

## Title Page

### **Can prebiotics assist in the Management of Cognition and Weight Gain in Schizophrenia?**

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## Abstract

Schizophrenia is among the top half of the 25 leading causes of disabilities worldwide with a 10-20 year decrease in life expectancy. Ineffective pharmacotherapy in the management of cognitive deficits and weight gain are known to be significant contributors; therefore interventions that may mitigate one, or both, of these parameters would be highly beneficial. Manipulation of the gut microbiome using dietary supplements such as prebiotics may be one such intervention. Preclinical studies have shown that a 2-4 week dietary supplementation with a prebiotic has beneficial effects on learning and memory, and prevents pro-inflammatory signals that are detrimental to cognitive processes. Furthermore, prebiotics influence metabolism, and in obesity they increase the expression of anorexigenic gut hormones such as peptide tyrosine tyrosine, glucagon-like peptide 1 and leptin, as well as decrease levels of orexigenic hormones such as ghrelin. Despite compelling evidence for the pro-cognitive and neuroprotective effects of prebiotics in rodents, their ability to alleviate cognitive deficits or enhance cognition needs to be evaluated in humans. Here we suggest that important symptoms associated with schizophrenia, such as cognitive impairment and weight gain, may benefit from concurrent prebiotic therapy.

### Keywords

prebiotics, immune, weight gain, schizophrenia

## **Abbreviations**

C-reactive protein (CRP)

N-methyl D-aspartate (NMDA)

gamma-aminobutyric acid (GABA)

brain-derived neurotrophic factor (BDNF)

galacto-oligosaccharide (GOS)

short-chain fatty acids (SCFAs)

G protein-coupled receptors (GPRs)

neuropeptide Y (NPY)

## 1.1 Introduction

The anti-psychosis actions of current front-line medications have greatly improved schizophrenia symptomatology by decreasing oscillations between relapse and remission (Komossa et al., 2010), thereby allowing patients to effectively engage in daily and social functions. However, long term use of antipsychotic agents, particularly second-generation medications, robustly confer significant weight gain (i.e., 7% increase) within three months of treatment (Allison et al., 1999; Arterburn et al., 2016), and may even exacerbate cognitive deficits inherent to the disorder (Zhang et al., 2017). Identifying interventions that attenuate weight gain and cognitive decline, which can be administered in parallel with normal pharmacotherapy but do not disrupt the therapeutic actions of antipsychotic medications, would be highly beneficial for patients.

The enteric microbiome has been explored in patients with schizophrenia wherein a significant elevation of *lactobacillaceae* abundance compared to healthy controls was observed (Schwarz et al., 2017). The study highlighted the clinical relevance of this elevation by demonstrating positive association with severity of psychotic symptoms, and negative association with global assessment of functioning. Interestingly, an increased abundance of *lactobacilli* has also been documented in the oropharyngeal environment of patients with schizophrenia, though relationships with symptomatology were not explored (Castro-Nallar et al., 2015; Yolken et al., 2015). However, since sampling from one microbial community along the human digestive tract may broadly reflect populations further downstream (Segata et al., 2012), it is conceivable that alterations in the oropharyngeal microbiome in schizophrenia patients (Castro-Nallar et al., 2015; Yolken et al., 2015) may also be associated with various schizophrenia symptomatology. Nevertheless, it remains uncertain whether alterations in microbial environments, which appears to be conducive to the growth of *lactobacillaceae*, is inherent to the disorder, the result of a homeostatic response to the illness, and/or the impact of pharmacotherapy. One physiological process that is significantly

influenced by gut bacteria and so perhaps may be linked to the pathophysiology and/or treatment of schizophrenia is the immune system.

