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The Human Gut Microbiome A Focus on Health and Disease with Relevance to Neuropsychiatric Disorders

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Abstract

The gut microbiome consists of a complex amalgamation of diverse bacterial species in the human gastrointestinal (GI) tract. Proliferation and normobiosis of bacteria are dependent on the nutrient intake supplied by the host, intra-and-inter metabolite signaling, crosstalk between neighboring species and environmental signals, and cues based on the geographical location along the GI tract. With the recent explosion of gut microbiome research, several research groups have identified and elucidated the critical role gut-metabolites play in modulating an individual's normal physiology and/or contribute to several diseased states, including neuropsychiatric disorders such as Major Depressive Disorder (MDD), and Generalized Anxiety Disorder (GAD) and neurodegenerative disease such as Parkinson's Disease (PD) and Alzheimer's Disease. The purpose of this review is to systematically identify recent advancements of major bacteria phyla such as *Baceteroidetes* and *Firmicutes* and its relevant genus and species in health and disease, and how some of the specific metabolites produced by the respective genus and species may mediate neuropsychiatric disorder. Further exploration of such metabolites and its dominant bacterial species may provide innovative areas for research and potential novel targets for therapeutics.

***Abbreviations**:*
Parkinson's Disease (PD), Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), gamma amino butyric acid (GABA), Human Microbiome Project (HMP), gastrointestinal (GI), Selective Serotonin Reuptake Inhibitor (SSRI)

2. Introduction

The gut microbiome is an exception to the common phrase that the whole is greater than the sum of its parts. The microbiome is established early in life and this dynamic relationship between the microbial flora and its host are subjected to environmental triggers and certain genetic predisposition which influence the microbiome and thus in-turn influence the overall health status of host. Therefore, in understanding this symbiotic relationship between the microbiome and host, comprehension of the dominant microbiota and its metabolites may provide insight into the pathogenesis of some diseases and expose avenues for therapeutic intervention. It is the

purpose of this review to compile the major bacterial species and genera within the gut microbiome to date, and to identify the metabolites they produce with the best of our knowledge. Furthermore, this review seeks to identify gaps and challenges in current literature, which may provide insight into the therapeutic targets in gut microbiome.

3. The Gut Microbiome

The human gastrointestinal tract is inhabited by a diverse assortment of organisms including bacteria, fungi and viruses. The composition of such microorganisms, within the gastrointestinal system are collectively known as the "gut microbiome." To understand the complex role of the microbiome NIH in early 2007, conducted a major study known as the Human Microbiome Project (HMP) to identify and map the microbial ecosystem in order to elucidate its role in health and disease. Identification and classification of species within the human gut have been carried out by through two primary sequencing methodologies, shotgun and 16S amplicon sequencing(ref.). With the data generated by HMP, researchers around the globe have been able to identify numerous microorganisms involved in pathogenesis of several diseases.

Bacteria are the predominant microorganisms in the human microbiota coexisting in a nearly 1:1 ratio in regard to human cells (1). In total, there are nearly 1000 different species of bacteria in the gut microbiome (2). The microbiome, once established early in life, tends to remain relatively constant however its composition is not static (3). The gut microbiome exhibits inter-individualistic differences and is also subject to divergence from the core microbiome over time due to factors such as: diet or dietary change, diseased state, and/or use of medication. This microbiome has been implicated in host-microbes' metabolic functions, protection from pathogens, and education of the immune system (2). One landmark study determined the major components of the gut microbiome to be from five bacterial phyla: *Bacteoridetes, Firmicutes, Actinobacteria, Proteobacteria,* and *Verrucomicrobia* (7). Of particular interest, are the two major phyla, which were identified in that study; *Baceteroidetes* and *Firmicutes,* which comprised approximately 90% of the gut microbes (7). In this review, these phyla will be the subject of analysis for available knowledge on metabolic function, and its role in neuropsychiatric disorder.

4. Inclusion Criteria

Two phases were utilized during this literature review. During the first phase, the designated phyla of bacteria were determined by the reports from Arumugam et al., in 2011 along with other concurring reports (7-11). After determining the major phyla, bacteria were further taxonomically organized based on *Bergey's Manual of Systematic Bacteriology* Volume 3 and Volume 4, with additional cross-referencing with NCBI's taxonomy database and the list of prokaryotic names with standing in nomenclature database. Furthermore, reported species were then compared to the International Code of Nomenclature of Prokaryotes to determine species, which have been accepted as valid. Only species which were considered valid were reported in this review. Minor amendments were also made based on updates to the species and categorizations performed since that publication in other relevant literature. The complete list of explored genera are composed in Figure 1.

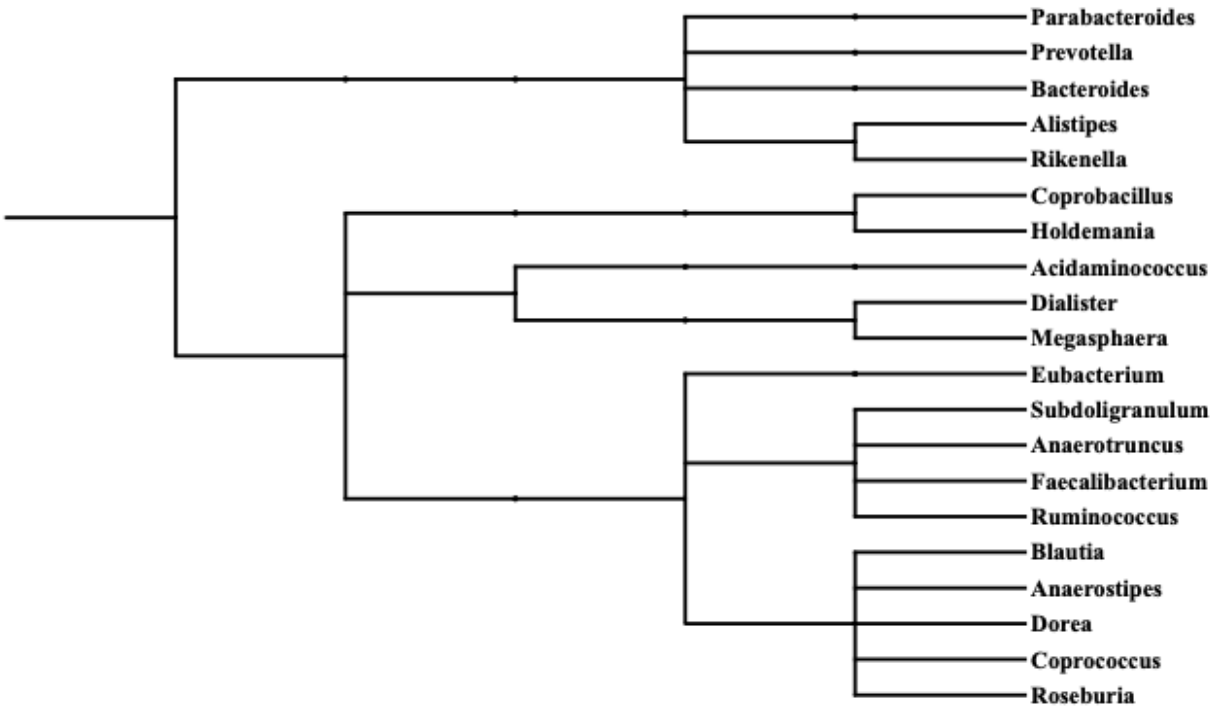

Figure 1. Phylogenetic tree of genera explored in this review. The two initial nodes represent the divergence of bacterial organisms within the phyla Bacteroidetes and Firmicutes, respectively. The terminal branches indicate the genera of bacterial organisms under exploration.

Search words included taxonomic organization, genus then species, the phrase "gut microbiome," and finally the taxonomic organization again in quotations. For example: "*Bacteroides vulgatas* 'gut microbiome' '*Bacteroides vulgatas.'"* A time range between 2005 and 2019 was set. Abstracts of publications matching those keywords were then screened for each matching key word. Each species was then characterized by the amount of resources devoted to its understanding. Search results greater than 100 in the last 15 years were considered abundant, whereas less than 100 search results in the last 15 years were considered sparse.

