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Review

Psychobiotics and the Microbiota–Gut–Brain Axis: Where Do We Go from Here?

Sylvie Binda [1,2,*], Annie Tremblay [2], Umar Haris Iqbal [2], Ola Kassem [2], Mélanie Le Barz [1], Vincent Thomas [1], Stéphane Bronner [2], Tara Perrot [3], Nafissa Ismail [4] and J. Alex Parker [5]

1 Lallemand Health Solutions, 19 Rue des Briquetiers, BP 59, 31702 Blagnac, France; mlebarz@lallemand.com (M.L.B.); vthomas@lallemand.com (V.T.)
2 Rosell Institute for Microbiome and Probiotics, Lallemand Health Solutions, 6100 Royalmount Avenue, Montreal, QC H4P 2R2, Canada; atremblay@lallemand.com (A.T.); iumarharis@lallemand.com (U.H.I.); okassem@lallemand.com (O.K.); sbronner@lallemand.com (S.B.)
3 Department of Psychology and Neuroscience, Dalhousie University, Halifax, NS B3H 4R2, Canada; tara.perrot@dal.ca
4 Department of Psychology, University of Ottawa, Ottawa, ON K1N 6N5, Canada; nafissa.ismail@uottawa.ca
5 Département de Neurosciences, Université de Montréal, Montreal, QC H3T 1J4, Canada; ja.parker@umontreal.ca
* Correspondence: sbinda@lallemand.com

Abstract: The bidirectional relationship between the gut microbiota and the nervous system is known as the microbiota–gut–brain axis (MGBA). The MGBA controls the complex interactions between the brain, the enteric nervous system, the gut-associated immune system, and the enteric neuroendocrine systems, regulating key physiological functions such as the immune response, sleep, emotions and mood, food intake, and intestinal functions. Psychobiotics are considered tools with the potential to modulate the MGBA through preventive, adjunctive, or curative approaches, but their specific mechanisms of action on many aspects of health are yet to be characterized. This narrative review and perspectives article highlights the key paradigms needing attention as the scope of potential probiotics applications in human health increases, with a growing body of evidence supporting their systemic beneficial effects. However, there are many limitations to overcome before establishing the extent to which we can incorporate probiotics in the management of neuropsychiatric disorders. Although this article uses the term probiotics in a general manner, it remains important to study probiotics at the strain level in most cases.

Keywords: psychobiotics; microbiota–gut–brain axis; stress; early-life stress; neuropsychiatric disorders; neuroinflammation; microglia; metabolic syndrome; obesity

Citation: Binda, S.; Tremblay, A.; Iqbal, U.H.; Kassem, O.; Le Barz, M.; Thomas, V.; Bronner, S.; Perrot, T.; Ismail, N.; Parker, J.A. Psychobiotics and the Microbiota–Gut–Brain Axis: Where Do We Go from Here? *Microorganisms* **2024**, *12*, 634. https://doi.org/10.3390/microorganisms12040634

Academic Editors: Marc G. J. Feuilloley and Mohamed Zommiti

Received: 21 February 2024
Revised: 19 March 2024
Accepted: 20 March 2024
Published: 22 March 2024

1. Introduction

The gut microbiota is composed of a highly complex community of microorganisms residing in the gastrointestinal (GI) tract of humans and other animals. Most of the microbiota is found in the large intestine, with a smaller fraction residing in the stomach and small intestine. The lifelong symbiotic relationship between microorganisms and the host begins as early as the time of birth, perhaps even in utero [1]. While the host provides the habitat and nutrition, these microorganisms return the favor with various significant benefits. The GI benefits provided by the resident microbiota include supporting digestion and metabolism, vitamin synthesis, maintaining the epithelial integrity of tight junctions (thereby preventing the absorption of harmful molecules or pathogens), colonizing the mucosal layer and competing with pathogens for food and space, and supporting the development of immunity. The systemic benefits of probiotics include enhancing the immune system and, for psychobiotics, influencing gut–brain communication to regulate mood, cognitive and neurological functions, and even brain structures [2–4].

