A Critical Literature Review of the Role of Gut Microbiota in Mood Disorders

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Abstract

Recent research has found a link between the gut and brain known as the gut-brain axis. Through this axis microbes in the gut have impacts upon the brain and behavior of individuals. Researchers have become increasingly interested in the implications of this axis on psychological disorders. This review will examine and evaluate research focusing on the role of gut microbes in three mood disorders: depression, bipolar disorder, and schizophrenia. A specific focus will be placed on the role of gut microbes in the onset and cause of each mood disorder as well as treatment options for each mood disorder that alleviate symptoms through altering the gut microbial environment. The prevailing hypothesis concerning the role of gut microbes in each mood disorder will be evaluated using the current literature. Treatment options for each mood disorder will explore probiotics as well as more traditional methods.
A Critical Literature Review of the Role of Gut Microbiota in Mood Disorders

Recently gut microbiota have become an area of interest in regards to understanding the etiology of psychological disorders as well as the treatment options available to those suffering from these disorders. Gut microbiota are largely influenced through the environment through diet and lifestyle and with a shift in recent years to an emphasis on natural diets and more health-conscious lifestyles, researchers are interested in the role of these microbiota on disorders and how these shifts might affect them and thus those with disorders. Microbiota have been shown to activate the immune system and the central nervous system as well as produce and deliver neurochemicals (Evernsel and Ceylan, 2015). These microbiota act upon the brain through the gut-brain axis, a bidirectional pathway between the brain and peripheral intestines. The brain can induce changes in the gut microbiota and the gut microbiota can induce changes in the brain (Carabotti, Scirocco, and Severi, 2015).

Research has found the vagus nerve to be one of the main pathways connecting the gut and brain. A study examining the impact of a probiotic on GABA receptors in the brains of mice found mice that underwent a vagotomy did not see any change in the expression of GABA receptors, however, mice with intact vagus nerves demonstrated a decrease in receptor expression (Bravo et al., 2011). A study by Bercik et al. (2012) examined the effect of microbiota on levels of Brain-Derived Neurotropic Factor (BDNF) and behavior is mice and found that activation of the vagus nerve was necessary for the microbiota to actually impact the functioning of the brain. Most of the microbes in the gut can be placed in the Bacteroidetes and Firmicutes phyla and in the Prevotella, Ruminococcus, and Bacteroides enterotypes or biomarkers (Arumugam et al., 2011). Bacteria in the Bacteroidetes phyla are associated with the absorption of nutrients as well as aiding in the maintenance and maturation of epithelial cells.
Bacteria in the Firmicutes phyla are associated with the maintenance of and protection of the epithelium of the colon (Eckburg et al., 2005). *Prevotella, Ruminococcus,* and *Bacteroides* have been found to be related to diet, lifestyle, and disease state within individuals (Gorvitovskaia, Holmes, & Huse, 2016).

Mood disorders have always been present in society and yet are not fully understood. While psychologists are aware of the chemical changes in the brain, it is not yet understood all mechanisms by which these changes occur. Furthermore, diagnosing mood disorders can prove to be somewhat tricky as it relies solely on subjective appraisal of symptoms by humans according to the *DSM-V.* Many researchers have become interested in the role gut microbiota play in the onset of mood disorders and how these microbiota could be targeted as treatment options for mood disorders in addition to or in place of traditional treatment options.

Major depressive disorder, MDD, is a very prevalent and detrimental mental disorder. It is estimated MDD affects about 15% of the general population and accounts for 12.3% of the burden of disease globally (Kessler et al., 2003). Symptoms of MDD are characterized by intense sadness, adhedonia, an overall delay of motor skill speed, and suicidal thoughts. Antidepressant medications, psychotherapies, as well as brain stimulation therapies are all used to treat MDD (National Insitute of Mental Health, 2017a). Bipolar disorder is significantly rarer than MDD only impacting an estimated 4.4% of U.S. adults at some point in their lifetime. Bipolar disorder is characterized by periods of mania (periods of hyperactivity, delusions, and other disturbances) followed by periods of depression with typical depressive symptoms. Bipolar disorder is typically treated through mood stabilizing medications, antipsychotic medication, and antidepressants. Those with bipolar disorder may also undergo cognitive behavioral therapy or other forms of psychotherapy (National Institute of Mental Health, 2017b). Schizophrenia
impacts between 0.25% and 0.64% of the US population. The symptoms of schizophrenia are categorized as positive and negative. Positive symptoms include behaviors not usually seen in healthy individuals, such as hallucinations, while negative symptoms include reductions in behaviors usually seen in healthy individuals, such as reduced speech or reduced feelings of pleasure. The symptoms of schizophrenia are usually treated through antipsychotic medications as well as psychosocial therapy which focuses on helping individuals cope with and learn how to function with their symptoms (National Institute of Mental Health, 2018).

The following review will examine literature referring to the role of microbiota in the onset/cause and possible treatment options for three mood disorders: Depression, Bipolar Disorder, and Schizophrenia. The sections will be centered around the evaluation of a hypothesis focusing on the interactions between the gut microbiota and the brain through the gut-brain axis in regard to each mood disorder.

**Depression**

A recent review conducted by Inserra, Rogers, Licinio, & Wong (2018) proposed what is known as the Microbiota-Inflammasome Hypothesis, the currently prevailing hypothesis. Their review of published studies lead to the conclusion that shifts in the composition of the gut microbiota caused by stress or the current condition of the gut leads to the upregulation of pro-inflammatory pathways mediated by Nod-like receptors containing NLRP3 inflammasome. The upregulation of these pathways is to blame for the depressive symptomatology which further compromises the gut environment perpetuating the symptoms (Inserra et al., 2018). The subsequent paragraphs will evaluate the hypothesis based on current research in the field regarding onset/causes of depression as well as current treatment options.

**Onset/Cause**
Initial experiments began exploring metabolites within human waste, both urine and feces, to identify what specific organisms were present in those with MDD and were either not present or not as prevalent in healthy controls. Zheng and colleagues (2013) examined the metabolites in urine as a potential biomarker for MDD. The purpose of the study was to examine the urine samples of one group of depressed participants and healthy controls, the training set, for specific metabolic differences and then use the results from that group to predict the metabolites found in urine samples of a different group of depressed participants and healthy controls, the test set. Results showed 23 different metabolites were distinguishable between depressed participants and healthy controls, however further analysis distinguished five as the most significant. Depressed participants had different levels of malonate, formate, N-methylnicotinamide, m-hydroxyphenylacetate, and alanine when compared to healthy controls. The panel was fairly successful and accurate when predicting the metabolic content and discrimination of the depressed participants and healthy controls in the test set, AUC of 0.89 (Zheng et al., 2003).