The second phase of this review targets dysbiosis of the major bacterial phyla involved in neuropsychiatric disorder and neuroinflammatory processes. Key words used in order to yield those articles included the genus of the bacteria as in phase one, then the disease or disorder, so that it appeared as follows "Genus Disease 'Disease'." The diseases and disorders included in the search were generalized anxiety disorder, major depressive disorder, and Parkinson's disease. A similar method was utilized in order to obtain search results for metabolites/molecules associated with the aforementioned pathologies. Those metabolites/molecules include serotonin, epinephrine, norepinephrine, dopamine, GABA, kynurenine, and glucuronic acid.

Finally, species of bacteria in the two major phyla that did not yield significant search results were not reported. Furthermore, genera that contained only one species, which yielded sparse search results were also excluded. For example, the genera Xylanibacter and Rikenella were not reported. However, it should be stated that they did receive exploration throughout this review.

5. Composition of the Gut Microorganisms

The gut microbiome is home to a variety of bacteria, which reside in the series of hollow organs spanning from the oral cavity to the anus. There is abundant evidence supporting a few dominant phyla within the gastrointestinal tract (7-11). Those dominant phyla include Bacteroidetes and Firmicutes, which compose, on average, 90% of gut microbiota. However, this statistic alone does sufficiently elucidate the gut microbiome composition. Bacteroidetes may vastly outnumber Firmicutes, or *vice versa,* depending on demographic and geographic factors such (11).

Furthermore, Bacteroidetes composition appears to exhibit inter-individual variation; whereas the Firmicutes appear to vary over time within individuals (8).

Although Bacteroidetes and Firmicutes are the dominant phyla, further diversity within the gut microbiome is promoted by a variety of factors. For instance, Bacteroidetes and firmicutes may compete for the same available resources, thus limiting dominance of other at the specific location. Another common phenomenon involves certain bacteriophages that play a vital role in inhibiting the growth of certain species in the human body (5). Regional conditions of the gastrointestinal tract also serve as selective pressures, which determine what microorganisms flourish. The duodenum is subjected to exposure to rapidly changing pH, digestive enzymes, bile, as well as varying levels of oxygen suggesting predomination of genera such as *Lactobacillus, Eubacterium,* and *Streptococcus* in the duodenum (12). In comparison, this composition changes somewhat in the jejunum and ileum where microaerophilic strains such as *Enterococcus, Lactobacillus, Streptococcus,* and *Gammaproteobacteria*, are more common (12,13). The large intestine is mildly acidic with stable pH and it is also a predominantly anaerobic therefore supporting the growth of obligate anaerobes strains such as *Bacteroides, Prevotella, Rikenella, Lachnospiracae,* and *Ruminococcus* (14).

5.1 Bacteroidetes

The taxonomic organization of the Bacteroidetes phylum has been subject to change in the last twenty years with the development of novel classification techniques. According to *Bergey's Manual of Systematic Bacteriology,* the Bacteroidetes phylum is composed of four Gram-stain-negative, rod-shaped classes. It includes: *Bacteroidia, Flavobacteriia, Sphingobacteriia, and Cytophagia* (15). *Bacteroidia* itself has five families, classified in the order *Bacteroidales,* those families include *Bacteroidacea, Rikinellaceae, Porphyromonadaceae, Prevotellaceae,* and *Marinilabiliaceae* (15). Recent work determining the composition of the gut microbiome determined the most common bacterial genera of the small intestine. Those genera included the *Bacteroides, Parabacteroides, Alistipes,* and *Prevotella* (9, 11). Of the samples obtained by Arumugam et al, the *Bacteroides* genera were disproportionately more abundant than any other genus within that phylum (9). However, one recent study showed that this relationship may be

expected as *Prevotella* and *Bacteroides* are, to some extent, antagonistic to one another. For example, mice were colonized by *Prevotella copri, Bacteroides thetaiotaomicron,* or both species. Individually, *Prevotella copri* and *Bacteroides thetaiotaomicron* flourished, but when combined in the same environment, populations decreased for both species (16).

5.1.1 Bacteroides

The *Bacteroides* genus is the largest of the genera constituting the family *Bacteroidacea* (15). It is comprised of >10 species of anaerobic, nonmotile, saccharolytic bacteria (15). Multiple sources have found *Bacteroides vulgatus*, *Bacteroides thetaiotaomicron*, *Bacteroides coprocola, Bacteroides caccae*, *Bacteroides uniformis*, *Bacteroides fragilis*, *Bacteroides eggerthii*, and *Bacteroides massiliensis, Bacteroides pyogenes*, *Bacteroides salyersiae*, and *Bacteroides nordii* were detected in stool samples (16,17). Of those found, the predominant species appeared to be *Bacteroides vulgatus*, *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, and *Bacteroides caccae* (17,18). However, it should be noted that individual variation in diet, such as increased fiber intake, vegan, vegetarian, or omnivorous may account for some discrepancies (18-20). Furthermore, differences in location of samples may also account for individual differences in *Bacteroides* species (20). *Bacteroides eggerthii,* among other species of bacteria, has also been implicated in the development of colitis in mouse models (21). *Bacteroides fragilis* and *Bacteroides thetaiotamicron* have also been the subject of study in regard to promoting intreaepithelial lymphocytes in the epithelial lining of the colon (22).

5.1.2 Alistipes

The *Rikenellaceae* family contains the genera *Alistipes* and *Rikenella. Alistipes* can be further classified into eight species of nonmotile, Gram-negative rods, which are obligate anaerobes (15). Those species are listed in Table 1.

As a whole, *Alistipes* have been of some interest in studying gut microbial composition in obesity patients, and *Alistipes* may play a role in ease of weight loss (23). Increased levels of *Alistipes* have also been identified in relation to MDD (24). However, current literature on specific species of *Alistipes* is more limited. For example, available publications for *Alistipes putredinis* seem to only identify its presence in stool samples (25, 26) or being used as a

reference genome. *Alistipes finegoldii* has recently been implicated as a colitis-protecting species within the gut microbiome of mice (21). *Alistipes onderdonkii* has also been the subject of interest as it has been shown to promote intraepithelial lymphocyte production (22). *Alistipes shahii* has been correlated with increased species richness, as well as elevated fruit consumption (27).

5.1.3 Prevotella

The family *Prevotellaceae* contains two genera, *Prevotella* and *Xylanibacter* (15). The family can be further subdivided into >20 anaerobic, rod-shaped, saccharolytic species indicated in Table 1.

Review of the available literature showed that specific roles of species in health and disease is limited to a small pool of species. However, information regarding the genus *Prevotella* is more abundant. As a whole, *Prevotella* has been implicated in obesity and weight loss, as a reduction in *Prevotella* may also be related to ease of weight loss (23). *Prevotella* has also been reported to primarily inhabit mucosal sites, such as the oral cavity, respiratory tract, and the gastrointestinal tract. Given its diverse nature, *Prevotella* appears to have a "finger in every pie." Recent studies and literature reviews have focused on the role of *Prevotella* in mediating an immune response resulting in inflammatory diseases such as rheumatoid arthritis, periodontitis, bacterial vaginosis, asthma, COPD, and inflammatory bowel disease (28, 29, 30). For example, a recent study on Chinese subjects showed increased levels of *Prevotella melaninogenica* and *Prevotella copri* have both been associated with the development of Ankylosing Spondylitis (31). *Prevotella copri* has also been strongly associated in the exacerbation of colitis in murine models and the onset of untreated rheumatoid arthritis (29). The topic of rheumatoid arthritis and *Prevotella* yielded a wealth of information. HIV was also associated with increased prevalence of specific lineages of Prevotellaceae, *Prevotella stercorea* and *Prevotella coprii* (32). During the course of this review a multitude of species of *Prevotella* were implicated in the oral microbiome and development of disease, such as *Prevotella pallens, Prevotella maculosa,* and *Prevotella buccalis* to name a few (33, 34).

5.1.4 Parabacteroides

Multiple species from *Bacteroides* have been relocated to the more appropriate family *Porphyromonadaceae.* This family is characterized as predominantly anaerobic, saccharolytic, nonmotile, gram-negative rods (15). *Porphyromonadacea* is composed of eight genera including: *Porphyromonas, Barnesiella, Dysgonomonas, Paludibacter, Petrimonas, Proteiniphilum, Tannerella,* and *Parabacteroides* (15). Of interest is the *Parabacteroides* genus, which is comprised of eight species of bacteria listed in Table 1.

