iThe Role of the Gut Microbiome in the Development of Schizophrenia

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Abstract:

Schizophrenia is a heterogenous neurodevelopmental disorder involving the convergence of a complex and dynamic bidirectional interaction of genetic expression and the accumulation of prenatal and postnatal environmental risk factors. The development of the neural circuitry underlying social, cognitive and emotional domains requires precise regulation from molecular signalling pathways, especially during critical periods or "windows", when the brain is particularly sensitive to the influence of environmental input signalling. Many of the brain regions involved, and the molecular substrates sub-serving these domains are responsive to life-long microbiota-gut-brain (MGB) axis signalling. This intricate microbial signalling system communicates with the brain via the vagus nerve, immune system, enteric nervous system, enteroendocrine signalling and production of microbial metabolites, such as short-chain fatty acids. Preclinical data has demonstrated that MGB axis signalling influences neurotransmission, neurogenesis, myelination, dendrite formation and blood brain barrier development, and modulates cognitive function and behaviour patterns, such as, social interaction, stress management and locomotor activity. Furthermore, preliminary clinical studies suggest altered gut microbiota profiles in schizophrenia. Unravelling MGB axis signalling in the context of an evolving dimensional framework in schizophrenia may provide a more complete understanding of the neurobiological architecture of this complex condition and offers the possibility of translational interventions.

Keywords: Schizophrenia, Psychosis, Microbiota, Microbiome, Gut-brain axis, Psychobiotics

Introduction:

Schizophrenia is complex heterogeneous neurodevelopmental disorder with deficits across many dimensions. The expression of the underlying genetic vulnerability is shaped by a multifaceted combination of prenatal and early postnatal environmental factors. These factors sensitise a developing brain and its information processing ability, to the subsequent accumulation of additional environmental insults, which may overwhelm compensatory capacities during adolescence and emerge as psychotic symptoms. Subtle deficits in cognition, social communication and functioning are often evident prior to the onset of overt psychotic symptoms and the majority of people experience recurring psychotic relapses with variable degrees of functional impairment. A precise integrative mechanistic understanding of the interaction of genetic and environmental processes across the neurodevelopmental trajectory in this condition remains elusive.

The microbial ecosystem is intrinsically linked to human health. Microbiology and neuroscience have converged to begin to elucidate the role of microbes in brain development and function (Dinan and Cryan, 2013). Microbes communicate with the brain via the gut-brain axis encompassing the immune system (Erny et al., 2015), tryptophan metabolism (O'Mahony et al., 2015), the hypothalamic-pituitary-adrenal (HPA) axis (Sudo et al., 2004), the vagus nerve (Bravo et al., 2011) and by the production of microbial metabolites, such as short chain fatty acids (SCFA's) (Stilling et al., 2016b). MGB axis signalling occurs throughout life, but is particularly important during the early postnatal period, as the trajectory of early postnatal brain development overlaps with the acquisition and expansion of the gut microbiome. Advances in preclinical research have revealed that neurotransmission, neurogenesis, myelination, dendrite formation and blood brain barrier organisation are under the influence of this MGB axis signalling system. At the behavioural level MGB axis signalling modulates cognitive function and patterns related to social interaction, locomotor activity and stress management.

Precisely determining the subtle complexities in gut microbiota acquisition and development and corresponding signalling via the MGB axis across the neurodevelopmental stages in schizophrenia is an exciting and evolving area of neuroscience research. Furthermore, unravelling microbiota-diet and microbiota-drug interactions could lead to clinical benefits. Navigating the emerging field of psychiatric microbiome research may yield novel insights into individual variations and perhaps enable the development of new interventions for certain dysregulated domains in psychotic disorders. This review synthesizes the preclinical and emerging clinical evidence implicating the microbiome in schizophrenia.

Maturation of gut microbiota

The evolutionary transition from unicellular to multicellular organization occurred approximately 3 to 3.5 billion years ago (Grosberg and Strathmann, 2007). This co-evolution has shaped evolving phenotypes in all life forms and resulted in an interlinked physiology between microbe and man. The human body contains as many bacterial cells as human cells, with a total mass of 0.2 kg (Sender and Fuchs, 2016). The majority of these microbes reside in the gastro-intestinal tract (GIT). This microbial ecosystem, regarded as an extra, albeit mutable organ (Clarke et al., 2014), varies in spatial organization and localization along the GIT, with low concentrations transiting from the ileum to the cecum of about 10^8 bacteria per gram to 10^{11} bacteria per gram in the stool (Sender et al., 2016). Thousands of new human microbiome species are being discovered (Forster et al., 2019, Pasolli et al., 2019) and while dominated by bacteria, other microbes such as viruses and bacteriophages, protozoa, archaea and fungi are also present (Lankelma et al., 2015). In terms of bacterial phyla composition, as measured by 16S rRNA gene sequencing and metagenomic shotgun sequencing of fecal samples, *Firmicutes*, *Actinobacteria*, and *Bacteroidetes* dominate, with lower relative abundances of *Verrucomicrobia* and *Proteobacteria* (Zhernakova et al., 2016).

Due to complex interindividual variation, comprising marked functional redundancy, it is difficult to precisely define a typical healthy adult gut microbiota (The Human Microbiome Project et al., 2012, Falony et al., 2016, Shanahan and Hill, 2019). However, in the gut, high compositional diversity and stability are associated with health benefits (Lozupone et al., 2012). Conversely, the impact of a narrowing of gut microbiome diversity and its functional repertoire is associated with indices of poor health (Vangay et al., 2018, Claesson et al., 2012, Kelly et al., 2016a, Kelly et al., 2019b). The gut is largely thought to be sterile in utero and colonized during birth and postnatally (Perez-Munoz et al., 2017, Bushman, 2019), though the maternal microbiota may indirectly exert effects on the developing fetus (Gomez de Aguero et al., 2016, Koren et al., 2012). For example, whether inflammatory responses arise as a consequence of bacterial translocation to the intrauterine environment during periods of excessive maternal gestational stress, resulting in deficits in neurodevelopment remains an open question (Chen and Gur, 2019).

Acquisition and expansion of the infant microbiome are key processes in the development of a healthy host-microbiome relationship. The gut microbiota in the initial days of life is unstable and of low diversity (Arrieta et al., 2014). Multiple maternal sources, such as vaginal, skin, oral, and gut communities all contribute to the early infant microbiome. However, a few days postpartum, the contribution of the vaginal and skin microbiome decreases, with gut strains showing more persistence in the infant gut (Ferretti et al., 2018, Yassour et al., 2018). Breast milk facilitates transmission of *bifidobacterial* communities, including *bifidobacterial* phages (Duranti et al., 2017). Microbial diversity increases over the first three to four year of life (Fouhy et al., 2019, Yatsunenko et al., 2012). There is a divergence in

intestinal microbiome assembly between different birth modes and between preterm and full-term infants, with implications for the associated microbial metabolite profile (Fouhy et al., 2019, Bokulich et al., 2016, Hill et al., 2017). However, full-term C-section infants gradually progress to harbouring a microbiota closely resembling full-term spontaneous vaginally delivered infants by week eight of life (Hill et al., 2017).