The five metabolites that were significantly decreased in depressed participants are specific to energy metabolism, bacterial metabolic processes in the gut, and tryptophan-nicotinic acid metabolism. Malonate is associated with the tricarboxylic acid cycle and inhibits succinate-coenzyme Q reductase, which plays a role in the citric acid cycle as well as the electron transport chain. Formate is an electron acceptor in the electron transport chain and is significantly decreased in MDD participants. Alanine is involved with the exchange of glucose between the tissues and the liver, another aspect of energy production, and is significantly increased in MDD participants. This suggests that the cycles producing energy in those with MDD could be different from the energy cycles in healthy controls and those with MDD may have a decreased
capacity for energy (Zheng et al., 2003). M-hydroxyphenylacetate is involved in metabolism in the gut and the decreased presence of this in MDD participants suggests that MDD is linked to the variation of microbes in the gut (Zheng et al., 2003). Finally, N-methylnicotinamide is involved in the metabolism of nicotinamide. Nicotinamide is involved in the tryptophan-nicotinic acid pathway which leads to the production of serotonin and nicotinic acid. The decreased presence of N-methylnicotinamide in MDD participants provides evidence for the well-known theory that deficiencies in serotonin contribute to the onset of MDD (Zheng et al., 2003). The study supported the claim that the gut environment and the metabolites produced in response to the environment can affect the brain through the gut-brain axis, either causing or perpetuating the symptoms associated with MDD. This study made great strides in understanding the scope of MDD in the body. Unfortunately, 13 participants in the study, 42%, were taking anti-depressant medication which could have impacted their microbial environment and skewed the results.

A similar study conducted by Jiang et al. (2015) examined the fecal samples of patients that were active-MDD (A-MDD), responded-MDD (R-MDD) and healthy controls. R-MDD participants were individuals that were receiving some other form of treatment for their depression but were still exhibiting symptoms of depression. Participants in the A-MDD group had more diversity in the bacteria in their fecal matter than controls. A-MDD and R-MDD participants had higher levels of bacteria the \textit{Bacteroidetes} phylum. Bacteria belonging to \textit{Bacteroidetes}, specifically \textit{Alistipes}, have been associated with the production of tryptophan which is a precursor of serotonin suggesting the increase of \textit{Bacteroidetes} in the gut could disrupt the serotonergic system. Participants in the A-MDD group had increased levels of bacteria in the \textit{Proteobacteria} phylum. Bacteria in this phylum are involved in inflammatory pathways and an increased presence of these could alter behavior and the brain through increased
levels of inflammation. Participants in the A-MDD group had decreased levels of bacteria in the *Firmicutes* phylum. Bacteria in this phylum have been associated with anti-inflammatory responses, therefore a decreased presence would allow the increased inflammation caused by bacteria in the *Proteobacteria* phylum to perpetuate for a longer amount of time. The levels of BDNF in A-MDD and R-MDD individuals was lower than those in controls (Jiang et al., 2015). As previously mentioned, BDNF has been linked to gut microbes previously and are found to interact through the vagus nerve. BDNF is linked to antidepressant and anxiolytic behavior at the level of the hippocampus (Bercik et al., 2011). The decreased level of BDNF in A-MDD and R-MDD participants caused by their altered gut microbes could explain their depressive behavior.

The study supports both a role of microbiota in depression as well as a role of inflammation in depression through the microbiota. To the researchers’ surprise, however, there was no significant difference between the levels of inflammatory markers present in each group. The researchers cite the use of antidepressants among the participants as the main reason for this which limits the validity of the study as was the case with the Zheng et al. study. In the A-MDD group, eight participants used SSRIs, 22 participants used atypical antipsychotics, and five used benzodiazepines. In the R-MDD group, 12 participants used atypical antipsychotics and seven used benzodiazepines (Jiang et al., 2015). A study consisting of only drug-naïve patients would confirm the results in the previous studies to ensure the microbiota listed above are independent of antidepressants or other forms of treatment.

A study conducted by Naseribafrouei, Hestad, Avershina, Sekelja, Linlokken, Wilson, and Rudi (2014) sought to examine the role of medication in the production of microbiota in the gut to see if the same microbiota were present in those receiving antidepressant treatment and those that were not receiving any form of treatment. Fecal samples were analyzed and
Bacteroidetes and Firmicutes were determined as the dominant phyla in both groups of depressed individuals and controls. Bacteroidales was underrepresented in depressed individuals while Alistipes and Oscillibacter were overrepresented. The researchers noted that Alistipes has previously been associated with inflammation therefore it could act on depressive symptoms independently as well as through inflammatory pathways. Oscillibacter has been found to bind with the GABAa receptor, it is reasonable to assume this bacterium acts on the brain through this receptor and not through other pathways such as inflammatory pathways. The researchers concluded there was no significant effect of the medication on the bacteria (Naseribafrouei et al., 2014).

This study addresses the previously mentioned concern of the possibility of antidepressants affecting and altering the gut environment in a way that could interact with the already present microbiota to influence symptoms. Clearly, Bacteroidales is a common bacteria among all individuals, both medicated and non-medicated. This study both supports and opposes the hypothesis in that one bacterium, Alistipes, did indeed impact the brain through inflammatory pathways, but another bacterium, Oscillibacter, influenced the brain without impacting the inflammatory pathways.

All studies up until this point have assumed the gut environment is not dependent upon gender and therefore depression affects both genders in the same way through the same microbiota. Chen and colleagues (2018) addressed this issue as they examined the metabolites present in fecal matter collected from depressed participants and healthy controls comparing males and females. The phyla and families of the bacteria were determined using the 16s rRNA gene. Operation taxonomic units or OTUS were assigned according to each bacteria’s phyla and family. There were significant differences between female depressed participants and healthy
controls as well as differences between male depressed participants and healthy controls, which was expected based on prior studies. In females, 57 OTUs were different between depressed participants and healthy controls. Twenty-nine OTUs were increased in depressed participants and belonged to the families of *Coriobacteriaceae, Lachnospiraceae*, and *Ruminococcaceae*. Twenty-eight OTUs were decreased and belonged to *Lachnospiraceae* and *Ruminococcaceae*. In males, 74 OTUs were different between depressed participants and healthy controls. Twenty-one OTUs were increased in depressed participants and belonged to the families of *Lachnospiraceae* and *Erysipelotrichaceae*. Fifty-three OTUs were decreased and belonged to *Lachnospiraceae* and *Ruminococcaceae*. In female depressed participants the most abundant bacteria belonged to *Actinobacteria* whereas in male depressed participants the most abundant bacteria belonged to *Bacteroidetes* (Chen et al., 2018).