Psychobiotics are defined as probiotics that confer mental health benefits to the host when consumed in a particular quantity through the interaction with commensal gut bacteria. Over the last decade, interest in psychobiotics has significantly increased, leading to major advances in understanding their therapeutic potential in indications related to the microbiota–gut–brain axis (MGBA). This bidirectional communication that exists between the brain and gut microbiota is thought to be primarily mediated by the enteric nervous system, the hypothalamic–pituitary–adrenal (HPA) axis, and the central and peripheric nervous systems, with influences from immune, endocrine, and molecular pathways (Figure 1) [5–7]. Numerous studies have associated the administration of psychobiotics with positive effects on areas of stress, anxiety, neuroinflammation, neurodegenerative diseases such as Alzheimer's and Parkinson's, and GI diseases [8–12]. The mechanism by which psychobiotics confer these benefits has been suggested to be mediated through their regulation of neurotransmitters such as serotonin, gamma-aminobutyric acid (GABA), brain-derived neurotropic factor (BDNF), as well as short-chain fatty acids (SCFAs) and enteroendocrine hormones [13–17]. Psychobiotics have also been shown to impact inflammatory pathways by normalizing the levels of pro-inflammatory cytokines as well as inducing increased amounts of anti-inflammatory cytokines such as IL-10 [14,18]. In addition to their anti-inflammatory role, psychobiotics have been shown to reduce the activation of the HPA axis in response to stressors [19–21].

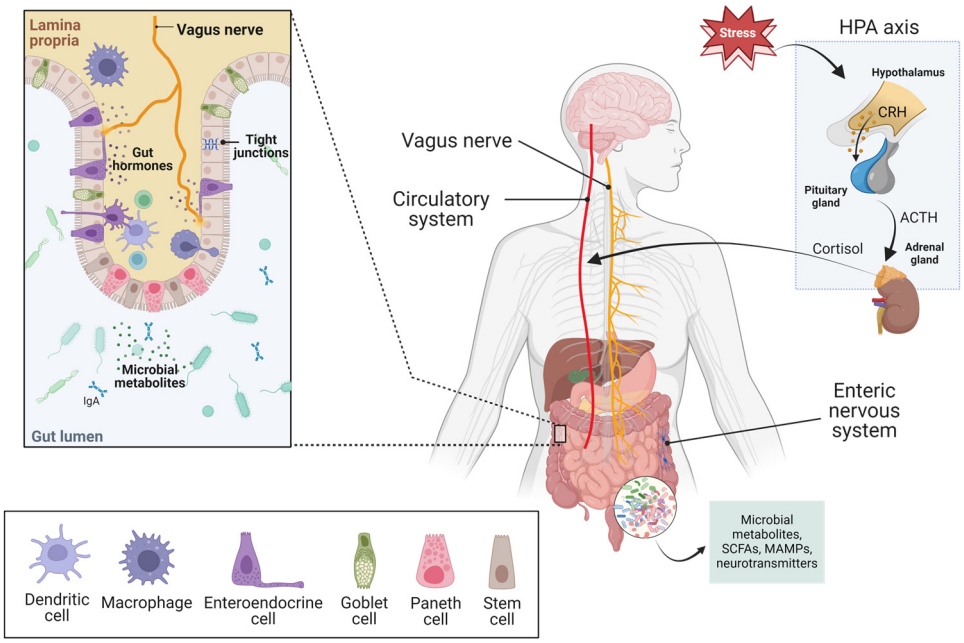

Figure 1. Schematic representation of the main components of the MGBA. The microbiota acts in the gut lumen and on the epithelial mucosa via the secretion of a variety of metabolites, including, but not restricted to, SCFAs and neurotransmitters. The microbial metabolites can cross the epithelial barrier to reach the lamina propria and the circulation. Other metabolites act directly on the epithelial barrier to strengthen tight junctions and stimulate the production of neuroendocrine and immune mediators that will influence vagal afferents or reach the circulation. In the lamina propria, immune cells secrete anti-inflammatory cytokines in response to the specific microbial signals received by the dendritic cells. Stress activates the HPA axis, which controls the circulating concentrations of cortisol, and affects intestinal motility through communication with the enteric nervous system.