There are several lines of evidence for inflammation as a core feature of schizophrenia, with genome-wide association studies showing genes involved in the adaptive immune response are associated with the disorder (e.g., HLA classes I, II, III, as well as extended classes I and II sub-regions) (Purcell et al., 2009; Shi et al., 2009; Shiina et al., 2009). Reports in schizophrenia patients reveal robust elevations in the levels of circulating C-reactive protein (CRP) that neither antipsychotic administration nor disorder progression were able to normalize (Fernandes et al., 2016; Miller et al., 2013; Miller et al., 2014). Biologically, CRP is a hepatocyte-derived pattern recognition molecule that identifies inflammatory stimuli and defends the host as part of the innate immune system (Black et al., 2004; Fernandes et al., 2016), thus making it a reliable biomarker for subclinical systemic inflammation. Since early life increases in CRP may be a risk factor for development of schizophrenia in later life (Khandaker et al., 2014), and may have a role in cognitive decline (Dickerson et al., 2007), compounds that normalise CRP levels may confer therapeutic benefits for patients. Prebiotics, which are substrates that are selectively utilized by host microorganisms which confers health benefits (Gibson et al., 2017), have been shown to decrease elevated CRP levels in various human health conditions (McLoughlin et al., 2017). These host microorganism populations can be found not only in the gastrointestinal tract, but in other major organs (e.g., skin, eyes etc.) as well. Although the manipulation of the gut microbiome through prebiotic supplementation has not been explored in schizophrenia patients, administration of minocycline, a broad-spectrum tetracycline antibiotic with anti-inflammatory properties, which limits the growth of a gamut of gut microbes, improved negative symptoms in one study of early stage schizophrenia patients treated with risperidone (Liu et al., 2014). This provides the precedence to explore other anti-inflammatory therapies for psychosis, such as prebiotics, to test if they too can attenuate symptoms that do not respond to current medication.

## 1.2 Cognitive Impairments in Psychosis

Neurocognitive impairments are core features of schizophrenia, with more than 80% of patients exhibiting significant deficiencies (Keefe and Fenton, 2007), even at first episode of illness and early schizophrenia (Aas et al., 2014). Robust impairments with large effect sizes (i.e., over -1.5) have been reported across a multitude of cognitive domains, including verbal memory, sustained attention, information processing, and particularly executive function (Dickinson et al., 2007), as well as general factors such as processing speed and general intelligence (i.e., IQ). It is important to recognize that performance across various neuropsychological tasks which are designed to measure independent abilities have a tendency to be moderately to highly inter-correlated, suggesting more generalized cognitive impairment in patients. Currently, there is very little evidence for front line pharmacological, or psychological, treatments improving these cognitive impairments, and some evidence suggests that antipsychotic medications even exacerbate these conditions. For instance, in two separate studies, six weeks of treatment with risperidone reduced spatial working memory in treatment-naïve schizophrenia patients (Reilly et al., 2006; Reilly et al., 2007), whilst another study showed that reducing the dose of risperidone or olanzapine by 50% resulted in improvements in global cognitive scores, with particular improvements in verbal working memory in patients with longstanding schizophrenia (Takeuchi et al., 2013).

Cognitive impairments may originate from the disruption of one or several amino acid neurotransmission pathways, but hypo-functioning of the glutamate ionotropic N-methyl D-aspartate (NMDA) receptor has gained particular attention. Membrane depolarization displaces the magnesium cation from the receptor channel permitting calcium influx upon the concomitant binding of glutamate, the major excitatory neurotransmitter, and a co-agonist (glycine or D-serine). Under normal physiological conditions, activation of the NMDA receptors is a major trigger of long-term potentiation at synapses made within hippocampal sub-regions, a fundamental cellular activity often interpreted as a reliable learning and memory correlate (Collingridge et al., 1983). Seminal

