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Role of Microbes in the Pathogenesis of Neuropsychiatric Disorders

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Abstract

Microbes inhabit different anatomical sites of the human body including oral cavity, gut, and skin. A growing literature highlights how microbiome variation is associated with human health and disease. There is strong evidence of bidirectional communication between gut and brain mediated by neurotransmitters and microbial metabolites. Here, we review the potential involvement of microbes residing in the gut and in other body sites in the pathogenesis of eight neuropsychiatric disorders, discussing findings from animal and human studies. The data reported provide a comprehensive overview of the current state of the microbiome research in neuropsychiatry, including hypotheses about the mechanisms underlying the associations reported and the translational potential of probiotics and prebiotics.

Keywords

Microbiome; Gut-Brain- Axis; Inflammation; Neuropsychiatric Disorders; Dysbiosis; Probiotics

1. Introduction

Microbes reside in the human body and not all of them are necessarily harmful. Their presence/absence and balance/imbalance are associated with health and disease. Recent estimates revealed that the number of microbial to human cells show a 1:1 proportion. Some microbes are beneficial and their diversity across human body sites contributes to the overall health status of an individual [1; 2]. Fluctuations in the relative diversity and composition of the microbiome across the human body are hypothesized to affect the risk of several diseases, including inflammatory bowel disease (IBD) [3], cancer [4], and immunological disorders [5].

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There is considerable literature supporting the association between human microbiome variation and mental health, also including several review articles focused on specific disorders or specific mental health domains, such as depression [6; 7; 8], mood disorders [9; 10], neurodegenerative disorders [11], and neurodevelopment [12]. However, to our knowledge, a review presenting the current state of microbiome research across multiple neuropsychiatric disorders and different body sites is missing. The current article aims to provide a compendium of the current state of human microbiome research across the neuropsychiatric spectrum to help investigators with different expertise to understand the evidence available to date. We include an initial overview of three microbiome domains (gut, mouth, and skin; Figure 1) and then review findings specifically related to eight neuropsychiatric disorders (Alzheimer's disease, attention deficit hyperactivity disorder, anorexia nervosa, autism spectrum disorder, bipolar disorder, major depressive disorder, schizophrenia, and substance use disorders; Table 1). Due to size constraints, we decided to focus on those psychiatric disorders that were investigated by numerous studies or that were not reviewed previously.

The studies reviewed were conducted using a wide range of different methods and designs. For example, diversity metrics include several measures of alpha diversity (e.g., the Shannon index assumes the observed abundances reflect random sampling of the microbiome and thus is maximized when abundances increase evenly across all taxonomic units; the Simpson index gives more weight to highly abundant taxanomic groups and is less influenced by very low abundance organisms; the Chao1 index uses a Poisson distribution to estimates the number of taxa in a sample by extrapolating the number of rare organisms that may have been missed due to under-sampling; rarefaction assesses species richness through construction of rarefaction curves). Beta diversity reflects a comparison of abundances between two microbiome samples (e.g., Jaccard distance is measures similarity in the presence or absence of taxonomic groups without regard to abundance; Bray–Curtis dissimilarity measures the differences in abundances of each taxonomic units; Unweighted UniFrac is the distance between two samples by calculating the fraction of the branch length in a phylogenetic tree that leads to descendants) [13]. Because analytic variability undermines comparison between studies and contributes to the lack of reproducibility among microbiome studies, investigators have highlighted the need for establishing standards for microbiome analysis and interpretation [14; 15]. Due to the difficulty of comparing results that used different statistics, we decide to compare the finding of the studies reviewed relying on the interpretation made by the authors.

2. Gut-Brain Axis

The gut microbiome is a reservoir of many microorganisms such as *Firmicutes, Bacteroides, Preveotella*, and *Bifidobacterium* associated with the healthy physical and mental state of an individual. [16]. Gut dysbiosis (i.e., altered abundances of gut microbial communities) has been hypothesized to be involved in gastrointestinal disease [16; 17], cardiovascular illnesses [18], metabolic disorders [19]and autoimmune diseases [19; 20]. With respect to neuropsychiatric disorders, the gut-brain axis (GBA) represents the link between the central and the enteric nervous system, linking emotional and cognitive centers of the brain with peripheral intestinal functions. The association between microbiota and

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GBA appears to be bidirectional with signaling from gut-microbiota to brain and from brain to gut-microbiota mediated neural, endocrine, immune, and humoral mechanisms [21]. The impact of gut microbes on human health also includes potential associations with increased vulnerability to psychiatric disorders. A well-known study on using a germ-free mouse model emphasized an altered hormonal response to stress, suggesting that microbiota influences the neuroendocrine hypothalamic–pituitary–adrenal (HPA) axis [22]. In additional mouse experiments, the lack of normal gut microbiota influences behaviors (e.g., motor activity) and brain transcriptomic profile involved in motor control and behavioral regulations [23]. Another study testing the administration of a mixture of nonabsorbable antimicrobials for 7 days to pathogen-free mice transiently altered the gut microbial composition and was associated with heightened exploratory behavior and hippocampal Brain-Derived Neurotrophic Factor (BDNF) expression [24; 25]. These changes were independent of other inflammatory activities and alterations at the level of gastrointestinal neurotransmitters. Accordingly, the intestinal microbiota was hypothesized to influence brain chemistry and behaviors independently of the autonomic nervous system and gut inflammation [25].