The results of this study suggest different types of bacteria are associated with depression in females and males. Unlike other studies, participants in this study were not receiving any type of medication, therefore the results are more robust and have greater external validity. The results also suggest the possibility of sex-specific biomarkers and treatments for MDD. Previously, MDD has been viewed as a one size fits all type of disease with no difference in treatment options or medications for males and females because the disease was assumed to affect all individuals in the same way. The discovery of different bacteria in males and females suggests the disease may work through different mechanisms depending on sex but that microbiota are still at the center of that mechanism. Several bacteria overlap between all studies mentioned up to the point. These are the phyla *Firmicutes, Bacteroidetes*, and *Actinobacteria*. Seeing as this study was conducted with patients who were not receiving antidepressants or
treatment, it is fair to assume the bacteria that are mentioned in other studies are further validated by this study as resulting from depression alone and not other forms of treatment.

Other studies have taken a much more invasive approach by introducing bacteria associated with depression into the gut environment of rats and mice to examine if the behavior shifts to depressive behavior. Kelly and colleagues (2016) took fecal matter collected from depressed patients as well as controls and introduced it into the gut of microbiota depleted antibiotic rats through oral gavage. The researchers then examined the behavior of the rats to see if those that received fecal matter from depressed patients began to show depressed symptoms. Results showed rats that received the fecal matter from depressed patients did indeed show symptoms such as anhedonia, as seen through the decreased interest in sucrose, and anxiety, as seen through decreased visits to the open arms in the elevated plus maze and less time spent in the center of the open field test. Rats that received depression fecal matter showed increased levels of C-reactive protein, an inflammatory marker, and increased intestinal transit time. Rats that received fecal matter from depressed individuals also showed a decreased variety of gut microbiota as compared to controls. Rats that received fecal matter from depressed patients specifically showed a decreased amount of microbes associated with tryptophan metabolism from the phyla *Actinobacteria*. As previously stated, this decrease can impact the production of serotonin which has been linked to depressive behavior (Kelly et al., 2016).

This study supports the hypothesis that gut microbes play a role in the onset and perpetuation of depression in humans. The communication between the gut and brain in rat models was significant enough that the rats began to exemplify behaviors associated depression in humans, despite the fact humans and rodents have vastly different microbiota present in the gut. Further research is needed to determine if one specific phyla or family is responsible for the
symptoms or if rather it is a combination of different phylae and families. This study also provides further support that the microbiota are the sole source of blame for the depression symptoms as opposed to a possible interaction between the microbiotic response to treatment and the microbes already present in the gut as the rats received no form of treatment.

**Treatment**

As more research has demonstrated the role of gut microbes in depression, many have explored the possibility of probiotics and other forms of bacteria as possible treatment options for depression that either act upon microbiota or inflammatory pathways.

Sun and colleagues (2018) examined the antidepressant effects of *Clostridium butyricum* on behavior when mice experienced chronic unpredictable mild stress. The study consisted of three groups: the control group, the chronic unpredictable mild stress (CUMS) group in which mice experienced chronic unpredictable mild stress with no treatment, and the *Cb* group in which mice experienced chronic unpredictable mild stress and received *Clostridium butyricum* as treatment. *Clostridium butyricum* decreased depressive-like behavior in CUMS mice in all behavioral assessments. *Clostridium butyricum* increased levels of serotonin in the brain as compared to CUMS group which had significantly reduced levels of serotonin compared to controls. This is suspected to have occurred through the gut-brain axis. *Clostridium batyricum* altered the microbes in the gut, specifically bacteria from the *Bacteroidetes* and *Actinobacteria*. CUMS mice had decreased levels of BDNF in the brain as compared to controls but this decrease was significantly reversed with *Cb* treatment. In the colon, CUMS mice had lower GLP-1 levels compared to controls but *Cb* mice had significantly higher levels. *Cb* mice has significantly higher levels of GLP-1R in the brain but CUMS mice had decreased levels. The results indicate
*Clostridium butyricum* acts as an anti-depressant in an animal model of depression (Sun et al., 2018).

The increased levels of serotonin help to regulate mood, emotion and behavior that is altered during a stress response. Serotonin is usually decreased in individuals that struggle with depression, hence their symptoms of mood and emotional dysregulation. BDNF is critical for neural survival, neurogenesis, synaptogenesis, and plasticity. Those that are depressed have decreased levels of BDNF but *Cb* combatted this effect. The glucagon-like peptide-1 receptor, GLP-1, has been identified as one of the main chemicals involved in the gut-brain axis as it interacts with the vagus nerve and has receptors in both the gut and brain. The GLP-1 is involved in a variety of functions across all areas of the body including feeding, glucose metabolism, stress, and cognitive functioning. (Sun et al., 2018). The increase of GLP-1 caused by *Cb* indicates the antidepressant effect works both at a brain and gut level. *Clostridium butyricum* could potentially decrease the symptoms of depression by interacting with the brain through the gut-brain axis by altering levels of chemicals in the brain through the gut environment. This treatment does not, however, address any inflammatory response in the gut-brain axis suggesting that the microbiota may work independently of the inflammatory response to produce depression symptoms, contradictory to the hypothesis.

A similar study by Li et al. (2018) studied the antidepressant effects of *Cistanche tubolsa* extract, CTE, in rats that experienced chronic unpredictable stress as compared to those that experienced stress without any form of treatment. CTE is an herb typically used in traditional Chinese medicine to treat a variety of ailments from kidney deficiency to infertility, however, the herb also has neuroprotective and anti-inflammatory purposes hence its use in this study. Rat behavior was analyzed (forced swim test (FST), novelty-suppressed feeding test (NSFT), sucrose
preference test (SPT), and open field test (OFT)) as well as hippocampal and colon levels of neurotransmitter and neurotrophic factors, and gut microbiota makeup. Rats that received CTE had decreased immobility time in the NSFT and latency to eat in the NSFT as compared to controls and increased sucrose preference in SPT and distance covered in OFT. High doses of CTE treatment increased serotonin and BDNF hippocampal levels as compared to controls. In the colon, CTE treatment in higher doses increased serotonin levels. More than 90% of the serotonin in the body is produced from enterochromaffin cells found in the gut and colon hence the rise of serotonin in the colon. CTE treatment also restored the gut microbiota environment to that of the pre-stress environment, meaning it restored homeostasis. Researchers stress that because this herbal remedy is a natural substance it would alleviate many of the negative side effects associated with traditional antidepressants while still affecting the body and brain in the same way (Li et al., 2018).