The trajectory of early postnatal brain development overlaps with the acquisition and reorganization of the gut microbiota (Borre et al., 2014, Chu et al., 2017). A recent cohort study in human infants aged 3 to 6 months (n=309) suggested an association between infant gut microbiome composition and communication, personal and social, and fine motor skills at age three years, mostly driven by taxa within the order *Clostridiales* (Sordillo et al., 2019). A study of normally developing 1-year-olds (n=89), identified 3 groups based on their bacterial composition, that differed on the Mullen scales of early learning (Carlson et al., 2018). Additionally, higher alpha diversity was associated with lower scores on the overall composite score, visual reception scale, and expressive language scale at 2 years of age, though there were minimal differences in regional brain regions, measured using structural MRI (Carlson et al., 2018). However, the physiologically relevant MGB axis signalling cascades remain to be sufficiently characterised (Dinan et al., 2018).

C-section alters the gut microbiota, and is associated with asthma, allergies and obesity in offspring (Bar-Meir et al., 2019, Yuan et al., 2016, Martinez et al., 2017). While obstetric complications are associated with schizophrenia (Cannon et al., 2002) the link between C-sections and schizophrenia is tenuous (Fond et al., 2017, O'Neill et al., 2015). Other important factors that shape the gut microbiome include breast- and formula-feeding (Timmerman et al., 2017), antibiotic usage in early life (Korpela et al., 2018, Bokulich et al., 2016, Stearns et al., 2017) and malnutrition (St Clair et al., 2005, Million et al., 2017). It has yet to be determined whether subtle alterations of the gut microbiome at birth and the proceeding early developmental phase, for example, by delivery mode, feeding mode, antibiotics, infections and stressors combine with other vulnerability factors, to increase the risk of schizophrenia (**Table 1**).

Microbiota, the immune system and schizophrenia

The gut microbiota performs a critical priming function in the development of the neuroimmune system, pivotal for myelination, synaptic pruning, and neuronal remodelling (Hoban et al., 2016c, Rea et al., 2016). This neuroimmune signalling during the early postnatal developmental stages is an important determinant of cognitive function and emotional behaviour (Spencer and Meyer, 2017). Alterations in the gut microbiota signature early in life can predispose to immune disorders (Penders et al., 2007, Fujimura et al., 2016, Al Nabhani et al., 2019).

Immune system alterations are implicated in the pathophysiology of schizophrenia (Corvin and Morris, 2014, Schizophrenia Working Group of the Psychiatric Genomics, 2014, Feigenson et al., 2014, Muller, 2014, Sekar et al., 2016, Benros et al., 2012). It is well established that certain infections increase the risk of schizophrenia (Meyer et al., 2009, Brown, 2012). A large epidemiological study (n=1,015,447), showed that treatment with anti-infective agents (primarily driven by infections treated with antibiotics), were associated with an increased risk of schizophrenia by a hazard rate ratio of 1.37 (Kohler et al., 2017, Kohler-Forsberg et al., 2018). A genetically programmed subtle alteration in the immune system, in combination with a precisely timed pathogen exposure may amplify susceptibility to schizophrenia. For example, the timing of maternal immune activation (MIA), triggered by prenatal infection may act as a "neurodevelopmental primer" (Meyer, 2014, Meehan et al., 2016, Meyer et al., 2006, Smith et al., 2007, Knuesel et al., 2014, Coiro et al., 2015, Pendyala et al., 2017).

The MIA rodent model displays deficits in social interactions, a tendency toward repetitive behaviour and reduced communication and serves as a useful model for neurodevelopmental disorders such as schizophrenia and Autism Spectrum Disorder (ASD). The commensal *Bacteroides fragilis* corrected gut permeability dysfunction and reversed the deficits in communicative, stereotypic, anxiety-like and sensorimotor behaviours in a MIA mouse model (Hsiao et al., 2013). In other ASD mouse models, *L. reuteri* treatment acted in a vagus nerve-dependent manner and ameliorated social interaction-induced synaptic plasticity in the ventral tegmental area of ASD mice, but not in oxytocin receptor-deficient mice (Sgritta et al., 2019).

In a recent fecal microbiota transplantation (FMT) study, GF mice colonized with human ASD microbiota displayed alternative splicing of ASD-relevant genes, social and repetitive behavioural abnormalities and altered metabolome profiles compared to GF mice transplanted with fecal samples from typically developing children (Sharon et al., 2019). Furthermore, administration of microbial metabolites (taurine, the metabolic product of cysteate or taurocholic acid, and 5AV, the fermentation product of proline - both GABA-A receptor agonists) to a BTBR autism mouse model, improved the ASD-like behaviours (Sharon et al., 2019). Taken together, these preclinical studies suggest that microbial-based strategies may show promise in ameliorating social dysfunction, characteristic of both ASD and schizophrenia.

Complement, Cytokines and Toll-Like Receptors (TLRs)

A low-grade inflammatory component both peripherally and centrally, in First episode psychosis (FEP) individuals (Di Nicola et al., 2013, de Witte et al., 2014), including those without medication (Upthegrove et al., 2014, Song et al., 2014) and chronic schizophrenia has been demonstrated (Rodrigues-Amorim et al., 2017, Miller et al., 2011, Gallego et al., 2018). Individuals exposed to elevated maternal levels of anti-inflammatory cytokines were significantly less likely to develop

psychosis in adulthood (Allswede et al., 2016), whereas elevated maternal blood levels of complement factor C1q increased the risk of psychosis (Severance et al., 2014). An intriguing translational study implicated dysregulated complement C4 activity, another component of the classical complement cascade, that recognizes and eliminates pathogens and cellular debris (Sekar et al., 2016). This study showed that excessive C4 mediated synapse elimination during postnatal development, was associated with the development of schizophrenia (Sekar et al., 2016). Among those at clinical high risk of developing psychosis, and then converted to psychosis, higher levels of plasma pro-inflammatory cytokines at baseline were predictive of steeper rates of gray matter reduction in the right prefrontal cortex (PFC) (Cannon et al., 2015).

However, the source of this low-grade inflammation is not fully known. Whether it reflects underlying pathophysiology or is due to other factors such as obesity, smoking, antipsychotic use, or stress has yet to be conclusively determined. The gut microbiota mediates many of these factors. Indeed, gut inflammation and permeability may be a contributing source, at least in subgroups. In a mouse model of social disruption, stress altered the gut microbial profile and increased levels of the pro-inflammatory cytokine IL-6 (Bailey et al., 2011). It noteworthy that a serological surrogate marker of bacterial translocation (soluble CD14) was elevated in schizophrenia compared to controls, though there were no differences in the levels of lipopolysaccharide binding protein (LBP) (Severance et al., 2013).

