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Review Paper

# Effect of Dysbiosis in Gastrointestinal (GI) Tract on the Severity of Negative Symptoms in Schizophrenia: A Literature Review

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## ABSTRACT

**Background:** Schizophrenia is a complex neuropsychiatric disorder with positive symptoms (hallucination and delusional thoughts) and negative symptoms such as cognitive deficits, apathy and social withdrawals according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and the International Classification of Diseases, 10th revision (ICD-10). Its specific etiology is still unclear but generally being attributed to the interaction between genetic and environmental factors which can effect as early as the gestational stage. Recent studies found increasing link between gastrointestinal (GI) microbiota and the gut-brain axis (GBA) to the early development of brain and onset of psychiatric disorders. There is a bidirectional communication between the central nervous system (CNS) and the peripheral gastrointestinal tract mediated by the GI microbiota via neural, hormonal and immunological pathways. **Method:** We searched the database of MEDLINE/PUBmed which consists more than 25 million references on biomedicine currently. MeSH terms such as "Brain-Gut-Axis", "Dysbiosis", "Negative Symptoms" and "Schizophrenia" were used. Boolean operator "AND" was used to join these MeSH terms to form a full search strategy. Studies linking dysbiosis of GI to negative symptoms of schizophrenia were included for this review while those elaborated on other psychiatric disorders and causes not linked to GI were excluded. Other database used includes Embase. **Results:** Studies showed microbiome of GI tract has an influence on the central Brain-Derived Neurotropic Factor (BDNF) level and the maintenance of N-methyl-D-aspartate (NMDAR) production. Both were found to play a role in cognitive function and synaptic plasticity and were linked to development of schizophrenia and other neurodegenerative disorders such as depression and dementias. In the absence of GI microbes, central BDNF level was reduced. Such reduction led to decreased NMDAR input onto GABA inhibitory interneurons, resulted in disruption of signal-to-noise ratio with consequence of aberrant synaptic behaviour and cognitive deficits. **Conclusions:** Dysbiosis of GI tract plays a role in the etiology of Schizophrenia and has an impact on the severity of its negative symptoms.

***Keywords:*** *Brain-Gut-Axis, Dysbiosis, Negative Symptoms, Schizophrenia*

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**Effect of Dysbiosis in Gastrointestinal (GI) Tract on the Severity of Negative Symptoms in Schizophrenia: A Literature Review**

Schizophrenia is a chronic abnormality of the brain characterised with heterogeneous psychiatric behaviours (R Caso, Balanza-Martinez, Palomo & Garcia-Bueno, 2016; Severance, Prandovszky, Castiglione & Yolken, 2015). Symptoms of schizophrenia can be classified dichotomously into positive and negative. Positive psychotic symptoms include hallucinations and delusions while negative symptoms involved cognitive disorganization, apathy and social withdrawal (APA, 2013). DSM-5 and ICD-10 further defined negative symptoms as lack of social involvement of any kind (asociality), poverty in speech (alogia), deficit in self-initiated and goal-directed acts (avolition), blunted affect and anhedonia (deficit in deriving pleasures from activities or relationships)(Mitra, Mahintamani, Kavoor& Nizamie, 2016).

Negative symptoms can be measured using various tools such as the Positive and Negtive Syndrome Scale (PANSS), Scale for the Assessment of Negative Symptoms (SANS), Brief Psychiatric Rating Scale and the Schedule for the Deficit Syndrome (SDS) (Mitra et al., 2016).

Recent studies showed that there is a bidirectional communication between the gut and the brain via microbiota residing in individuals' GI forming the brain-gut axis (Carabotti, Scirocco, Maselli & Severi, 2015; Lv, Chen, Wang, Jiang, Tian, Li& Zhuo, 2017) also termed "microbiota-gut-brain axis" (Zhu, Han, Du, Liu, Jin & Yi, 2017). It was found that gut microbiota played a role in individuals' mental well-being and has effect on the proper functioning of the central nervous system (Lv et al., 2017; Maqsood & Stone, 2016). Significant differences in composition of microbiota were found in faecal samples of schizophrenic patients and that of the healthy controls (Schwarz, Maukonen, Hyytiäinen, Kieseppä, Orešič, Sabunciyan & Suvisaari, 2018; Nguyen, Kosciolek, Maldonado, Daly, Martin, McDonald& Jeste, 2018).

