Gut Microbiome in Schizophrenia

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The gut microbiome (GMB) plays an important role in developmental processes and has been implicated in the etiology of psychiatric disorders.

gut microbiome | gut–brain axis | schizophrenia | antipsychotics | prebiotics | probiotics | psychobiotics

1. Introduction

A relationship by which the gut microbiota (GMB) may interact with the central nervous system (CNS) through the gut–brain axis has long been construed. The gut–brain axis is a complex bilateral communication network that ensures proper maintenance of the gastrointestinal (GI) homeostasis. The fundamental mechanisms of the gut–brain axis communications involve neuro-immunoendocrine mediators through the CNS, the autonomic nervous system, the enteric nervous system and the hypothalamic pituitary adrenal axis [1]. In recent decades, studies have reported causal effects of the GMB on human behaviour and on the structure and function of the brain along with elucidating the underlying molecular mechanisms [2][3][4].

Current evidence indicates that communication from the GMB to the brain primarily occurs through neuroimmune and neuroendocrine mechanisms, often involving the vagus nerve [5]. This bottom-up communication is mediated by several microbial-derived molecules, with the best-elucidated examples including short-chain fatty acids, secondary bile acids and tryptophan metabolites [6][7][8]. While some of these microbial-derived molecules interact directly with enteroendocrine cells, enterochromaffin cells and the mucosal immune system, others may penetrate the intestinal barrier to enter systemic circulation. Although some of the molecules are able to cross the blood–brain barrier, it remains unclear whether they interact with brain sites directly or only through neural signaling via spinal and/or vagal afferents [5]. Additionally, the GMB can independently produce or contribute to the production of several neuroactive molecules such as serotonin (5HT), norepinephrine, dopamine and γ-aminobutyric acid [9][10][11]. However, it is unknown if they reach significant concentrations or relevant receptors to elicit a response. Through evolution, the human immune system has maintained a symbiotic relationship with the microbiota. The GMB was shown to play an important role in regulating various immune functions in mice such as autoimmunity, defense and inflammation. The GMB has been implicated in the development and function of the CNS immune cells, specifically microglia [12]. Relative to controls, GF mice have diminished microglia maturation leading to higher risk of pathogen exposure. Adult specific pathogen-free mice treated with antibiotics led to microglia re-entering immature status which can be rescued through recolonization with a complex microbiota. Treatment with

antibiotics reverts microglia back to an immature state, suggesting continuous signaling of the GMB is needed for microglial function [12]. Disruption of the dynamic interaction between the two can result in profound effects on human health.

2. The Gut Microbiome in Behavior and Psychiatric Diseases

Several experimental approaches in animal models have been used to study the influence of the GMB on the gut–brain axis, including fecal microbial transplantation [13][14], colonization with human [14][15] or synthetic [16] microbiota, manipulation of the GMB with antibiotics [13][17][18] and probiotics [19][20][21] and germ-free (GF) animal models [13][22][23][24]. It was demonstrated that the absence of normal GMB in GF mice has significant effects on behaviour such as abnormal memory, sociability, anxiety-like behaviours and motor performance [23]. These behavioural abnormalities could be rescued by colonization at the neonatal stage. In addition to anxiety-like behaviours [19], the GMB is also implicated in relation to stress-responsiveness [19][22] and depression-like behaviours [25][26].

3. Antipsychotics and the Potential Role of the Gut Microbiome

3.1. Antipsychotic-Induced Metabolic Side Effects

Psychiatric patients have a higher relative risk of metabolic syndrome, a combination of cardiovascular risk factors such as dyslipidemia, hypertension, stroke and obesity, than the general population [27]. Moreover, the prevalence of metabolic side effects, type 2 diabetes and antipsychotic-induced weight gain (AIWG), is increased with the use of antipsychotics, specifically with olanzapine and clozapine [27][28][29]. Although the exact mechanisms by which metabolic dysfunction occurs remain unclear, several specific mechanisms of AIWG are supported by research evidence. One mechanism proposed is the antagonism of serotonergic and histaminergic receptors, resulting in increased appetite [30]. Additionally, genetic factors such as associations with 5HTR2C gene promoter polymorphisms or MC4R gene variants have been found to be associated with AIWG [30][31][32].