The gut epithelium plays a key role in the GBA regulation because it is the primary target for changes induced by dietary, microbial, and inflammatory components. Enterochromaffin (EC) cells function as chemo- and mechanosensory neuroendocrine cells that release serotonin in order to modulate other gastrointestinal neurons, in order to effect peristalsis and mucus secretion. Serotonin released from EC cells in the mouse colon has been attributed to neuroinflammation [26; 27]. There is evidence of sex-differences in this hormonal response to microbiome perturbations. Female germ-free mice showed greater serotonin concentrations and elevated plasma levels of tryptophan (i.e., the serotonin precursor) than conventionally colonized control animals [28]. In mouse models of stroke and multiple sclerosis, the perturbation of gut microbiota appears to interfere with communicative and sensorimotor behaviors via immunomodulation [29].

The gut consists of a high concentration of immune cells, providing an additional layer of defense from pathogens. Production of pro- and anti-inflammatory cytokines is influenced by gut microbiota which can lead to brain dysfunction through the circulatory system [30]. Inflammation caused by cytokines can result in the release of corticosteroids accelerating stress-induced anxiety and depression [31]. Gut microbiota regulates metabolism of neuroactive compounds (e.g., short-chain fatty acids, indoles, bile acids, choline metabolites, lactate) and their release of these neuroactive compounds can promote additional neuroinflammation [32; 33].

Microbes residing in the gut often metabolize tryptophan, the serotonin precursor, along with a host of other neurotransmitters and neuromodulators [34]. These compounds permeate the gut wall that is innervated by the enteric nervous system (ENS) [35; 36]. This interaction can trigger bidirectional gut-brain communication resulting in inflammation of the gut and brain epithelia and production of stress peptides resulting in anxiety-driven behaviors [21]. Gut-brain module analysis based on human fecal metagenomes identified microbial production of 3,4-dihydroxyphenylacetic acid (a dopamine metabolite), which correlated positively with self-reported quality of life; this study also indicated the role

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of microbial γ-aminobutyric acid production in psychopathology [33; 37]. Among the pathogenic processes involved in the disruption of gut-brain axis equilibrium, inflammation plays a key role in altering the microbiome homeostasis in response to specific pathogens [38], immune activation [39], and antibiotic supplementation [40]. This altered microbial environment due to gut infection can be restored via beneficial microbes called probiotics [41]. Although this field is still in infancy, it has great potential for the development of future therapeutic applications [42; 43; 44].

3. Oral Microbiome

The human oral cavity is a complex environment presenting a variety of habitats hosting different kinds of microorganisms [45]. Highly prevalent microorganisms in the oral cavity include *Staphylococcus* [46; 47] and *Streptococcus* [48]. Data regarding different oral microbiome species are available from the Human Oral Microbiome Database (HOMD) [49]. Compared with the gut microbiome, few studies examined the oral microbiome in the context of neuropsychiatric disorders [50]. The microbiome in the oral cavity has been associated with systemic inflammation linked to altered cognitive functioning [51]. This may be due to indirect factors such as diet, lifestyle, and oral hygiene, but the fact that the association was related to a specific species (i.e., *Neisseria subflava*) suggests the possibility of a direct link. Unfortunately, to date the underlying mechanisms are still unclear. Due to many confounders that can affect the human variation of oral microbiome composition, most of the current studies should be considered as preliminary evidence that needs confirmation in a larger and more carefully characterized samples [52].

4. Skin Microbiome

Skin serves as a barrier preventing the invasion of external pathogens and also acts as the primary habitat for the commensal microbiota [53]. Sebaceous sites in the skin are reservoirs of specific bacteria like lipophilic *Propionibacterium*, *Staphylococcus*, and *Corynebacterium* species [54]. Skin microbiome diversity is generally conserved at the community level and despite external perturbations like diet, antimicrobial therapy, and long-term environmental interactions, it is considered stable over time in healthy individuals [55]. Alteration of skin microbiota is observed when individuals are affected by wounds, lesions, and/or dermatological disorders. Very few studies investigated the impact of skin microbiome dysbiosis with respect to psychiatric disorders. However, some of them hypothesized the presence of a gut-brain-skin axis related to immune response and inflammatory processes linking these organs [56; 57; 58]. Bidirectional communication between skin and gut microbiota has been reported in the context of immune-related disorders [1; 59; 60]. For example, variation in gut microbiome in patients with skin lacerations has been reported to alter the skin microbiota [57; 61; 62]. Persistent changes in both gut and skin microbiome can lead to neuro-modulatory effects associated with decreased cognitive function via inflammatory cytokines (i.e., TNF-α, IL-1β, IL-6, IFN-α) [56]. These factors have been associated with gut inflammation, increasing the permeation of the gut-brain barrier resulting in the release of neurotransmitters [63; 64; 65]. In patients with psoriasis, alterations in the skin and intestinal microbiome play a role in the pathogenesis of psoriasis,

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where inflammatory and immune mechanisms are associated with the dysregulation of the hypothalamic-pituitary-adrenal axis [66; 67].

