Psychobiotics As Integrative Therapy for Neuropsychiatric Disorders with Special Emphasis on the Microbiota-Gut-Brain Axis

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Equal contribution.

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Introduction

The human body is colonized by numerous microbial communities residing in both internal and external areas. The total of microorganisms in the intestinal tract is known as the gut microbiota. A complex interaction exists between host and gut microbiota, and this field of research is of growing interest to clinicians and researchers. The gut microbiome consists of the collective genome of about 100 trillion microorganisms residing in the gastrointestinal tract, and contains 150 times as many genes as the human genome. Amongst microbial communities, the gut microbiota is considered of particular importance to the host. Humans are in a symbiotic relationship with gut microbes, in which we provide them with a continuous source of nutrition and in return they provide us with health benefits.

For a better understanding of the complex interaction between gut microbiota and the host, and its role in health and disease, a complete description of the microbiome ecology is needed. Both metagenomic and molecular methods have been used for this purpose. It is estimated that our microbiome consists of more than 1000 species and more than 7000 strains. The human gut is home to 10^13-10^15 microorganisms, consisting of mainly anaerobic bacteria, but also viruses, protozoa, fungi and archaea.

The gastrointestinal tract of the fetus is considered sterile and gut colonization of the infant begins at birth with the exposure of the newborn to maternal and hospital environment. It is important to note that there is data suggesting the presence of a prenatal mother-to-child microbiota transmission. As infants are exposed to a variety of environmental factors, gut microbiota is growing in terms of size and diversity, and around the age of 1 to 2 years an adult-like microbiome is noticeable. The gut microbiome has a dynamic nature and can be influenced by a variety of factors, including route of birth delivery, maternal transfer, genetics, diet, infection, medications such as antibiotics, age and stress. These factors can alter the composition of the gut transiently, as well as permanently. The gut microbiome is dominated by two bacterial phylotypes, Firmicutes and Bacteroidetes, with other phyla such as Proteobacteria, Actinobacteria, Fusobacteria and Verrucomicrobia present in significantly lower amounts. Although there are interindividual variations in gut microbiota composition, humans have been classified into three enterotypes, dominated respectively by Prevotella, Ruminococcus and Bacteroides.

Gut microbiota plays an important role in host physiology. A balanced gut microbial composition could be a marker associated with health, as microbiota dysbiosis is seen, for example, in Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD). Possibly, the individual microbiota profile could represent a valuable tool in assessing risk to disease and response to therapy. Gut microbiota lowers the risk of infection by defending against pathogen colonization and protects against bacterial penetration by embellishing the intestinal epithelial barrier. These microorganisms contribute also to metabolism by aiding in the breaking down of indigestible fibers and by producing essential metabolites, such as small chain fatty acids (SCFAs). In addition, gut bacteria are the main source of vitamin K and a less vital source of the B complex. Gut microbiota is a key modulator of the development and function of the host immune system. Indeed, in Germ-Free (GF) mice immune defects are seen at a structural, as well as cellular level. Interestingly, gut microbiota is also critical to brain development and function. Bidirectional communication between gut and brain has been long recognized and most of the communicational pathways have been established. However, the term microbiota-gut-brain axis is emerging due to a growing body of experimental data focusing on the role of gut microbiome in the brain-gut communication. Moreover, several studies have pointed out the importance of gut microbiota to Central Nervous System (CNS) function by being involved in the regulation of neuroinflammation, neuroendocrine stress response, and neurodevelopment. Gut microbiota also has the potential to modulate mood and behavior, which implicates it in neurological disorders, such as stress, anxiety, depression and autism that result in disruption of...
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of social behavior. Current and future animal and clinical studies dedicated to elucidating the microbiota-gut brain axis will be a breakthrough in preventing and treating mental illness.

There seems to be a balance in the enteric microbiota that confers health benefits and participates in the preservation of homeostasis. Dysbiosis and dysregulation of the microbiota-gut-brain axis have been implicated in gastrointestinal disorders, such as IBD, metabolic, and neurological disorders, such as autism. Luckily, we have the opportunity to target and modulate gut microbiota. Emerging research data is suggesting the use of psychobiotics, defined as probiotics that produce health benefits in patients suffering from psychiatric illnesses, or prebiotics as a suitable therapeutic intervention for depression and related disorders. The bacteria most commonly exploited as probiotics belong to the *Bifidobacterium* and *Lactobacillus* families. However, more research is required to assess the potential therapeutic effects on patient population.