## METHOD AND LIMITATIONS

Literatures used for this project were searched mostly from the database of MEDLINE/PUBmed which consists more than 25 million references on biomedicine currently. MeSH terms such as "Brain-Gut-Axis", "Dysbiosis", "Negative Symptoms" and "Schizophrenia" were used. Boolean operator "AND" was used to join these MeSH terms to form a full search strategy. Studies linking dysbiosis of GI to negative symptoms of schizophrenia were included for this project while those elaborated on other psychiatric disorders and causes not linked to GI were excluded. Other database used includes Embase which is highly versatile with comprehensive coverage of biomedical literature.

## DISCUSSIONS

Recent studies showed dysregulation of microbiota or dysbiosis played a vital role in the pathogenesis of various neurological diseases including schizophrenia.

Mitra and colleagues (2016) summarised how negative symptoms of schizophrenia originated (see **Figure 1**) while Lv and colleagues (2017) proposed possible mechanisms gut microbiota involved in the pathogenesis of schizophrenia (see **Figure 2**).

Mitra and colleagues (2016) found that severity of negative symptoms in schizophrenia is correlated positively to white matter volume loss in the prefrontal particularly the orbitofrontal area. Studies on germ-free mice with deficiency of microbiota throughout life experienced upregulation of myelination in the prefrontal cortex, a region of the brain in charge of emotional regulation, planning, cognitive behaviours and modulation of social behaviours (Lv

et al., 2017). Thus, the composition of individuals' microbiota has an implication on the neuropsychiatric well-being of these people and played a role in the onset of neuropsychiatric disorders which include schizophrenia (Hoban, Stilling, Ryan, Shanahan, Dinan, Claesson& Cryan, 2016). Further, Labus and colleagues (2017) established the correlation between microbial composition and regional brain volume of patients with irritable bowel syndromes (IBS). Increased *Firmicutes*-associated *Bacilli* was found in patients with IBS and such increase was positively correlated to volume of right nucleus accumbens and subregions of the frontal gyrus but negatively correlated to that of the prefrontal cortices and volume of the posterior cingulate cortex.

Other evidence on role of microbiota in the pathogenesis of psychiatric disorders includes findings on effects of bacteria-derived metabolites on the Central Nervous System (CNS) expression of brain-derived neurotrophic factor (BDNF) and other proteins which played a vital role in cognition and subsequent behaviours of the hosts (Lv et al., 2017). Short chain fatty acids (SCFAs) such as acetate, propionate and butyrate are metabolites which have been implicated to have indirect influence than direct action on the hypothalamic pathway due to the blood-brain barriers (Groen, de Clercq, Nieuwdorp, Hoenders& Groen, 2018). Translocation of these commensal metabolites from leaky gut into the systemic circulation could interfere with CNS function and immune regulation (Borre, O'Keeffe, Clarke, Stanton, Dinan & Cryan, 2014).

Bercik and colleagues (2011) experiment with germ-free BALB/c mice (timid strain) and Swiss mice (adventurous strain) found that via faecal transplant with faeces of the earlier species to the latter greatly reduced the exploratory behaviours of the latter. This was explained as due to level of hippocampal brain-derived neurotrophic factor (BDNF) being lowered resulted from the faecal transplant. Zheng and colleagues (2016) further corroborated such evidence. Groen and colleagues (2018) found microbial composition differences between patients with psychotic disorders and healthy controls involving bacteria populations *Bacteroides spp*., *Lactobacillus, Lachnospiraceae* and *Ruminococcaceae*. Nguyen and colleagues (2018) found negative correlation between *Ruminococcaceae* and severity of negative symptoms.

Conversely, *Lactobacillus* correlates positively with the severity of different symptom domains in schizophrenic patients but negatively with their global assessment of functioning (Schwarz et al., 2018).

Studies also found a bidirectional interaction between the guts and brain, modulating each other's functions. For example, the brain modulates the functions of the guts in terms of mucus and acid secretions, motility, bicarbonates production and immune response through the autonomic nervous system (ANS). Maqsood and Stone (2016) found that cortisol released from adrenal glands during stress is able to alter the gut permeability, altering its mucus secretion leading to changes in the composition of microbial living environments and dysbiosis. This interaction between the guts and the brain can form a feedback loop, affecting the microbiota community with mounting evidence corroborating its role in diverse neuropsychiatric disorders (Lv et al., 2017).