5. Alzheimer's disease

Alzheimer's disease (AD) is a leading cause of death worldwide, with an estimated incidence of 1–3% and a prevalence of 10–30% of the population > 65 years of age in the United States [68; 69]. The role of altered gut microbiota and its subsequent impact on the HPA axis has been studied in the context of AD pathophysiology [70]. The leading hypothesis is that the composition of the intestinal microbiome plays a role in the neuroinflammation of the amyloid plaques deposition [71]. Indeed, microbiota-mediated inflammation associated with AD appears to act at the level of the blood-brain barrier (BBB) [72]. Some bacteria are capable of directly crossing the BBB, giving rise to infections of the central nervous systems (CNS) [73]. Certain molecules generated by bacteria (e.g., lipopolysaccharide, LPS) potentially stimulate BBB disruption in patients affected by neurodegenerative disorders. [74]. Consistent with this, the bacterial metabolite propionate, a short-chain fatty acid (SCFA), appears to protect the BBB from damage via inhibiting oxidative stress thereby maintaining its integrity. [75]. LPS is typically associated with pathogenic strains, while commensal or non-pathogenic flora produce SCFAs. In rats, peritoneal LPS administration resulted in increased levels of inflammatory factors, notably IL-1, IL-6, and TNF-α, in the hippocampus, suggesting a role for the microbiome in the initiation of an innate immune response in AD [76]. Zhao and colleagues found immunohistochemical evidence of microbiome-derived LPS within the perinuclear region of human AD brains [77].

The natural biodiversity of the gut microbiome tends to decline with aging, with a relative reduction in commensal species, such as *Bacteroides*, *Bifidobacteria*, and *Lactobacilli*, and a relative increase in opportunists and potentially pathogenic species such as *Enterobacteria, C. perfringens*, and *C. difficile* [78]. In the ELDERMET cohort comprised of individuals over 65 years of age, there was a shift in the gut microbiota toward a *Bacteroidetes*-predominated population in older individuals compared to younger participants[79]. The variation in microbial composition is also dependent on diet and lifestyle [80]. Diet-induced perturbation in the gut microbiome alters the shikimate metabolic pathway (responsible for the *de novo* synthesis of aromatic compounds in microorganisms [81]), which was associated with elevated levels of the cytotoxic amine tryptamine and increased symptoms among individuals affected by AD [82]. In human brain samples, a large bacterial load of *Firmicutes* species and *P. acnes* was observed in the cerebral cortex of AD patients [83].

Ongoing studies are exploring the role of probiotics used in gastrointestinal (GI) diseases for the treatment of AD patients. [84]. Certain probiotic formulations displayed neuroprotective effects in a transgenic mouse model of AD, including attenuation of microglial activation, reduction in Aβ load, and preservation of dendritic spine structure and function [85; 86]. A relatively larger randomized controlled trial (N=60) revealed that intake of milk supplemented with *Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum, and Lactobacillus fermentum* produced significant, albeit small magnitude improvement in Mini-Mental Status Examination scores (widely used to test cognitive function among the

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elderly [87]) and improvement on various metabolic measures in AD patients [88]. With respect to the oral microbiome, a large scale retrospective case-control study of Alzheimer's disease (AD) including participants from Taiwan's national insurance database (*N*=209,112 cases and 836,448 dementia-free controls) found negative associations with the per-person cost of dental care, number of root canals, and number of tooth extractions, and positive associations with the cost of dental imaging and dental emergencies [89].

6. Attention Deficit Hyperactivity Disorder

Attention-deficit hyperactivity disorder (ADHD) is a heterogeneous neurodevelopmental disorder [90]. Diet potentially plays an important role in ADHD-related behavioral processes via its effect on the composition and functioning of the gut microbiome [91]. Apart from diet, host-microbe interaction with the gut-brain axis could be directly involved in the development of ADHD [92]. The host-microbiome interactions have implicated effects on hormones and neurotransmitter levels thought to be involved in the pathophysiology of ADHD [93; 94]. For instance, GABA production has been associated with different microbial genera including *Bifidobacterium*, *Lactobacillus*, and *Escherichia coli* [95]. Gut dysbiosis in combination with immune dysfunction caused by constant pathogen exposure could contribute to hyperactive behaviors observed in ADHD affected patients [96]. A study administering probiotics to ADHD patients showed that early intervention with *Lactobacillus* reduced the risk of ADHD development later in childhood [97]. ADHD has been associated with abnormalities in the predicted dopamine and noradrenaline synthesis, whose precursors are provided by the gut bacteria [90]. ADHD is often found to be associated with gut dysbiosis like enrichment or depletion of certain bacteria like *Bifidobacterium* [94].