Parabacteroides distasonis has received significantly more attention than any of the other species. *Parabacteroides distasonis* has been implicated in playing a role in reduction of cytokines in murine models of acute and chronic colitis induced by dextran sulphate sodium (35). However, another recent study reported that *Parabacteroides distasonis* may play a role in promoting colitis (21). *Parabacteroides goldsteinii* has also been of some interest, with a few recent studies aimed on the role of *Parabacteroides goldsteinii* in obesity and hepatitis. For example, one study determined that the oral administration of *Parabacteroides goldsteinii* to high-fat-diet mice resulted in increased adipose tissue thermogenesis (36). Furthermore, this bacterium was correlated with reduced inflammation and improved insulin sensitivity (36). It is possible that if underlying mechanisms are elucidated in this process, that it may be of some use in maintenance of obesity, colitis, or even diabetes mellitus. *Parabacteroides johnsonii* research is also abundant and diverse. One study focused on the effects of administration of Resveratrol on glucose homeostasis and gut microbial composition (37). Those results showed that the level of *Parabacteroides johnsonii* were reduced, along with an alteration in the *Bacteroidetes* to *Firmicutes* ratio (37). Another study observed the differences in the gut microbiome of subjects with alopecia aureate, in which enriched levels of *Parabacteroides johnsonii,* among other non-*Parabacteroides* species, were detected (38). The study of *Parabacteroides merdae* has been diverse and abundant as well. Studies on *Parabacteroides merdae* have ranged from enzymatic analysis, to its effects on hypertension, and to a review on its relation to the ketogenic diet in seizure patients (39-41).

Phylum	Genus	Species	Associated Literature
Bacteroidetes			
	Bacteroides	*vulgatus*	16, 17, 18
		thetaiotamicron	16, 17, 18, 22
		coprocola	16, 17, 114
		caccae	16, 17, 18
		uniformis	16, 17, 18
		fragilis	4, 6, 16, 17, 18, 22
		eggerthii	16, 17, 21
		massiliensis	16, 17, 114
		pyogenes	16, 17
		salyersiae	16, 17
		nordii	16, 17
	Alistipes	*putredenis*	25, 26
		finegoldii	21
		onderdonkii	22
		shahii	27
		ihumii, indistinctus, inops, timonensis	Scarce results
	Prevotella	*pallens*	33, 34
		melaninogenica	31
		coprii	16, 29, 31, 32, 114
		buccalis	33, 34
		maculosa	33, 34
		stercorea	32
		veroralis, albensis, denticola, multiformis, corporis, disiens, aurantica, falsenii, intermedia, nigrescens, bergensis, oris, salivae, bryantii, multisaccharivorax, baroniae, buccae, dentalis, enoeca, pleuritidis, tomonensis, loescheii, shahii, brevis, ruminicola, amnii, bivia, dentasini, fusca, jejuni, marshii, nanceiensis, oryzae, oulorum, paludivivens, saccharolytica, scopos	Scarce results
	Parabacteroides	*merdae*	39, 40, 41
		distasonis	35
		goldsteinii	36
		jhonsonii	37, 38
		gordonii, chartae, chichillae, faecis	Scarce results

Table 1. Compiled list of the species within each genera of the Bacteroidetes. Each genus and its respective species explored in this review. Each species has associated literature compiled, unless otherwise indicated by "scarce results."

5.2 Firmicutes

The Firmicutes phylum has also been subject to change in the last decade, having previously been comprised of three classes, according to *Bergey's Manual of Systematic Bacteriology* Volume 3. These three classes included: Bacilli, Clostridia, and Erysipelotrichia (42). However, four more additions to the class have been made since that publication. Those classes were obtained from the NCBI Taxonomy Browser and include: Negativicutes, Limnochordia, Thermolithobacteria, and Tissierellia. The majority of these classes are gram positive, though a few exceptions are made (42). Bacilli is further subdivided into the orders: *Bacillales* and *Lactobacillales*. *Lactobacillales* is comprised of six families, of which focus will remain on a specific subset. Importantly, *Lactobacillales* contains the family *Streptococceae,* which includes the genera *Streptococcus, Lactococcus,* and *Lactovum.* Based on the study performed by Arumugam et al., 2013, focus will be placed on *Streptococcus,* along with: *Faecalibacterium, Roseburia, Blautia, Coprococcus, Ruminococcus, Eubacterium, Dorea, Subdoligranulum, Anaerostipes, Holdemania, Anaerotruncus, Acidaminococcus, Megasphaera, Dialister,* and *Coprobacillus* (9).

The class Clostridia is further subdivided into the orders: *Clostridiales, Halanaerobiales,* and *Thermoanaerobacterales.* Of significance, the *Clostridiales* order is comprised of the *Ruminococcoceae*, *Lachnospiriceae,* and *Eubacteriaceae* families. Within the *Ruminococcaceae* family are the genera *Faecalibacterium, Ruminococcus, Subdoligranulum,* and *Anaerotruncus*. Within the *Lachnospiriceae* family is *Roseburia, Blautia, Coprococcus, Dorea, Anaerostipes,* Within the *Eubacteriaceae* family is the genus *Eubacterium.*

Erysipelotrichia is composed of the order *Erysopelotrichiales,* which is further made up of the family *Erysopelotrichaceae*. Importantly, this family contains the genera *Coprobacillus* and *Holdemania.*

The class Negativicutes is comprised of three orders: *Acidiminococcales, Selenomonadales,* and *Veillonellales.* Particular attention will be made to the orders *Acidiminococcales* and *Veillonellales. Acidiminococcales* is importantly composed of the family *Acidiminococcaceae,*

which contains the genus *Acidiminococcus. Veillonellales* contains the family *Veillonellaceae*, which contains the genera *Megasphaera* and *Dialister.*

5.2.1 Faecalibacterium

The genus *Faecalibacterium* is composed of nonmotile, strictly anaerobic, rod shaped cells of varying length, some of which are gram negative staining (42). This genus contains one species, *Faecalibacterium prausnitzii.* However, as the sole species of its genus this bacterium has garnered significant attention in gut microbiome. *Faecalibacteirum prausnitizii* is widely regarded as the most prominent bacteria in the gastrointestinal tract, accounting for approximately 5% of faecal microbes (43). This statistic has been supported by another study, which proposed that the abundance and transcriptional activity of *Faecalibacterium prausnitzii* appears to be more important than the mere presence or absence of that species (44). Publications in this time range tend to focus on the role of *Faecalibacterium prausnitzii* in production of butyrate and inflammatory processes. This metabolite has been implicated as an anti-inflammatory in the colonic mucosa (45); as such *Faecalibacterium prausnitzii* has been subject to study in inflammatory processes such as irritable bowel disease (44, 46). More specifically, *Faecalibacterium prausnitzii* was shown to have a protective effect against development of Crohn's disease in murine models via blockage of NF- KB and IL-8 (47).

5.2.2 Ruminococcus

The genus *Ruminococcus* is classified as strictly anaerobic, chain-forming cocci, which are gram-stain-positive in some cases and gram-stain-negative in many cases (42). *Ruminococcus* contains eleven species, which are listed in Table 2.

