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# ARE THEY ALSO MIND COLONIZERS? EXPLORING THE ASSOCIATION BETWEEN GUT MICROBIOTA AND DEPRESSION

**Tolulope E. Fadeyi and Funmilola A. Ayeni**

Department of Pharmaceutical Microbiology, Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria

Author's email: fadeyitolulopeelizabeth@gmail.com, funmiyeni@yahoo.co.uk

**ABSTRACT**

The association of the gut microbiota with many diseased and healthy state is currently of global interest. Depression is a disorder that is etiologically heterogeneous. There is a correlation between gut microbiota, immune responses, behaviour and pathophysiology of depression. These shows the link of microbiome and mental health, which point to a possible future of manipulation of gut microbiota for better health. This mini review compiled some existing literature on the relationship between depression and human gut microbiota.

**Keywords**: Depression, Brain, Gut microbiota. Probiotics

## THE HUMAN INTESTINAL MICROBIOTA

The microbiome is a trillion set of human-hosted, beneficial- and pathogenic microorganisms and humans host have nearly 100 trillion microbes in their digestive tract, most of which are bacterial species (Thursby and Juge, 2017). In comparison, human genes are 150-fold larger than the bacterial genes in the digestive tract (Backhed *et al.,* 2011). The microbiota of the intestines starts at birth, as the intestinal tract is sterile in the utero. The gut microbiota is fairly stable after 3 years, but may be influenced by factors such as feeding style (Marques *et al.* 2010, Ayeni *et al.,* 2018), gestational age (Barrett *et al.,* 2013), lifestyle (Afolayan *et al* 2019), delivery methods, (Dominguez-Bello *et al.,* 2010) e.t.c.. The intestinal barrier acts as a protection that the intestinal microbiota or its metabolites can alter (Tlaskalová-Hogenova *et al*., 2011, Jakobsson *et al*., 2015). The microbiome lives in symbiosis with its host; the host provides the gut microbiota a protected and energy-rich environment and the gut microbiota modulates gut motility, regulates absorption of nutrients and contributes to neural communication, especially as some bacterial strains can produce neurotransmitters (Barrett *et al.,* 2012). Such physiological effects of the microbiota lead to the host's excellent safety and wellbeing. Hence, disruptions of the bowel or dysbiosis can interfere with the health of the host in various ways, including behavioural changes and brain function. The aim of this mini review is to explore depression with its associated factors and the link between gut microbiota and depression.

### Gut-brain axis

There is a bi-directional contact between the brain and intestines called the intestinal microbiota axis, which acts as a key signalling factor (Clarke *et al.,* 2013). In addition, a cross-talk between the gut and the brain is mediating in single aminogenesis and the hypothalamic pituitary-adrenal axis (HPA) (Mayer, 2011). Amygdala comprises the network that integrates and transmits homeostatic information from the intestinal tract, including visceral pain and food intake (Mayer, 2011). Homeostatic changes in the gut are communicated to the brain through the enteric nervous system (ENS), a system comprised of 200-600 million neurons (Mayer, 2011). Multiple potential brain-gut signaling pathways have been proposed, which may help modulate the brain and behaviour (Mayer *et al.,* 2014). The directionality of the gut-brain axis allows both "bottom-up" and "top-down" communication e.g. the administration of certain bacterial strains to a murine host changes the neural activity and behaviour. Mice with *Campylobacter jejuni* displayed an improved anxiety-like activity and altered brain activation in one such study (Sylviaa and Demasa 2018). Studies have also shown "top-down" communication by primarily studying how psychological stress can influence the microbiota. Early life stress in a murine 3 model, via maternal separation alters immune and microbiota profiles (O' Mahony *et al.,* 2009), increase intestinal permeability of mice and alter behavioural profiles (De Palma *et al.,* 2015). The gut microbiota is intrinsically connected with gastrointestinal and central function. Although associations within the gut-brain axis have been established, further mechanistic and translational studies are needed to render plausible applications to psychiatric conditions in humans.