7. Anorexia Nervosa

Anorexia nervosa (AN) is a mental illness characterized primarily by feeding restriction, distorted perceptions of and preoccupation with body weight and shape, and obsessive behaviors related to food [98]. Metabolic, immunologic, and weight regulating effects of the microbiome could influence the course and prognosis of the disease. Additionally, the interplay between stress-coping mechanisms and gut microbiome can also have important implications for AN [99].

AN patients have demonstrated altered diversity of bacterial species within the gut [100; 101; 102]. In particular, AN patients showed high gut levels of the archaeon *Methanobrevibacter smithii* [103]. This methane-producing archaeon is associated with food transformation processes in a very low-calorie diet [104]. AN patients also have significantly low amounts of total bacteria and obligate anaerobes, e.g. *Clostridium coccoide*s group [105]. The reduced microbial diversity is associated with impaired immune response and reduced capacity to absorb calories from the diet [106]. Additionally, the genera *Roseburia, Ruminococcus*, and *Clostridium* were reduced in line with the AN depletion of total short-chain fatty acids, butyrate, and propionate [101]. Butyrate concentrations inversely correlated with anxiety levels, whereas propionate was positively associated with insulin levels and with an increased presence of *Roseburia inulinivorans* [101].

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Due to its therapeutic potential, the interaction of the human microbiome with dietary habits is a rapidly expanding research area in AN [107; 108]. For example, *Roseburia sp.* represents one of the candidates for AN probiotic intervention due to the lower rate of anxiety associated with affected patients [109]. However, more studies are needed to clarify whether the differences observed are a cause or consequence of the disease. Additionally, it will be important to understand how changes in AN microbiota are affected by the interactions among nutritional supply, nutritional supplements, probiotics (i.e., live bacteria), and prebiotics (i.e., fibers supporting the growth of certain types of bacteria) [110].

8. Autism Spectrum Disorder

Autism spectrum disorder (ASD) is characterized by impairment in communication, speech, social interaction, and the presence of restricted interests and repetitive or stereotyped behaviors [111; 112]. Due to the high prevalence of GI symptoms in ASD-affected individuals, considerable attention has been paid to the gut microbiome [113]. Altered age-related patterns have been associated with ASD-affected individuals, including cognitive impairments, difficulty in speech and motor coordination skills [114; 115]. A higher representation of *Bacteroidetes*, *Proteobacteria, and Firmicutes* has been reported in ASD patients when compared with healthy controls [116]. Conversely, ASD showed a reduction of *Bifidobacterium, Klebsiella, Enterobacter, Prevotella, Coprococcus*, and *Veillonellacea* [117; 118; 119]. Earlier studies also suggested that the imbalance in *Bacteroides* and *Firmicutes* gut has been associated with increased autism severity in ASD patients [120]. However, this finding was not replicated in certain cohorts, possibly due to different living conditions and eating habits [121]. Pyrosequencing of fecal microflora of ASD children showed a higher abundance of *Desulfovibrio* species and *Bacteroides vulgatus* when compared with healthy controls [122]. Late-onset autism patients presented a high incidence of *Clostridium* and *Ruminococcu*s species with a particular enrichment for *Clostridiu*m cluster groups I and XI and *Clostridium bolteae* [123]. The accumulation of neurotoxin-producing bacteria such as *Clostridia* are associated with ASD symptoms [124]. Toxic molecules released by such microbes affect serotonin signalling [125], potentially leading to ASD behavioral patterns such as decreased socialization, decreased response to pain, abnormal language, and self-abusive or repetitive behaviors. ASD-affected individuals show altered levels of other potentially toxic compounds produced by several bacteria (e.g., *Bifidobacterium*, *C. difficile*, and *C. histolyticum*) [126; 127; 128; 129]. Among them, increased abundance of urinary and fecal paracresol (p-cresol) and its conjugated derivative p-cresylsulfate inhibit the enzyme dopamine-beta-hydroxylase [130]. Additionally, increased *Clostridia*-derived metabolite 3-(3-hydroxyphenyl)-3-hydroxy propionic acid has been detected in ASD-affected individuals, potentially reflecting an altered catecholamine metabolism. Treatment with vancomycin and probiotic *Bifidobacterium* was associated with normalized metabolite levels, decreased constipation, and a reduction in severity of ASD features [131].