Evidence also suggests that peptide hormones might mediate AIWG as studies have found correlations between antipsychotics, weight gain and expression of peptide hormones such as leptin and C-peptide [33][34]. Antipsychotics can disrupt mitochondria function, related enzyme activity and ATP levels through downregulation in genes encoding subunits of the electron transport chain [35]. Our groups initiated a pilot study examining the effects of antipsychotics in patients with early psychosis, as well as in patients starting clozapine and in patients being chronically treated with clozapine in order to better understand the potential causal roles of antipsychotic medications and induced metabolic abnormalities [36].

The GMB has been proposed as a potential target in relation to AIWG and other metabolic dysfunction due to its ability to regulate metabolism, homeostasis and energy balance [37][38][39][40]. Morgan et al. (2014) demonstrated that the presence of a gut microbiome was necessary and sufficient for olanzapine-induced weight gain in GF

mice. They proposed olanzapine's effect on AIWG to be through its in vitro antimicrobial activity against resident enteric bacteria [41]. Sex may play a role as females have been observed to be more susceptible to metabolic side effects such as weight gain than males in both animal and human models, with some studies reporting a decrease in body weight in male rats [29][39][41][42][43]. Evidence suggests a lipogenic effect when administering olanzapine in rodents; however, significant weight gain is only seen in female rats [42]. Furthermore, co-treatment of minocycline with olanzapine prevents AIWG in mice. However, coadministration of tetracycline, a closely related antibiotic showed no effects on AIWG, suggesting the mechanism behind minocycline is distinct from its antibiotic properties [44]. Olanzapine was also observed to alter the GMB profile in both male and female-treated rats, specifically increased levels of *Firmicutes* and decreased levels of *Bacteriodetes* [37]. Furthermore, treatment with prebiotics or antibiotics attenuated the olanzapine-induced metabolic dysfunction, including AIWG in female rats [38][45]. However, Kao et al. (2018) observed no change in GMB composition after olanzapine treatment, which may have been due to the short duration and variable dose of olanzapine treatment. The prebiotic mixture alone was reported to have some notable effects such as increasing *Bifidobacteria* spp. and reducing species within the *Firmicutes* (*Coprococcus*, *Oscillibacter*, *C. coccoides*, *Roseburia intestinalis cluster*, *Clostridium XVIII cluster*) and *Proteobacteria* (*Escherichia*/*Shigella* spp.) phyla [45]. Furthermore, olanzapine was observed to attenuate this effect of the prebiotic mixture, which suggests the antipsychotic does influence the GMB.

3.2. Effects of Antipsychotics on the Microbiome

Variety of antipsychotics used in various research studies may play a role in this inconsistency as different antipsychotics have been shown to have different effects on the GMB [38][39][43]. A study examining the effects of APs on the GMB in patients with bipolar disorder found a significant decrease in species diversity in females [46]. Recent in vitro work extensively examined over 1000 marketed drugs and found that 24% of the drugs with human targets inhibited the growth of at least one strain [47]. Among these drugs, APs were overrepresented with 26 out of 37 having antibacterial activity and displayed a similar pattern when targeting specific species. The authors hypothesized that direct bacterial inhibition may not only be a side effect of the APs, but also be part of their mechanism of action [47]. However, clozapine, risperidone and olanzapine were reported to lack any antibacterial activity.

When investigating the GMB in first-episode SCZ patients, chronic SCZ patients and healthy controls, Ma et al. (2020) found that chronically antipsychotic-treated SCZ patients had increased abundance in family *Enterococcaceae* and *Lactobacillaceae* and in genus *Enterococcus*, *Escherichia*, *Lactobacillus*, *Shigella*, *Streptococcus* and *Veillonella* relative to first-episode SCZ patients [48]. The same microbiota levels were similar or increased in abundance in first-episode SCZ patients compared to healthy controls, suggesting that antipsychotics may have negative effects on microbiota levels. In a similar fashion, relative abundances of family *Peptostreptococcaceae* and *Veillonellaceae* and genus *Fusobacterium* and *Megasphaera* were increased in chronic SCZ patients compared to first-episode SCZ patients but remained unchanged between first-episode SCZ patients and healthy controls, suggesting a normalizing effect of antipsychotics on these microbiota levels [48].