### Blood brain barrier and microbiome

The blood brain barrier (BBB) is a complex neurovarietal community composed of the central nervous system (CNS) cells that separate the blood vessel from the CNS (Bauer *et al.,* 2014). The discovery of connections between bowel microbiota and the CNS contributes to a profound shift in neuroscience with potential implications for both pathophysiology and stress-related mental disorders. The effect on endocrine (neuro) or immunosignal enhanced neuro-endocrine stress response may be a variable risk arising from a marginal shift in early-life microbiota acquisition and maintenance (Farzi *et al.,* 2018). According to Kelly *et al.*

(2015) review, the most important effects of microbiota can happen in early life during critical neurodevelopment processes (Borre *et al.,* 2014) and the gut microbiota is needed for pituitary supercarenal hypothalamic axis (HPA) development as early colonisation is required to ensure normal development of this important pathway at certain times (Moloney *et al.,* 2014). This also correlates to the 'old friendship hypothesis' (Bloomfield *et al.,* 2016) that was first proposed in the late 1980s (Strachan 1989). It is suggested that less biodiversity may lead to inflammatory disorders, including depression (Williamson *et al.,* 2015). Antibiotics use reduces gut microbial diversity in children who used antibiotic therapy in their first year of life as they are more likely to have behavioural problems and depression. At the age of three, the results were clear (Slykerman *et al.,* 2017). Animal studies have identified similar phenomena of antibiotic induced dysbiosis and behavioural issues (Guida *et al.,* 2018) and stress influence the gut microbiota contents in animal studies (Marin *et al.,* 2017). However, it has been shown that chronic-stress-induced depression in animals were improved with the use of lactobacilli (Liang *et al.,* 2015).

**Gut microbiota and behaviour**

Depression is a complex, persistent worsening mood condition associated with many environmental and genetic factors for a minimum of two week or longer with at least five associated symptoms which cause a clinically substantial daily deterioration (societal, work or other main functional areas, considerable weight loss, or weight gain). Depression can be defined as mood disturbance, tiredness, lack of energy, sense of truth or unfailing guilt, decreased capacity to think or focussed, and repeated death thought (APA, 2013). In stress disorders which involves extreme chronic and stress-related major depression, gut microbiota is recommended in behaviour regulation (Dash *et al.,* 2015),

Changes in the HPA axis in patients that have severe depressive disorders (e.g. elevated levels of cortisol, higher levels of CRF in the brain) are frequently found. In fact, pro-inflammatory cytokines are not only signs of disease, but are signs of severe depression in susceptible people with no prior history of mental disorder, which indicates that depression is involved in the brain cytokine system (Dantzer *et al.,* 2008). In animal models, a correlation between altered gut microbiota and depression has been identified over the years. Three potential pathways have been proposed for how gut microbiota causes depression. One of these is inflammations mediated by IgA and IgM is increased by lipopolysaccharide in depressed people. Lower adaptability due to abnormalities in cytokines circulation can also lead to depression. HPA is an important element in the neuroendocrine stress reaction mechanism and therefore plays a key role in mood regulation. Therefore, as mentioned above, changes in HPA are caused by several mental conditions (including anxiety and depression). Treatment with probiotic bacteria *L. farciminis* has been shown to minimize HPA pressure by preventing intestinal barrier impairment and reducing circulating lipopolysaccharide levels (Ait-Belgnaoui *et al.,* 2012). Direct interference with neurotransmitter signaling is another potential mechanism. Depression neurobiology in the mouse model was observed as depressive behaviour and as a consequence of the two-sided surgical removal of olfactory amputation; it has been shown that anxiety and depression influence the composition of the microbiota in the colon (Park *et al.,* 2013, Marin *et al.,* 2017) and changes in the proportion of certain bacterial phyla was due to the microbial composition, not to their presences or absences (Park *et al.,* 2013). Furthermore, stressed animals have lower lactobacilli abundances than control animals, thereby showing their effect on the dietary and strains in gastrointestinal tract (Marin *et al.,* 2017). Unfavourable experiences in early life are correlated with a slower response to stress and a consequent increase of the risk to disease in the future, thereby influencing the brain-gut axis as demonstrated in maternal separation of male rat pups (during the 2-12 postnatal period, separation from the mothers 3 hours a day) caused stress while animal control were left undisturbed (O'Mahony *et al.,* 2011).