Obesity- or diet-induced changes in the offspring gut microbiome have been examined as a potential mediator of the association of maternal obesity with ASD. In rodent models, offspring of mothers who were fed high fat diets showed altered gut microbial composition and deficits in social behaviors and social reward pathways thought to be relevant to ASDs

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[132]. Fecal inoculation from offspring whose mothers were fed a typical diet (through either cohabitation or fecal transplant) were associated with normalization of social (but not repetitive) behaviors [132].

The gut microbiome metabolizes three classes of short-chain fatty acids (SCFA): propionic acid (PPA), acetic acid, and butyric acid. PPA and SCFA in general are capable of gaining access to the brain and inducing widespread effects on CNS function, including neurotransmitter synthesis and release, calcium influx, intracellular pH maintenance, lipid metabolism, intercellular gating, immune activation, and gene expression [133]. Perfusion of PPA in rats induced ASD symptoms, supporting the importance of gut-acquired factors [119; 134].

A small open-label clinical trial evaluated the impact of microbiota transfer therapy (MTT; a combination of antibiotics, a bowel cleanse, a stomach-acid suppressant, and fecal microbiota transplant) on gut microbiota composition, GI symptoms, and ASD symptoms in eighteen affected individuals. [135]. The GI symptom rating scale exhibited an approximately 80% decrease of GI symptoms at the end of treatment, including significant improvements in symptoms of constipation, diarrhea, indigestion, and abdominal pain [135]. Additionally, ASD symptoms improved significantly and remained constant 8 weeks after treatment ended [135]. The overall bacterial diversity and the abundance of *Bifidobacterium*, *Prevotella*, and *Desulfovibrio* among other taxa increased following MTT, and these changes persisted after treatment stopped [135]. Parracho and colleagues conducted a double-blind placebo crossover trial in the United Kingdom with 22 children with ASD aged between 3–16 years using *Lactobacillus plantarum WCFS* as a probiotic [136]. Although no major differences were observed in GI symptoms, a significant increase in *Lactobacilli*/*Enterococci* and a decrease in the *Clostridium coccoides* were reported in the stool samples of children with ASD when compared with the placebo group.

Another interesting area of ASD research is related to maternal immune activation (MIA) triggered by infectious or infection like stimuli [137]. A MIA mouse model showed significant behavioral changes in offspring of potential relevance to ASD [29]. These changes are accompanied by altered gut microbial composition. Oral treatment with human *Bacteroides fragilis* improved the communicative and stereotyped behaviors, as well as altered intestinal permeability associated with microbial composition [29]. The behavioral deficits appeared to be due to the *Clostridiu*m-associated metabolite 4-ethylphenyl sulfate, a molecule like p-cresol (4-methylphenol) [29]. This is a chemically related metabolite reported being a possible urinary ASD biomarker [138; 139]. In another study conducted on ASD-affected children (N=22), a sugar-free diet and probiotic capsules of *L. acidophilus* were associated with significant improvement in concentration and the ability to follow instructions in affected patients [128; 140]. In an additional clinical trial, an oral liquid dose of vancomycin 500 mg/day and followed by probiotic therapy (a mixture of *L. acidophilus, L. bulgaricus, and B. bifidum*) was associated with an improvement in the cognitive functioning of ASD patients [141].

Beyond the gut environment, microbiome variation in other body sites was also investigated with respect to ASD. For example, certain components of the oral microbiome (abundance

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of *Rothia, Neisseria, Moraxella, Megasphaera*, and *Gemella*) were associated with autism in children [142].

9. Bipolar Disorder

Bipolar disorder (BD) is a chronic mood disorder characterized by periods of abnormally elevated mood in addition to periods of depression, and it is associated with high morbidity [143]. Several lines of evidence support the presence of chronic low-grade inflammation among BD-affected persons, with increased plasma cytokines, soluble cytokine receptors, chemokines, acute phase reactants, and T-cell activation. It is unclear the extent to which these findings may be linked with dysbiosis.

In a study comparing the gut microbiota of 115 BD patients and 64 healthy controls [144], *Faecalibacterium* levels were decreased in BD patients and abundance was negatively correlated with self-reported symptoms of depression severity. In a separate study, higher microbial variation was observed in BD-affected patients when compared to healthy controls [145]. Among patients affected by episodes of both mania and depression, the relative increase of *Escherichia coli* and *Bifidobacterium adolescentis* was higher in individuals with manic episodes, while *Stercoris* was higher in individuals with depressive symptoms [145; 146]. *Flavonifractor* genus was associated with BD patients [147]. However, no difference in gut microbiota were observed between unaffected first-degree relatives of BD patients and healthy controls [147].

Few studies have examined microbiome interventions in BD. An investigation of 20 euthymic BD-affected individuals, who received a probiotic supplement over 3 months, showed significant improvement in cognition and psychomotor processing speed [148]. Additionally, one observational study of atypical antipsychotic treatment showed a decreased alpha diversity of gut microbiota in BD female patients and altered abundance of *Lachnospiraceae* and *Akkermansia* in the whole BD group [149].