Although, there is still no confirmative findings on the actual cause or pathogenesis of schizophrenia to date, there are findings which indicate the link between decreased BDNF expression and hypoactivity in the N-methyl-D-aspartate (NMDA) receptor with pathogenesis

of schizophrenia. Decreased level of plasma BDNF in schizophrenic patients were noted (Lv et al., 2017).

Nevertheless, Cui and colleagues (2012) in their systematic review highlighted inconsistent findings with regard to role of BDNF in pathogenesis of schizophrenia from different studies.

Nguyen and colleagues (2018) also found that schizophrenia and other mental illnesses have association with oxidative stress, chronic systemic and gastrointestinal inflammation and metabolic dysfunction. It was further found that at phylum level, *Proteobacteria* was relatively decreased in schizophrenic patients compared to the healthy controls. At genus level, *Anaerococcus* was relatively increased in individuals with schizophrenia while *Haemophilus*, *Sutterella* and *Clostridium* were found decreased in comparison to normal controls.

Several studies evidenced association between schizophrenia and elevated serological biomarkers of microbial translocation with implication of leaky guts or increased permeability of intestinal lumen causing dysbiosis of the GI system and affects systemic physiological functioning (Severance et al., 2015). Leaky gut effects a role in gut-brain axis with activation of systemic immune-inflammatory processes (Maes, Kanchanatawan, Sirivichayakul & Carvalho, 2018). Maes and colleagues (2018) found increased plasma IgM/IgA responses to Gram-negative gut commensal bacteria such as *Hafnei alvei*, *Pseudomonas aeruginosa*, *Morganella morganii* and *Klebsiella pneumoniae* are correlated to negative symptoms, neurocognitive impairments and the deficit phenotype.

Moreover, GI inflammation environment can be elicited by neurotropic gut pathogen *Toxoplasma gondii*. This could affect functioning of the brain as GI inflammation will activate innate immunity including activation of complement C1q which also function at synapses of the brain (Severance et al., 2015) In addition, gut diseases such as colitis, celiac disease and irritable bowel syndrome are highly prevalent comorbidities in schizophrenic individuals with implication of relationship between the guts and the brain (Nguyen et al., 2018). Severance and colleagues (2015) posited that modification in migrants' dietary consumption resulted in gluten indigestion could alter main bacterial composition and lead to "migrant status" being a risk factor of getting schizophrenia.

Schwarz and colleagues (2018) also witnessed different microbial composition in guts of those at risk of getting or with schizophrenia compared to those who are not. People with chronic GI inflammation such as having celiac disease, ulcerative colitis and Crohn's disease associated to autoimmune diseases are at higher risk of getting schizophrenia. It was further found that individuals in first-episode schizophrenic (FES) experience showed maximum abnormalities in their guts' microbial composition (in comparison to profiles of normal controls) with severe psychotic symptoms, worst global functioning at hospitalisation and low remission rate after one year follow-up compared to schizophrenic patients who were not in FES phase.

Current literature showed inconsistent findings on the effect of dysbiosis of GIT on the severity of negative symptoms in schizophrenia and unestablished evidence on the use of psychobiotics as therapeutic intervention (Remington et al., 2016).

Ng and colleagues (2019) systematic review on three randomised control trials (Dickerson et al., 2014; Severance et al., 2017; Tomasik, Yolken, Bahn & Dickerson, 2015) found non-significant effect of probiotics on schizophrenia symptoms with pooled standardized mean difference -0.0884 (95% CI -0.380 to 0.204, $p = 0.551$) despite findings of BDNF increase with probiotics supplementation (Tomasik et al., 2015). BDNF increase was found to promote adult neurogenesis and ameliorate negative symptoms (Tomasik et al., 2015).