The focus of this review is the role of gut microbiota in specific neurological disorders and the preventive and therapeutic potential deriving from modulation of gut composition in such psychiatric conditions.

Communication Between Gut Microbiota and Brain

The notion that brain can regulate gastrointestinal activity is well established. A variety of studies conducted both on animals and humans have shown that gut microbiota is critical for normal brain development and function. In the past decade research has focused on the reverse pathway, how gut microbiota can affect the brain, and what are the mechanisms behind this. The bidirectional communication between the gut and the brain is known as the gut-brain axis. This term has been expanded to microbiota-gut-brain axis, since gut microbiota is of primary importance to this pathway. The main components of the axis include neural, neuroendocrine, neuroimmune and metabolic pathways. All of these components interact to form a complex reflex network with afferent fibers projecting to CNS structures for integration and efferent projections to the smooth muscle.

The CNS communicates with and influences the gut principally through neural and endocrine pathways. The autonomic division of the autonomic nervous system (ANS) primarily innervates the vascular beds of the gastrointestinal tract (GI) and the enteric nervous system (ENS), and secondarily the lamina propria and Peyer’s patches. The sympathetic nervous system and hypothalamus-pituitary-adrenal axis (HPA) can modulate GI motility, secretion and epithelial permeability.

Gut microbiota can regulate CNS activity through different pathways. The vagus nerve and the ENS are implicated in transmitting the effects of gut microbiota on the brain and vice versa. The majority of vagus nerves (80%) are sensory neurons carrying out information from the gut to the CNS. Many of the effects of gut microbiota and probiotics have been confirmed as dependent on vagal activation. However, vagus independent pathways also exist, as vagotomy has failed to influence certain communicational aspects. Furthermore, gut microbiota can stimulate secretion of cytokines and chemokines that can affect the integrity of the epithelium, and thus elicit an immune response by entering into the systemic circulation. Indirect stimulation of the innate immunity can alter the levels of cytokines, such as interleukin-1 (IL-1) and interleukin-6 (IL-6), which can directly influence the brain by acting on the HPA axis. In addition, gut microbiota are important factors in the development and regulation of the HPA axis, which is the major stress response system of our body and is itself involved in the bidirectional communication between brain and gut. Finally, gut microbiota can produce neurotransmitters and neuroactive compounds, such as SCFAs that can also modulate brain function. Alterations in microbiota composition may lead to impairment of the communicational pathways, which can lead to disturbances in the gut-brain axis and ultimately to disease. Dysregulation of this pathway has been linked to gastrointestinal, as well as stress-related disorders. Modulation of the gut microbiota is revealing new possible therapeutic targets for mood and other disorders.

Gut Microbiota and Stress

Gut microbiota plays an important role in brain development, behavior and mood. Moreover, compiling data indicates that intestinal microbes can affect social interaction and stress management (Table 1).

Stress is defined as “a state of threatened homeostasis”, and inability to properly respond or adapt to it may lead to disease. Indeed, exposure to stress can impair a number of functions and induce GI and mental disorders, such as depression, anxiety, post-traumatic stress disorders and drug addiction.

The HPA axis is the major neuroendocrine stress response system of our body. It consists of the hypothalamus, pituitary gland, adrenal cortex, regulatory inputs and secreted factors and
hormones. When activated, cells of the paraventricular nucleus (PVN) release corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). These stimulate the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH) into the systemic circulation. ACTH in turn stimulates the adrenal cortex to release cortisol, which has a wide range of functions. Apart from glucocorticoids, catecholamines are also released into the circulation. Both psychological and physical stressors can activate the HPA axis. The response to psychological stress is mediated by neurotransmitters, such as serotonin or 5-hydroxytryptamine (5-HT) and norepinephrine (NE). On the other hand, response to physical stressors, for instance to infections, is activated via pro-inflammatory cytokines.