Toll-Like Receptors (TLR) are pattern recognition receptors (PRR), which may have evolved to control resident beneficial microbes rather than invasive pathogens (Bosch, 2014). TLRs recognize microbe-associated molecular patterns and serve as molecular communication channels between the gut microbiota and immune system homeostasis. TLR4 binds lipopolysaccharide in gram-negative bacteria, whereas TLR2 recognizes lipoproteins and peptidoglycans (PGN) from gram-positive bacteria, leading to the production of cytokines. Furthermore, TLR's are able to modulate neurodevelopmental processes. TLR2 and TLR4 knockout mice showed subtle impairments in behaviour and cognitive functions (Too et al., 2016, Park et al., 2015). PRR's, such as TLR2 in the developing brain can recognize bacterial PGN. A study in mice, suggested that PGN from commensal bacteria can enter blood and cross the BBB during postnatal development in healthy animals (Arentsen et al., 2017). Furthermore, the PGN-sensing molecules in the developing striatum are partially under the influence of the gut microbiota, and knockdown of the PGN-recognition protein 2 (Pglyrp2) was associated with the development of sex dependent changes in social behaviour and alterations in the expression of the ASD risk gene c-Met (Arentsen et al., 2017).

Human studies are few, but drug-naïve patients with schizophrenia exhibited an increased percentage of TLR4 and TLR5 monocytes and TLR5 T reg/Tact cells compared to matched controls, with higher percentages of TLR4 and TLR5

monocytes correlating with more severe cognitive deficits (Kéri et al., 2017). There are alterations in TLR agonist-mediated cytokine release in whole blood in patients with psychosis compared to healthy controls (McKernan et al., 2011). Moreover, alterations in the expression of the initial elements of the TLR4 signalling pathway in post-mortem PFC samples from psychosis patients have been shown, though may have been influenced by antipsychotic treatment status (García-Bueno et al., 2016).

Microbiota and Microglia

The gut microbiota is also involved in the maturation and activation of microglia (Cryan and Dinan, 2015, Erny et al., 2015). In PET studies, subjects at high risk of psychosis, and those with schizophrenia showed evidence of altered microglial activation compared to healthy controls (Bloomfield et al., 2016, van Berckel et al., 2008). However, not all studies are consistent (Collste et al., 2017, Holmes et al., 2016, Notter and Meyer, 2017, Narendran and Frankle, 2016). Interestingly, GF mice display underdeveloped and immature microglia in the cortex, corpus callosum, hippocampus, olfactory bulb, and cerebellum (Erny et al., 2015). There was an upregulation of microglia transcription and survival factors, and downregulation of cell activation genes and genes for type 1 IFN receptor signalling compared with those isolated from conventionally colonized control mice. These defects were partially restored by recolonization with a complex microbiota, and SCFAs reversed the defective microglia in absence of complex microbiota (Erny et al., 2015). A recent study showed that the prebiotic (inulin) administered to mice for 14-weeks altered the gut microbiota and ameliorated stress-induced immune priming in middle-aged mice (10 months), while reducing brain infiltration of Ly-6Chi monocytes and reversing increases in a subset of activated microglia (Ly-6C+) (Boehme et al., 2019). Collectively, these studies suggest that subtle alterations in gut microbiota acquisition and development, by regulating neuro-inflammatory processes, may act as additional vulnerability factors that predispose to schizophrenia.

Blood Brain Barrier (BBB)

BBB dysfunction has been associated with psychotic disorders (Pollak et al., 2017). Although the direction of causality has not been determined, it has been postulated the BBB dysfunction may be linked to disrupted neuronal and synaptic function, increased permeability to inflammatory molecules, disrupted glutamate homoeostasis, and impaired action of antipsychotics (Pollak et al., 2017). Approximately, 30%-40% of patients with velocardiofacial syndrome (22q11 deletion syndrome) have schizophrenia (Monks et al., 2014, Schneider et al., 2014). 22q11 is associated with haploinsufficiency of the claudin-5 gene, which produces claudin-5, a tight junction (TJ) protein, found in endothelial cells forming part of the BBB. Greene and colleagues showed that claudin-5 suppression in mice resulted in impairments in learning and memory, anxiety-like behaviour and sensorimotor gating (and seizures), and that antipsychotic medications dose-dependently increased claudin-5 expression in vitro and in vivo (Greene et al., 2018). Further, they showed aberrant, discontinuous expression of claudin 5 in the post mortem

brains of schizophrenic patients compared to age-matched controls (Greene et al., 2018).

Preclinical evidence from GF mice suggests that the microbiota can modulate the BBB. Exposure of GF adult mice to the fecal microbiota from pathogen-free donors decreased BBB permeability (Braniste et al., 2014). Moreover, monocolonization of the intestine of GF adult mice with SCFA-producing bacterial strains normalised BBB permeability, whilst sodium butyrate was associated with increased expression of the TJ protein occludin in the frontal cortex and hippocampus (Braniste et al., 2014). Intragastric antibiotic treatment of adult mice showed that antibiotic-induced gut alterations reduced the expression of claudin and occludin mRNA in the hippocampus and increased the expression of TJ protein 1 and occludin mRNA in the amygdala (Frohlich et al., 2016). Low dose penicillin administered to mice during the perinatal period (1 week before birth to weaning) showed that the antibiotic induced gut microbiota alterations, increased cytokine expression in the frontal cortex, modified BBB integrity and decreased anxiety-like and social behaviours, including a reduced preference for social novelty in the offspring (Leclercq et al., 2017). Concurrent supplementation with *L. rhamnosus* (JB-1) attenuated the penicillin induced decrease in social novelty preference behaviour (Leclercq et al., 2017).

Stress sensitivity, the microbiome and schizophrenia

Environmental stressors act on genetic vulnerabilities to shape the neurodevelopmental trajectory in schizophrenia (**Table 1**). Early life environmental insults are particularly important as they sensitive the developing brain. Stressful life events can precipitate psychotic symptoms and sensitivity to minor stressful events are associated with more intense psychotic experiences in FEP (Reininghaus et al., 2016b). The interaction of the mediating role of the gut microbiota, stress sensitivity and environmental stressors has not been explored in schizophrenia. Stress can reshape gut microbiota composition and alter gut barrier permeability (Galley et al., 2014a, Galley et al., 2014b, Wang and Wu, 2005, O'Mahony et al., 2009, Golubeva et al., 2015, Frohlich et al., 2016, Bailey and Coe, 1999, Bailey et al., 2011, Kelly et al., 2015). Preclinical evidence suggests that the gut microbiota signature acquired and maintained during the pivotal early developmental stage may also affect stress sensitivity. GF rodents demonstrate abnormal behavioural and neuroendocrine responses to stress (Crumeyrolle-Arias et al., 2014, Moloney et al., 2014, Sudo et al., 2004, Nishino et al., 2013) and the normal development of the HPA axis is contingent on microbiota colonisation at specific neurodevelopmental time points (Sudo et al., 2004). Furthermore, the expression of anxiety like behaviour in a mouse model of early life stress is partially dependent on the gut microbiota (De Palma et al., 2015).

