psoriasis) were 25% and 18%, respectively.\textsuperscript{63} The average length of PANS flare-up is significantly shorter when treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or prednisone.\textsuperscript{63} Past infection has also been related to future onset of OCD in adults. For example, a large prospective cohort study revealed that intestinal infection (odds ratio [OR] = 1.34, $P < .01$) was associated with subsequent onset of an anxiety disorder (including OCD).\textsuperscript{64}

![Microbial differences observed in people with autism spectrum disorder per varying taxonomic levels.](image-url)
Toxoplasma gondii infection has also been associated with OCD (OR = 3.4, \( P = .0004 \)).

Numerous studies have also reported an altered inflammatory cytokine profile in adult patients with OCD. The only study evaluating primary pediatric OCD reported increased levels of IL-17A (\( P = .03 \)), TNF-alpha (\( P = .01 \)), and IL-2 (\( P = 0.02 \)) in patients with OCD than in controls; symptom severity and illness duration were not significantly correlated with cytokine levels. This may be further supported by the finding in patients with early-onset OCD revealing increased production of inflammatory cytokines by monocytes when stimulated with lipopolysaccharide (LPS) or dexamethasone and LPS. As such, patients with OCD may possess an intrinsic vulnerability to monocyte activation, which may generate an increased inflammatory response. In adult populations, results of studies investigating cytokines are inconsistent; however, many believe that this may be consequent to the confounding effects of medications and comorbid conditions (specifically mood disorders, which have been associated with low-grade inflammation) in study populations. For example, a meta-analysis revealed decreased levels of IL-1 beta while showing no differences in levels of...
IL-6 and TNF-alpha between cases and controls, suggesting a noninflammatory profile. However, a stratified subgroup analysis revealed moderating effects of age and inclusion of patients on pharmacological treatment and with comorbid mood disorders. A recent study in drug-naive, comorbidity-free patients with OCD revealed increased plasma levels of IL-2, IL-4, IL-6, IL-10, and TNF-alpha compared to age- and sex-matched controls, suggesting immune dysregulation as increased levels of the anti-inflammatory cytokine IL-10 may have been in response to an overall proinflammatory cytokine profile. A positive association between some autoimmune conditions (systemic lupus erythematosus, thyroid dysfunction, and multiple sclerosis) and OCD has also been suggested. Although circulating cytokines do not provide a clear picture of increased inflammation in OCD, these bodies of evidence further the role of immune dysregulation, and as an extension, the inflammatory response in OCD.

Beyond this, the role of inflammation in OCD may also be supported by treatment response observed in trials using immunomodulating compounds. In a 28-week crossover, randomized controlled trial (RCT), intake of Trichuris suis ova (studied in autoimmune disorders) in patients with ASD was shown to reduce scores on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) compulsion subscale ($d = 0.52$). Adjuvant celecoxib (200 mg twice daily), a NSAID, has also been shown as superior to fluvoxamine monotherapy (200 mg/day) after 10 weeks of treatment while also having an earlier response. Similarly, an earlier study had shown adjunctive celecoxib (200 mg twice daily) was superior to 8 weeks of fluoxetine (20 mg/day) monotherapy.

**WHAT DOES THIS MEAN FOR TREATMENT?**

At the present time, there are no published studies evaluating the gut microbiome in OCD. As such, we can only consider theoretical treatments that either alter the gut microbiota or have shown promise in conditions in which microbial disruption has occurred. Potential therapies include antibiotics, probiotics, and fecal transplantation.

**Antibiotics**

With the ability to eliminate microbial pathogens, antibiotic treatment can dramatically alter the gut microbiota and landscape both in the short and long term, in part by reducing bacterial densities. Given that microbiome dysbiosis does not preclude the overgrowth of certain microbial components at the root of any observed dysbiosis, antibiotics targeting a given class of bacteria could theoretically offer benefit by “normalizing” the microbial profile.

The extant literature supports the use of antibiotics in ASD, MDD, and BD conditions in which microbial dysregulation has been identified. In one study, 8 weeks of open-label treatment with vancomycin (500 mg/d) in children with regressive-onset autism ($n = 11$) revealed short-term improvements in communication and behavior. Like imipramine, the tetracycline antibiotic doxycycline was shown to reverse LPS-induced behavioral effects (ie, depressive behavior) in mice. Similarly, minocycline is known to alter glutamate transmission and has a regulatory effect on proinflammatory cytokines. It has also been evaluated in psychiatric conditions revealing antidepressant effects when used as a monotherapy in patients with HIV with mild-to-moderate depression, as an adjunctive therapy in patients with unipolar psychotic depression, and in rats based on the forced swim test. Eight weeks of open-label adjunctive treatment with minocycline also revealed significant changes in the Montgomery-Asberg Depression Rating Scale in bipolar I or II disorder patients in the midst a major depressive episode.