This treatment did not in any way affect inflammatory pathways, instead it acted on the brain primarily through neurotransmitters and gut microbiota alone. This does not support the inflammation aspect of the hypothesis as the treatment was still effective without any interaction with inflammatory pathways. The success of this treatment suggests there is another pathway through the gut-brain axis that works independently of inflammatory pathways to reduce depressive symptoms.

A study conducted by Abildgaard, Elfving, Hokland, Wegner, and Lund (2016) explored the antidepressant effects of probiotic treatment in rats with a control and high fat diet to simulate the types of diet depressed individuals might have. Rats that received probiotic treatment exhibited an antidepressant effect through less immobility time in the force swim test regardless of what type of diet the rat was on. The Barnes maze consisted of a center disc
surrounded by 18 holes with only one hole leading to an escape box. The rat was guided to the escape hole with spatial cues for a learning phase consisting of eight trials. After a delay of seven days, the rat was placed back into the box to measure its spatial memory. Due to the association between the impairment of spatial memory and bipolar disorder, this maze was used to model the impact of the treatment on a specific symptom of bipolar disorder. In the Barnes maze, rats on the high fat diet improved their time faster day by day during the learning phase but there were no probiotic effects in either diet meaning the increase in time was not due to alleviation of the symptoms but rather the diet itself. During the recall-session, rats on the high fat diet that received the vehicle completed the maze faster than those that received the probiotic. Probiotics increased the levels of IL2, IL4, and IFN specifically but not the total number of cytokines in general. There was no effect of diet. Probiotics lowered the expression of HPA axis regulating genes but had no effect on the concentration of lipopolysaccharide, an endotoxin known for producing depressive-like symptoms. Two tryptophan metabolites and a metabolite associated with amino acid metabolism were increased by probiotic treatment. The probiotic treatment decreased depressive behavior as well as several physiological markers of depression (cytokines, levels of expression of HPA regulatory genes in the hippocampus, and metabolites) regardless of the type of diet the rats were assigned to (Abildgaard et al., 2017).

This study suggests probiotics as a very robust treatment option for depressed patients. When considering gut microbes, diet plays a large role in constructing that environment. Finding a treatment option that works independently of the type of diet of the individual is imperative to the implementation of a treatment protocol that will be applicable to and successful for a wide variety of patients. These findings are also aligned with the inflammation aspect of the hypothesis seeing as how probiotics did not increase the level of cytokines in general meaning
the level of inflammation was maintained which could have also contributed to the antidepressant effects.

Another study focusing on the effects of probiotics on decreasing depressive symptoms by Akkasheh and colleagues (2015) found contrary results. Participants received either placebo or probiotic treatment for eight weeks at which point their symptoms, plasma glucose, insulin metabolism markers, lipid concentrations, high-sensitivity C-reactive protein, and markers of oxidative stress were assessed. Participants that received the probiotic had decreased symptoms, insulin levels, high-sensitivity C-reactive protein levels and oxidative stress levels.

This treatment option supports all aspects of the microbial inflammatory hypothesis as the probiotic alleviated symptoms both through microbial elements and inflammatory pathways. Diet was not regulated as a part of the experiment, which therefore could be a limitation to the results as diet could have impacted the microbial environment in addition to the probiotic.

After reviewing literature addressing both onset and causes of depression as well as treatment, the microbiota-inflammasome hypothesis is a valid hypothesis but does not cover the entire story behind the gut-brain axis and depression. Several studies examining human waste in humans found microbiota that impacted depressive symptoms independently of inflammatory pathways (Jiang et al., 2015, Naseribafrouei et al., 2014). Other studies transplanting fecal matter and bacteria from depressed patients into rats or mice found the model animals began to express the symptoms regardless of whether the bacteria were associated with inflammatory pathways (Kelly et al., 2016). Treatment options have proven successful without acting on inflammatory pathways and acting on microbiota alone (Li et al., 2018, Sun et al., 2018). The hypothesis is not completely wrong however as studies focusing on human waste have found bacteria that acts upon inflammatory pathways (Naseribafrouei et al., 2014). Studies focusing on probiotics as a
form of treatment have found that probiotics decrease depressive symptoms by action upon microbial and inflammatory targets (Abilgaard et al., 2017, Akkasheh et al., 2015). Perhaps the hypothesis could be expanded to address the possibility that there is another pathway in the gut-brain axis, independent of inflammatory pathways, that gut microbiota act upon the brain and therefore reduce depressive symptoms. There should also be further exploration into different hypotheses for males as females as there is a possibility that depression is represented differently in the bacteria found in the gut according to gender (Chen et al., 2018).

**Bipolar Disorder**

As research regarding the role of gut-brain axis in depression has increased, many have turned to examine other mood disorders for pathways through the gut-brain axis for possible causal or treatment connections, specifically those that have similar symptoms or elements of depression. A letter to the editor of an Australian and New Zealand journal described a woman that was admitted with manic symptoms despite having no previous personal or familial psychiatric history. The woman had, however, recently undergone a subtotal gastrectomy for morbid obesity. Doctors hypothesized the inflammation caused by the disruption of the gut environment following the surgery was the cause of the mania. They chose to treat the patient with activated charcoal, known for absorbing inflammatory cytokines, which alleviated her manic symptoms (Hamdani et al., 2015). The success of this treatment in a woman that was exhibiting symptoms similar to those in bipolar disorder sparked interest in other researchers to explore the interactions between gut microbiota and symptoms of bipolar disorder.

**Onset/Causes**

Early explorations into the relationship between gut microbes and bipolar disorder began focusing on inflammation in the gastrointestinal tract (GI). Severance et al. (2014) examined
levels of anti-*Saccharomyces cerevisiae* antibodies (ASCA), a marker of GI inflammation, in non-psychiatric controls, bipolar disorder participants without a recent psychosis, and bipolar disorder participants with a recent psychosis. Results showed a significant increase in ASCA levels between both groups of bipolar disorder patients as compared to controls. To ensure this effect was due to bipolar disorder and not medication, bipolar disorder participants were further divided according to their current medication used for treatment of their symptoms. No significant difference was observed between the different medication groups in regard to ASCA levels meaning the GI inflammation was related solely to bipolar disorder. Results also showed a significant correlation between ASCA and immune reactivity to wheat glutens and bovine milk, specifically those bipolar disorder participants that reported other GI symptoms (Severance et al., 2014).

While this study does not focus on specific microbes, it does demonstrate that those with bipolar disorder, regardless of the presence of psychosis and type of medication, have a different gut environment than controls. The heightened levels of the GI inflammation marker as well as the unique immune reaction to wheat and milk seen in those with bipolar disorder suggests that a level of inflammation is already present in the gut and the addition of foods only increases this inflammatory immune response.