Prenatal stress also impacts the gut microbiota with implications for physiological outcomes in the offspring (Golubeva et al., 2015). In a mouse model of prenatal

stress, maternal stress decreased the abundance of vaginal *Lactobacillus*, resulting in decreased transmission of this bacterium to offspring, which corresponded with changes in metabolite profiles involved in energy balance, and with disruptions of amino acid profiles in the developing brain (Jasarevic et al., 2015). Human infants of mothers with high self-reported stress and high salivary cortisol concentrations during pregnancy had significantly higher relative abundances of *Proteobacterial* groups known to contain pathogens and lower relative abundances of lactic acid bacteria (*Lactobacillus*), *Actinobacteria* and *Bifidobacteria* (Zijlmans et al., 2015). In addition, those infants with altered microbiota composition exhibited a higher level of maternally reported infant GI symptoms and allergic reactions, highlighting the functional consequences of aberrant colonisation patterns. However, a recent study of seventy mothers, did not find any differences in *Proteobacteria*, *Actinobacteria* or *Lactobacilli* and psychosocial stress variables (Hechler et al., 2019).

Microbiota and Neurochemistry

At the cellular level, brain development and function requires a complex and coordinated birth, migration and differentiation of both neurons and glia followed by synaptic integration and neural circuit formation. Schizophrenia is associated with dysregulation of synaptic function and structure (Habela et al., 2016, McGlashan and Hoffman, 2000, Faludi and Mirnics, 2011). The gut microbiota plays a role in developmental programming of the brain, specifically, synapse maturation and synaptogenesis (Diaz Heijtz et al., 2011) (**Figure 1**). Synaptophysin, a marker of synaptogenesis, and PSD 95, a marker of excitatory synapse maturation, were decreased in the striatum in GF mice compared to specific pathogen free (SPF) mice (Diaz Heijtz et al., 2011). Reduced levels of synaptophysin have been demonstrated in the cerebral cortex of post-mortem samples from schizophrenia subjects (Hu et al., 2015).

Dopaminergic pathways

Dopaminergic dysfunction is a key pathophysiological process underpinning the manifestation of psychotic symptoms (hallucinations and delusions). A primary circuit involved in psychosis includes the thalamus and prefrontal cortex feeding into the associative striatum. Excessive D2 signalling in the associative striatum appears to be critical for the manifestation of psychotic symptoms, with limbic regions such as the hippocampus and amygdala connecting to this circuit, contributing to altered sensory perception and emotional context (Kesby et al., 2018). Antipsychotics reduce psychotic symptoms primarily by blocking D2 but have little impact on negative and cognitive symptoms.

Preclinical studies using GF rodents, antibiotics and probiotics have shown that dopaminergic circuits are sensitive to changes in gut microbes (Gonzalez-Arancibia et al., 2019) (**Table 2**). GF mice have altered dopaminergic neurotransmission in the hippocampus, striatum and the PFC (Diaz Heijtz et al., 2011, Nishino et al., 2013)

(Crumeyrolle-Arias et al., 2014). Similarly, antibiotic treated rodents demonstrate altered dopamine metabolite levels in the hippocampus, amygdala and striatum (Hoban et al., 2016a, Desbonnet et al., 2015). Although unlikely to cross an intact BBB in appreciable quantities, it is nonetheless interesting to note from an evolutionary interconnectivity perspective, that the gut microbiota plays a role in the production of biologically active free catecholamines, including dopamine (Asano et al., 2012). Collectively, these preclinical studies, suggest that the dopaminergic system, of direct relevance to the pathophysiological trajectory of psychosis, is under the partial influence of the gut microbiota.

Glutamatergic and gamma-aminobutyric acidergic (GABA) pathways

The glutamate hypothesis of schizophrenia implicates hypofunction of signalling through NMDA receptors (NMDARs) on inhibitory neurons, leading to disinhibition of glutamate neurons, increasing synaptic activity of glutamate, especially in the PFC (Moghaddam and Javitt, 2012, Jackson et al., 2004). This proposes that NMDA receptors contribute to psychotic symptoms as well as cognitive deficits in schizophrenia (Gonzalez-Burgos and Lewis, 2012, Thomas et al., 2017). Indeed, NMDA receptor antagonists, such as ketamine can manifest aspects of schizophrenia in healthy volunteers, including some of the attentional and memory problems, and can exacerbate symptoms in individuals with schizophrenia (Malhotra et al., 1997, Breier et al., 1997). Rats that received intraperitoneally injected ketamine had amplified *Lactobacillus*, *Turicibacter* and *Sarcina* and decreased opportunistic pathogens *Mucispirillum* and *Ruminococcus* compared to mice that received saline (Getachew et al., 2018). Phencyclidine, another NMDA receptor antagonist, causes hyperlocomotion, social withdrawal and cognitive impairment in rodents. Sub-chronic phencyclidine (subPCP) treatment altered cognition and gut microbiota composition in rodents, whereas administration of ampicillin abolished the subPCP-induced memory deficit (Pyndt Jorgensen et al., 2015).

A preclinical study showed a decrease in the NMDAR subunit NR2B mRNA expression in the amygdala in GF mice (Neufeld et al., 2011). The prebiotics galacto-oligosaccharide (B-GOS) and fructo-oligosaccharide (FOS) elevated NMDAR subunits, implicated in synaptic plasticity, in the hippocampus, with B-GOS additionally increasing NR2A subunits in this region, and NR1 and D-serine in the frontal cortex (Savignac et al., 2013). B-GOS administration to rats improved performance in a set-shifting task, associated with an increase in cortical NMDA receptor function (Gronier et al., 2018).

A recent FMT study showed that gut microbiome transfer from individuals with schizophrenia to GF mice modulated the glutamate-glutamine-GABA cycle associated with increased startle responses and locomotor hyperactivity (Zheng et al., 2019a). This study found elevated glutamine in the serum and hippocampus and decreased glutamate (glutamic acid) in the stool and hippocampus, in GF mice that

received an FMT from schizophrenia patients compared to health controls (Zheng et al., 2019a). This study also showed that GABA, known to be dysfunctional in schizophrenia (Schmidt and Mirnics, 2015), was increased in the hippocampus in GF mice that received the FMT from schizophrenia patients (Zheng et al., 2019a). Preceding preclinical studies showed *L. rhamnosus* (JB-1) increased GABA receptor levels in the hippocampus in mice (Bravo et al., 2011) and increased central GABA levels as measured non-invasively by magnetic resonance spectroscopy (MRS) (Janik et al., 2016). However, unfortunately *L. rhamnosus* has not, as yet, translated into the clinic (Kelly et al., 2017a, Kelly et al., 2016b, Kelly et al., 2019a). Prebiotics can also alter GABA in animal models. Fructo-oligosaccharide (FOS) and galacto-oligosaccharide (GOS), increased GABA-B1 and GABA-B2 receptor gene expression in the hippocampus (Burokas et al., 2017).