10. Major Depressive Disorder

Major Depressive disorder (MDD) is the 4th leading course of disability around the world [150]. Multiple studies reported associations between microbiome variation and certain biological changes associated with MDD pathogenesis (e.g., neurotrophic factor alterations neuroanatomical abnormalities, and endocrine and immune system dysfunction) [151; 152]. Depression appears to be generally associated with reduced microbial diversity [153]. The relative abundance of *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* phyla were increased in MDD patients whereas that *Firmicutes* abundance was significantly reduced [152]. MDD group also showed elevated levels of *Enterobacteriaceae* and *Alistipes* but reduced levels of *Fecalibacterium*, which were also negatively associated with MDD symptoms [152]. *Coprococcus, Pseudobutyrivibrio, Dorea*, and *Clostridium* genera were reported as overrepresented in MDD patients [154]. Conversely, MDD-depleted bacterial genera include butyrate-producing bacteria like *Dialister, Fecalibacterium*, and *Butyvibrio* [155; 156]. In female MDD patients, it was observed enrichment for Bacteroidetes, proteobaeteria, and Fusobacteria and depletion for Firmicutes and Actinobacteria phyla

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[157]. In mouse models, the microbiome profile associated with depressive symptoms has been associated with specific changes in microbial genes and changes in gut metabolism of carbohydrate and amino acids [158; 159]. The composition of gut microbiota is significantly altered in MDD mice versus healthy GF (germ-free) controls [153; 160]. In mouse models, LPS-administration induces neuroinflammatory changes that effect synaptic and non-synaptic plasticity in basolateral amygdala projection neurons associated with anxiety-related behavior [161]. Additionally, the endocrine system communicates bidirectionally with the gut microbiota also via sex hormones, like androgens, estrogens, and others, which can influence MDD-related neuroinflammation [162; 163]. Indeed, androgens seem to exhibit anxiolytic properties whereas estrogens have been found to elevate HPA activity [164]. Fluctuations in levels of oxytocin are correlated positively with changes in the gut bacterial taxa whose abundance was altered in clinical depression [160].

Probiotics consumption for extended periods showed beneficial effects on depression-related behaviors, [165]. One of the other potential therapeutic approaches for depression based on FMT microbial manipulation is the. This therapeutic approach showed positive effects in treating *Clostridium difficile* mediated infection[166]. GF mice receiving FMT from patients with depression exhibited greater depressive behaviors compared to GF mice receiving FMT from healthy control individuals [158].

11. Schizophrenia

Schizophrenia (SCZ) is a chronic psychiatric disorder characterized by a range of symptoms, including delusions, hallucinations, disorganized thoughts, and cognitive deficits [167]. The role of microbial diversity in contributing to SCZ has been widely discussed. Imbalance of microbes produced either by pathogen invasion, stress, immune gene activation, or endothelial barrier compromise is associated cognitive impairments and has been hypothesized to occur in individuals with SCZ [168]. In 1845, Jean-Étienne Esquiro was the first to suggest that infectious diseases are involved in the vulnerability to psychoses [168]. More recently, SCZ risk has been associated with the exposure to neurotropic viruses (e.g., herpes simplex viruses, cytomegalovirus, Epstein-Barr virus, measles, and rubella) [169; 170; 171; 172]. Nevertheless, viral load in post-mortem brain samples did not show any significant difference between SCZ patients and healthy controls [173]. In addition to the established SCZ-associated pathogens, gut microbes could activate cytokine and complement systems, causing neuroinflammation and increasing the risk of psychotic symptoms [174]. In one study, maternal complement was elevated in peripheral blood at time of birth in mothers whose children went on to develop severe psychoses [175]. This complement activation during pregnancy can affect the development of neuronal networks [176]. Metagenomic studies showed increased fecal abundance of *Lactobacillus* among individuals with first-episode psychosis, as well as diminished response to treatment in those with the strongest evidence of dysbiosis [177]. Additionally, *Lactobacillus* phage *phiadh* showed increased abundance in the oropharyngeal microbiomes of SZ-affected individuals [177; 178].

Candida albicans and *Saccharomyces cerevisiae* were observed to be elevated in SCZ patients [179]. In a double-blind, placebo-controlled study, *C. albicans* was elevated in

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SCZ and was associated with more severe cognitive impairments and psychiatric symptoms [180]. Probiotic treatment reduced C. *albicans* antibodies over the 14-week study period in males, but not in females.

Another study showed an association of the oropharyngeal microbe *Ascomycota*, being more abundant in SCZ patients than in non-affected individuals [181]. Significant enrichment of lactic acid-producing microbes like *Candida* and *Eubacterium* compared to *Neisseria*, *Haemophilus*, and *Capnocytophaga*, also suggests a specific dysbiosis signature in SCZ patients. Recently, the oropharyngeal microbiome showed an underrepresentation of *Neisseria Weeksellaceae*, and *Prevotella* in SCZ and individuals with manic episodes [51].