Much of the work on species of *Ruminococcus* has focused on the role that *Ruminococcus albus, Ruminococcus flavifaciens,* and *Ruminococcus champanellensis* species play in digestion of complex polysaccharides such as cellulose (48, 49). This cellulolytic action aids in the continual recycling of the most abundant biopolymer in nature, which explains why many resources have gone into the understanding of these species. Other species of *Ruminococcus* are non-cellulolytic, such as *Ruminococcus bromii. Ruminococcus bromii* has also been focused on for its

role in degradation of starch in the human GI tract. *Ruminococcus bromii* has been shown to degrade starches that are typically resistant to degradation earlier in the GI tract, as well as improve the ability of other species of starch-digesting species of bacteria to digest resistant starches (50). Furthermore, this species has been shown to increase in abundance to exposure to resistant starches (51). *Ruminococcus gnavus* has been the subject of study in Crohns disease and Ulcerative Colitis (52). The abundance of this species in these diseases may be related to its ability to affect mucin expression in the intestines of mouse and human models, as well as utilize mucin-derived glycans for metabolic purposes (53-55). Another study found that *Ruminococcus gnavus* appears to be more aerotolerant than its classification may suggest (55). These reports may be two sides of the same coin, as increased mucin expression by intestinal goblet cells may protect the bacteria from the reactive oxygen species involved in IBD as well as providing an ample growth medium. However, studies have not yet shown whether the abundance of *Ruminococcus gnavus* is coincidental or incidental to the worsened disease state. Thus, further investigation is required. Of interest, one publication determined that the amplification of RNA derived from *Ruminoccocus gnavus* was significantly greater than that of other indicated species in Crohns disease and IBD (44). Thus, small changes in the abundance of *Ruminoccocus gnavus* in the intestine may have greater effects than other species (44). Similar to *Ruminococcus gnavus, Ruminococcus torques* is a mucin-degrading bacterial species, which has been implicated in subjective, worsened symptom reports by individuals with IBD (56). *Ruminococcus torques* has also received some attention in regard to its ability to produce butyrate, and in one study was shown to have reduced abundance in Crohns disease subjects (57). *Ruminococcus lactaris* search results were abundant, however, multiple mentions of the phrase "*Ruminococcus lactaris"* were in passing or in regard to a species that bore resemblance to *Ruminococcus lactaris. Ruminococcus faecis* shares a similar story, although it has received some attention due to its isolation from the human gut (58).

5.2.3 Roseburia

Roseburia is a genus composed of five slightly curved, rod-shaped, gram-negative or gram-variable, motile, obligate anaerobic species, which are also known to hydrolyze starch (42). The five species, which can be found in Table 2. As a whole, these species have received moderate

attention due to their role in the production of the short chain fatty acid, butyrate (58, 59). Given this reputation, these species have been the subject of multiple studies.

One recent study sought to understand factors that can affect the Firmicutes to Bacteroidetes ratio via administration of a whole-grain barley vs brown rice diet (58). The results of that experiment showed a gradual increase in both the *Roseburia faecis* and *Roseburia intestinalis* species, among other Firmicutes (58). This point serves to show that the gut microbiome is not static, and changes in diet may alter the normal gut microbiome ratio. Furthermore, *Roseburia faecis* has been shown to produce a bacteriocin-like substance against *Bacillus subtilis*, which may allow it to successfully compete with other bacteria in the intestines of its host (60).

Roseburia hominis was recently determined to affect host gene expression in the innate immune system, the gut barrier, and T cells of murine models (61). More specifically, *Roseburia hominis* was shown to upregulate gene activity in *Roseburia hominis* mono-colonized mice (61). Furthermore, *Roseburia hominis* levels have been shown to be reduced in subjects with IBD (61). That reduction of the gut barrier-promoting bacterial species could bely an effect on the severity of IBD (61). Of interest, search results for *Roseburia hominis* yielded a patent for production of a probiotic used for modulating host immunity, satiety, and IBD, to name a few (62).

The extent of study of *Roseburia inulinivorans* appears to revolve around its role as a butyrate-producing bacterium (58, 59). One recent study, for example, showed that along with reduced levels of *Ruminococcus torques, Roseburia inulinivorans* abundance in the intestines of Crohns disease subjects was reduced in those with positive C reactive protein levels (57). Continuing with the theme of butyrate, *Roseburia intestinalis* is no exception. This species has been the focus of multiple studies regarding its ability to synthesize butyrate. In one study, *Roseburia intestinalis* colonization in murine models was shown to be a protective factor from atherogenesis (63). In that study, *Roseburia intestinalis* mice exhibited a 30% reduction in the area of atherosclerotic plaques (63). It was suggested that this reduction was mediated via the fourfold production of butyrate when compared to a core bacterial community (63). This species was also determined to be one of the major inhabitants of intestinal mucins, which may be due to

its possession of a flagella (64). Only one species yielded sparse search results, *Roseburia cecicola*.

5.2.4 Blautia

The genus *Blautia* is a relatively novel genus and has been met with some scrutiny. In this review, *Blautia* will be covered as though it was entirely accepted. This genus is composed of 13 species of bacteria, which are characterized as mostly Gram-positive, anaerobic, and coccobacillus shaped (65-69). The species included in this genus are listed in Table 2.

Information on specific species of *Blautia* is difficult to determine given the instability of the current acceptance of *Blautia.* Thus, available literature tends to look at *Blautia* on the genus-level, rather than on species level. As previously mentioned, there are some dominant bacteria in the human host, which may differ based on geographic location. In one study, researchers focused on the group *Clostridium coccoides* in a Japanese population, and the subgroups and species that compose it (69). That group has been reported to contain several genera, including *Eubacterium, Blautia, Clostridium,* and *Dorea,* to list a few. Fecal samples obtained from their subjects showed that the genus *Blautia* was the most common subgroup of intestinal microbes regardless of age (69). Furthermore, *Blautia* was also found to decrease in abundance with age (69). The species of *Blautia* included in that study were: *Blautia hydrogenotrophica, Blautia luti, Blautia obeum, Blautia schinkii, Blautia hansenii, Blautia producta,* and *Blautia coccoides* (69). This study also supported previous hypotheses that overall counts of *Clostridium coccoides* group between children and adults is relatively stable (69). However, it also seemed to oppose the idea that the gut microbiome is of a stable composition, since the *Clostridium coccoides* group diminished into later age (69). These results suggest that the gut microbiome is still subject to change throughout the human lifetime, which supports the need to further refine the study of stability of the populations of the gut microbiome depending on age. *Blautia hydrogenotrophica* has received some attention due to its ability to synthesize acetate from hydrogen (70). It may be speculated that this carbon-cycling activity within the host could contribute to the growth of species that utilize acetate. In contrast, it could also contribute to the loss of species that compete for the same resources, such as methanogens.

5.2.5 Coprococcus

Coprococcus is a genus composed of three species of bacteria characterized as nonmotile, obligately anaerobic, chemoorganotrophic, Gram-stain positive cocci (42). These bacteria include: *Coprococcus eutactus, Coprococcus catus,* and *Coprococcus comes.* Altogether, these species are known for their production of short chain fatty acids, such as butyrate, acetate, formic acid, and propionic acid (42).

Coprococcus eutactus has been studied for its varied presence, or decreased abundance, in subjects with IBS. *Coprococcus eutactus* has been shown to occur normally within the intestines of healthy control subjects compared with IBS subjects (71). Another recent study appeared to confirm this difference; *Coprococcus eutactus* was shown to have reduced abundance in subjects with IBS who also hosted *Ruminococcus torques* (56). As previously mentioned, *Ruminococcus torques* is a mucin-degrading species, thus it may occur in competition with *Coprococcus eutactus,* or subject to competition by another species of bacteria. Therefore, it may be worth investigating the localization of the *Coprococcus eutactus* to determine its abundance and dependence on mucin as well as its aerotolerance. One study suggested a relationship between Gram-negative bacteria and Gram-positive bacteria such as *Coprococcus eutactus.* In that study, *Bdellovibrio bacteriovorus,* a predator of Gram-negative bacteria, were introduced to rat models, which resulted in a gradual increase in the abundance of *Coprococcus eutactus* (72). However, that study was unable to determine the exact cause of the increase in that species. *Coprococcus catus* has been the subject of study in regard to its production of short chain fatty acids in multiple studies including its potential role in obesity of children, ability to survive and produce short chain fatty acids in varying pH, and possible effect on preeclampsia (73-75). *Coprococcus comes* also appears to have been subject to studies interested primarily in its role in the production of short chain fatty acids (76).

5.2.6 Dorea

The genus, *Dorea,* is composed of two species characterized as nonmotile, obligately anaerobic, chemoorganotrophic, Gram-stain positive rods (42). These bacteria include: *Dorea longicatena, Dorea formicigenerans.*

Dorea longicatena has received some attention, and this species is considered to have an abundance of information. Similar to other species of bacteria in different genera, *Dorea longicatena* has been the subject of study in regard to Crohns disease. This species was recently found to increase in abundance in the ileal mucosa of subjects experiencing Crohns disease remission (77). In another study, both *Dorea longicatena* and *Dorea formicigenerans* were implicated in cytokine activity; an abundance of these species was associated with elevated levels of interferon gamma in response to fungal-derived stimuli (78). As stated by those authors, the ability of *Dorea longicatena* and *Dorea formicigenerans* to metabolize sialic acid of mucins may be related to increased gut permeability (78).