Groundbreaking studies revealed that the gut microbiota is essential to the stress response by being implicated in the development and programming of the HPA axis and in the stress response later in life. They also determined that there is a narrow window of early life colonization that ensures the normal HPA axis development. Sudo et al. demonstrated that GF mice exposed to mild restraint stress showed an excess corticosterone and ACTH release, compared to the specific pathogen free (SPF) controls. This response in GF mice was partly reversed by colonization with SPF animal fecal matter, and fully reversed by association with Bifidobacterium infantis in a time dependent manner. A similar study found that expression of the glucocorticoid receptor in the hippocampus of GF rats was lower than in SPF controls, whereas CRH expression was increased in the hypothalamus of GF animals.

Both the intestinal microbiota and the stress response develop in parallel during the postnatal period. Therefore, stress, both acute and chronic, and the associated HPA axis can affect gut microbiota composition and function. Most of the related studies have been performed using animal models. Stress can alter intestinal permeability, allowing bacterial translocation across the intestinal mucosa and thus immune system activation, which can have direct effects on CNS. Another study showed that pretreatment with the probiotic Lactobacillus farciminis in rats reduced intestinal permeability that results from restraint stress and abated HPA axis response. Similarly, the combination of L. helveticus and L. rhamnosus prevented intestinal abnormalities and bacterial translocation to mesenteric lymph nodes, caused by chronic stress.

Baily et al. demonstrated that prenatal stressors can alter the microbiome in rhesus monkeys by reducing the overall numbers of Bifidobacteria and Lactobacilli. Maternal separation model studies in rodents have shown that neonatal stress can significantly change the diversity and composition of gut microbiota, as well as the stress response. Moreover, in a mouse model exposed to chronic psychological stress, the gut microbial profile was altered, a decrease in Bacteroides and an increase in Clostridium genus was found, and pro-inflammatory cytokine IL-6 levels were increased. Humans under stress also show a modified microbial profile.

Probiotic treatment has been able to reverse many of the stress related effects both in animals and humans. However, probiotic effect on corticosterone level seems to be strain specific.

L. helveticus and B. longum combined decreased stress-induced corticosterone secretion, whereas in another study Bifidobacteria were not found to affect the hormone levels. In a double blind, randomized parallel group study, healthy human subjects were given L. helveticus R0052 and B. longum in combination, or placebo for 30 days. The twenty-four hour urinary free cortisol (UFC) output was reduced in the group taking the probiotic combination.

A complete understanding of the mechanisms underlying the interaction between gut microbiota and stress responses could provide with novel approaches to prevent and treat stress related defects with the use of psychobiotics.

### Gut Microbiota and Anxiety

Multiple pathways mediate the effects of gut microbiota on the CNS, and many of these are implicated in the pathogenesis of mood disorders, including anxiety. Accumulating evidence indicates the role of gut microbiota in the pathophysiology of anxiety and other mood disorders, as well as the potential anxiolytic effects arising from its modulation (Table 2a, 2b).

Experiments conducted on animal models with altered gut microbial composition (GF, probiotics and/or antibiotics treated mice, enterically infected mice, fecal transplant), clearly showed a relation between gut microbiota and anxiety-related behavior. However, GF rodent models have given somewhat contradictory results. From one side, independent studies have demonstrated a reduced anxiety-like behavior in GF mice, as seen by increased exploration of generally aversive zones in the elevated plus maze (EPM), the light/dark test (L/D) and the open field (OF). Although GF mice have a reduced anxiety-like behavior, corticosterone plasma levels were significantly increased as compared to their SPF counterparts. On the other side, in one study female GF mice gave different results, and in another study GF rats showed both an increase in serum corticosterone and anxi-
Table 2a. Potential beneficial effects of different probiotic species on anxiety in mice.