Bahr et al. (2015) reported that chronic treatment of risperidone in male children (n = 18) was associated with a lower a *Bacteroidetes*:*Firmicutes* ratio and an increase in BMI. Furthermore, a gradual decrease in the *Bacteroidetes*:*Firmicutes* ratio was seen over the course of risperidone treatment [39].

Yuan et al. (2018) looked at the effects of risperidone in drug-naive, normal weight, first-episode SCZ patients. After a 24-week treatment plan, there were significant increases in relative abundance of fecal *Bifidobacterium* spp. and *Escherichia coli* and significant decreases in the abundance of fecal *Clostridium coccoides* group and *Lactobacillus* spp. Increases in body weight, BMI, blood-glucose, triglycerides and C-reactive protein were observed as well. Antipsychotic-naive patients with first-episode SCZ were found to have reduced levels of *Bifidobacterium* spp., *Escherichia coli* and *Lactobacillus* spp. and increased levels of *Clostridium coccoides* group compared to matched healthy controls. However, levels of *Lactobacillus* spp. and *Bifidobacterium* spp. were elevated in first-episode psychosis patients compared to controls following antipsychotic treatment [49][50]. Weight gain was found to be correlated with GMB composition of first-episode SCZ patients treated with risperidone. Specifically, increase in the relative abundance of *Bifidobacterium* spp. strongly correlated with weight gain.

However, another study conducted by Pelka-Wysiecka et al. (2019) showed differing results. The study analyzed the effect of olanzapine on the GMB in 20 SCZ patients [50]. Patients underwent a 7-day washout of all psychiatric medication, received standard hospital diet and were administered olanzapine treatment. Stool samples were taken at baseline after the washout and after 6 weeks of treatment. Similar to previous studies, only women experienced a significant increase in BMI. No significant changes were observed in alpha diversity and GMB composition [51]. However, the absence of significant changes may be due to the short intervention period.

Zhu et al. (2020) looked at the effects of APs on the GMB by following up with 38 medication-free patients with SCZ at baseline and 3 months after treatment. 26 microbial species were identified to differ between medication-free SCZ patients and HCs at baseline [52]. However, 20 species remained altered after 3 months of AP treatment compared with controls. Throughout AP treatment, authors reported 28 differentially abundant bacterial species, five of which were included in the 26 operational taxonomic unit SCZ classifiers [52]. The authors suggest that the GMB is influenced by APs but is not completely restored from SCZ-associated alterations.

Current clinical studies provide little evidence on the relationship between the APs, GMB and metabolic changes. Given the inconsistent findings highlighted in this review, future studies should ideally address the following: larger patient samples, with standardized medications, use of homogeneous populations (e.g., age, sex, BMI, symptom severity), comparable study designs and accounting for geographical diversity.

4. Evidence for Psychobiotic Intervention in Schizophrenia

A GMB is essential for optimal function of the immune system and immune dysfunction has been implicated in SCZ. Consequently, alterations in the GMB may play a key role in the etiology and treatment response of SCZ through bacterial infections and contributes to a chronic inflammatory state. The studies by Shen et al. (2018) and Zhang et al. (2020) found reduced levels of the genera: *Roseburia* and *Faecalibacterium* [53][54]. Notably, both

genera play an important role in maintaining the intestinal barrier through the production of butyrate [55][56]. Braniste et al. (2014) concluded that not only the presence of a GMB is essential for normal development of the blood–brain barrier, but studies also indicated that the GMB can also regulate its permeability [57]. Therefore, through such mechanisms, disturbances to the GMB can lead to CNS infection and inflammation.

Although many findings were inconsistent, a few taxonomic groups were repeatedly reported to be altered in SCZ patients (Table 1). Multiple studies reported increased species within the *Fusobacterium*, *Lactobacillus*, *Megasphaera* and *Prevotella* genera, most of which are gram-negative bacteria [58][59][52][53][54][60][48][61]. While gram-negative bacteria are common in normal gut flora, increased permeability of the gut wall may result in systemic circulation of enteric inflammatory molecules such as lipopolysaccharides (LPS). An in vitro study examined the effects of LPS on intestinal epithelial cells and found that acute administration of LPS resulted in altered and reduced distribution of tight junctions [62]. LPS has been shown to be an effective neurodevelopmental model of SCZ in rodents [63][64][65]. In addition, to LPS, SCZ patients have been shown to have increased inflammatory cytokines which may contribute to the change in gut permeability and development of a “leaky gut” [66].