work in rodents has illustrated that pharmacological inhibition of hippocampal long-term potentiation using amino-phosphono-valeric acid caused significant deficits in spatial learning and memory, cementing the critical role of NMDA receptors in synaptic plasticity and cognition (Morris et al., 1986). Indeed, hypo-activation of these receptors has been posited as a likely origin of schizophrenia pathophysiology. In neonatal rodents, transient blockade of NMDA receptors resulted in cognitive deficits in later life, which is in keeping with the neurodevelopmental theory of schizophrenia (Reiprich et al., 2005). Additional evidence for the key role of NMDA receptors in cognition and their dysfunction in psychosis originates from pharmacological studies of NMDA receptor antagonists in humans. Sub-anaesthetic doses of psychosis-inducing agents such as phencyclidine (Javitt and Zukin, 1991) and ketamine (Corlett et al., 2007; Hu et al., 2015; Krystal et al., 1994) results in cognitive impairments in healthy volunteers that is analogous to those seen in psychosis. Increased levels of endogenous antagonists such as N-acetyl-aspartyl-glutamate and kynurenic acid have been documented in brain tissue and cerebral spinal fluid of schizophrenia patients (Erhardt et al., 2001; Schwarcz et al., 2001; Tsai et al., 1995). Hypofunction of NMDA receptors has also been attributed to auto-antibodies (Al-Diwani et al., 2017; Khandaker et al., 2015), or receptor desensitization that resulted from abundant agonist levels (Nahum-Levy et al., 2001) that may contribute to psychosis, as well as cognitive decline. While in-depth mechanisms of schizophrenia pathophysiology are currently underway examining the crosstalk between gamma-aminobutyric acid (GABA) and glutamate regulation (Howes et al., 2012), there is already reasonable evidence to suggest that NMDA receptors play an integral role in both the clinical presentation of psychosis as well as the development of cognitive deficits during the disorder.

Since D-serine and brain-derived neurotrophic factor (BDNF) both play a role in regulating glutamate synaptic activity, aberrant expression of either molecule and/or individual receptor subunits may result in hypo-functioning of the glutamatergic system, contributing to cognitive decline and accelerated aging (Islam et al., 2017). Therefore, the augmentation of BDNF expression, as well as

NMDA receptor subunits, via the administration of prebiotics, may reasonably justify exploratory examinations on schizophrenia symptomatology and cognitive dysfunction, both conditions heavily dominated by glutamate receptor signalling. Behavioural changes as a result of prebiotic administration have recently been reviewed, highlighting the limited number of animal studies that explore the neuropsychological effects of prebiotics (Kao et al., 2016). In a recent investigation examining an executive function in rats, three weeks of daily prebiotic supplementation increased cortical NMDA receptor functioning and improved cognitive flexibility (Gronier et al., 2017). Similarly, in the frontal cortex and hippocampal subfields of rats fed with a *bifidobacteria*-enhancing prebiotic, the expression of NMDA receptor subunits (i.e., GluN1, GluN2B), co-agonist D-serine, and BDNF were elevated (Savignac et al., 2013; Vazquez et al., 2015; Williams et al., 2016). However, this has not been consistently replicated as no significant changes in BDNF levels have also been reported (Mudd et al., 2016). Cognitive improvements in spatial learning and memory post-prebiotic intervention have been reported in both rats (Jia et al., 2016; Vazquez et al., 2015) and mice (Vazquez et al., 2015; Yen et al., 2015). Most recently, pro-cognitive effects of prebiotic administration was explored in an Alzheimer's mouse model; significantly restoring the latency time in a water maze test, suggesting improvements in learning and memory (Chen et al., 2017). This particular study did not report any significant alterations in levels of monoamine neurotransmitters in the brain including norepinephrine, dopamine, as well as serotonin (5-HT) suggesting other possible mechanisms that results in cognitive enhancement, such as the immune pathways. With regards to the translatability of animal data, one study has demonstrated that healthy volunteers on a daily, three week course of a prebiotic, showed decreased levels of waking cortisol, and increased attentional bias to positive emotional stimuli (Schmidt et al., 2015). This was therefore consistent with rodent work suggesting anxiolytic and cognitive (attention) effects of prebiotics.

It may also be worth noting the beneficial effects of probiotic supplementation (i.e., live bacterial cultures) in humans have been more extensively reported, and have shown improved mood and



alleviation of psychological distress (Benton et al., 2007; McKean et al., 2017), and even cognitive reactivity to low mood (Steenbergen et al., 2015).