On the contrary, Steenbergen and colleagues (2015) found statistically significant overall reduction in cognitive reactivity to sad mood after four weeks of administration of multispecies probiotic containing *Lactobacillus brevis W, Bifidobacterium lactis W, Lactobacillus acidophilus W37, Bifidobacterium bifidum W2, Lactobacillus salivarius W2, Lactobacillus casei W5, and Lactococcus lactis (W19 and W58)* to 20 healthy individuals. Any corroboration of findings in the literature requires further studies in future especially on effect of specific probiotics on specific negative symptoms of schizophrenia as well as confounding factors modulated by individuals' diet, medications and any underlying comorbidities.

## CONCLUSION

In conclusion, there are converging evidences showing association between dysbiosis and severity of psychotic symptoms of schizophrenia and confirmative findings on existence of bidirectional communication between the guts and the brain. Lower expression of DBNF and hypoactivity of NMDA receptors, GI inflammation associated with autoimmune diseases, elevated plasma IgM/IgA responses to gut commensal Gram-negative bacteria, tryptophan metabolism have all been implicated in affecting the severity of negative symptoms of schizophrenia. There are also various pathways implicated in the aetiology of psychotic symptoms with dysbiosis of gut flora being the initial trigger.

Nguyen and colleagues (2018) proposed oxidative stress, chronic systemic GI inflammation and metabolic dysfunction as part of the causes of schizophrenia while Severance and colleagues (2014) found diet modification leading to gluten indigestion being a risk factor in getting schizophrenia as in those with "migrant status". People in FES phase has also been found having the most profound differences in gut microbial composition compared to similar profiles from the normal controls and schizophrenic individuals in stable phase (Schwarz et al., 2018).

Further, Lv and colleagues (2017) found correlation between gut microbial composition and volume loss of the prefrontal region of the brain which played a pivotal role in determining the severity of negative symptoms in schizophrenia. Last but not least, Bercik and colleagues (2011) established the effect of gut microbial composition on behaviours via their experiment with germ-free BALB/c mice (timid strain) and Swiss mice (adventurous strain).
Despite these findings, number of empirical studies on microbial communities in schizophrenic patients is very limited with most studies using animal models (Nguyen et al., 2018). The role of BDNF in pathogenesis of schizophrenia is also inconclusive (Cui, Jin, Wang, Weng & Li, 2012). Availability of literature with use of human samples and consistent findings is limited. Other constraints include methodology challenges faced in experiments.

Future research should use more human samples and bridging the gap of inconsistent findings.