Table 1. List of taxonomic groups that were significantly increased/decreased in multiple studies.

Taxa	Increased in Schizophrenia	Decreased in Schizophrenia
Phylum: *Firmicutes*	Castro-Nallar et al., 2015 (Oral) [59]	Shen et al., 2018 [53]
Phylum: *Proteobacteria*	Shen et al., 2018 [53] Ma et al., 2020 (vs HC only) [48] Zhang et al., 2020 (FSCZ) [67]	Nguyen et al., 2019 [54]
Class: *Deltaproteobacteria*	Xu et al., 2020 [61] Zhang et al., 2020 (FSCZ) [67]	
Order: *Actinomycetales*	Xu et al., 2020 [61] Zhang et al., 2020 (FSCZ) [67]	
Order: *Clostridiales*	He et al., 2018 (High-risk for SCZ) [58]	Shen et al., 2018 [53]

Taxa	Increased in Schizophrenia	Decreased in Schizophrenia
Family: *Enterobacteriaceae*	Shen et al., 2018 [53] Ma et al., 2020 (vs. HC only) [48]	Zheng et al., 2019 [60]
Family: *Enterococcaceae*	Ma et al., 2020 [48]	Xu et al., 2020 [61]
Family: *Lactobacillaceae*	Shen et al., 2018 [53] Ma et al., 2020 [48]	
Family: *Lachnospiraceae*		Shen et al., 2018 [53] Zheng et al., 2019 [60] Zhang et al., 2020 (FSCZ) [67]
Family: *Prevotellaceae*	Shen et al., 2018 [53] Zheng et al., 2019 [60]	
Family: *Rikenellaceae*	Zheng et al., 2019	Xu et al., 2020 [61]
Family: *Veillonellaceae*	Shen et al., 2018 [53] Zheng et al., 2019 [60] Ma et al., 2020 (vs. FSCZ only) [48]	
Genus: *Acidaminococcus*	Shen et al., 2018 [53] Zhu et al., 2020 (FSCZ) [52]	
Genus: *Akkermansia*	Zheng et al., 2019 [60]	

Taxa	Increased in Schizophrenia	Decreased in Schizophrenia
	Zhu et al., 2020 (FSCZ) [52]	
Genus: *Anaerotruncus*	Zhang et al., 2020 (FSCZ) [67] Zhu et al., 2020 (FSCZ) [52]	
Genus: *Bifidobacterium*	Castro-Nallar et al., 2015 (Oral) [59] Zhu et al., 2020 (FSCZ) [52]	Yuan et al., 2018 (FSCZ) [49]
Genus: *Blautia*	Nguyen et al., 2019 [54] Zhang et al., 2020 (FSCZ) [67]	Shen et al., 2018 [53] Zheng et al., 2019 [60]
Genus: *Citrobacter*	Shen et al., 2018 [53] Ma et al., 2020 (vs. FSCZ only) [48] Zhu et al., 2020 (FSCZ) [52]	Zheng et al., 2019 [60]
Genus: *Clostridium*	Shen et al., 2018 [53] Ma et al., 2020 (vs. FSCZ only) [48]	
Genus: *Coprobacillus*	Ma et al., 2020 (vs. HC only) [48] Zhu et al., 2020 (FSCZ) [52]	
Genus: *Coprococcus*	Zhang et al., 2020 (FSCZ) [67]	Shen et al., 2018 [53] Zheng et al., 2019 [60]
Genus: *Eggerthella*	Xu et al., 2020 [61]	

Taxa	Increased in Schizophrenia	Decreased in Schizophrenia
	Zhang et al., 2020 (FSCZ) [67]	
Genus: *Enterococcus*	Ma et al., 2020 [48] Zhu et al., 2020 (FSCZ) [52]	Xu et al., 2020 [61]
Genus: *Fusobacterium*	Shen et al., 2018 [53] Zheng et al., 2019 [60] Ma et al., 2020 (vs. FSCZ only) [48]	
Genus: *Lactobacillus*	Castro-Nallar et al., 2015 (Oral) [59] He et al., 2018 (High-risk for SCZ) [58] Shen et al., 2018 [53] Ma et al., 2020 [48] Zhu et al., 2020 (FSCZ) [52]	Yuan et al., 2018 (FSCZ) [49]
Genus: *Megasphaera*	Shen et al., 2018 [53] Nguyen et al., 2019 [54] Zheng et al., 2019 [60] Ma et al., 2020 (vs. FSCZ only) [48] Xu et al., 2020 [61]	
Genus: *Prevotella*	He et al., 2018 (High-risk for SCZ) [58] Shen et al., 2018 [53]	Yolken et al., 2020 (Oral) [68]