5.2.7 Anaerostipes

Anaerostipes is a genus composed of four species of nonmotile, Gram-positive in exponential phase but not in the stationary phase, obligately anaerobic rods, which sometimes occur in chains of 2-4 cells (42). These species are also known to produce the short chain fatty acid, butyrate (42). These species can be found in Table 2.

Anaerostipes caccae has received the most attention within the genus *Anaerostipes.* One recent study utilized *Anaerostipes caccae* and *Akkermansia muciniphila* co-cultures to determine that mucin-degrading species can promote the growth of butyrogenic species by providing a nutritional supply (79). Furthermore, the presence of the *Anaerostipes caccae* induced changes in the expression of the mucin-degrading genes via upregulation of the response regulator Amuc_1010 (79). This study again highlights one of the many possible relationships that gut commensal bacteria can provide to other species and could elucidate the previously mentioned

increase in levels of *Ruminococcus gnavus*. *Anaerostipes hadrus* also has an abundance of information regarding its role as a butyrate-producing bacterium (41, 80).

Anaerostipes butyraticus was isolated in 2010 from the cecal content of a broiler chicken, which may contribute to the sparse results for this topic (81). However, this species has received some attention for its reputation as a "hyper-butyrate producer" (82). It seems likely that more attention will focus on this species and other producers of short chain fatty acids as more knowledge about the role of SCFA's in pathogenesis is elucidated.

5.2.8 Eubacterium

The genus *Eubacterium* is composed of >15 different species of bacteria, characterized as Gram-positive, obligately anaerobic, chemoorganotrophic rods (42). These species are also known to produce the short chain fatty acids butyrate, acetate, and formate (42). These species can be found in Table 2.

Eubacterium coprostanoligenes is well-known for its role in the reduction of cholesterol to coprostanol (83, 84). As such, it has been utilized in studies in order to determine its effects on hypercholesterolemia, as is the case with the series of studies of hypercholesterolemia by Li et al., 1995, 1996, and 1998. In the first study, rabbits received an oral administration of *Eubacterium coprostanoligenes,* which resulted in a significant decrease in the plasma cholesterol concentration (85). Furthermore, the hypocholesterolemic effect lasted for another 34 days after the last oral administration (85). However, the effect of oral administration of *Eubacterium coprostanoligenes* on cholesterolemia still appears to be somewhat unclear; as the follow-up studies determined that oral administration of *Eubacterium coprostanoligenes* to hens and murine models was unable to affect plasma cholesterol levels (86, 87). Current research on the pathways and the enzymes involved in this conversion are not fully elucidated. Furthermore, the impact on the formation of cholesterol-derived hormones; glucocorticoids, mineralocorticoids, androgens; and species capable of reducing cholesterol in the gut microbiome is a topic that has not seen much exploration (88).

Eubacterium limosum has been implicated as a species that increases in abundance throughout age, thus supporting the notion that the gut microbiome has a dynamic composition that may change with age. In that study, the abundance of *Eubacterium limosum* was determined to be 10-fold of that compared to the two younger groups (89). At this point in time, much work has been devoted to understanding the metabolic relationship between *Eubacterium ramulus* and dietary polyphenols, but *Eubacterium limosum* has also received some attention as well. However, studies of this topic have been confounded by the inability to control the host microbiome, as well as account for the variability in the host. One recent study focused on the role of *Eubacteirum limosum* and *Eubacterium ramulus* in the catabolism of polyphenols (90). *Eubacterium ramulus* was determined to have the capacity to metabolize the polyphenols Xanthohumol, 8-prenylnaringenin, and desmethylxanthohumol *in vitro* (90). Furthermore, *Eubacterium ramulus* utilizes the product 8-prenylnaringenin formed by *Eubacterium limosum* to create *O*-desmethyl-α,β-dihydroxanthohumol (90). This relationship also supports the cooperativity exhibited by species of bacteria, which occurs in the host.

The species *Eubacterium rectale* has received significantly more attention than any other species in the genus *Eubacterium.* This abundance may be, in part, due to the role of *Eubacterium rectale* in production of the short chain fatty acid butyrate (91). One recent study found that abundance of *Eubacterium rectale* increased in one group of subjects that were producing high amounts of butyrate in response to the gradual administration of a resistant starch diet (91). However, in another group of subjects deemed the “elevated” group, abundance of *Bifidobacterium adolescentis* and *Ruminococcus bromii* were found rather than the *Eubacterium rectale* (91). It is possible that this difference is due to the sample size, thus further exploration of this topic will be required.

Eubacteirum ventriosum has been found in association with obesity in multiple studies (92, 93). In a recent study on obese Japanese subjects, this species along with *Blautia hydrogenotorophica*, *Coprococcus catus*, *Eubacterium ventriosum*, *Ruminococcus bromii*, and *Ruminococcus obeum* were found to be associated with obesity (92). However, the directionality of this relationship was unable to be established. This again reinforces the need for continued study of these organisms and the effect on the development of disease. This study did

appear to confirm a previous association made in 2012 in a study performed on monozygotic twins (94). This study also determined that higher BMI twins had increased abundances of *Eubacterium ventriosum* and *Roseburia intestinalis* (93).

Although literature regarding *Eubacteirum eligens* and *Eubacterium siraeum* are considered abundant, the majority of the literature utilized the species as a representative species for *Eubacterium* or provided passing mention of the species. It is also likely that the inclusion of the phrase "gut microbiome" is including additional search results that are absent of the phrase "*Eubacterium eligens*" or "*Eubacterium siraeum.*"

5.2.9 Acidaminococcus

The genus *Acidaminococcus* is composed of two species of coccoid, Gram-negative, nonmotile, anaerobic, chemo-organotrophic cells (42). These two species include *Acidaminococcus fermentans* and *Acidaminococcus intestini.*

Of the aforementioned species, the most well-studied is *Acidaminococcus fermentans.* This species has received moderate attention for its role as one of the most prominent bacteria involved in the hydrolysis of amino acids (94, 95). This species was recently found to occur in abundance in fecal samples of subjects with ankylosing spondylitis, along with *Parabacteroides distasonis, Eubacterium siraeum, Acidaminococcus fermentans and Prevotella copri* (96). Although, aforementioned reports have suggested that *Prevotella copri* may exhibit an antagonistic response to *Bacteroides thetaiotamicron*. One may speculate that if such competition occurs in the gut microbiome, that the prevalence of another bacteria that is antagonistic to a competitor of *Acidaminococcus fermentans* may account for the increased abundance of this, or other, species.

5.2.10 Megasphaera

Megasphaera is a genus, which is comprised of nine species of obligately anaerobic, nonmotile, Gram-negative, short-chain-fatty-acid-producing cocci (42). Those nine species can be found in Table 2.

The species *Megasphaera elsdenii* has been of particular interest in ruminant animals, as it was initially identified in the rumen of cattle (97). There is some available literature on the role of this species in the gut of non-ruminant animals such as kittens, rats, and pigs (97-99). One study from 2003 identified changes in the abundance of this species in fecal samples of kittens, which showed reduced percentages of that sequenced bacteria in fecal samples at twelve weeks of age (98). Taken together, the role of this butyrate-producing bacteria may still have an unidentified role in the human gut microbiome.

Megasphaera massiliensis yielded scarce search results, since its isolation in 2013 from the stool of an HIV infected patient (100). However, this species has seen some recent interest due to its role in the production of butyrate and valeric acid. In one study, this bacterium was shown to have the strongest enhancing function on histone deacetylases in comparison to *Roseburia intestinalis* and *Bacteroides massiliensis* (101).

5.2.11 Dialister

The genus *Dialister* is composed of five species of obligately anaerobic, nonmotile, small, Gram-negative coccobacilli (42). Those species can be found in Table 2.

Dialister invisus was initially isolated from the human oral cavity, although it has also been isolated in the intestine and has been implicated in IBS and DM1 (44, 103, 104). One recent publication reporting that *Dialister invisus* occurred in abundance within subjects with IBS (44). However, this species was relatively inert and did not exhibit gene expression within the host (44). This report would suggest that *Dialister invisus* is either non-growing or a dead population and therefore is not contributing to the disease state. This study also highlights an important aspect of the gut microbiome; it is not sufficient for one species to be abundant in the gut, but it must also be transcriptionally active. One study associated *Dialister invisus* abundance with increased permeability of the gut in Diabetes Mellitus Type 1 subjects but were unable to elucidate the specific role this species played (104). Thus, it is possible that *Dialister invisus* may contribute to dysbiosis and the disease state.