The parasitic protozoan *Toxoplasma gondii,* known to alter the gut microbiota (Molloy et al., 2013) is associated with an increased risk of schizophrenia (Torrey and Yolken, 2003, Severance et al., 2016a, Monroe et al., 2015, Bhadra et al., 2013). Latent *T. gondii* can upregulate cerebral complement factor C1q (Xiao et al., 2016), alter dopamine metabolism (Prandovszky et al., 2011) and is associated with reduced psychomotor performance (Beste et al., 2014, Havlicek et al., 2001). A translational study showed that *T. gondii* infection produced sustained, strain-specific, anti-NMDAR immune responses, in conjunction with alterations in surrogate markers of blood-gut (gluten IgG) and BBB (S100B) function in mice (Kannan et al., 2017). In the human part of the same study, NMDAR IgG and markers of barrier permeability were significantly associated with *T. gondii* exposure in subgroups of individuals with schizophrenia compared with controls, independently of antipsychotic medication (Kannan et al., 2017).

Brain-Derived Neurotrophic Factor (BDNF)

A key regulator of synaptic plasticity and neurogenesis in the brain, throughout life, is the neurotrophin BDNF (Monteggia et al., 2004). Given the role of BDNF in the regulation of synaptic strengthening and pruning, maintaining appropriate levels of BDNF and other neurotrophins, especially during critical neurodevelopmental windows is vital for schizophrenia (Nieto et al., 2013). Meta-analysis showed reduce blood levels in both medication naïve and medicated adult individuals diagnosed with schizophrenia (Green et al., 2011). Preclinical studies show that BDNF levels are influenced by the gut microbiota (**Table 2**).

Serotonin (5-HT) and Kynurenine pathway

The indolamine 5-HT has a wide range of physiological functions, including anxiety and fear modulation, stress responsivity, reward, cognition and social behaviour (Asan et al., 2013, Dayan and Huys, 2008, Lucki, 1998). In schizophrenia, a meta-analysis of post-mortem studies found an elevation in prefrontal 5-HT1A receptors and a reduction in prefrontal 5-HT2A receptors (Selvaraj et al., 2014). The largest

reserve of 5-HT is located in enterochromaffin cells in the GIT (Berger et al., 2009), where 5-HT plays an important role in secretion, sensing and signalling (Mawe and Hoffman, 2013). 5-HT, and its precursor tryptophan, are critical signalling molecules in the MGB axis and under the influence of gut microbiota, especially, but not limited to, periods prior to the emergence of a stable adult-like gut microbiota (O'Mahony et al., 2015, Clarke et al., 2013, Desbonnet et al., 2008, El Aidy et al., 2012, Hata et al., 2017) (**Table 2**). A metabolomics study showed a three-fold increase in plasma serotonin levels when GF mice were colonized by gut microbiota (Wikoff et al., 2009). Bacterial metabolites, such as SCFA's can increase tryptophan hydroxylase 1 transcription, the rate limiting for mucosal 5-HT synthesis in chromaffin cell cultures (Reigstad et al., 2015) and increase colonic and blood 5-HT in GF mice (Yano et al., 2015).

The regulation of circulating tryptophan availability, and the distribution and subsequent kynurenine pathway metabolism, in the periphery and CNS, is tightly regulated during all stages of life (Badawy, 2017, Ruddick et al., 2006, Kennedy et al., 2017). The enzyme indoleamine 2,3-dioxygenase (IDO) found in macrophages and microglia cells is the first and rate limiting step in the kynurenine pathway of tryptophan catabolism. The expression of tryptophan-2,3-dioxygenase (TDO) can be induced by circulating glucocorticoids (O'Connor et al., 2009) and has been reported to be regulated by the gut microbiota during colonization (El Aidy et al., 2014). Under normal physiological conditions, approximately 99% of tryptophan is metabolized to kynurenine in the liver by TDO. However, proinflammatory cytokines, known to be associated with schizophrenia (discussed above) can induce IDO resulting in the metabolism of tryptophan along the kynurenine pathway (Schwarcz et al., 2012). Kynurenine, tryptophan and 3-hydroxykynurenine (3-HK) can cross the BBB and tryptophan's conversion to kynurenine and 3-HK in the peripheral circulation can therefore contribute to CNS levels (Schwarcz et al., 2012, Myint and Kim, 2014). In the brain, the end result of the metabolic pathway in astrocytes is Kynurenic acid (KYNA) (Gramsbergen et al., 1997), whereas, in microglia, it is quinolinic acid (Alberati-Giani et al., 1996). A recent study in mice exposed to chronic social defeat stress, known to increase colitis susceptibility, showed an accumulation of KYNA in the gut, which activated protein-coupled receptor 35 (GPR35) signalling to induce autophagy-dependent degradation of NLRP3 in macrophages, leading to IL-1β production (Zheng et al., 2019b).

The regulation of the kynurenine pathway is important throughout life, but especially during sensitive periods of early neurodevelopment (Notarangelo et al., 2019). Abnormal KYNA levels are implicated in the pathophysiology of schizophrenia. KYNA is an NMDA and alpha7 nicotinic (α7nACh) receptor antagonist, both important in modulating brain development with implications for cognition, social behaviour and anxiety-like behaviour (Myint and Kim, 2014, Pershing et al., 2015, Pocivavsek et al., 2014, Notarangelo and Pocivavsek, 2017, Pershing et al., 2016, Forrest et al., 2015, Erhardt et al., 2016, Notarangelo and Schwarcz, 2017). In schizophrenia, increased KYNA levels in the CSF, including in drug naïve patients

(Nilsson et al., 2005), and in post-mortem brain samples have been shown (Erhardt et al., 2001, Plitman et al., 2017). Furthermore, the plasma kynurenine/tryptophan ratio was significantly higher in patients diagnosed with schizophrenia (n=34) compared to healthy controls (n=36) (Barry et al., 2009). In a clinical study, patients with schizophrenia (n=64) were more intolerant to a psychological stress challenge than healthy controls, and while salivary KYNA levels increased significantly between baseline and 20 minutes following the stressor in both groups, patients who were unable to tolerate the stressful tasks showed significantly higher levels of KYNA, compared to patients who tolerated the psychological stressor or healthy controls (Chiappelli et al., 2014).

In a recent post-mortem study, the kynurenine/tryptophan ratio, KYNA levels, and TDO mRNA and kynurenine aminotransferases (KATI/II) mRNA, were significantly increased in the PFC in the schizophrenia subgroup with high cytokine mRNA levels (Kindler 2019). In plasma, the high cytokine schizophrenia subgroup displayed an elevated kynurenine/tryptophan ratio, which correlated inversely with attention and dorsolateral prefrontal cortex (DLPFC) volume (Kindler et al., 2019). Collectively, these preclinical and clinical studies highlight the importance of the kynurenine pathway during neurodevelopment with the associated implications for schizophrenia. Exploration of the microbial regulation of this pathway is emerging as an important objective in schizophrenia research.