Taxa	Increased in Schizophrenia	Decreased in Schizophrenia
	Zheng et al., 2019 [60] Zhang et al., 2020 (FSCZ) [67]	
Genus: *Ruminococcus*	Nguyen et al., 2019 [54] Ma et al., 2020 (vs. FSCZ only) [48]	Zhang et al., 2020 (FSCZ) [67]
Genus: *Streptococcus*	Ma et al., 2020 [48] Yolken et al., 2020 (Oral) [68]	Shen et al., 2018 [53]
Genus: *Veillonella*	Ma et al., 2020 [48] Zhu et al., 2020 (FSCZ) [52]	
Species: *Akkermansia muciniphila*	Xu et al., 2020 [61] Zhu et al., 2020 (vs. HC only) [52]	
Species: *Bacteroides eggerthii*		Shen et al., 2018 [53] Zheng et al., 2019 [60]
Species: *Bifidobacterium adolescentis*	Shen et al., 2018 [53] Xu et al., 2020 [61] Zhu et al., 2020 (vs. HC only) [52]	
Species: *Escherichia coli*	Zhu et al., 2020 (vs. FSCZ only) [52]	Yuan et al., 2018 (FSCZ) [49]
Species: *Eubacterium hallii*	Castro-Nallar et al., 2015 (Oral) [59]	Zhu et al., 2020 (vs FSCZ only) [52]

Notably, SCZ patients were reported to have lower levels of the family *Lachnospiraceae*, which has been reported to be beneficial in health such as butyrate and other short-chain fatty acid production. As previously mentioned, the

Taxa	Increased in Schizophrenia	Decreased in Schizophrenia [55][56]
Species: *Lactobacillus gasseri* [69] [74][75]	Castro-Nallar et al., 2015 (Oral) [59] [19][22][70][71][72][73] Xu et al., 2020 [61]	
Species: *Lactobacillus ruminis*	He et al., 2019 (High-risk for SCZ) [58] Zhu et al., 2020 (vs. HC only) [52]	[76] Zhu et al., 2020 (vs FSCZ) [52]
Species: *Lactobacillus salivarius*	Castro-Nallar et al., 2015 (Oral) [59] Zhu et al., 2020 (vs. HC only) [52]	[45]
Species: *Haemophilus parainfluenzae*	[80]	Nguyen et al., 2019 [54] Zheng et al., 2019 [60]

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rhamnosus and *Bifidobacterium animalis*. Probiotic supplementation led to a reduction of the acute phase reactant von Willebrand factor in SCZ patients, suggested to be the secondary effect of probiotic-induced improvement of intestinal epithelium integrity. Patients treated with probiotics also were less likely to develop severe bowel difficulties [81]. Bowel difficulty was reported to be positively correlated with seropositivity of *Candida albicans* [82]. Positive symptoms of SCZ were significantly improved in males who were seronegative for *Candida albicans* compared to those who were seropositive within the 13-week timepoint. However, no significant effects on the PANSS scores were seen for the full duration of the study.

In a more recent study, probiotic *Bifidobacterium breve* A-1 was given to SCZ patients for 4 weeks and improvements were seen in anxiety, depression and PANSS scores [83]. Elevated levels of various interleukins were also measured, including IL-22 and tumour necrosis factor-related activation induced cytokine (TRANCE). The authors suggested that the reported symptom improvements could be due to the critical roles IL-22 and TRANCE play in the function of the gut epithelial barrier.

Ghaderi et al. (2019) investigated probiotic supplement treatment in SCZ patients by administering a combination of vitamin D and probiotic mixture containing *Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *Lactobacillus fermentum* and *Lactobacillus reuteri* for 12 weeks [84]. A significant decrease in metabolic abnormalities and circulating C-reactive protein were noted, indicating reduced inflammation, alongside improvements in general and total PANSS scores and plasma total antioxidant capacity. However, it is uncertain whether vitamin D, probiotic supplement, or a combination of both are responsible for the observed improvements.

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