Another study by Severance et al. (2016) examined the immune reaction to *Candida albicans* in individuals with bipolar disorder, schizophrenia, and healthy controls. *Candida albicans* is a yeast that is found in the human respiratory, gastrointestinal (GI), and genitourinary tracts but when left unchecked can produce severe infections. Levels of antibodies in the blood were measured to determine the immune response. Results showed a significant increase in
antibodies among bipolar males as compared to control males, however there was no significant difference between female groups (Severance et al., 2016).

This study again demonstrated a role of gut microbes in bipolar disorder through the heightened inflammatory immune response to *Candida albicans*. This response indicates the presence of microbiotic dysbiosis in bipolar participants that is not seen in healthy controls. The researchers explained the lack of significance in the female groups by noting the higher occurrence of yeast infections in women as compared to men. Women are naturally prone to an overgrowth of *Candida albicans* and thus a heightened immune response regardless of their disease state (Severance et al., 2016). The studies from Severance and colleagues in 2014 and 2016 provided evidence for a role of the gut-brain axis in bipolar disorder and laid the foundation for later more specific studies.

A study conducted by Evans et al. (2018) examined the microbiota present in stool samples taken from bipolar participants and controls. Bipolar participants and controls had significantly different microbiota present. There was also a significant difference between bipolar individuals that reported a high burden of disease and those that reported a low burden of disease with those with a high burden of disease having a lower amount of *Faecalibacterium* present in their sample. The researchers note that *Faecalibacterium* has been shown to have anti-inflammatory properties and hypothesize that these properties are the reason those that have a higher abundance of it report a lower burden of disease (Evans et al., 2018).

The correlation between severity of illness and abundance of *Faecalibacterium* in bipolar participants suggests that the inflammatory hypothesis is correct. As was the case with depression, there is the possibility that other microbiota are working on another pathway to also
produce symptoms as *Faecalibacterium* was not the only microbiota that varied between bipolar participants and controls, it was just the most significant.

Another study, by Painold et al. (2018), also looked at stool samples of male bipolar patients, all receiving a traditional form of treatment, and healthy controls. There was an association between the level of specific inflammatory markers and types of microbiota present in the gut. Bipolar individuals with increased IL-6 levels had increased levels of *Lactobacillales*, *Streptococcaceae*, and *Bacilli*. *Lactobacillales* has been found to produce acetylcholine and GABA. *Streptococcus* synthesizes 5-HT and *Bacillus* produces dopamine. Those with a lower diversity of microbiota had longer illness duration and the converse was also true. *Faecalibacterium* was higher in controls as compared to bipolar participants (Painold et al., 2018).

There is a clear interaction between inflammation and gut microbes in the previously mentioned study. However, the reappearance of *Faecalibacterium* suggests two pathways are at work here. Evans et al. also found *Faecalibacterium* as a discriminating factor not only between bipolar participants and controls but also between highly affected and less affected bipolar participants. Seeing as how the same symptoms were present in both studies, without the inflammatory markers present in the Evans et al. (2017) study, it can be assumed there are two independent pathways at work in bipolar individuals.

Another study, conducted by Coello and colleagues (2018), compared the microbiota in stool samples from bipolar participants, first-degree relatives of the bipolar participants that were healthy, and healthy controls that were not related to the bipolar participants. Results showed that communities of bacteria did differ between bipolar participants and healthy controls. Initial analysis showed a difference between the bacteria communities present in bipolar participants
and their relatives with *Flavonifractor* as the determining factor between the bacterial communities. Unfortunately, however, further analysis controlling for confounding variables found the differences between the communities in bipolar participants and their relatives was not associated with presence the disorder but rather was associated with their smoking habits (Coello et al., 2018).

The other previously mentioned study comparing gut microbes in bipolar patients and controls did not find *Flavonifractor* in their stool samples, however the participants in that study were significantly older than the participants in this study (Evans et al., 2017). It could be that *Flavonifractor* presence is a function of the progression of the illness. Coello et al. (2018) did not replicate the findings of lower levels of *Faecalibacterium* suggesting the presence of this is also a function of the progression of the illness or rather caused by the longer period of time that the participants in Evans et al. (2017) have been taking the antidepressant medication due to their increased age.

In order to expand the availability of research on the role of microbes and bipolar disorder, some researchers have begun to examine links between microbes and mania, a symptom of bipolar disorder. Khambadkone et al. (2018) focused on the association between nitrates in meat products and mania in humans as well as behavioral patterns and brain gene expression in rats. Human participants were individuals with mania or a similar psychiatric disorder and healthy controls. Participants were asked how often they consumed nitrated dry cured meat, other non-treated meat products, and fish. A strong association between eating nitrated dry cured meat and mania was observed. This association was specific to nitrated dry cured meat and was not observed with other non-treated meat products or fish. To provide further evidence for this association, researchers compared the behavior of rats that were fed
nitrated dry cured meat products and control rats. Rats that ate the meat exhibited behaviors comparable to the behaviors observed in manic humans (Khambadkone et al., 2018).

These results suggest the microbes either introduced to the gut my nitrated meat or the microbes that are upregulated to aid in the digestion of the nitrated meat in the gut could have a role in mania symptoms. While mania is a symptom of bipolar disorder only a small cohort of bipolar individuals experience this symptom. While this finding does not apply to all, it does provide support for interactions between the gut and brain in bipolar disorder through mania symptoms. Further research is needed in this field to explore the possibility of diet as a component of the onset and causality of bipolar disorder through the effects of diet on the gut’s microbial environment.

**Treatment**

Researchers have explored alternative treatment options, such as probiotics, that decrease bipolar symptoms through the gut microbiota and inflammatory pathways to understand their mechanism and how effective they are. Other researchers have focused on how typical medication, such as atypical antipsychotics, interact with the gut microbiota and inflammatory pathways through the gut to decrease symptoms and illness severity.

Probiotic supplements have also been explored as a possible treatment option for bipolar individuals in regard to their cognitive impairment. Participants were given probiotic supplements over a period of three months with cognitive assessments before giving the supplement, one month later, and at the conclusion of the study. The supplements did indeed improve the cognition of the bipolar participants. Due to this study being a pilot, researchers plan to replicate this study with a wider variety of bipolar participants to see how the probiotic effects those with varying levels of illness severity. This is a promising novel treatment as the
researchers believe improving the cognition of these individuals will also improve their ability to interact with society and lower their burden of disease. While it is unclear the mechanism of action for the supplement, researchers hypothesize it acts on the gut microbiota that are directly associated with or homologs to neurotransmitters in the brain (Reininghaus et al., 2018).