Phylum	Genus	Species	Associated Literature
Firmicutes			
	Faecalibacterium	*prausnitzii*	43, 44, 45, 46, 47, 124
	Ruminococcus	*bromii*	50, 51, 92
		champanellensis	48, 49
		faecis	58
		flavefaciens	48, 49
		torques	56, 57
		gnavus	44, 52, 53, 54, 55, 126, 127
		albus, bicirculans, callidus, gauvreauii, lactaris	Scarce results
	Roseburia	*faecis*	58, 60
		hominis	61, 62, 125
		inulinivorans	57, 58, 59
		intestinalis	58, 63, 64, 93, 125
		cecicola	Scarce results
	Blautia	*coccoides, hansenii, hominis, luti, obeum, producta, shinkii*	69
		hydrogenotrophica	69, 70, 92
		caecimuris, faecis, glucerasei, stercoris, wexlerae	Scarce results
	Coprococcus	*eutactus*	56, 71, 72
		catus	6, 73, 74, 75, 92
		comes	76
	Dorea	*longicatena*	77, 78
		formicigenerans	78
	Anaerostipes	*butyraticus*	81, 82
		caccae	79
		hadrus	80
		rhamnosivorans	Scarce results
	Eubacterium	*coprostanoligenes*	83, 84, 85, 86, 87
		limosum	89, 90
		ramulus	90
		rectale	91
		siraeum	96
		ventriosum	92, 93
		aggregans, barkeri, callenderi, eligens, halli, multiforme, oxidoreducens, plexicaudatum, pyruvitavorans, rangiferina, ruminatium, uniforme, xylanophilum	Scarce results
	Acidaminococcus	*fermentans*	94, 95, 96
		intestini	Scarce results
	Megasphaera	*elsdenii*	97, 98, 99, 100
		massiliensis	101, 102
		cerevisiae, hexanoica, indica, micronicifformis, paucivorans, stantonii, sueciensis	Scarce results
	Dialister	*invisus*	44, 103, 104, 105
		microaerophilus, pneumosintes, propionicifaciens, succinatiphilus	Scarce results

Table 2. Compiled list of the genera of Firmicutes and their associated species. The major genera explored in this study were subdivided into their corresponding species. Each species has associated literature, unless otherwise indicated by "scarce results."

6. Neuropsychiatric Disorders and Gut Dysbiosis

Indeed, gut microbiome dysbiosis has been linked to multiple facets of systemic disorders. However, more recent studies have sought to understand the relationship between the gut microbiome and neuropsychiatric disorder such as, Major Depressive Disorder, and Generalized Anxiety Disorder and as a comorbidity of neurodegenerative disorders such Parkinson's disease. One founding hypothesis for the "gut-brain axis" was proposed by Braak and colleagues (105). They suggested a relationship between neuropsychiatric disorder and the gut was linked by the connection of the intestines via parasympathetic fibers from the vagus nerve to the spinal cord. In the gut, sensory information is registered via the nodose ganglion, and is then transmitted to the nucleus tractus solitarius of the brain. Braak and colleagues cemented their hypothesis in the wake of isolating Lewy bodies (protein aggregates composed primarily of alpha synuclein and ubiquitin) from the enteric nervous system, spinal cord, prefrontal cortex, and mid-brain of subjects with early PD (105). Following that study, it was shown that the injection of alpha synuclein into the gut wall in rat models migrated to the brain stem through the vagus nerve (106). The aforementioned hypothesis addresses the "highway" that connects the gut to the brain and does not account for the microbiota and their potential influence on that axis. Thus, we incorporate the findings of a few recent studies. The first showed that changing diet to a combination of high fat and high sugar diet in rat models resulted in dysbiosis of the gut microbiome. They suggested that dysbiosis may account for activation of microglia in the nodose ganglia that causes an inflammatory response that is responsible for changes in vagal afferent fibers (107).

Other explanations for the relationship between the gut microbiome and nervous system have explored bacterial production of molecules that may act as local neurotransmitters in the gut. For example, serotonin has been shown to mediate the enteric nervous system, as well as activity of the vagus nerve. This notion has been supported by the recent work by Neufeld and colleagues (108). In that study, they demonstrated that administration of oral selective serotonin reuptake inhibitors increases the rate of action potential production in the vagal nerve afferents harvested from the jejunum of mouse models. Furthermore, direct administration of SSRIs such as sertraline or fluoxetine to the lumen of the jejunum also resulted in increased rate of action

potentials (108). For example, *Lactobacillus reuteri* has been shown to be capable of producing GABA from L-Glutamate, and *Clostridia* has been shown to produce GABA from glutamic acid (110, 111). Not only have bacteria been shown to directly produce these molecules, they have also been shown to influence their synthesis within cells of the gastrointestinal tract. A study by Asano and colleagues have shown that bacteria, such as *Clostridia,* possessing β glucuronidase are capable of liberating conjugated neurotransmitters including dopamine and norepinephrine in the intestine of mouse models (112). Of importance, these bacteria are capable of producing or influencing production of neurotransmitters, which are implicated in disorders such as PD, MDD, and GAD. Thus, we will now explore which bacterial phyla are capable of producing such metabolites.

6.1 Bacteroidetes in Neuropsychiatric Disorder and Metabolic Products

One recent publication showed a reduction in the level of *Bacteroidetes* in subjects with MDD. However, they also indicated that bacteria belonging to the genus *Prevotella* were found to have increased in abundance in the obtained fecal samples (112). Although important, it should be underscored to report all observable changes in the microbiome, rather than generalized changes in abundances of bacteria. There were no indications that *Prevotella* abundance is altered or affects GAD. However, one publication reported that levels of *Prevotella copri* in comparison to control were elevated in subjects with PD (113). Given this information, and the role that *Prevotella* have been reported to play in other inflammatory diseases, that changes in the level of this species could induce inflammatory changes contributing to the pathogenesis of PD (28-31).

The genus *Alistipes* has been implicated in MDD. In one recent study, it was shown that *Alistipes,* along with *Enterobacteriaceae* had increased in abundance in patients with that disorder (24). There was little available information to support a role for *Alistipes* in GAD. However, the abundance of the genus *Alistipes* along with other genera has also been associated with subjects with PD when compared to healthy controls (114, 119).

Literature regarding the role of *Bacteroides* in MDD is available. However, according to one recent comprehensive review, there are conflicting results on the roles of *Prevotella, Alistipes,*

and *Bacteroides* in MDD (115). These genera have all been shown to have results that support both increases and decreases in abundance in subjects with MDD (115). Thus, further research into the roles of these genera will be necessary to accurately determine their roles in this disorder. One study has shown that abundance of *Bacteroides* in fecal samples has been shown to increase in subjects with GAD (116). In regard to PD, one recent study showed reduced abundance of multiple species of *Bacteroides* including *Bacteroides massiliensis* and *Bacteroides coprocola* in fecal samples of subjects with PD compared to healthy controls (114). As a whole, the genus *Bacteroides* was also found to be reduced in abundance (114). Another older study also found that levels of *Bacteorides fragilis* in subjects with PD were reduced in abundance when compared to controls (4). However, these results conflict with an earlier study that showed that the genus *Bacteroides* increased in abundance in fecal samples obtained from PD patients (6). It is apparent that *Bacteroides* dysbiosis is present when comparing diseased-state subjects to controls. However, further analysis will be required to determine the exact role of the species and genus *Bacteroides.* It may be reasonable to conclude, that although relative decreases at the genus level are being recorded, increases in abundance of one or more species in that genus may be hidden indicators of the diseased state. This statement therefore highlights the caution that should be taken when reporting genus-level changes in abundance.

There was little information available regarding the role of the genus or species of *Parabacteroides* in GAD and MDD. However, the genus *Parabacteroides* has been shown to increase in abundance in fecal samples from subjects with PD when compared to healthy controls in multiple studies (117-119). Thus, there may be room for exploration of species of *Parabacteroides* and how the changes in their relative abundance relate to PD.