Also, in transplanting microbiota of depressed patients and healthy individuals into germ-free mouses, Zheng and colleagues found that depressed mice had a microbiota distinct from that of healthy rats. These differences are similar to their donor differences and may lead to depression by metabolism change (Zheng *et al.,* 2016). Kelly and colleagues also studied another model where the depressed patient faecal microbiota are transplanted to rats that have been infected with gut microbiota using antibiotic cocktails. The receiving rats had obvious symptoms such as anhedonia, elevated anxiety and metabolic tryptophane disorders, all of which were close to those of their microbiota providers (Kelly *et al.,* 2016). Both of these studies have shown that depression-related symptoms of psychological and physiological conditions can be spread among different subjects. Specific microbiota are acquired by offsprings from parents in the natural conditions by longitudinal and horizontal gene transfer (Yatsunenko *et al.,* 2012).

Correlations between gut microbiota and anxiety have been observed in inflammatory and intestinal barrier safety studies (Maes *et al.,* 2013). Wide-ranging use of antibiotics in mice induces dysbiosis, depression, and impaired neuronal shooting of the hippocampus following the probiosis procedure with a reverse-type of the *Lactobacillus casei DG* (Guida *et al.* 2018). Transplanting depressed and healthy microbiota from human to germ free rats have resulted in behavioural disorder in the affected animals with depressed microbiota (Kelly *et al*, 2016, Zheng *et al.,* 2016). Behavioural associations from baby colic (Mi *et al.,* 2015) to neuro-developmental behavioural abnormalities (Hsiao *et al.,* 2013) have been shown. Some studies have found that microbiota diversity and abundance have diminished in depressed patients (Jiang *et al.,* 2015). At the phyla level, the abundance of Bacteroidetes and Proteobacteria has been increased, while the abundance of Firmicutes has decreased whereas Prevotelaceae have increased in relative abundance, whereas *Faecalibacterium* and *Ruminococcus* have decreased (Zheng *et al.,* 2016, Liu *et al.,* 2016). Abundance also decreased in *Lactobacillus* and *Bifidobacterium* (Aizawa *et al.,* 2016). In all of these studies, there have been evidence of

intestinal microbiota mal-normalities, but there are still some discrepancies in intestinal regulation and regulation variations that are possibly due to differences in diagnostic criteria, grouping criteria, faecal methodologies in microbiota detection, e.t.c. Animal experiments have also shown microbiological variations between depressing models and control animals. The phenomenon has been shown by various models of depression, such as the Bilateral olfactory bulbectomy model (Park *et al.,* 2013), the maternal separation model (O'Mahony *et al.,* 2009), and social interrupting model (Bharwani *et al.,* 2017). The abundance of Bacteroidetes is increasing but the abundance of Firmicute declines and abundance of *Lactobacillus* decreases (Yu *et al.,* 2017), which indicates the depressed animal microbiota is close to that of depressed humans. All these findings indicate that certain phenotypes of the intestinal microbiota are potentially associated with depression.

Colonised mice follow the behavioural characteristics of the donor mice thus, giving a proof of how gut microbiota affects the "bottom-up" axis of gut brain communication. More precisely, it is supported by the colonization with more exploratory and less nervous NIH Swiss mice of GF Balb / c mice, usually shy and nervous. The Balb / c mice recipient thus took on their NIH Swiss donor's role, with the Balb / c mouse exhibiting reduced anxiety and more exploratory activity. In addition, the study has also demonstrated an increased anxiety-like activity of Swiss mice colonized with Balb / c microbiota and a decreased brain hippocampal neuro-trophic factor (BDNF) (Bercik *et al.,* 2011). In comparison, a study demonstrates how mice raised in a hostile environment exhibited a changed microbiota composition and a rise in depressive behaviour, as well as an example of "top down" gut brain-axis contact (Bendsten *et al.,* 2012).