12. Substance Use Disorders

Gut dysbiosis has been reported among subjects with substance use disorders (SUD) and hypotheses have been made regarding whether these differences are consequences of substance use or they contribute to the psychopathology observed among the patients investigated [182]. As such, this section includes both studies of SUD-affected patients and the effects observed among users of addictive substances. Comparing intestinal microbiota in SUD patients and healthy controls, the species diversity index and the abundance of *Thauera*, *Paracoccus*, and *Prevotella* were increased in SUD individuals with over-representation of microbial pathways related to translation, DNA replication and repair, and cell growth [183]. Changes in microbiome community composition suggest negative impact of alcohol dependence on gut microbiota [184]. Alcohol dependent subjects also show altered gut permeability, which is related to higher scores greater acute depression, anxiety, and alcohol craving after abstinence [185]. Gut permeability appears to induce neuroinflammation associated with changes in mood, cognition, and alcohol abuse [186]. Among the gut-derived bacterial products, the permeation of lipopolysaccharides and peptidoglycans was observed to stimulate certain inflammatory pathways in peripheral blood mononuclear cells associated with alcohol craving [187; 188].

While tobacco smoking generally decreases gut microbiome diversity, it increases the abundance of *Proteobacteria*, *Clostridium*, *Bacteroides*, and *Prevotella* [189]. Cigarette smoking is also associated with changes in the oral microbiome with differences between active smokers, former smokers, and never smokers. Active smokers show a depletion of *Proteobacteria*, *Capnocytophaga*, and *Peptostreptococcus* and *Leptotrichi*a and an enrichment of *Atopobium and Streptococcus* [190]. Smoking-associated changes in oral microbiomes were related to changes in microbial genes associated with carbohydrate, energy, and xenobiotic metabolisms [190].

Taking the advantage of the resting-state functional magnetic resonance imaging technique for the analysis of brain functional networks, changes in brain functional connectivity (mainly including connectivity between brain default network and other task-positive networks) were observed to be associated with microbial imbalance caused by nicotine dependence in smokers [191]. A consistent association between gut microbiota and opioid-related traits has been reported across multiple studies [192]. Mu-opioid receptors in neurons within the myenteric ganglia or on nerve terminals innervating smooth muscle cells appear

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to affect analgesic tolerance to opioids [193]. In patients affected by type-2 diabetes, the abundance of *Bifidobacterium* and *Prevotella* genera in the gut microbiome appears to be regulated by the interaction of exogenous opioids with mu-opioid receptors in the gut [194]. In male C57Bl6/J mice treated with intermittent morphine, depletion of the gut microbiota showed increased neuroinflammation, reduced opioid analgesic potency, and impaired cocaine reward [195]. In mice, the bacterial depletion with oral gavage of an antibiotic cocktail reduced gut bacteria and morphine-induced gut permeability, also showing the ability to prevent tolerance while not altering naloxone withdrawal susceptibility [196]. In a self-directed intake model, a diet enriched for omega-3 polyunsaturated fatty acids increases microbial richness, phylogenetic diversity, and evenness, improving oxycodone-seeking behaviors [197].

In cannabis users, the abundance of *Prevotella* genera in gut microbiome was positively correlated with fluid cognition which is associated with the capacity of an individual to process information, flanker inhibitory control, working memory, and cognitive flexibility [198]. These associations were not present in cannabis non-users.

13. Conclusions

The study of the human microbiome in the context of psychiatric disorders is an emerging and promising field of study. To date, most studies are focused on the gut-brain axis and neuroinflammation, highlighting potential pathogenetic mechanisms in the context of psychiatric traits [63; 70]. Although there are a limited number of investigations, oral and skin microbiome can also affect mental health [56; 89; 199]. The current state of microbiome research in neuropsychiatry presents several major limitations. There is a general lack of statistical power in human studies due to the limited number of individuals tested [153]. Studies conducted examining the association of microbiome variation with psychiatric disorders often fail to account adequately for potential confounding factors, such as diet, age, sex, comorbidities, and their associated medications [200]. Another important limitation that is not limited to neuropsychiatry research in is the lack of established standards for microbiome analysis and interpretation that makes difficult to compare findings generated using different analytic frameworks [14; 15]. Although the number of associations between microbiome variation and psychiatric disorders is rapidly growing, there is a systematic lack of mechanistic studies to understand the underlying processes by which the human microbiome affects mental health. These should include human, *in vitro*, *in vivo*, and computational approaches focused on understanding the implications of microbiome function in the context of disease and behavior. A better comprehension of the relationship between the human microbiome and mental health will permit the use of many probiotics and prebiotics, which may augment the effects of current treatment approaches for neuropsychiatric disorders. This could particularly benefit a consistent portion of psychiatric patients not responding to current pharmacological therapies.