As previously stated, if bacteria in the class *Clostridia* or genus *Lactobacillus,* have been shown to produce compounds that affect the brain-gut axis, a loss of corresponding species could possibly confer negative effects for the host. However, available literature has not supported this assertion for the genus *Prevotella.* There was no available indication that *Prevotella* was capable of producing neurotransmitter-like compounds including GABA, dopamine, serotonin, norepinephrine, or epinephrine. That genus has also not had any indication in the ability to

produce short-chain-fatty acids. There were no reports of species of *Prevotella* with β glucuronidase activity.

In contrast to *Prevotella*, the genus *Alistipes* may play a role in the metabolism of the neurotransmitters GABA and serotonin. In one review and one recent experiment, *Alistipes* was reported to utilize the enzyme glutamate decarboxylase (121, 122). That enzyme is responsible for the production of GABA (121). Furthermore, another study also suggested that *Alistipes* may be capable of producing indole, a derivative of tryptophan (24). Thus, it is worth speculating that this production of indole from tryptophan may cause a reduction in the availability of tryptophan for serotonin synthesis. However, indole has also been shown to be re-converted back into tryptophan. Thus, an alternative suggestion may be necessary. Perhaps, an over-abundance of *Alistipes* may cause an imbalance the normal formation and conversion of tryptophan to indole. If that occurs, it is reasonable to then suggest that and over-abundance of *Alistipes* could contribute to a decrease in tryptophan available for serotonin synthesis. That deficit in serotonin, or the aforementioned production of GABA may then contribute to the pathogenesis of neuropsychiatric disorder. Although, there is some evidence that the genus *Alistipes* may play a role in the reactivation and level of serotonin in the gut. Thus, this activity and the role of *Alistipes* in the gut microbiome will require further exploration. It would be reasonable to propose that an over-abundance of *Alistipes* in the gut microbiome may contribute to deficits in serotonin or other metabolites that contribute to the pathogenesis of neuropsychiatric disease. Furthermore, this proposal is supported by multiple publications that have found a positive correlation between the over-abundance of the genus *Alistipes* in patients with depression (24, 120).

Two available sources reported that both *Bacteroides* and *Parabacteroides* may be capable of producing GABA, the former was able to further specify that those species contained the *gadB* and *gadC* genes (121, 122). The latter study was able to utilize *Parabacteroides* and *Bacteroides* obtained from fecal samples of healthy individuals to draw the conclusion that they are, indeed, capable of producing GABA (122). Thus, abnormalities or dysbiosis may result in abnormal amounts of synthesized GABA in the gut that could potentially contribute to neuropsychiatric disorder. There have also been reports that the subspecies *Bacteroides fragilis* is capable of

producing the short chain fatty acid propionate from succinate. Information regarding the role of *Bacteroides* and *Parabacteroides* on the production of serotonin was sparse. *Parabacteroides* and *Bacteroides* also yielded sparse search results when reviewing available literature for kynurenine and the kynurenine pathway.

Taken together, it may appear that the role of *Bacteroidetes* in the synthesis or reactivation of molecules and compounds associated with neuropsychiatric disorder is supported. Thus, further study will be required to elucidate the roles that species of the aforementioned genera play in that biosynthesis. Possible future directions may focus on the effect of those synthesized molecules on local nervous tissues such as the vagus nerve.

6.2 Firmicutes in Neuropsychiatric Disorder and Metabolic Products

Clostridia and *Lactobacillus* are two genera within the phylum *Firmicutes.* As previously mentioned, these species have already been implicated in the neuropsychiatric disorder. Thus, it is worth exploring the possibility that other well-cited *Firmicutes* may also be associated with neuropsychiatric disorder.

In one recent study, reduced abundance of *Faecalibacterium prausnitzii* was shown to be associated with MDD (24). However, other supporting studies are scarce, and further exploration will need to be done before confirming this species role. There was no available information to support the role of this species in GAD. However, one study has shown an association between reduced abundance of *Faecalibacterium* in colonic mucosa samples of PD subjects (6). Thus, it may be worth investigating the metabolic roles of this species, as well as its function within the mucosa of the intestine. As previously stated, it is also possible that this species is subject to predation or may be antagonistic to other species of bacteria. Thus, relationships between this species and other gut commensals should also be explored.

The genus *Ruminoccocus* was one of several genera shown to be elevated in healthy controls compared to subjects with active MDD (24). Furthermore, *Ruminococcus* was also shown to be of decreased abundance in responded MDD (24). However, this genus suffers the same lack of

supporting studies as *Faecalibacterium.* There was no supporting information for the role of this genus in GAD or PD.

As reported by Jiang et al. in 2015, *Roseburia* was also shown to be of increased abundance in subjects with active and responded MDD (24). Again, recent exploration of the role of this genus in depression and MDD remains relatively unexplored. There was no supporting information for the role of this genus in GAD. However, one study showed an increased abundance of *Roseburia* in healthy controls when compared to PD (6). Unfortunately, additional studies supporting this association were scarce. Thus, future directions may focus on the role of this species in PD progression. It may also be worth exploring the relationships between this gut microorganism and other commensal bacteria. Through that method, it may be possible to determine whether this species abundance is the result of PD progression or bacterial predation or antagonism.

In the same study, the genus *Blautia* was shown to increase in abundance in subjects with active and responded MDD (24). However, there was a lack of supporting studies regarding the association between *Blautia* and MDD. There was no available information regarding the role of *Blautia* in GAD. However, levels of *Blautia* have been shown to be altered in subjects with PD compared with healthy subjects. In that study, *Blautia* was significantly more abundant in those healthy controls (6). However, there were no supporting studies to confirm this role. Thus, there may be some association between PD and reduced abundance of *Blautia,* but that will require further exploration. Furthermore, other factors such as metabolic roles and antagonistic effects between bacteria should be explored.

Information regarding the role of *Coprococcus* in MDD and GAD was scarce. However, this genus may be open to exploration in those disorders given the aforementioned roles of the species *Coprococcus catus* and *Coprococcus comes* in the production of short chain fatty acids. To the contrary, decreased levels of *Coprococcus* has been associated with PD. In the study performed by Keshavarzian and colleagues in 2015, *Coprococcus* was shown to be reduced in abundance in fecal samples of PD subjects when compared to healthy controls (6). Unfortunately, there was no available information to support or refute this relationship. Thus,

further exploration of this relationship will be required to determine the extent of the role of *Coprococcus* in PD.

Similar to the *Bacteroidetes*, *Firmicutes* may also play a role in metabolites associated with neuropsychiatric disorder. The genus *Faecalibacterium* has been implicated in decreased levels of serotonin. As one study has shown, after modeling IBS by administration of dinitro-benzene sulfonic acid, *Faecalibacteirum prausnitzii* was administered to the colon of germ-free murine models. After administration, reduced levels of serotonin were recorded (123). If this species is truly associated with decreases in GI serotonin, further exploration should focus on determining the metabolic capabilities of *Faecalibacterium prausnitzii. Faecalibacterium prausnitzii* have also been explored for their role in the production of butyrate (45). There was no available information regarding the role of this genus in synthesis or metabolism of GABA, dopamine, epinephrine, or norepinephrine. *Faecalibacterium prausnitzii* was not associated with beta-glucuronidase activity. Furthermore, one study exposed this species to growth conditions restricted to glucuronic acid, and determined

Faecalibacterium praustnitzii showed a limited range of growth from none to very poor (123). Therefore, it is unlikely that this species contains the enzymes necessary to utilize glucuronic acid as an energy source.

It is possible that serotonin level within the gut may also be influenced by the presence of *Ruminococcus.* Specifically, *Ruminococcus gnavus* has been well-documented in utilizing the enzyme tryptophan decarboxylase (125). This enzyme is responsible for converting tryptophan into tryptamine. Tryptamine, then may act as a neurotransmitter capable of stimulating further release of serotonin by enterochromaffin cells of the GI (125). It would not be unreasonable then, to suggest that serotonin is capable of affecting the gut-brain axis mediated by the vagus nerve. There was no available information regarding the role of *Ruminococcus* in synthesis or metabolism of GABA, dopamine, epinephrine, or norepinephrine. However, there are reports of beta-glucuronidase activity in *Ruminococcus gnavus* (126). With this activity, it is possible that *Ruminococcus gnavus* is capable of reactivating glucuronide-conjugated compounds.