Other studies have shown that Lactobacillales, Streptococcaceae, and Bacilli are bacteria present in the gut that are associated with production of important neurotransmitters such as GABA, 5-HT, and dopamine (Painold et al., 2018). These specific bacteria were associated with elevated levels of markers for inflammation in the gut, suggesting the probiotic may in some way interact with the microbiota through inflammatory pathways as previously hypothesized.

A study conducted by Flowers and colleagues examined how atypical antipsychotics (AAPs) interact with the gut microbiome to treat bipolar symptoms. Fecal samples were collected from bipolar participants that were currently taking medication and bipolar participants that were not currently taking any medication. In individuals currently taking AAPs, Akkermansia was significantly decreased. Akkermansia has been found to have an inverse relationship with inflammation, meaning as abundance of Akkermansia decreases the amount of inflammation increases. Female participants taking AAPs had a decreased diversity in microbiota however males taking AAPs had an increased diversity (Flowers et al., 2017).

The hypothesis that bipolar disorder is caused by inflammation in the gut is not supported by the results of this study as the bacteria known for controlling inflammation was decreased in individuals taking AAPs, suggesting the symptoms are being controlled by some other mechanism. The sex differences in the results are interesting, however it is unclear if the differences are caused by AAPs or the difference in diets between the two sexes as diet was not controlled for.
As compared to depression, very little research is available discussing the role of gut microbes in bipolar disorder as this is a very novel field. Also, much less of the population is affected by bipolar disorder as compared to depression meaning there is a larger need for understanding possible causes and treatments of depression as compared to bipolar disorder. Most research has focused on inflammation caused outside of the gut rather than inflammation inside the gut caused by/interacting with microbiota. The limited research available, however, does suggest, as was the case with depression, that two independent pathways may be present. Beginning studies focused on the relationship between GI inflammation and bipolar disorder in order to demonstrate the influence of the gut-brain axis in bipolar disorder. Severance et al. (2014) found higher levels of anti-\textit{Saccharomyces cerevisiae} antibodies in bipolar participants as compared to healthy controls. The increase in the level of antibodies in bipolar participants was explained by a different microbial gut environment in these individuals as compared to controls (Severance et al., 2014). In 2016, Severance and colleagues examined the immune response to \textit{Candida albicans} in bipolar participants, schizophrenics, and controls. In men, a significant increase in antibodies was observed in bipolar participants as compared to controls. The immune response observed in bipolar participants indicated the presence of microbiotic dysbiosis in these individuals (Severance et al., 2016). The 2014 and 2016 studies demonstrate, at a very basic level, the axis connecting the gut and brain is present and partially responsible for the symptoms of bipolar disorder however these studies failed to deduce what specific microbes were influencing the brain from the gut. Painold and colleagues (2017) found that levels of inflammatory markers were associated with levels of microbiota, suggesting an interaction between the two that influences the brain through neurotransmitters. Both Painold et al. (2017) and Evans et al. (2018) found \textit{Faecalibacterium} to be a discriminating factor not only between
controls and bipolar individuals but also within degrees of illness severity of Bipolar individuals. While *Faecalibacterium* has been associated with anti-inflammatory properties, it is uncertain if these are only properties of the bacterium. Also, in the Evans et al. (2018) study, other microbiota varied between healthy controls and bipolar participants aside from *Faecalibacterium*. While *Faecalibacterium* was the main focus, as it was the most significant, the presence of other alterations in microbiota rule out the possibility that inflammation in the gut is the sole cause and proponent of Bipolar symptoms. The consumption of nitrated dry cured meats was linked to mania in humans and was further supported by the demonstration of mania behaviors in rats that were fed nitrated dry cured meats. This suggested that diet could play a role in the cause of bipolar disorder through the effects of diet on the microbial environment of the gut (Khambadkone et al., 2018). The study by Flowers and colleagues (2017) supports this claim as *Akkermansia*, a bacterium known for suppression inflammation was depleted in those taking AAPs suggesting the medication acted upon some other pathway to alleviate the symptoms. While it does seem as though the association with symptoms and the interaction between inflammation and microbiota is stronger than the association between symptoms and microbiota alone, due to the limited evidence available based on limited research it would be unwise to rule out the association with only microbiota completely.

**Schizophrenia**

Due to its close relatedness to bipolar disorder, schizophrenia has also become of interest in terms of interactions between the microbiota of the gut and brain through the gut-brain axis. Much like previous bipolar research, previous schizophrenia research has focused on inflammation and immunity pathways outside of the gut that do not interact with gut microbes. Research examining the interaction between inflammation and microbiota is new and very
limited. Due to the association between inflammation and the immune system outside of the gut, like bipolar disorder, many believe the microbiota in the gut will interact with the brain through inflammation and inflammatory markers. The following articles will describe explorations into this relationship through research examining associations and treatment options.

Onset/Causes

Initial studies focused on gut microbiota in animal models of schizophrenia. Jorgensen et al. (2014) induced schizophrenic-like behaviors in rats through subchronic phencyclidine, subPCP, treatment. They analyzed the microbes present in their fecal matter as well as their behavior through the novel object recognition test, NOR, and locomotor activity. The novel object recognition test is used to assess the cognitive impairment caused by SubPCP which models the cognitive impairment caused by schizophrenia. Rats are habituated to a box which contains two identical objects. After the rat is returned to the home cage a third item is placed into the box. This new item is either a triplicate of the object already in the box or a novel item. The rat is then returned to the box with the three items and its behavior is monitored. If a rat treated with SubPCP explores both the novel and familiar objects in a similar fashion or if the rat explores all three familiar items extensively, its cognition is perceived as impaired. If the rat focuses on the novel object more than the familiar object or does not explore any of the three versions of the familiar object, its cognition is perceived as normal. Locomotor activity was measured through the rat’s movement in a cage that it was previously habituated to. The decrease of movement in rats treated with SubPCP models the negative symptom of decreased movement in human schizophrenics. To further investigate the relationship, rats were then treated with antibiotics to restore gut homeostasis and functioning was evaluated through NOR and locomotor activity. SubPCP rats showed impairments in performance in the NOR task directly
after treatment but these impairments decreased over time. SubPCP rats also showed increased locomotor activity both immediately after antibiotic treatment and longer after antibiotic treatment. There was a significant correlation between gut microbiota and memory performance in the NOR directly after treatment. After SubPCP rats received antibiotic treatment their performance in the NOR, specifically memory, was equal to that of controls suggesting the antibiotics reversed the schizophrenic symptoms caused by the SubPCP. There was no effect of antibiotics on locomotor activity performance (Jorgensen et al., 2014).

The results suggest a relationship between gut microbiota and the cognitive symptoms associated with schizophrenia, through the impairment of memory when treated with SubPCP and the alleviation of these impairments when antibiotics were given. This supports, at least in regard to cognitive impairment, gut microbiota play a role in schizophrenia. However, no inflammatory pathways were implicated suggesting, as has been the case throughout this review, two separate processes may be present within the gut-brain axis.