<table>
<thead>
<tr>
<th>Species</th>
<th>Preclinical studies</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. Rhamnosus JB-1</td>
<td>Mice</td>
<td>anxiolytic effects on EPM test ◀ stress-induced corticosterone levels</td>
<td>(34)</td>
</tr>
<tr>
<td>L. Helveticus R0052 and B. Longum R0175</td>
<td>Male Wistar rats</td>
<td>◀ stress/anxiety behavior in conditioned defensive burying test</td>
<td>(61)</td>
</tr>
<tr>
<td>L. Helveticus NS8</td>
<td>Male SPF Sprague-Dawley rats</td>
<td>◀ anxiety-like behavior in hyperammonemia rats assessed by EPM test ◀ concentration of 5-HT, PGE2 and IL-1β in specific brain regions</td>
<td>(62)</td>
</tr>
<tr>
<td>B. Longum NCC3001</td>
<td>Male AKR mice</td>
<td>vagally mediated anxiolytic effect of B. Longum in a chronic colitis model</td>
<td>(63)</td>
</tr>
</tbody>
</table>

Table 2b. Potential beneficial effects of different probiotic species on anxiety in humans.

<table>
<thead>
<tr>
<th>Species</th>
<th>Preclinical studies</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. Casei strain Shirota</td>
<td>35 CFS patients</td>
<td>▲ fecal total amount of Bifidobacteria and Lactobacillus ◀ anxiety symptoms assessed by BAI</td>
<td>(64)</td>
</tr>
<tr>
<td>L. Helveticus R0052 and B. Longum R0175</td>
<td>55 healthy Caucasian subjects</td>
<td>◀ HADS global score due to a lower HADS-Anxiety subscore ◀ UFC levels</td>
<td>(61)</td>
</tr>
</tbody>
</table>

L., Lactobacillus; EPM, Elevated Plus Maze; B., Bifidobacterium; SPF, Specific pathogen free; 5-HT, 5-hydroxytryptamine, Serotonin; PGE2, Prostaglandin E2; IL, Interleukin.

Gut Microbiota and Depression

Depression is a mood disorder of complex pathophysiology, causing significant disability and having severe social consequences. Important pathophysiological mechanisms involved in depression include neurotransmitter deficiencies, HPA axis dysfunction, reduced BDNF levels, increased proinflammatory cytokine levels and decreased neurogenesis.

As reported previously, it is evident that gut microbiota, through their link to the microbiota-gut-brain axis, can affect mood and behavior and thus the pathophysiology of depression, introducing the concept of psychobioma. Moreover, studies performed both in animals and humans, have demonstrated that depression is associated with an altered gut microbiota composition. A study performed on both depressed and healthy subjects, analyzed fecal microbiota and found a significant increase...
in the order Bacteroidales, specifically in Alistipes genus, and a decrease in Lachnospiraceae family in depressed individuals. Fecal samples of depressed and healthy individuals were analyzed in a similar study and showed that depressed patients had increased Bacteroidetes, Proteobacteria and Actinobacteria levels, and that Firmicutes levels were reduced. In more detail, they showed increased levels of Enterobacteriaceae and Alistipes, and reduced Fecalibacterium levels. This reduction negatively correlated with depressive symptoms severity.

The use of probiotics has been extensively studied in animal models for both depression and anxiety symptoms (Table 3a, 3b).

Depression is frequently associated with HPA axis dysfunction, and normalization of the adverse effects resulting from this can contribute to the resolution of the disease. A hyperactivity of this axis is seen in GF mice, and its normalization is achieved with probiotics, such as B. infantis, suggesting antidepressant potential.

In a maternal separation model during the neonatal period in rats, chronic treatment with B. infantis reduced depressive-like symptoms, as seen by reduced immobility in the forced swim test (FST). The outcome was similar to that of citalopram. Probiotic treatment also normalized the immune response and NE concentrations in the brainstem. Administration of L. rhamnosus in healthy male BALB/c mice decreased anxiety- and depressive-like behavior in the EPM, OF and FST. The mice spent less time immobile in the FST. Probiotic treatment induced region-dependent alterations in gamma-aminobutyric acid (GABA) mRNA in a vagal-dependent manner. GABA<sub>rh</sub>mRNA was increased in cortical cingulate and prelimbic regions, while it was decreased in the hippocampus, amygdala and locus coeruleus. Interestingly, in depressed animal models GABA<sub>rh</sub> receptor expression was lower in frontal cortices. It was further observed that stress-induced elevation in corticosterone was reduced in L. rhamnosus fed mice. What is more, probiotic combination of L. helveticus and B. longum reversed the depressive behavior and restored intestinal barrier integrity in myocardial infarction (MI) rats. The study was performed in order to evaluate the preventive effect of probiotics on post-MI depressive behavior.