Short Chain Fatty Acids (SCFA's)

SCFA's (butyrate, acetate and propionate) are neurohormonal signalling molecules produced by microbial fermentation of indigestible dietary fibres. SCFAs can reach the circulation, cross the BBB (Frost et al., 2014, Vijay and Morris, 2014, Steele, 1986) and have a wide range of physiological functions (Koh et al., 2016). Butyrate, in addition to functioning as a ligand for a subset of G protein-coupled receptors (Bourassa et al., 2016), acts as a potent inhibitor of Histone deacetylases (HDACs). Histone acetylation initiates or assists in chromatin relaxation, allowing access of the transcription mechanisms to specific positions. Conversely, HDACs inhibit this transcriptional activity due to the enhanced binding of histones to the DNA structure (chromatin condensation). HDAC inhibition has been proposed as a mechanism by which the microbiota via SCFA production may act as a mediator of gene-environment interactions (Stilling et al., 2016a, Stilling et al., 2014). While the physiological levels of SCFAs may be subtle, cumulative chronic delivery may produce long-lasting stable effects on gene expression (Stilling et al., 2014).

Post-mortem analysis of human brain tissue showed that HDAC1 levels are elevated in the PFC and hippocampus of patients with schizophrenia (Sharma et al., 2008, Benes et al., 2007). Similarly, HDAC1 mRNA and protein levels were elevated in the PFC of patients with schizophrenia and in blood from patients with schizophrenia who had experienced early life stress (Bahari-Javan et al., 2017). In the preclinical

arm of the same study, mice subjected to a maternal separation paradigm, had increased HDAC1 levels in the PFC, which were associated with deficits in novel object recognition and prepulse inhibition (Bahari-Javan et al., 2017). In addition, the administration of an HDAC inhibitor (MS-275) ameliorated some of the early life stress-induced behavioural deficits. It would be interesting to determine whether SCFA's could also ameliorate these schizophrenia-like behavioural deficits. It has previously been shown that supra-physiological levels of SCFA's produce marked deficits in cognitive performance, social interaction and locomotor activity in rodents (Macfabe, 2012, MacFabe et al., 2007, Thomas et al., 2012). More recently, administration of a mixture of acetate, propionate and butyrate, to mice, following a 3-week social defeat and overcrowding procedure, alleviated heightened stress-responsiveness and stress-induced increases in intestinal permeability, while also, decreasing anxiety-like behaviour in the open field test and decreasing depressive-like behaviour in the forced swim test (van de Wouw et al., 2018).

Microbiota and Social Behaviour

The PFC, the amygdala and temporoparietal junction form key components of the neural circuitry underlying social cognition and behaviour and have been shown to be abnormal in people with schizophrenia (Rasetti et al., 2009, Aleman and Kahn, 2005). The amygdala, vital for social behaviour, acts as an emotional salience encoder. Schizophrenia is associated with decreased activation of the amygdala to emotional stimuli (Aleman and Kahn, 2005) and decreased interactions between the amygdala and the medial PFC (Williams et al., 2004). The amygdala is particularly sensitive to changes in microbiome composition (Cryan and Dinan, 2018, Cowan et al., 2018). In GF mice, amygdala neuronal activity (Stilling et al., 2015) and dendritic morphology is altered (Luczynski et al., 2016). In these mice, expression of immediate early response genes such as Fos, Fosb, Egr2 or Nr4a1 were increased in the amygdala, in conjunction with increased signalling of the transcription factor CREB (Stilling et al., 2015). Differential expression and recoding of several genes involved in fundamental brain processes ranging from neuronal plasticity, metabolism, neurotransmission and morphology were identified and a significant downregulation was noted for immune system-related genes (Stilling et al., 2015). Moreover, GF mice show attenuated social stimulus-dependent transcriptional regulation in the amygdala, and an increase in expression of splicing factors and exon usage, compared to control mice (Stilling et al., 2018). Additionally, myelination, a process tentatively linked to brain dysconnectivity in schizophrenia (Konrad and Winterer, 2008, Hakak et al., 2001, Mighdoll et al., 2015, Kelly et al., 2018), is partially under the influence of the gut microbiota (Hoban et al., 2016b). GF mice exhibited an upregulation of genes linked to myelination and myelin plasticity, with hyper-myelinated axons within the PFC (Hoban et al., 2016b).

At the behavioural level, GF mice display abnormal social behaviours, including social motivation and social novelty preference (Desbonnet et al., 2014). This decreased sociability has been reproduced in GF rats (Crumeyrolle-Arias et al.,

2014). In addition to an altered transcriptional profile in the amygdala, GF mice have been shown to exhibit reduced freezing behaviour during a cued amygdala-dependent memory retention test, while colonized GF mice were behaviourally comparable to conventionally raised mice during the memory retention test (Hoban et al., 2017). In a recent FMT study, GF mice transplanted with gut microbiota from schizophrenia patients, displayed locomotor hyperactivity, decreased anxiety and depressive-like behaviours, and increased startle responses (Zheng et al., 2019a).

The urban environment has long been regarded as a risk factor for the development of psychotic disorders (**Table 1**) (Vassos et al., 2012, Pedersen and Mortensen, 2001, Krabbendam and van Os, 2005, Peen et al., 2010, Newbury et al., 2016, Omer et al., 2016). However, a recent meta-analysis showed that this elevated risk may not apply to developing countries and highlighted the variable urban-rural patterns of cannabis use, racial discrimination, and socioeconomic disparities between developing and developed nations (DeVylder et al., 2018). In healthy controls, current city living was associated with increased amygdala activity, whereas urban upbringing affected the perigenual anterior cingulate cortex (ACC) (Lederbogen et al., 2011). Alterations in gray matter volume in the right DLPFC and in the perigenual ACC have also been associated with urban upbringing (Haddad et al., 2015). Moreover, urban upbringing leaves an immunoregulatory imprint. Healthy controls with an urban upbringing, without exposure to pets, was associated with a more pronounced increase in the number of peripheral blood mononuclear cells and plasma IL-6 concentrations, following acute psychosocial stress induced by the Trier social stress test, compared to rural upbringing in the presence of farm animals (Böbel et al., 2018).

Urbanisation is also associated with an increased risk of immune and metabolic disorders, including obesity, while reducing microbial diversity and impacting the overall functionality of the gut microbiome (Mancabelli et al., 2017, Clemente et al., 2015, Yatsunenko et al., 2012, Sonnenburg and Sonnenburg, 2019). Whether differential environmental exposure to microbes in the urban compared to the rural environment interact with differences in social stressors to alter social stress neural circuitry remains to be seen (Stamper et al., 2016). Similarly, unravelling the microbial mediated contribution to social stress related to migration, another risk factor for schizophrenia (Cantor-Graae and Selten, 2005) is an intriguing endeavour. A recent study showed that migration from a non-Western country to the United States was associated with immediate loss of gut microbiome diversity and function (Vangay et al., 2018). Specifically, bacterial enzymes associated with plant fiber degradation, and a displacement of *Prevotalla* with *Bacteroides* strains occurs over time (Vangay et al., 2018). It is interesting to note that Zheng and colleagues showed that individuals with schizophrenia had reduced gut microbiota alpha diversity compared to healthy controls (Zheng 2019), echoing the concept that a more diverse ecosystem may be a health promoting factor (Dantzer et al., 2018). Whether a more diverse microbial biodiversity, with its corresponding MGB axis signalling, especially during specific vulnerable neurodevelopmental periods has implications for the trajectory of schizophrenia remains to be seen.