It is well recognized that through the concept of interoception, the brain can sense and process information related to the internal physiological state of the body [22,23]. This was previously thought to be primarily mediated by fine, unmyelinated vagal and sympathetic afferent neurons. However, we now know that besides those direct neurons, the gut microbes and their metabolites provide a key source of such interoceptive information;

psychobiotics can affect the brain through vagal afferents since some of their effects can be alleviated by vagotomy in animal models [24]. Interestingly, in addition to perception, the gut microbiota can even influence the anatomical structure and development of the brain, which subsequently impacts physiological functions, as shown in animal models of early-life stress. Abnormalities in delicately tuned interoceptive signaling could result in disordered MGBA communications and disease conditions such as irritable bowel syndrome (IBS), functional dyspepsia, chronic abdominal pain, psychiatric disorders, and neurodegenerative and developmental disorders [6,25].

A solution, as proposed also for GI diseases, would be to restore the "normal" or baseline gut microbiota composition and functions, and/or to restore proper communication between the brain and the gut by correcting the imbalanced microbiome population (aka dysbiosis) to that observed in healthy individuals. Accordingly, psychobiotics have emerged as potential tools to mitigate the symptoms of various mental and neuropsychiatric conditions.

2. Psychobiotics and Neuropsychiatric Disorders (NPDs)

A recent systematic review by Ribera et al. (2024) [see [26], and references therein] identified 43 clinical trials assessing the effects of various psychobiotics (probiotics or synbiotics) on clinically diagnosed NPDs. Major depressive disorder (MDD) was the most studied disorder, with 17 trials. Other disorders were deemed understudied, which prevented formal conclusions about the positive effects of psychobiotics on schizophrenia (10 studies), bipolar disorder (5 studies), anorexia nervosa (4 studies), attention deficit hyperactivity disorder (ADHD) (3 studies), anxiety disorders (2 studies), Tourette syndrome (1 study) and insomnia (1 study) from being formed. The authors concluded that psychobiotics are beneficial in MDD patients, but that more well-designed studies are required in other indications. Overall, these studies used probiotic formulations containing various amounts of *Lactobacilli* and *Bifidobacteria* strains at various dosages. This is one difficulty inherent to systematic reviews, as the differences between studies in terms of psychobiotic regimens do not allow a specific probiotic strain or dose to be recommended. The typical limitations identified in the systematic reviews are listed in Box 1.

Box 1. Typical limitations of psychobiotic studies in NPD indications [26].

- High variability in strain, dose, and duration of supplementation.
- Use as an adjuvant to pharmacologic treatments or alone, or with nutraceuticals without a corresponding nutraceutical control arm.
- Heterogeneity in the prior or co-administered pharmacologic treatments.
- Heterogeneity in outcome measures and outcome assessment tools.
- Lack of patient-centered outcomes, such as social functioning.

Among the studies that included mechanistic outcomes, it was common for inflammatory markers as well as biochemical markers of glucose metabolism to be assessed; this is because these pathways, for which many probiotics show regulatory effects, have also been linked with the pathophysiology of several NPDs. Ribera et al. (2024) excluded studies on populations with non-medically diagnosed conditions; however, psychobiotics have been shown to exert positive effects also in sub-clinical contexts [27,28]. In systematic reviews considering both sub-clinical and clinical populations, conclusions are limited by the heterogeneity between populations in addition to the limitations presented in Box 1. Overall, despite several encouraging results, the application of psychobiotics in mental and neurological diseases in clinical trials is primarily perceived to be of a supportive nature rather than a treatment. As research progresses towards a better understanding of the holistic nature of mental health maintenance, with the reciprocal impacts of stress, sleep, lifestyle factors, eating habits, early-life environment, upbringing conditions, and other comorbidities, the integration of psychobiotics into the NPD treatment armamentarium

will be facilitated and possibly tailored to the specific modes of actions of each strain or specific mix.