Acknowledgements and Declaration of Interest

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Highlights

- The human microbiome in the context of psychiatric disorders is an emerging field of study.
- The gut-brain axis has been associated with several neuropsychiatric disorders.
- Oral and skin microbiome could affect mental health via inflammatory pathways.
- Large samples and appropriate designs are needed to verify the microbiome-brain association.

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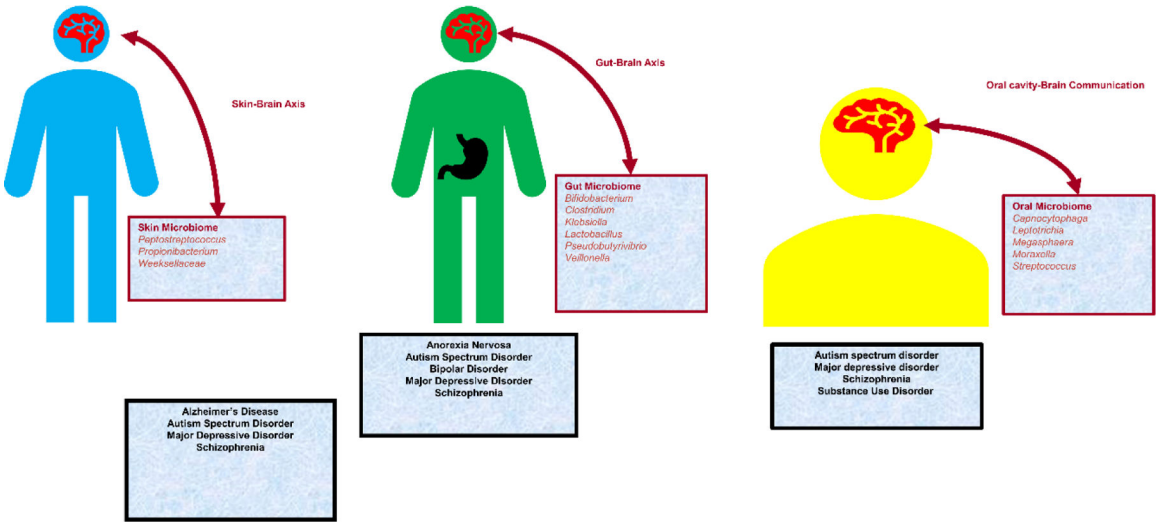

Figure 1:
Microbiome across different anatomical sites and associated psychiatric disorders

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Table 1:

Microorganisms, anatomical sites, and associated psychiatric disorders.

Microorganism	Type	Anatomical sites	Psychiatric Disorders
Lactobacillus fermentum	Commensals	Gut	AD
Lactobacillus acidophilus			AD, ASD
Lactobacilli			
Roseburia inulinivorans			AN
Roseburia			
Methanobrevibacter smithii			
Ruminococcus			AN, ASD
B. bifidum			ASD
Bifidobacterium			
Collinsella stercosis			
LactoBacillus bulgaricus			
Lactobacillus fermentum			
Lactobacillus plantarum WCFS			
Veillonella			
Bifidobacterium adolescentis			
Preveotella			
Akkermansia			BD
Faecalibacterium			
Flavonifractor			
Lachnospiraceae			
Butyrivibrio			MDD
Coprococcus			
Dorea			
Pseudobutyrivibrio			
Lactobacillus phage phiadh			SZ
Leptotrichia		Gut, Oral Cavity	SUD
Peptostreptococcus		Gut, Oral cavity, Skin, Vagina	
Propionibacterium acnes		Gut, Skin	AD
Corynebacterium		Skin	ASD, AD, MDD
Weeksellaceae			SZ
Enterobacteria	Pathogens	Gut	AD, ASD
Clostridium difficle			
Enterobacter			AD, MDD, ASD
Clostridium			AN, ASD
Clostridium bolteae			ASD
Klebsiella			
Clostridium coccoides			

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Microorganism	Type	Anatomical sites	Psychiatric Disorders
Clostridium histolyticum			
Escherichia coli			
Alistipes			MDD
Measles morbillivirus			SZ
Saccharomyces cerevisiae		Gut, Skin	SZ
Streptococcus		Oral cavity	ADHD, ASD, BD, MDD
Neisseria			ASD
Megasphaera			ASD, SZ
Moraxella			ASD, SZ, BD
Capnocytophaga			SUD
Rothia			
Capnocytophaga			SZ
Haemophilus			
Herpes simplex virus		Oral cavity, Skin, Vagina	
Cytomegalovirus		Oral cavity, Urinary tract	
Epstein–Barr virus		Oral cavity, Vagina	
Rubella		Urinary tract	
Candida albicans		Vagina	

Abbreviations- AD: Alzheimer's disease, ADHD: Attention Deficit Hyperactivity Disorder, AN: Anorexia Nervosa, ASD: Autism Spectrum Disorder, BD: Bipolar Disorder, MDD: Major Depressive Disorder, Schizophrenia: SZ, SUD- Substance Use Disorder.