Microbiota and Cognition

Social cognition is just one of the multiple cognitive domains that are impaired in schizophrenia (Kahn and Keefe, 2013). Evolving cognitive activity during neurodevelopment is dependent on the microbiota and its metabolic outputs (Sordillo et al., 2019, Fouhy et al., 2019). The combination of acute stress and infection can impact cognition. *Citrobacter rodentium* infected C57BL/6 mice that were exposed to acute stress exhibited memory dysfunction (Gareau et al., 2011). Moreover, GF Swiss-Webster mice displayed memory impairment at baseline, in the absence of acute stress (Gareau et al., 2011). In male C57BL/6 mice, higher percentages of *Clostridiale*s and lower levels of *Bacteroidales* in high-energy diets were related to the poorer cognitive flexibility (Magnusson et al., 2015). In BALB/c mice, treatment with *B. Longum* resulted in an improvement in stress related behaviour and cognition (Savignac et al., 2015).

Hippocampal volume reduction is associated with schizophrenia (Velakoulis et al., 2006, Adriano et al., 2012). Indeed, hippocampal neurogenesis, a pivotal process in learning and memory consolidation (Deng et al., 2010, Hueston et al., 2017, Levone et al., 2015, Anacker and Hen, 2017) has been shown to be regulated by the gut microbiota, mediated at least partially via the vagus nerve. Subdiaphragmatic vagotomised adult male BALB/c mice had decreased BDNF mRNA, reduced proliferation and survival of newly born cells and a decreased number of immature neurons in the hippocampus (O'Leary et al., 2018). FMT from mice exposed to unpredictable chronic mild stress, to antibiotic treated mice, showed decreased adult hippocampal neurogenesis and depressive-like behaviours compared to mice that received non-stressed FMT (Siopi et al., 2019). Moreover, subdiaphragmatic vagotomy abolished the microbiota-induced effects on behaviour and neurogenesis (Siopi et al., 2019). GF mice exhibit increased adult hippocampal neurogenesis in the dorsal hippocampus, and post-weaning microbial colonisation failed to reverse the changes in adult hippocampal neurogenesis (Ogbonnaya et al., 2015). Furthermore, exercise or probiotics were able to ameliorate deficits in neurogenesis and behaviour in antibiotic-treated mice (Mohle et al., 2016). *L. johnsonii* CJLJ103 attenuated memory impairment and colitis in mice by inhibiting gut microbiota lipopolysaccharide production and NF-κB activation (Lim et al., 2017).

Antibiotic-induced alterations of the microbiota-gut-brain axis also modulate cognition. Using an antibiotic (ampicillin, metronidazole, vancomycin, ciprofloxacin, imipenem) treated rat model, gut microbiota depletion during adulthood resulted in deficits in spatial memory as measured by the Morris water maze (Hoban et al., 2016a). In another preclinical antibiotic study (ampicillin, bacitracin, meropenem, neomycin, and vancomycin), novel object recognition, but not spatial memory, was impaired in the antibiotic-treated mice and this cognitive deficit was associated with brain region-specific changes in the expression of BDNF, NMDAR subunit NR2B, serotonin transporter and neuropeptide Y system (Frohlich et al., 2016).

Clinical Schizophrenia studies and gut microbiota

Several preliminary clinical studies investigating the microbiome across the different stages of schizophrenia, from at risk states to FEP to established schizophrenia, have emerged (**Table 3**). The most recent study showed that patients with schizophrenia (n=63) had lower alpha (within-sample) diversity compared to health controls (n=69), and that several species (*Aerococcaceae*, *Bifidobacteriaceae*, *Brucellaceae*, *Pasteurellaceae*, and *Rikenellaceae*) reportedly discriminated individuals from healthy controls (Zheng et al., 2019a). As well as, demonstrating the gut microbiota's influence over amino acid pathways in schizophrenia (discussed above), this study showed altered lipid metabolism in serum and hippocampus in GF mice that received the FMT from a random sample of five schizophrenia patients (Zheng et al., 2019a). Specifically, glycerophospholipids including phosphatidylethanolamines, phosphoserines, phosphatidylcholines and phosphatidylinositol were all decreased. Interestingly, recent data from the Avon Longitudinal Study of Parents and Children, showed that dysregulated blood phosphatidylcholines and lysophosphatidylcholines at age 12 years, contributed to psychotic experiences at age 18 years (Madrid-Gambin et al., 2019). It would be an appealing prospect to decipher the mediating role of the gut microbiota in this sample.

A recent study showed increased abundances of *Clostridiales*, *Prevotella* and *L. ruminis* in fecal samples, in an ultra-high-risk (UHR) group (n=19) compared to health controls (He 2018). Levels of choline measured by MRS in the ACC were also elevated in the UHR group compared to the healthy control group. There were no significant differences between the high-risk group and healthy group (He 2018). In people diagnosed with FEP (n = 28), the of majority of whom were prescribed antipsychotics, there were significantly increased *Lactobacillaceae* and decreased *Veillonellaceae* at the family level and increased *Lactobacillus* at the genus level compared to healthy controls (n = 16) (Schwarz et al., 2018). This decrease in *Veillonellaceae* in FEP contrasts with the increase in the Zheng et al study. The authors report that *Lactobacillus* group bacterial numbers correlated positively with severity of psychotic symptoms measured using the Brief Psychiatric Rating Scale, and negatively with global assessment of functioning scale. *Lactobacilli* and *Lactobacilli phage phiadh* were also found in greater abundances in the oropharyngeal microbiome in people diagnosed with schizophrenia (Castro-Nallar et al., 2015, Yolken et al., 2015).

Translation:

Will definitive developments that will impact patient care emerge? There has been one clinical interventional study investigating probiotics in patients diagnosed with schizophrenia (**Table 3**). This 14-week, randomized, double-blind, placebo-controlled trial (n = 65), used *L. rhamnosus strain GG* and *B. animalis* subsp. lactis strain Bb12, added to antipsychotic treatment as usual (Dickerson et al., 2014). The

probiotics improved GI symptoms, and increased levels of serum BDNF (Tomasik et al., 2015), but failed to impact positive or negative symptoms (Dickerson et al., 2014). However, male participants in the probiotic group had significantly reduced *C. albicans* antibodies and there was a trend towards improvement in the Positive and Negative Syndrome Scale (PANSS) positive symptom subset score in seronegative males (Severance et al., 2017). In contrast, the same research group, randomized patients hospitalized for a manic episode (n=66), to receive 24 weeks of adjunctive probiotics (*L. rhamnosus strain GG* and *B. animalis* subsp. lactis strain Bb12) or adjunctive placebo at discharge (Dickerson et al., 2018). The probiotic group had lower rates of re-hospitalization compared to the group that received the placebo.