Another study analysed the faecal microbiota of depressed patients and healthy controls and found that depressed subjects had a significant association with presence of both *Oscillibacter* and *Alistipes* and exhibited an overrepresentation of the order Bacteroidales but an underrepresentation of the family Lachnospiraceae (Naseribafrouei *et al.,* 2014). This study was important in establishing correlations between depression and specific organisms. Similarly, another study analysed gut microbiota composition of depressed and healthy subjects and found that depressed subjects had increased α-diversity and altered levels of bacterial species, as compared to healthy controls (Jiang *et al.,* 2015). Moreover, there was a negative correlation between serum BDNF and *Clostridium XIVb* as well as a negative correlation between depression severity and *Faecalibacterium*. In another study between depressed individuals and healthy controls, Bacteroidales were increased and the family Lachnospiraceae abundance were decreased in depressed patients (Naseribafrouei *et al.* 2014). A high level of Enterobacteriaceae and *Alistipes* were found in relation to depression and the severity of depression symptoms were negatively correlated to *Fecalibacterium* population (Jiang *et al.* 2015). These studies established a link between altered gut microbiota and mood disorders in humans. A study published in 2016 found that rats colonized with gut microbiota from patients with major depressive disorder displayed significantly greater depressive-like behaviour, TNF-α concentration, and kynurenine/tryptophan ratio than rats colonized with healthy control gut microbiota (Kelly *et al.,* 2016). However, in the paper, the colonized rats were not germ-free but simply treated with antibiotics prior to colonization, and the faecal microbiota used for colonization was a pool of several donors samples, thus the operational taxonomic units (OTUs) of individual patients, or the differences between them, could not be delineated.

**The relationship between the gut microbiota, barrier function and stress**

Stress is theoretically associated with an increased intestinal permeability and may affect the development course of the intestinal barrier (Lennon *et al.,* 2013, Kelly *et al.,* 2015). The occurrence of anxiety later in life was strongly associated with traumatic early-life events (Syed and Nemeroff, 2017). There are well known associations between stress, HPA and immune systems (Baes *et al.,* 2014). The composition of gut microbiota was shown to be restructured by stress (De Palma *et al.,* 2015).

Many neurobiological changes have been associated with the production and persistence of depression over the past few years. Inflammation seems to be a fundamental process which connects many of these findings. Both biological causes like the accumulation of excessive neurotransmitters, psychological mechanisms like adult stress reactivity and childhood trauma have been correlated to chronic inflammation. An inflammatory disorder driven by the microbiota can be caused by defective gut barrier with brain consequences. A single source was not the source of low-grade inflammation reported during depression. Whatever the order, the intestinal microbiota might be active in both processes.

A fine balance between the microbiome and the mucosal immune system is found in homeostatic conditions; however, perturbations of the microbiota can result in immune activation, such as activation of toll-like receptors and consequent release of pro-inflammatory cytokines (Dinan *et al.,* 2013). This cascade of events leads to inflammation and can often be accompanied with altered behaviour. For example, rodents that received peripheral proinflammatory cytokines exhibited symptoms of depression, disrupted circadian rhythm, and appetite loss (Bilbo and Schwarz, 2012). Furthermore, animal models of intestinal inflammation often present with concurrent anxiety. Mouse models of experimental colitis display intestinal inflammation and anxious behaviour with changes in central BDNF, but mice with colitis treated with probiotic *Bifidobacterium longum*, exhibited normalized anxiety-like behaviour and BDNF levels (Bercik *et al.,* 2011). Higher immune responses (IgA and IgM production) against lipopolysaccharide (LPS) of commensal Gram-negative gut-bacteria due to bacterial translocation has been linked to depression (Maes *et al.* 2012). Toll like receptor -4 (TLR-4) signaling up- regulation was observed in depressed patients which could be linked to

bacterial translocation as against healthy controls (Kéri *et al.*, 2014).

There is a link between proinflammatory pathways, gut microbiota, barrier behaviour and co-morbid anxiety in relation to alcohol dependence with greater bowel permeability in a subgroup of subjects who relied on alcohol (Leclercq *et al.,* 2014, Kelly *et al.* 2015). Also, enteric pathogenic contaminations appeared to impact the intestinal barrier (Wu *et al.,* 2011). Gastrointestinal contamination has been noted to deliver high nervousness behaviour in mice (Lyte *et al.,* 2006). The heterogeneity of gut microbiota arrangement may likewise be affected by anti-infection agents with potential consequences for neurochemistry and activities ((Willing *et al.,* 2011, Bercik and Collins, 2014, Kelly *et al,* 2015).