When considering antibiotics as a treatment for OCD, much support stems from PANDAS, where systematic evidence alludes to their benefit in acute episodes. However, open-label and RCT data suggest that the therapeutic benefits of minocycline may also translate to non-PANDAS OCD. In a 10-week RCT, minocycline additive to fluvoxamine in moderate-to-severe OCD ($n = 51$) revealed significantly higher rates of remission, partial ($35\%$ reduction in Y-BOCS score) and complete response ($35\%$ reduction in Y-BOCS score) ($P < .001$) than placebo ($n = 51$). With antibiotics eliciting anti-inflammatory effects and symptomatic relief achieved in psychiatric conditions in which microbial dysbiosis has been suggested, it is possible that these effects may be regulated by the microbiome.

**Probiotics**

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.
There is much animal data illustrating the behavioral effects of probiotics, and some evidence suggesting probiotics may ameliorate anxiety and depressive symptoms in primarily healthy populations. A 3-week RCT (n = 124) involving daily intake of a probiotic milk (containing Lactobacillus casei) or placebo did not demonstrate an overall change in mood or cognition. However, lower baseline mood, as per the profile of mood states, revealed greater improvements in the group receiving the probiotic drink than the placebo group (P < 0.025). In addition to improved “obsessive-compulsive” subscores on the HSCL-90, Messaoudi et al. also noted improvements in depression, anxiety, and paranoid-ideation subscores and urinary free cortisol levels in healthy adults randomized to a probiotic formulation containing Lactobacillus helveticus and Bifidobacterium longum or placebo. Steenbergen et al. had 20 healthy participants consume either a multispecies probiotic or placebo for 4 weeks and found that the probiotic group had reduced cognitive reactivity to sad mood. Significant pre- to post reductions in anxiety and depressive symptoms were also reported in a sample of petrochemical workers after intake of a probiotic capsule or yogurt; however, no significant between-group differences were seen post-intervention, as all three groups had reductions in the mean scores on the General Health Questionnaire and the Depression Anxiety Stress Scale.

Presently there is only one RCT showing benefit of a probiotic in patients with MDD. In this study, 40 patients with MDD (who met Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria, and had a 17-item Hamilton Depression Rating Scale score ≥15) and were randomized to receive a probiotic capsule (Lactobacillus acidophilus, L. casei, and B. bifidum) or placebo (n = 20) for 8 weeks. At endpoint, those receiving probiotics reported significantly lower scores on the Beck Depression Inventory total scores (-5.7 ± 6.4 vs -1.5 ± 4.8, P = .001) compared to placebo. Significant decreases in serum insulin levels (-2.3 ± 4.1 vs 2.6 ± 9.3 μIU/mL, P = .03) and serum high-sensitivity C-reactive protein concentrations (-1138.7 ± 2274.9 vs 188.4 ± 1455.5 ng/mL, P = 0.03) were noted, in addition to an increase in total plasma glutathione levels (1.8 ± 83.1 vs -106.8 ± 190.7 μmol/L, P = 0.02).

There are a variety of mechanisms by which probiotics may elicit these effects, many which involve the gut microbiota. Although the exact mechanism of action remains unknown, strains of lactobacilli and bifidobacterium have been shown to produce gamma-amino butyric acid, the primary inhibitory neurotransmitter in the central nervous system, and oral administration of Bifidobacterium infantis has been shown to increase levels of tryptophan, a precursor to serotonin. Based on such evidence, probiotics may act as a direct delivery vehicle for neuroactive compounds. They may also inhibit proinflammatory cytokines such TNF-alpha and IL-6, some of which have been implicated in psychiatric conditions, including OCD.

**Fecal Microbiota Transplant**

Fecal microbiota transplant (FMT), also known as bacteriotherapy, involves the transfer of fecal microbes from a healthy person to an ailing person. Although many patients view this treatment negatively, it is has proven to be a reliable an inexpensive option with a low side-effect profile. It has been used to mainly treat recurrent Clostridium difficile infections. Although there are no existing clinical trials evaluating the effects of FMT in neuropsychiatric conditions, this may change as the body of microbiome research in psychiatric conditions continues to grow. This notion is supported by the wealth of rodent data suggesting significant changes in immune response and behavior after FMT. More interestingly, FMT of pooled fecal samples from five nonmedicated patients with MDD and five healthy controls into GF-mice revealed behavioral differences 2 weeks post-FMT. Recipients of the MDD fecal samples illustrated more depression-like symptoms compared to recipients of “healthy” microbiota, and the initially observed microbial differences in the stool samples were maintained. This finding promotes the possible involvement of the gut microbiome in neuropsychiatric illness and suggests FMT as a viable treatment option as the relationship between psychiatry and the gut microbiome continues to develop.

**CONCLUSION**

The interest in the gut-brain axis and potential role of the gut microbiome in psychiatry has gained much traction in recent years, as evidenced by the growing scientific literature suggesting dysbiosis in conditions such as ASD, MDD, and BD. Although promising, it should be noted that many of these studies (in particular those for MDD and BD) are accompanied by several limitations. In addition to small sample sizes, much of the existing literature fails to evaluate many factors known to alter the gut microbiome, such as diet and medications, leaving the results muddled with confounding effects of such variables.

Although the state of the gut microbiome in OCD has not yet been evaluated,