After animal models suggested a difference in gut microbiota, research shifted to analyzing inflammation in the gastrointestinal tract of humans. Severance et al. (2013) examined markers of translocation of microbes across the gastrointestinal barrier which cause inflammation and a low-grade immune response. Researchers compared the levels of soluble CD14 (sCD14) and lipopolysaccharide binding protein (LBP), two markers of translocation in participants with schizophrenia as compared to healthy controls. The levels of sCD14 and LBP were compared to the level of C-reactive protein (CRP) as a means to measure the inflammation in the body. Schizophrenics were further separated into individuals that were experiencing their first episode while not taking antipsychotics and individuals that were experiencing their first episode while taking antipsychotics. Results showed that schizophrenic participants had
significantly higher levels of sCD14 and LBP as compared to controls. Results also showed that higher levels of sCD14 and LBP were significantly correlated with higher levels of CRP in schizophrenics (Severance et al., 2013).

This study was among the first to demonstrate the increase immune response and inflammation observed in Schizophrenia could be due to microbes in the gut. The heightened level of markers of translocation indicate individuals with schizophrenia most likely have a very different microbial gut environment as compared to controls. This study provided significant evidence for a role of the gut-brain axis in schizophrenia in humans and not just animals models of schizophrenia.

As previously mentioned when discussing bipolar disorder, Severance et al. (2016) examined the immune reaction to *Candida albicans* in participants with bipolar disorder, schizophrenia, and controls. Levels of antibodies in the blood were measured to determine the immune response to the native yeast *Candida albicans*. In addition, the cognitive functioning of schizophrenic participants was evaluated through the Repeated Battery for the Assessment of Neuropsychological Status (RBANS) as cognitive impairment is a well-known symptom of schizophrenia. The RBANS measures cognitive function through attention, language, visuospatial/constructional abilities, and memory. Male schizophrenic participants had heightened levels of antibodies as compared to controls. There was no significant difference between the groups of females, but the level of antibodies found in all female participants was equivalent to the levels observed in male schizophrenic participants. The researchers explained the heightened levels in females by the higher probability of a yeast infection in females as compared to males. Females will already have heightened levels of antibodies due to the yeast infections and not the presence or absence of schizophrenia. Results showed the levels of
antibodies was associated with cognitive impairment in schizophrenic females despite the lack of significant difference between the groups (Severance et al., 2016).

As was the case with bipolar disorder, the heightened response to *Candida albicans* is symbolic of a microbiotic dysbiosis present in schizophrenic individuals (Severance et al., 2016). This dysbiosis indicates a different microbial gut environment is present in schizophrenic individuals that is not present in healthy individuals. This varied gut environment could play a role in schizophrenia either independently or through the inflammatory response caused by the microbes in the gut.

A study conducted by Schwarz et al. (2016) compared the microbiota present in the fecal matter of those experiencing their first episode of psychosis, FEP, and controls. While the participants experiencing psychosis were not diagnosed as schizophrenic, their symptoms were comparable as they experienced delusions and hallucinations. In terms of families of bacteria, FEPs had increased levels of *Lactobacillaceae, Halothiobacillaceae, Brucellaceae,* and *Micrococcineae* with decreased levels of *Veillonellaceae*. The strongest association between FEP and difference in bacteria abundance was with *Lactobacillaceae*. There was a positive correlation between *Lactobacillaceae* abundance and severity of symptoms and negative correlation between abundance and global assessment of functioning (Schwarz et al., 2016). Unfortunately, these findings were not supported by later studies focusing on those diagnosed with schizophrenia.

Shen et al. (2017) compared the microbes present in the fecal matter of schizophrenics and healthy controls. The phylum of *Proteobacteria* was more abundant in schizophrenics as compared to healthy controls. The abundance of *Succinivibrio, Megasphera, Collinsella, Clostridium, Klebsiella,* and *Methanobrevibacter* were significantly higher in Schizophrenic
participants as compared to healthy controls. On the contrary, *Blautia*, *Coprococcus*, and *Roseburia* were significantly more abundant in healthy controls as compared to Schizophrenics. The researchers note that *Collinsella* has been shown to be related to pro-inflammatory cytokines (Shen et al., 2017).

The study demonstrates a role of microbiota in schizophrenia, however the mechanism is still unclear. While one bacteria, *Collinsella*, has been linked to inflammation, other microbiota help discriminate between Schizophrenics and controls, the mechanism of action of which are not fully understood. So, while there is evidence to support the microbiota interact with inflammatory pathways to create the symptoms, one cannot be fully certain as the other possibilities have not been fully explored.

**Treatment**

Many studies have examined the use of probiotics as a treatment option for schizophrenia. Initial studies focused on probiotics as a supplement in addition to normal treatment methods as a way to control some of the more disturbing GI symptoms but then as more research supported the idea of microbiota playing a role in schizophrenia, studies shifted to focus on probiotics as the sole treatment procedure.

In 2014, Dickerson and colleagues compared schizophrenics who received probiotic treatment to those that received a placebo in order to test probiotics as a way to treat the GI distress associated with schizophrenia. Participants receiving probiotics did indeed see a decrease in their gastrointestinal problems but no notable difference was observed in terms of psychiatric symptoms, given that all participants were currently receiving antipsychotic medication this was not surprising (Dickerson et al., 2014).
This study was the first study exploring the effect of probiotics on any symptom associated with schizophrenia. While it did not focus solely on psychiatric symptoms, it did illustrate that probiotics could be used as a form of treatment for schizophrenia and opened the door to explore probiotics as a treatment for the psychiatric symptoms.

To study the immunomodulatory effects of probiotics in those with schizophrenia, Tomasik et al. (2015) compared the serum proteins in Schizophrenics who received a probiotic supplementation in addition to their antipsychotic medication to the proteins of schizophrenics who received a placebo in addition to their antipsychotic medication. Those that received the probiotic treatment showed decreased levels of Willebrand factor, monocyte chemotactic protein-1, T-cell-specific protein RANTES, and macrophage inflammatory protein-1 beta. BDNF was increased in the probiotic treatment group. Willebrand factor, monocyte chemotactic protein-1, T-cell-specific protein RANTES, and macrophage inflammatory protein-1 beta are released by the immune system in response as they either have anti-inflammatory properties or aid in the healing of a physical wound. Thus, the decreased presence of these in individuals treated with the probiotic reflect the reversal of the heightened inflammatory response caused by the schizophrenia. BDNF is related to antidepressant effects in the hippocampus as well as neural survival and synaptogenesis. BDNF is usually decreased in schizophrenics. The increase in BDNF through the treatment implies the effects of the probiotic reach the brain through the gut-brain axis. Again, there were no psychiatric effects as all participants’ symptoms were managed with their antipsychotic medication (Tomasik et al., 2015).