**Irritable bowel syndrome, depression and cytokines**

There is an association between irritable bowel syndrome (IBS) and gut microbiota. Since the 1950s, it was postulated that IBS was associated with psychiatric disease, but the exact mechanism is still not very clear (Mudyanadzo *et al.,* 2018). Patients with gastric-disease disorders such as IBD, experience sicknesses such as major depressive disorder. Inflammatory-bowel disease patients were shown to suffer depression three times higher than the general population, with up to 17% of IBD patients experiencing depression and suicidal thought symptoms (Byrne *et al.,* 2017). The irregular intestinal microbiota profiles in patients with IBD indicate that the gut microbiota may play an important role in the disease (Distrutti *et al.,* 2016). The microbiome itself might not be associated, but may affect the efficacy or harmful effects of pharmacologic agents for the treatment of certain disorders (Flowers and Ellingrod, 2015). Furthermore, substantial numbers of IBS patients suffer from depressive and anxious symptoms as well as increased frequency and severity of gastrointestinal symptoms (Lucas *et al.,* 2014, Pinto-Sanchez *et al.,* 2015). Mood, pain and hippocampal visuospace memory alterations were also observed in depressed patients (Tillisch *et al.,* 2013, Kennedy *et al,* 2014, Kelly *et al.* 2015). The greatest positive risk of IBS is the mixture of intestinal permeability, Rome I parameters and fecal calprotectin (Sood *et al.,* 2015).

In a review by Kelly *et al.* (2015), high Firmicute/Bacteroidetes ratio is correlated with IBS ((Jeffery *et al.*, 2012) and a correlation has been shown between some members of Firmicutes and Proteobacteria with IBS symptoms (Rajilic-Stojanovic *et al.*, 2011). There is an inverse relationship between the order *Actinomycetales*, family *Actinomycetaceae* and significant depression (Jeffery *et al.*, 2012). The working role of microbiota in the presentation of psychiatstic comorbidities was explored through the use of germ-free mice in IBS patients with comorbid anxiety (IBS-A). It was found that mice which were colonized with IBS-A microbiota displayed higher anxiety and altered colonic expression of innate immune genes (De Palma *et al.,* 2017). People with already existing psychological disorders have an higher risk of having post-infection IBS (PI-IBS) and differences observed in some genetic characteristics e.g. cadherin-1, TLR9, IL-6 are risk factors in PI-IBS occurrence (Villani *et al.*, 2010, Kelly *et al.* 2015).

It has been noted that humoral activity markers have a positive correlation with depression symptom (Vicario *et al.*, 2015). A pro-inflammatory cytokine formed primarily by activated macrophages, is the tumor necrosis factor (TNF)-α. The large size of TNF-α limits their flow through the blood-brain-barrier but can affect the brain either through the circumventricular organs (parts of the more permeable blood-brain-barrier) or through different fibers of the vagus nerve (Himmerich *et al.*, 2019). It is possible that depression may result from exacerbated inflammation, as mediated by maladaptive or increased cytokine activation. Indeed, studies have found that mood depressive disorder patients have greater blood concentrations of TNF-α than healthy controls (Miller and Raison, 2016). Animal studies have shown the potential for depressive activity with increased pro-inflammatory cytokines. Mice treated with LPS, for example, shows increased depressive-like behaviour (that triggers the development of pro inflammatory cytokines), although motor activities and sicknesses return to normal (Remus and Dantzer, 2016). Infliximab, a chimeric mouse-human antibody targeting TNF-α, has been used to treat IBD for over a decade with accepted efficacy and safety (Fidder *et al.,* 2009). Interestingly, patients with IBD and IBS often present with comorbid depression and anxiety, with increased psychiatric symptoms during severe periods of active disease (Graff *et al.,* 2009). A study reported that anti-TNF therapy, including infliximab, decreased depressive symptoms and increased quality of life in IBD patients (Horst *et al.,* 2015). Moreover, infliximab treatment has been found to decrease depressive symptoms in mood depressive disorder patients with high baseline inflammatory biomarkers (Raison *et al.,* 2013). Animal studies have also shown that infliximab has the potential to alleviate psychiatric symptoms that are even not inflammatory bowel disease. For example, infliximab-treated rats that underwent chronic mild stress (CMS) exhibited a reduction in depressive and anxiety-like behaviour, as compared to placebo-treated rats (Karson *et al.,* 2013). Both clinical and animal studies provide support that inflammation, mediated via TNF-α, may contribute to the expression of depression and anxiety.