3. Psychobiotics and Microbiota in Sleep Quality, Stress and Mental Health

A systematic review by Scott et al. (2021) including 65 studies reported that improving sleep quality leads to better mental health [29], and Staines et al. (2022), based on 43 studies, found that improving sleep quality was associated with a reduction in anxiety symptoms [30]. A 2022 systematic review of 34 studies exploring the associations of stress with poor sleep quality and/or insomnia in undergraduate students found a strong association between insomnia and stress, and a moderate pooled association between sleep quality, insomnia and stress [31]. There is not much debate around the negative effects of stress and the importance of good sleep for overall and mental health. However, more research is required to determine the efficacy of specific stress reduction and sleep interventions and assess the effect of incorporating sleep improvement strategies into mental health services [29].

A large evidence base supports the ability of psychobiotics to counteract stress-induced GI and behavioral symptoms. It is believed that one of the key factors mediating the adverse effects of stress on mental health is the gut microbiome [32]. In mice, exposure to stressful environmental factors, such as chronic sleep disruption, during puberty induces depression-like behavior. However, probiotic supplementation during puberty significantly mitigates the latter effect in both males and females to a level comparable to rested mice [33,34]. These findings suggest that, as opposed to pharmacologic treatments that have been shown to negatively affect the microbiome, psychobiotics exert their benefits both in the gut and at a systemic level. Exposure to chronic sleep disruption also induces a significant decrease in the tryptophan concentration in the prefrontal cortex and in the glucose and lactate concentrations in the hippocampus, both of which can be mitigated by probiotics supplementation [33]. Probiotics have also been shown to mitigate the detrimental effects of maternal separation in animals, modeling early-life stress and its lifelong consequences [27]. Mental and neurological well-being in adulthood is significantly impacted by stress exposure in early life. During this period, the ongoing development of the nervous system allows for programming by internal and external events. Based on animal models, it appears that the impact of this programming is not limited to the exposed individual but also imposes a trans-generational effect. For instance, the induction of stress during gestation or pregnancy, which subsequently impacts the fetus, can result in epigenetic changes in adult offspring that are then passed on to the subsequent generation [35]. Mechanistic insights from animal studies include altered SCFA production, the disruption of T helper 17 cell differentiation and maternal immune activation, or alterations in tryptophan metabolism and serotoninergic signaling [36]. However, which outcomes do we measure, and when, to validate this lifelong and transgenerational process in humans? The study of the role of probiotics on epigenetics in epithelial intestinal cells in vitro suggests that they can modulate the global histone methylation and acetylation status [37], which is of the utmost interest from a neurodevelopmental biology perspective.

Nevertheless, for clinical trials, prerequisite research questions have yet to be answered: in what manner do GBA interactions in early life influence individuals' subsequent vulnerability to developmental and neurological disorders, and how do we factor the interindividual differences in resilience into this assessment? Indeed, one hypothesis is that early-life stress reduces one's ability to cope with subsequent life stressors. Moreover, a statistical report published by the U.S. National Institute of Mental Health highlights the age- and sex-dependent nature of mental illnesses. In 2021, just after the devastating worldwide pandemic, the prevalence of mental illness was reported to be higher among females (27.2%) compared to males (18.1%), with young adults aged 18–25 years having the highest prevalence (33.7%). An estimated 49.5% of adolescents had a mental disorder, out of which 22.2% experienced severe impairment and/or distress [38]. In Canada, this age group reported the most important decline in mental health after the pandemic, and those

already experiencing poor mental health before COVID-19 were impacted even more [39]. Conceivably, a stressful environment during the early years of life, followed by the physiological changes and psychosocial stressors that occur during puberty, such as significant hormonal changes, heightened emotional sensitivity, academic pressure, social and peer pressure, and concerns about self-image, all contribute to the high prevalence of mental illnesses in adolescents and young adults. A main issue pertaining to this group is limited proper diagnosis due to significant physical, emotional, and social changes, which make it difficult for caregivers to distinguish potential mental illness symptoms and (ab)normal expected adolescent behaviors. However, in infants and children, the microbiota composition in early life was associated with temperament in six studies, which is important considering that childhood temperament is believed to lay the grounds for individuals' later personality, behavior and risk of psychopathology [40].