Serotonin has an important role in the regulation of mood, and many antidepressants lead to serotonin increase as part of their mechanism of action. In the same study as mentioned previously, B. infantis resulted in increased levels of tryptophan, the precursor of serotonin, in the plasma of rats, thus indicating that probiotics can exert antidepressant effects by acting on the serotonergic system. Depression has been also associated with inflammation, seen by elevated levels in IL-6, tumor necrosis factor (TNF-α) and C reactive protein (CRP). It has been demonstrated that Lactobacillus and Bifidobacterium probiotics can stimulate anti-inflammatory IL-10 production in rodents, thus attenuating inflammatory responses. Additionally, low levels of BDNF is a hallmark of depression. Interestingly, gut microbiota seems to influence BDNF expression. A seminal study conducted in 2004 reported that GF male mice had a decrease in BDNF and expression of N-methyl-D-aspartate receptor subunit 2A in the hippocampus and the cortex, compared to controls. In another study, an increase in

### Table 3a. Potential beneficial effects of different probiotic species on depression in mice.

<table>
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</thead>
<tbody>
<tr>
<td>L. Helveticus R0052</td>
<td>Male Sprague–Dawley rats</td>
<td>↓ IL-1β associated with positive effect on post-MI depression model</td>
<td>(76)</td>
</tr>
<tr>
<td>L. Longum R0175</td>
<td></td>
<td>↓ corticosterone, ACTH circulating levels</td>
<td></td>
</tr>
<tr>
<td>L. Helveticus NS8</td>
<td>Male SPF Sprague-Dawley rats</td>
<td>↑ IL-10 levels and Bdnf m-RNA expression; restored 5-HT and NE levels in hippocampus</td>
<td>(77)</td>
</tr>
<tr>
<td>B. Infantis</td>
<td>Male Sprague-Dawley rats</td>
<td>↓ depression-like behavior in MS model assessed by FST</td>
<td>(78)</td>
</tr>
<tr>
<td>L. Rhamnosus JB-1</td>
<td>Mice</td>
<td>↓ expression of GABA&lt;sub&gt;rh&lt;/sub&gt;mRNA in specific brain regions possibly related with an antidepressant-like effect</td>
<td>(34)</td>
</tr>
<tr>
<td>L. Plantarum PS128</td>
<td>Adult mice</td>
<td>↓ ELS-induced depression-like behaviors, restored HPA axis and immune regulated levels of DA and 5-HT in the PFC</td>
<td>(79)</td>
</tr>
</tbody>
</table>

L., Lactobacillus; B., Bifidobacterium; IL, Interleukin; MI, Myocardial infarction; SPF, Specific pathogen free; ACTH, Adrenocorticotropic Hormone; Bdnf, Brain-derived Neurotrophic Factor; 5-HT, 5-hydroxytryptamine, Serotonin; NE, Norepinephrine; SPT, Sucrose preference test; MS, Maternal separation; FST, Forced swim test; GABA, gamma-aminobutyric acid; ELS, early life stress; HPA, Hypothalamic pituitary adrenal; DA, Dopamine; PFC, Prefrontal Cortex.

### Table 3b. Potential beneficial effects of different probiotic species on depression in humans.

<table>
<thead>
<tr>
<th>Species</th>
<th>Preclinical studies</th>
<th>Effects</th>
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</tr>
</thead>
<tbody>
<tr>
<td>L. Acidophilus, L. Casei, B. Bifidum</td>
<td>40 patients with MDD</td>
<td>↓ BDI total scores; ↓ hs-CRP serum levels</td>
<td>(80)</td>
</tr>
<tr>
<td>L. Helveticus R0052</td>
<td>55 healthy Caucasian subjects</td>
<td>↓ global severity index of HSCL-90 due to lower values for somatization, depression and anger-hostility</td>
<td>(61)</td>
</tr>
</tbody>
</table>