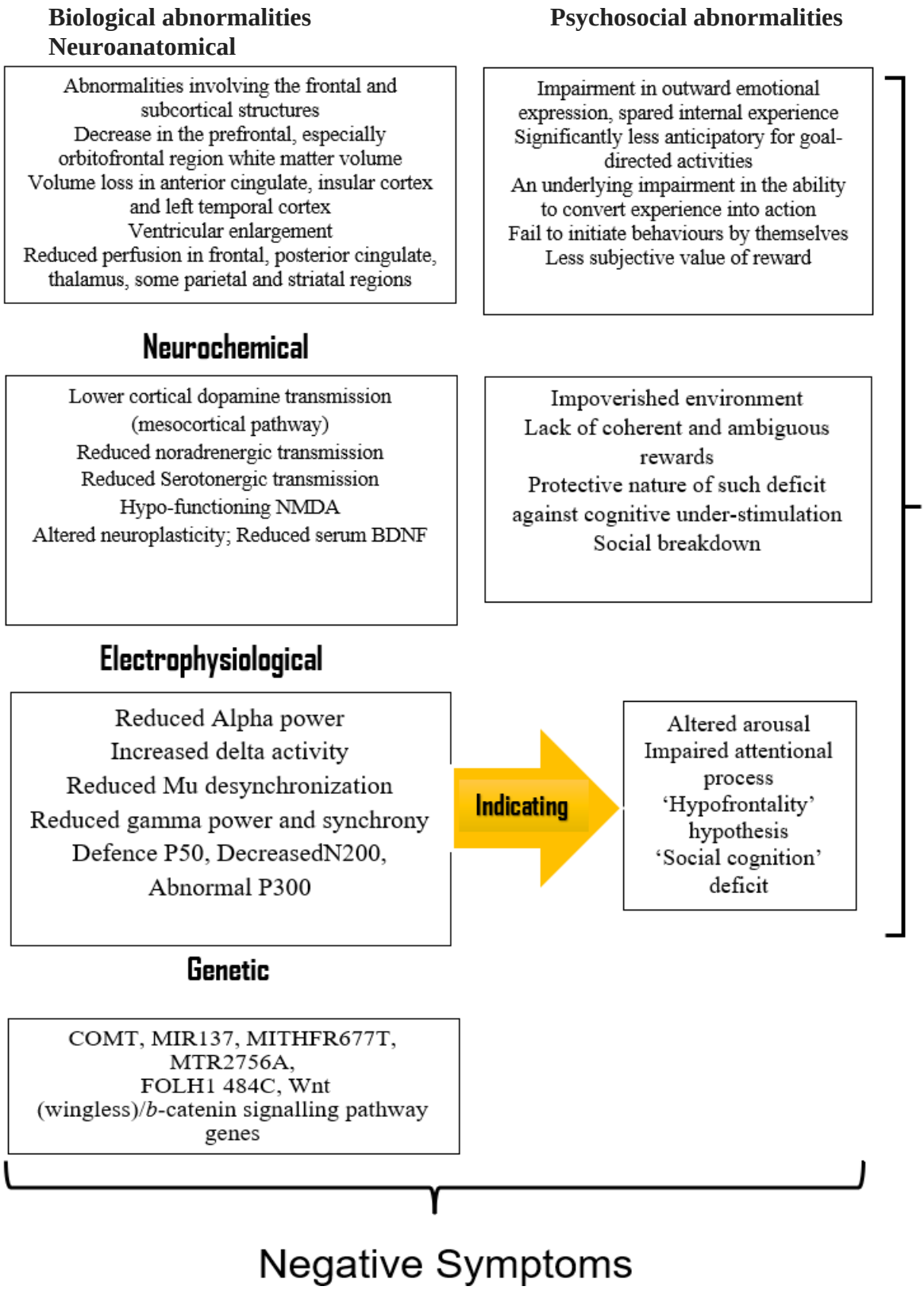


***Figure 1: The Aetiology of Negative Symptoms***

Mitra, S., Mahintamani, T., Kavoor, A. R., & Nizamie, S. H. (2016). Negative symptoms in schizophrenia. *Industrial psychiatry journal*, *25*(2), 135

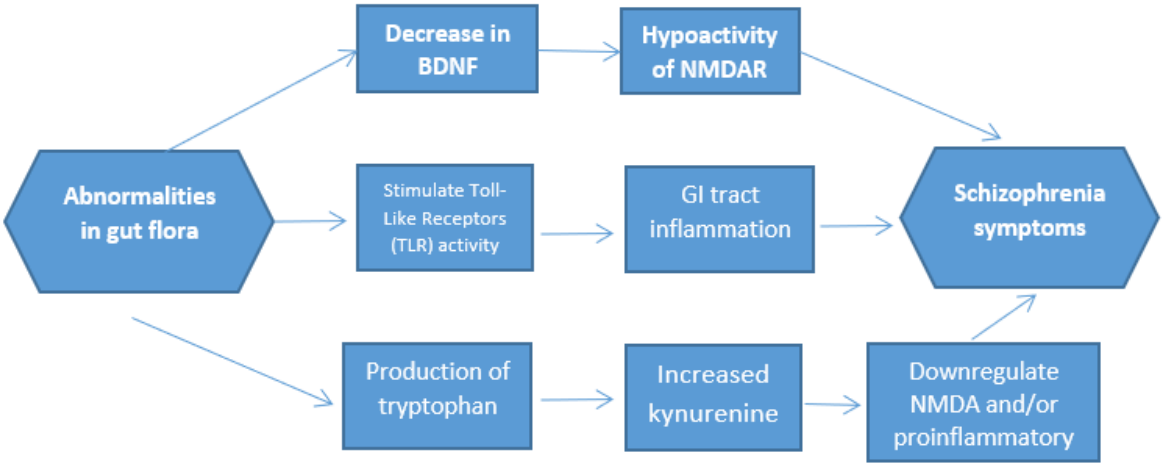


***Figure 2: Possible mechanisms of gut microbiota in the pathogenesis of schizophrenia through (1) modulation of BDNF (2) immune response of the guts (3) kynurenine pathway of tryptophan metabolism.***

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***Conflict of Interest***

The author(s) declared no conflict of interest.

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