### 1.3 Metabolic Concerns in Schizophrenia

Some antipsychotics, particularly second-generation agents, robustly confer more than 7% increase in body weight within the first year of treatment, significantly elevating the risk of developing metabolic syndrome and cardiovascular disorders (De Hert et al., 2012; Tschoner et al., 2007). While the mechanistic details of the weight gain are currently unclear, disruption in the neuroendocrine and inflammatory systems have been suggested. This includes disruption of hormones in appetite regulation pathways, leptin and ghrelin, as well as processes involved in adipose deposition and hepatic glucose sensitivity (Reynolds and McGowan, 2017). Chronic, systemic, low-grade inflammation is a well-known feature of obesity, possibly originating from the immunomodulatory role of leptin on monocytes (Juge-Aubry and Meier, 2002). The expansion of visceral adipose tissues, a physical feature of weight gain, releases cytokines into circulation which may contribute to the overall inflammatory state of human obesity (Fain, 2006). Although antipsychotic medications may confer anti-inflammatory properties (Maes et al., 2000), and thereby limit cytokine-mediated weight gain, groups have posited that disruptions in cytokine signaling, particularly IL-1, IL-6, and TNF $\alpha$ , lead to a shift towards fat accumulation (Fonseka et al., 2016). Leptin, a hormone that is released by adipocytes in response to increased fat deposition to regulate body weight, is often reported to be elevated in people taking antipsychotics (Ragguett et al., 2017). This elevation likely appears to be a consequence, rather than cause, of weight gain as leptin and leptin-receptors also influence many downstream cascades including neuropeptide Y, agouti-related peptide, pro-opiomelanocortin (POMC), ghrelin and orexin; each responding to changes in leptin levels to ultimately regulate body weight. Moving from the peripheral tissues, the central system may also contribute to weight gain. Differential binding affinities of antipsychotic agents for the serotonin and/or dopamine receptors

(Meltzer and Massey, 2011) could potentially predict the unique weight gain profiles associated with each individual different compounds, in particular the serotonin 2C receptor (5-HT<sub>2C</sub>) (Reynolds et al., 2006). In one recent study, female *Htr2c*-null C57BL/6 mice treated with lorcaserin, a 5-HT<sub>2C</sub> receptor agonist, ameliorated olanzapine-induced hyperphagia and weight gain (Lord et al., 2017).

Binding affinities for the histamine receptor H<sub>1</sub> (H<sub>1</sub>R) may also predict weight gain, with the blockade of the H<sub>1</sub>R is believed to attenuate olanzapine induced weight gain (Kroeze et al., 2003). Similarly, anti-depressants with high H<sub>1</sub> binding affinity has also been reported to be the strongest predictor to medication-associated weight gain (Salvi et al., 2016). Administration of beta-histines, which agonistically modulate the H<sub>1</sub>R, also ameliorates olanzapine-induced weight gain, possibly involving the increased action of neuropeptide Y (NPY) (Lian et al., 2014), a potent orexigenic agent that exerts physiological action through its Y<sub>1-5</sub> receptors in the hypothalamus. However, in an eight week mice study, prebiotic intervention did not appear to alter the mRNA levels of hypothalamic orexigenic (NPY) and anorexigenic (CART, POMC) peptides (de Cossio et al., 2017).

Furthermore, recent research has illustrated that the gut microbiome is also altered by antipsychotic medication. Atypical antipsychotics may be associated with decreased species richness (Flowers et al., 2017) as well anti-commensal (Maier et al., 2018) and anti-microbial (Morgan et al., 2014) activity. Pertinent to antipsychotic-induced weight gain, olanzapine, a drug well documented for conferring clinically significant weight gain, has been shown to shift the gut microbiome composition towards an obesogenic bacterial profile that is documented in both mouse and humans (Morgan et al., 2014). This describes an increase in the relative abundance of *Erysipelotrichi* from phylum *Firmicutes* and class *Gammaproteobacteria* from phylum *Proteobacteria*, and a decrease in class *Bacteroidia* from phylum *Bacteroidetes*. However, the impact of antipsychotic medications, on the microbiota composition will require further exploration as olanzapine has also been reported to confer no significant changes in phyla composition (Kao et al., 2018). Together this highlights the

need to further explore mechanisms of how the intestinal architecture may affect medication-related weight gain.