These results express the strongest support for the interaction between gut microbiota and inflammatory pathways not only in schizophrenia, but across all discussed diseases, as well as an independent mechanism of microbes. The probiotics acted through the gut microbiota to
decrease inflammation throughout the body. The probiotic was also related to an increase in BDNF, a chemical in the brain that helps with neural activity. Unlike other studies, the mechanisms of action were fully understood and discussed. It would be interesting to see how the reduction of inflammation would affect symptoms if the study were to be replicated using drug-naïve individuals.

Severance et al. (2017) finally viewed probiotics as an entire treatment plan, focusing on gastrointestinal symptoms and psychiatric symptoms. This study not only compared probiotics to placebos, it also compared males and females. Males that received the probiotic had decreased levels of *Candida albicans*, a common yeast species found to be associated with gastrointestinal distress, which was associated with few gastrointestinal issues. The results also hinted at a relationship between levels of *Candida albicans* and severity of positive psychiatric symptoms in males, with higher levels of *Candida albicans* being associated with the most severe symptoms. Males that received the probiotic did indeed have decreased severity of positive symptoms as their levels of *Candida albicans* decreased as well. The female results were inconclusive, the researchers supposed this was due to increased susceptibility to yeast infections in females as compared to males (Severance et al., 2017).

This was the first study to look at probiotics as a full treatment procedure that could address psychiatric as well as physical symptoms of schizophrenia. While the data were only significant for males, there is reason to believe that choosing to examine a different type of organism, instead of yeast, that women will also see significant improvements in their symptoms. This treatment also supports a role of microbiota in schizophrenia, both physically and psychologically. While the mechanism is not fully understood, the success of the treatment does
indicate pathways between the microbiota in the gut and the brain in the gut brain axis. Further replication of the study is needed to fully understand how the probiotics work in the body.

While research regarding the relationship between gut microbiota and schizophrenia is very new, it is clear a relationship between the two does indeed exists. In rat models, the fecal microbiota of rats that were in an induced state of schizophrenia was significantly different from that of rats that were controlled. Furthermore, correction of the gut disturbance with antibiotics alleviated the symptoms in rats (Jorgensen et al., 2014). There are several differences between the microbiota found in the fecal matter of schizophrenics and controls (Schwarz et al., 2016, Shen et al., 2017). Research regarding probiotics as a treatment option for Schizophrenia have shown probiotics to treat all symptoms of schizophrenia, physical, immunological, and psychology (Dickerson et al., 2014, Severance et al., 2017). It seems, unlike depression, the interactions that occur between the gut microbiota and brain are mediated by the inflammatory pathways in the immune system. This strong association was also seen in research focusing on bipolar disorder. This could be, however, due to the novelty of the field and the association between only the microbiota and the brain just has not been fully explored through research. Perhaps as time progresses and the field grows, a clearer image of the relationship between schizophrenia and gut microbes will be visible.

Discussion

It is clear gut microbiota play a role in depression, bipolar disorder, and schizophrenia, however the mechanisms of which differ slightly between the three disorders. While the mechanisms are not all fully understood, especially in bipolar disorder and schizophrenia, it is important to remember this field is still very new and growing.
The microbiota-inflammasome hypothesis for depression was somewhat supported by the current literature. While it was clear that some gut microbiota interacted with inflammatory pathways to cause the symptoms of depression, other microbiota still produced the same symptoms without interaction with inflammatory pathways. Treatment options have been found to be successful without acting upon inflammatory pathways and acting solely upon microbiota present in the gut. While there is evidence to support the interaction between gut microbes and inflammatory pathways, there is evidence to suggest this is not entire story. The hypothesis should be expanded to include that microbiota may act upon the brain independent of inflammatory pathways.

The limited research available on bipolar disorder painted a different picture from depression. There was a much stronger association between inflammatory pathways and microbiota within the literature as compared to microbiota acting alone. These findings make sense as the immune system plays a very large role in the symptoms of bipolar disorder outside of the gut, so for the same processes to be present within the gut is not very surprising. It is possible, however, that as more research is performed there may be more evidence that microbiota act alone as well, as is the case with depression. Most research available now is geared toward the interaction between inflammatory pathways and microbes because of the findings surrounding the role of the immune system outside of the gut.

Most research surrounding schizophrenia has been focused in a similar way to research on bipolar disorder, with an emphasis on the interaction between gut microbiota and inflammatory pathways due to the large role of the immune system in schizophrenia. Research may not be performed yet focusing on the independent role of gut microbiota on the brain in schizophrenia. The only relatively understood mechanism of action between the gut and brain in
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schizophrenia is through inflammatory pathways but this does not mean it is the only pathway. For example, it might be of interest to explore the relationship between microbes and dopamine in schizophrenia. The dopamine hypothesis is one of the prevailing hypotheses in schizophrenic research and states that the positive symptoms of schizophrenia can be explained by overactive dopamine D2 receptors in the subcortical area of the brain and limbic system while negative symptoms and cognitive impairment can be explained by underactive D1 receptors in the prefrontal cortex (Toda & Abi-Dargham, 2007). A study by Xue et al. (2018) found that after gut microbes were removed from the gut through antibiotic treatment, dopamine synthesis was significantly reduced in participants suffering from hepatitis. While the study did not examine this relationship in schizophrenic it provides evidence that gut microbes may influence dopamine production in the brain. If this relationship can be demonstrated in schizophrenic individuals, a new hypothesis concerning the relationship between microbes and the gut through the production of dopamine could be published. The hypothesis could detail how the different microbial gut environment of schizophrenic individuals effects the production of dopamine in their brain which could contribute to their positive symptoms, negative symptoms, or cognitive impairment.

Much more research is performed focusing on depression as compared to bipolar disorder and schizophrenia in regard to the role of gut microbes in the disorder. As previously mentioned this is most likely due to the significant difference in size of the population that is affected by depression as compared to bipolar disorder and schizophrenia. Hopefully as the field progresses and grows, more research will focus on bipolar disorder and schizophrenia. Across all three mood disorders, there is a clear relationship between gut microbiota and the brain through inflammatory pathways that act both within and outside of the gut. Likewise, for all three disorders, treatments that target these microbiota, like probiotics, have proven successful in
alleviating symptoms without as many negative side effects as more traditional methods of
treatment. As the field progresses it would be interesting to see if biomarkers could be developed
for each mood disorder to allow for a more empirical, less error prone method of diagnosis.
References