Antipsychotics:

Antipsychotics alter the gut microbiota and the metabolic side-effects of commonly used antipsychotics are at least partially mediated by the gut microbiota (Cussotto et al., 2018, Cussotto et al., 2019, Dinan and Cryan, 2018, Maier et al., 2018, Nehme et al., 2018). In a preclinical study, chronic olanzapine treatment altered gut microbiota composition and induced significant body weight gain in female rats, while both males and females had olanzapine-induced increases in adiposity (Davey et al., 2012). Pre-treatment with an antibiotic cocktail attenuated this weight gain (Davey et al., 2013). Another study using GF mice, demonstrated that the gut microbiota is necessary and sufficient for weight gain caused by oral olanzapine, which shifted the microbiota profile towards an "obesogenic" bacterial profile (Morgan et al., 2014). Weight gain was attenuated when olanzapine was co-administered with prebiotics. B-GOS, known to induce the growth of beneficial bacteria, including *Bifidobacteria*, reduced weight gain in olanzapine treated rats (Kao et al., 2018).

Similarly, FMT from risperidone-treated mice to risperidone naive recipients resulted in a 16% reduction in total resting metabolic rate (Bahra et al., 2015). The same research group translated the findings into an adolescent clinical cohort to show that chronic risperidone treatment was associated with an increase in body mass index and a significantly lower ratio of *Bacteroidetes:Firmicutes* compared to antipsychotic-naive psychiatric controls (Bahr et al., 2015). In first episode schizophrenia, 24 weeks of risperidone resulted in weight gain, increased C-reactive protein, increased fasting lipids and glucose and gut microbiota changes (Yuan et al., 2018). Another clinical study of atypical antipsychotics in bipolar affective disorder (n=117), showed overall differences in *Lachnospiraceae, Akkermansia*, and *Sutterella*, and decreased species richness in female antipsychotic treated patients (Flowers et al., 2017).

There is growing interest in the influence of the microbiome on drug metabolism and absorption (Clarke et al., 2019, Zimmermann et al., 2019). An elegant study highlighting the role of gut microbiota metabolism in drug availability, showed gut bacterial tyrosine decarboxylases modulated levels of levodopa in Parkinson's disease

(van Kessel et al., 2019). Indeed, we look forward to the results of a translational study, currently underway in Toronto, investigating the interaction of the gut microbiome and clozapine (Gorbovskaya et al., 2019).

The antibiotic minocycline, notwithstanding a complex mechanism of action, is known to modulate the MGB axis (Wong et al., 2016). Preliminary studies of this antibiotic showed potential in reducing negative and cognitive symptoms in schizophrenia (Levkovitz et al., 2010, Miyaoka et al., 2008, Khodaie-Ardakani et al., 2014, Jhamnani et al., 2013). Disappointingly, a recent well-powered (n=207) RCT of minocycline augmentation, in early stage schizophrenia spectrum disorder, did not impact symptoms or biomarkers (Deakin et al., 2018). However, it is important note that minocycline reduces gut microbiome diversity and does not preclude future studies of microbiome-based therapies in the form of prebiotics, live biotherapeutics or small molecules in the amelioration of cognitive or negative symptoms in subgroups with psychosis spectrum disorder.

Conclusions and Perspectives

The term schizophrenia, traditionally reserved for the severe end of the psychosis spectrum, is not a unified entity (Anttila et al., 2018, Jauhar et al., 2017, Hulshoff Pol et al., 2012) and is associated with stigma, negative bias and public mis-understanding (Takahashi et al., 2009). Unravelling the mysteries of schizophrenia will require a systems level dimensional approach, incorporating the impact of genetics and environmental inputs throughout the neurodevelopmental trajectory. Considering the microbiome contributes to the modulation of many of the processes during neurodevelopment, including neurogenesis, myelination, dendrite formation and blood brain barrier development and plays a role in cognitive function, social interaction, locomotor activity and stress management, the integration of the microbiome as an additional unit of analysis in the evolving dimensional framework, may provide a more complete understanding of the neurobiological architecture of this complex condition (Insel et al., 2010, Severance et al., 2016b, Kahn et al., 2015, Kelly et al., 2017b) (**Table 4**).

Deconstructing heterogenous traditional categorical diagnoses into dimensions, to uncover the interaction of biological mechanisms with environmental inputs is particularly challenging in the trajectory of psychosis spectrum disorders but may offer potential to advance the precision-personalized-preventative health framework (Ford et al., 2014, Cohen et al., 2017, Reininghaus et al., 2016a, Öngür, 2017, Silbersweig and Loscalzo, 2017). In other areas of medicine, the integration of the gut microbiome into predictive models using machine learning techniques has been shown to be clinically useful, for example; predicting post-prandial glucose levels (Zeevi, David 2015), steady-state plasma glucose (a measure of peripheral insulin resistance) (Schüssler-Fiorenza Rose et al., 2019) and triglyceride levels and high-density lipoproteins (Fu et al., 2015). In keeping with this advance towards a

precision-personalized-preventative health strategy, probiotics have also been shown to have an individualized impact on mucosal community structure and gut transcriptome (Zmora et al., 2018, Johnson et al., 2019).

While emerging preliminary clinical studies suggest that an altered gut microbiota is physiologically relevant in schizophrenia, the full neuropsychiatric implications of subtle alterations in MGB axis signalling, at early developmental stages or during adolescence have yet to be fully explored. For example, do microbial signature aberrations serve as additional risk factors or mediators in the development of psychotic disorders or in conjunction with stress, as contributory triggers for psychotic relapse? Or could the microbiota signature aberration occur early but remain clinically silent? Could a microbial based therapy reduce conversion to psychosis in subgroups at risk of developing the disorder. Furthermore, diet-microbiota and drug-microbiota interactions in psychosis are promising avenues of clinical research (**Table 5**).

It is perhaps not surprising that a consistent microbial biosignature has not emerged. There are notable limitations in the clinical studies (**Table 3**). The vast majority of participants were prescribed antipsychotic medication, which as discussed above, can alter gut microbiota composition. Furthermore, detailed dietary information is lacking. However, the most problematic issue relates to sample size. Well powered, longitudinal studies, including medication free individuals, and detailed dietary analysis, encompassing neuroimaging markers would be required to determine if targeting the MGB axis signalling system by psychobiotic strategies (probiotics, prebiotics, diet) translates into clinical utility. This will require functional and compositional microbiome analysis and standardised specimen preparation and analytical protocols (Costea et al., 2017). Pioneering the nascent field of microbiome research has potential to contribute to the evolution of precision-personalized-preventative psychiatry.

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Contributors

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Conflict of Interest

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