L., Lactobacillus; B., Bifidobacterium; MDD, Major Depressive Disorder; BDI, Beck Depression Inventory; hs-CRP, high-sensitivity C-Reactive Protein; HSCL, Hopkins Symptom Checklist.
hippocampal BDNF mRNA\textsuperscript{60} was seen in female mice. Changes in the serotonergic system have also been observed in male but not female mice.\textsuperscript{67} Altogether there seems to be a sex dependent regulation of the microbiome-gut-brain axis. One possible antidepressant mechanism of gut microbiota is through the production of the SCFA butyrate. Sodium butyrate has been seen to produce an antidepressant effect in the murine brain, by affecting BDNF levels through its inhibitory action on histone deacetylase.\textsuperscript{84}

An antidepressant effect was demonstrated by chronic administration of \textit{L. helveticus} in a chronic-stress-induced depression model. Results showed that \textit{L. helveticus} NS8 resulted in lower plasma corticosterone and ACTH levels, higher plasma IL-10 levels, normalized hippocampal 5-HT and NE levels, and increased hippocampal BDNF mRNA expression.\textsuperscript{77} Finally, \textit{L. plantarum} PS128 was found to normalize HPA axis exaggerated response and depression-like behavior induced by early life stress (ELS). Moreover, chronic probiotic administration also repaired some ELS-induced immune and neurochemical changes.\textsuperscript{79} These studies clearly indicate a link between gut microbiota and the pathogenesis of depression.

Although less evidence exists for probiotic actions on human population, they seem to have similar anxiolytic and antidepressant effects as those seen in preclinical studies. For instance, a probiotic mixture of \textit{L. helveticus} and \textit{B. longum}, given to healthy subjects for 30 days, showed an amelioration in psychological distress compared to subjects on placebo. The assessment was performed by validated questionnaires and measurement of UFC.\textsuperscript{81} In a similar study, healthy subjects consumed a probiotic-containing milk drink of \textit{L. casei} Shiratai or placebo for 3 weeks. Mood was assessed both pre- and post-treatment, and subjects who scored in the lowest third for depressed mood showed a significant improvement at the end of treatment.\textsuperscript{85}

In a randomized, double-blind, placebo-controlled clinical trial performed in patients with major depressive disorder, probiotics were administered to determine effects on depressive symptoms. The probiotic formulation contained \textit{L. acidophilus, L. casei} and \textit{B. bifidum} in a capsule. Patients who received the probiotic supplement had significantly decreased Beck Depression Inventory (BDI) scores.\textsuperscript{80}

The “leaky gut” concept\textsuperscript{86} represents another link between gut and depression. Thus, probiotics able to reduce intestinal permeability could be considered useful in preventing depressive symptoms arising from intestinal dysfunction. However, there is a need for more clinical studies performed on affected population in order to make solid conclusions on the use of psychobiotics for depression.

**Conclusions**

Experimental research up to date has strongly demonstrated that gut microbiota is a key mediator of the bidirectional communication between the gut and the nervous system, thus leading to a paradigm shift in modern medicine and science. Moreover, gut microbiota has the ability to influence mood and behavior and it has been tightly associated with disease, ranging from gastrointestinal, through metabolic, to mental disorders, including anxiety and depression. Preclinical data has proven the role of gut microbiota in such disorders, as well as the use of probiotics as a therapeutic tool for improving related symptoms and as preventive means. However, caution must be exercised when translating preclinical results to clinical. Clinical research is still limited, but has provided with ambitious results regarding probiotic effects on neuropsychological disorders. Probiotics of the \textit{Bifidobacterium} and \textit{Lactobacillus} genera appear to have the most valuable benefits over anxiety- and depression-like behavior. It seems like gut microbiota is of crucial importance to a deeper understanding of the role the brain has in health and disease. Furthermore, modulation of the microbial composition with probiotics can offer new therapeutic and preventive approaches to combat mental diseases. Future clinical research focusing on the effects of psychobiotics on anxiety and depression in patient population will provide valuable information.

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**References**


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