Searching the available literature for *Roseburia* did not yield information regarding a role in serotonin, dopamine, GABA, norepinephrine, or epinephrine synthesis or metabolism. However, there was available information to indicate beta glucuronidase activity in *Roseburia intestinalis* and *Roseburia hominis* when exposed to differing growth media (124). This varied activity may suggest an environmental or dietary sensitivity, which determines the level of activity of this enzyme.

Similar to *Ruminococcus, Blautia* has also been proposed to contain a tryptophan decarboxylase homolog capable of producing tryptamine (125). If correct, this could have a similar effect on enterochromaffin cell serotonin production in the GI as *Ruminococcus*. However, no available sources indicated a role in GABA, dopamine, epinephrine, norepinephrine, or glucuronic acid synthesis or metabolism.

Similarly, the genera *Eubacterium*, *Coprococcus, Megasphaera,* and *Dialister* did not yield any associations with production of dopamine, serotonin, GABA, norepinephrine, epinephrine or glucuronic acid. However, *Megasphaera elsdneii* has been shown to be involved in metabolism of amino acids in the human GI. Thus, it may be possible that species of *Megasphaera* function to reduce the availability of amino acids to be used by the surrounding tissue. Furthermore, utilization of the amino acids by these species supports competition between other genera that are also capable of utilizing amino acids, such as *Acidaminococcus* and *Lactobacillus* (127).

7. Therapeutic Applications

Consider a generic extended release medication. Now, imagine that delayed release agent but living in unison with the commensal bacteria of the GI. In that case, the medication may be continuously synthesized in the GI of the host and be reabsorbed by the intestinal wall. Essentially, this method achieves the same effect of an oral extended-release therapeutic, but it allows for continued synthesis of the medication within the host. However, this is not a permanent change, as we know the commensal bacteria continuously divide and die within the host. The genetically modified bacteria are no different. This exemplifies the use of bacteria in personalized medicine. Each bacterium can be uniquely modified to produce certain metabolites

at a regulated rate. Furthermore, the metabolites produced have been specifically chosen for that bacteria and have been shown to provide therapeutic effect. The modification of *Escherichia coli (E.coli)* Nissle by Isabella et al., in 2018 is one example of utilization of a bacterial species for treatment of a disease; in this case, it was synthesized for management of phenylketonuria (128). Previous studies have demonstrated *E.coli* Nissl as a probiotic, was a model candidate for treatment of GI conditions, given its effects on IBS (128). Furthermore, this species is readily eliminated from the body within a period of one week and does not colonize the human GI tract (128). With some modification based on the conditions of the GI tract, the *Escherichia coli* Nissle SYNB1618 strain was produced for management of phenylketonuria (128). This strain was genetically engineered to utilize phenylalanine ammonia lyase and L-amino acid deaminase in order to degrade phenylalanine in the GI (128). Although it has not yet been tested in human clinical trials, is has shown some promise in decreasing phenylalanine levels in the intestines of phenylketonuria mouse models (128). Non-human primate models have also shown support for the benefits of that same strain in improving phenylketonuria (128).

One similar route of therapy has been taking markets, grocery stores, and other health-focused stores by storm. That form of therapy is colloquially known as over-the-counter probiotics. These probiotics are carefully composed of species of bacteria, which have been determined to produce metabolites that have some therapeutic action. The aforementioned patent for a probiotic containing *Roseburia hominis,* exemplifies this new form of therapy, which has been proposed as a treatment for a wide range of disorders. Some of those disorders include modulating host immunity, satiety, and IBD (62). However, probiotics themselves are not a “one shoe fits all” form of therapy. If we accept that each individual has a unique gut microbiome, then each person may require a carefully formulated probiotic in order to avoid dysbiosis. This is one of the hallmark limitations of a generalized probiotic therapy. Although *Roseburia hominis* may produce beneficial metabolites within the host, it may only be possible to administer it to individuals who already have a high prevalence of *Roseburia hominis*. Administration of this probiotic to an individual with a relatively low level of *Roseburia hominis* could result in dysbiosis and subsequent worsening of their condition. However, the previous statement will require further study and clinical trials in order confirm or rule out that precaution.

Another strategy for therapeutics is cell-based therapy, in which living cells are administered to the host for some therapeutic purpose. The stem cell derivatives, among other types of cells, can promote healing through two major pathways after administration; via replacement of damaged cells or recruitment of local cytokines and growth factor (129). This form of delivery directly corresponds to the idea of administration of commensal bacteria. However, a key difference between bacteria and the cells, lies in integration. The bacteria are not truly becoming "one" with the host, but merely living in symbiosis with it and replacing something that was previously there. However, in stem-cell therapy sometimes the cells become part of the host by replacing defective cells. From a lay-man's perspective, it is also possible the idea of ingesting a probiotic on a regular schedule may appear less stressful than changing themselves at the cellular level. Furthermore, a once weekly oral probiotic may be more appealing than taking an oral or injected medication for management of disease.

Here, we propose a bridge between the two previously mentioned forms of bacterial metabolic therapy. It may be possible to create a bacterial strain that can produce metabolites with therapeutic capabilities, which can colonize in the gut with some assistance from a regularly scheduled probiotic. One outstanding difference between the proposed method of a probiotic bacterial metabolite-therapy and the applied *Escherichia coli* Nissle SYNB1618 strain is the ability to colonize. If species of the host commensal bacteria of the GI can be identified, then it may be possible to engineer a personalized strain of bacteria that mimics the host microbiome. Given the capacity for the original species to live in symbiosis in the host, the modified strain may be able to survive in the host and produce the metabolites necessary for treatment of the disease for that individual.

Indeed, we have identified several bacterial genera that are reportedly capable of producing and reactivating key metabolites for the synthesis of other biologically active molecules. Those genera are identified in Table 3.

Phylum	Genus	Metabolic Activity	References
Bacteroidetes			
	Alistipes	glutamate decarboxylase, GABA production	121, 122
		indole production	24
	Bacteroides	glutamate decarboxylase, GABA production	121, 122
	Parabacteroides	glutamate decarboxylase, GABA production	121, 122
Firmicutes			
	Ruminococcus	tryptophan decarboxylase	125
		beta glucuronidase	126
	Roseburia	beta glucuronidase	124
	Blautia	tryptophan decarboxylase	125

Table 3. Metabolic Activity of Bacteroidetes and Firmicutes by Genera. Above contains the major genera involved in affecting compounds identified in this study, including GABA, Serotonin, and glucuronic acid conjugates and their corresponding references.

8. Conclusions

The purpose of this review has been to identify key bacterial phyla, genus and species in in current literature, and then determine which of those species are capable of producing or reactivating metabolites that correspond to neuropsychiatric disease. This has been done in order to find species that may be genetically modified and utilized for live probiotic-based therapy. Although multiple species of bacteria were identified and characterized based on their abundance in available literature, we were not able to readily identify species that could be used for therapeutic purposes. It is possible that species of bacteria, which are capable of producing the aforementioned metabolites were not part of the original inclusion criteria. Furthermore, it is possible that the aforementioned species and genera are known to be involved in production of other metabolites not explored in this review. Despite the scarcity of information at the species level, we were able to determine multiple genera that may show some promise in the future for development of therapeutic agents.

This review was not without limitations, and those limitations will be explored hereafter. Within the design of the review, the number of publications needed in phase one was chosen based on the fact that research in the gut microbiome is a growing field. The number chosen did not represent recent or current trends in research that may have shown increased exploration in

certain areas. Therefore, species or genera considered scarce at the time of this review may reach criterion in a few months. Despite this, we encourage continued research in all of the aforementioned species, especially those which have shown scarce results.

In regard to the role of bacteria and their association with neuropsychiatric disorder, continued work is still needed. Multiple studies, some of which were reported here, and many that were not reported, were correlational. Although correlation may be an important step in identifying a relationship, it should be followed with experimental design in order to elucidate an actual causal relationship. For example, does the increase in abundance of a certain bacterial specie or strain in patients with MDD, truly cause the disease or is there an underlying predatory relationship with decrease in abundance of another commensal neighboring species. By exploring the relationship between host and microbe and innovating creative strategies to study the interactions i.e. developing novel animal models, metagenomic/metabolomic algorithms, and imaging tools, we will be able to push the boundaries of neurobiology and microbiology.

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