Anti-obesity and weight loss effects have been shown in a few studies which alters the gut microbial composition through the use of prebiotics and other similar compounds (i.e., probiotics). Enhancing the growth of specific microbial populations leads to the production of short chain fatty acids, and several downstream metabolites that enter the circulation and confer peripheral and central physiological benefits. These intermediate protein communicators may be able to mitigate, or attenuate, antipsychotic-induced weight gain. In a randomized, placebo-controlled trial, prebiotic supplementation led to reductions in self-reported appetite and caloric-intake as well as decreased overall weight in both overweight adults (Parnell and Reimer, 2009) and, most recently in overweight and obese children (Hume et al., 2017). Kellow and colleagues note in their systematic review of human studies with weight gain as a clinical outcome (Kellow et al., 2014) that extended trials lasting between 12 to 17 weeks in obese patients (Genta et al., 2009; Parnell and Reimer, 2009) were more likely to see reductions in body weight compared to trials that ranged from 4-8 weeks in normal patients (de Luis et al., 2011; Dehghan et al., 2014; Seidel et al., 2007), thereby indicating a possible floor effects in the latter. However, the authors continue to stipulate that there was insufficient evidence to recommend dietary prebiotics for reducing body weight and increasing anorexigenic gut hormones (i.e., PYY, GLP-1). It is also worth noting that are many additional mechanisms through which the gut microbiota may influence metabolism such as pathways involving fatty acid oxidation and lipogenesis (Dahiya et al., 2017). Future studies may therefore benefit from not only examining circulating satiety biomarkers (i.e., PYY and GLP-1) but from also exploring the expression of hepatic adenosine monophosphate kinase and acyl-CoA carboxylase, both markers for fatty acid oxidation.

Consistent with the view of obesity as a low grade inflammatory disorder, manipulation of the gut microbiome has shown anti-inflammatory effects, a mechanism that possibly contributes to its anti-obesity profile. In a recent Alzheimer mouse model, significant decreases in inflammatory cytokines have been reported in serum after eight weeks of prebiotic administration, though significant alterations in body weight was not observed (Chen et al., 2017). In addition, prebiotic administration in SOD193A transgene mice, a widely used model of amyotrophic lateral sclerosis, ameliorated several potentially harmful biomarkers (Song et al., 2013). Animals that received a ten-week oral administration of 2% galacto-oligosaccharide (GOS) experienced delayed disease onset and extended life span by almost two weeks, possibly through attenuation of motor neuron degeneration and significantly decreased cellular correlates of activated astrocytes and microglia in lumbar spinal cord section. Together with an increase in anti-apoptotic factors (i.e., Bcl-2) and decreased inflammatory markers (i.e., iNOS and TNF $\alpha$ ) in the spinal cord of GOS-fed mice and significant reductions in the levels of pro-apoptotic factors (e.g., cleaved caspase-3, Bax), the neuroprotective profile of prebiotics, and the microbiome in large, warrants further investigation (Song et al., 2013).

Prebiotic administration has also been explored in the context of its anti-oxidant potential, wherein significantly lower levels of reactive substances and carbonyls have been observed in various brain regions of overweight mice (Franco-Robles et al., 2018). Complementary evidence to decreased oxidative stress molecules has also been reported where increased anti-oxidant enzyme activity such as glutathione peroxidase and super oxide dismutase resulted after prebiotic administration (Jia et al., 2016). Together, this highlights that anti-inflammatory, and possibly anti-oxidant, profiles of prebiotics could be a key mediator that confers health benefits to the host from the gut.