β-defensins are antimicrobial peptides that limit microbial colonization in epithelial tissues and at high concentrations generate pro-inflammatory signals. Because inflammation has been proposed to play a role in the expression of depression and anxiety, it is possible that innate immune activation may also be involved. Calprotectin is a protein that exists in the cytosol of inflammatory cells. Fecal calprotectin has been widely accepted as a biomarker for overt intestinal inflammation and differentiates IBD, such as Crohn's or colitis, from IBS (D'haens *et al.,* 2012).

**Depression, probiotics, diet and short chain fatty acids**

A probiotic is defined as a live bacterium, which provides the host with a health benefit when administered adequately (WHO, 2001). Many lactic acid bacteria strains have been

extensively studied for their probiotic potentials (Ayeni *et al.* 2011, Adetoye *et al.* 2018, Adeoshun *et al.* 2019, Ayeni *et al.* 2019). Lactic acid bacteria also have antagonistic activities against intestinal pathogens (Adeoshun and Ayeni, 2016; Ayeni and Ayeni, 2017, Afolayan and Ayeni, 2017). Probiotics could be an adjunctive or alternate treatment for depression (Vlainić, *et al.,* 2016). A study by Orel and Kamhi, (2014), provide some evidence of therapeutic significance of probiotics in IBD. Some probiotics can ameliorate certain IBS symptoms (Didari *et al.* 2015). At least some of these positive effects may affect inflammatory effects of microbes (Chen *et al.,* 2017). There has been suppression of stress-induced hyperpermeability and prevention of HPA stress response by the use of *Lactobacillus farciminis* in rats (Ait-Belgnaoui *et al.,* 2012). The beneficial effects of probiotic strains in the gut microbiota in relation to stress response and depressive symptoms in bipolar disorder has been reported (Aizawa *et al.,* 2016). Prebiotics modify bowel movement, reduce low inflammation and improve metabolism (Bindels *et al.,* 2015). A probiotic organism (*Bifidobacteria infantis)* has been observed to attenuate pro-inflammatory responses and increased serotonergic precursor (Desbonnet *et al.,* 2008). Diabetic rats had substantially improved spatial memoir loss and restoration of hippocampal long-term potentiation through administration of probiotics in improved brain functions (Davari *et al.,* 2013). Administration of *Lactobacillus helveticus* in fermented milk improved sleep in elderly volunteers (Yamamura *et al.* 2009). In another study of volunteers with symptoms of stress, the use of probiotics reduced abdominal pains, vomiting and nausea in the volunteers (Diop *et al.,* 2008).

Many unhealthy diets, industrial and processed, excess fat-containing foods, sugar and food additives kill normal bowel microbiologies and increase risk of depression as fast foods can increase depression behaviour and intestinal permeability (Noble *et al.,* 2017). Poor food are possibly closely related to the functioning of the gut-brain axis (Bereswill *et al.,* 2014). A high fat diet results in modification of the composition of gut microbiota and consequently affects behaviour in an animal study (Pyndt *et al.,* 2014).

Microbiota are responsible for producing a number of bioactive metabolic materials, including polysaccharides, lycosylceramide and short chain fatty acids (SCFA) (Russell *et al.,* 2013). Short chain fatty acids are products of fermentation of non-digestible polysaccharides. They can serve as regulatory compounds that have the ability to influence emotion, inflammatory and cognition through the gut-brain axis (Skonieczna-Żydecka *et al.,* 2018). The SCFAs are neurohormonal signalling molecules produced by certain groups of bacteria, such as *Prevotella, Roseburia, Clostridium, Lactobacillus, Eubacterium, Propionibacterium, Bifidobacterium* and *Bacteroides* (Galland, 2014). They can be transported through BBB through monocarboxylate transporters and thereafter influence *BBB* integrity through inhibition of pathways associated with inflammatory responses (Dalile *et al.* 2019). Ironically, although butyrate is important in maintenance of intestinal barrier and reduction of bacterial translocation, there is a reduction of butyrate producing bacterial in IBS patients in a study (Pozuelo *et al.* 2015).

## CONCLUSION

The scientific studies done on both animal and human models have established a relationship between depression and human gut microbiota. More clinical researches still need to be done to further clarify this claim and explore the pathway by which gut microbiota affects depression. A possible therapeutic future in depression management might be gut microbiota manipulation

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