## 1.4 Enteric Inflammatory and Endocrine Communication to the Brain

Before we further explore the potential mechanisms of prebiotics beneficial effects on cognitive performance and obesity, we should take a step back and discuss the way in which intestinal microbes may communicate with the brain. The vagal nerve, the main afferent pathway from the abdominal cavity to the brain, is vital for communication between gut and brain. Vagotomised mice, following manipulation of the gut microbiome using probiotics, do not exhibit the same neurochemical and behavioural effects as healthy rodents (Bravo et al., 2011). Short-term vagal nerve stimulation in rodents can result in anti-depressant effects (Biggio et al., 2009; Krahel et al., 2004) and has been approved by the FDA as an alternative treatment for intractable depression, an approval that appears to be controversial (Martin and Martin-Sanchez, 2012). Additionally, the immunomodulatory function of the vagus nerve has garnered considerable attention where electrical stimulation has resulted in anti-inflammatory efferent responses (Forsythe et al., 2014). Some bacteria in the intestines are able to synthesize neurotransmitters and neuropeptides that are structurally identical to those produced by humans highlighting a fascinating putative mechanism..

Alterations in composition of the microbiome may increase gut permeability thereby introducing lipopolysaccharide into the systemic circulation, a molecule that stimulates pattern recognition receptors resulting in a low-grade inflammatory state (Cani et al., 2008). These cytokines may interact with elements of the endocannabinoid system to modulate adipogenesis, and in turn lead to obesity (Dahiya et al., 2017). Studies employing high fat diets to examine weight gain in rodents have often reported decreased gut permeability and accompanying metabolic distress, such as elevated cytokines and oxidative stress markers (Park et al., 2016). This is in-keeping with potential anti-obesity effects of gut-targeted interventions which appear to decrease levels of circulating cytokines (Vulevic et al., 2013) as well as restores intestinal integrity through increasing expression of  $\alpha$ -occludin and JAM-A, two transmembrane tight junction proteins at the apical membrane (Ait-Belgnaoui et al., 2014). Of particular relevance to prebiotic ingestion, fermentation of these dietary

fibres in the gut lumen releases short-chain fatty acids (SCFAs) such as acetate, butyrate, and propionate. Originating in the lumen, SCFAs likely enter the systemic circulation, although the receptors responsible for the uptake of SCFAs from blood into tissue have not yet been characterised. Involvement of G protein-coupled receptors (GPRs) is likely, as acetate and propionate have been shown to activate GPR41/43 *in vitro* (Brown et al., 2003) and *in vivo* (Belorkar and Gupta, 2016; Tazoe et al., 2009). The expression of these receptors are tissue-specific wherein GPR41 has been documented predominately in adipose tissue and GPR43 in immune cells including monocytes and neutrophils (Nilsson et al., 2003). Several reports have shown that GPR43 activation confers anti-obesity effects in adipocytes through reduction of lipolytic activity (Ge et al., 2008) or suppressing insulin signalling (Kimura et al., 2013; Priyadarshini et al., 2015), both factors relevant to antipsychotic-related weight gain (especially clozapine, olanzapine). However, additional research is required to identify the specificity of the prebiotic effect, as elevated levels of acetate, as the result of a high fat diet, have been associated with metabolic dysfunction and weight gain (Perry et al., 2016), whereas prebiotic administration has shown significant anti-obesity effects in animals (Kao et al., 2018), obese adults (Vulevic et al., 2013), and overweight children (Hume et al., 2017).

The endocrine and immune system may also be influenced by SCFAs. Since GPR43/41 are also expressed on L-cells and/or white adipose tissues, SCFA interactions with these cells may cause the release of anorexigenic hormones PYY and GLP-1 (Lu et al., 2016), thereby reducing food intake. As shown in rodents (Batterham et al., 2002) and obese subjects (Batterham et al., 2003), peripheral administration of PYY led to marked reductions in food intake. Neutrophils also express GPRs, which can result in the reduced secretion of pro-inflammatory cytokines upon activation by SCFAs (Vinolo et al., 2011). Notably, due to the widespread expression of GPRs, the physiological effects of their activation may be both protective and causative (Ang and Ding, 2016). In addition to the well-documented roles of PYY and GLP-1 in regulating appetite, cognitive functioning may also be influenced since PYY has been shown to readily cross the blood-brain barrier (Nonaka et al., 2003)

and its receptors Y1 and Y2 have been documented in the brain (Shaw et al., 2003). The administration of PYY may influence information processing speed and cognition through molecular signalling of the Y1 and/or Y2 receptor (Stadlbauer et al., 2015). The NPY/Y receptor system has been further suggested to include secretion of auto-antibodies against appetite-regulating neuropeptides/peptides as a potential mechanistic pathway allowing the gut to communicate with the brain (Holzer and Farzi, 2014). While the removal of these pathogenic antibodies through immunotherapy in anti-NMDA receptor encephalitis have been associated with good clinical outcome (Titulaer et al., 2013) the application of immunotherapies to schizophrenia has yet to be shown, though a few case studies exist to support this (Zandi et al., 2011).

Further gut-brain-immune interactions occur between enteric bacteria interacting with the immune system to influence expression of neurotransmitters including serotonin, dopamine, and glutamate (Miller et al., 2013), as well as jeopardise the health of neural tissue by precipitating inflammation (Felger and Lotrich, 2013). Though there is debate as to whether central levels of 5-HT receptors are affected by systemic inflammation, some groups have shown lipopolysaccharide-induced systemic inflammation results in increased cortical 5-HT<sub>2A</sub> receptor transcripts (Savignac et al., 2016) and hippocampal 5-HT release (Linthorst et al., 1995), and beneficially manipulating the microbiome with prebiotics normalizes receptor expression along with accompanying IL-1 $\beta$  and TNF $\alpha$  levels (Savignac et al., 2016). Since the 5-HT<sub>2A</sub> receptor is a target for second generation antipsychotic agents, it is important that interventions to ameliorate obesity or cognitive decline through anti-inflammatory mechanisms should not interfere with antipsychotic sites of action such as serotonin and dopamine receptors. A recent study in rats found that prebiotic supplementation attenuated olanzapine-induced weight gain but did not affect central 5-HT<sub>2A</sub> receptors which bind this antipsychotic (Kao et al., 2018).

## 1.5 Conclusion

There are many lines of evidence to suggest that prebiotic supplementation could be a useful adjunct to the treatment of schizophrenia, with the potential to help with the significant problems of weight gain and cognitive impairment that is so commonly seen in the disorder. It is important to highlight prebiotic use is not advocated *in lieu* of antipsychotic medication, but rather in parallel, and there have not been any reports of adverse or inhibitory effects due to such concurrent use. It is likely that SCFAs play a role in weight management of prebiotics as GPR expression is widespread and may therefore, be involved in a variety of physiological functions. However, there are several mechanisms through which SCFAs, and in turn prebiotics, may influence obesity such as those that involve adipose tissues and hepatic processes and documenting biomarkers in these regions could enrich the data to date. Furthermore, whether this pathway is a main contributor to influencing neurobiology, and thereby cognition, requires additional investigations using neuropsychiatric inventories to explore effects on executive functioning and memory. The immune system also appears to be relevant in the development of psychosis as well as cognitive impairments seen as part of the disorder. While studies directly demonstrating the central anti-inflammatory properties of prebiotics are currently few, studies of peripheral proxy markers, such as IL-6 and CRP have shown encouraging associations in clinical populations. Recent meta-analyses have provided supporting evidence for the use of prebiotic supplementation in humans, with studies showing systemic anti-inflammatory effects (McLoughlin et al., 2017), and to a lesser extent metabolic benefits (Kellow et al., 2014). There are a multitude of possible mechanisms that orchestrate the bidirectional communication between the gut microbiome and the brain (Kao et al., 2016; Sarkar et al., 2016), with additional studies required to untangle this connection and advance our understanding of this fundamental, and fascinating relationship.



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