A recent systematic review by Augusti et al. (2023) identified 13 longitudinal, cross-sectional and case–control studies assessing the relationship between ELS, either prenatal (four studies) or postnatal (nine studies), and the gut microbiome composition [41]. Several limitations were identified, notably the high heterogeneity between studies in terms of ELS stressors, as well as that in the microbiome sample collection and analyses (Box 2). On the contrary, several commonalities between studies were also identified, with only two of the studies not finding any association. Despite some conflicting results, ELS was mostly associated with lower *Bifidobacterium* species and higher levels of Proteobacteria (typically Enterobacteriaceae) in newborns exposed to ELS. No studies using psychobiotics (interventional) were found and few were monitoring probiotics use. In fact, the included studies generally lacked the monitoring of important confounding factors such as diet and antibiotic use.

Box 2. Limitations of human studies on ELS and microbiome composition [41].

- High heterogeneity in the ELS stressors studied, with some stressors assumed (i.e., effect of long-term institutionalized care on microbiome in children) but not confirmed (i.e., no emotional state measure reported).
- Few studies used adult biomarkers of stress to complement/confirm self-reported or interview-reported ELS.
- Heterogeneity in the collection, processing, and analyses of stool samples.
- The impact of medications is difficult to estimate (e.g., antiretroviral therapy, antidepressants, antibiotics, etc.).
- Diet not monitored.
- Participants age range very large (from newborns to adults with PTSD ‡)

‡ **based on the retrospective history of ELS exposure.**

While behavioral assessments on their own provide limited mechanistic information in humans, identifying specific biological markers such as inflammatory and other circulating molecules, beyond the ones we already have, for use as proxies in clinical trials is a must to gather a more comprehensive picture [42]. A number of psychobiotics have shown their potential to positively impact ELS-induced consequences. Liu et al. found that the administration of a *Lactiplantibacillus plantarum* strain in mice subjected to maternal separation significantly reduced inflammation while increasing levels of serotonin in multiple areas of the brain [43]. Another group has also shown that supplementation with a probiotic formulation containing *Lactobacillus helveticus* and *Lacticaseibacillus rhamnosus* alleviates the deleterious impacts of ELS on the fear retention, extinction trajectory and neuronal activation of the brain [44]. Another study found that administering this same probiotic formulation to rats subjected to chronic unpredictable stress reduced microglia immunoreactivity, suggesting both the neuroprotective effect of the psychobiotic as well as a reduction in the neuroinflammatory pathways associated with microglia activation [45].

Under chronic stress, the microglia remain in a constant state of activation, which has been associated with the increased production of inflammatory cytokines, creating a

hostile environment that promotes neuronal damage. Microglia activation can come from pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) [46]. These can become more prevalent in the brain in a state of chronic stress or in certain neurodegenerative diseases (NDDs), but can also reach the brain from other sources. In the gut, stress can affect the integrity of epithelial tight junctions [7], in addition to impairing the differentiation of intestinal stem cells into protective cells by stimulating indole-3-acetic acid (IAA) production by some *Lactobacilli* strains [47]. These effects increase intestinal permeability, also known as "leaky gut", which in turn causes more microbial products to reach the bloodstream. It is believed that some of those bacterial products that should not normally reach systemic circulation may accentuate stress-induced microglial activation and exacerbate neuroinflammation. Psychobiotics could counteract these effects by acting on both the intestinal barrier and by secreting molecules that positively regulate brain function and reduce inflammation.

4. The Immune System and NDDs

Recent research has emphasized the essential role of inflammation and immune system dysregulation in the pathogenesis of common NDDs, including Alzheimer's disease (AD), frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD). Evidence suggests that the early activation of innate immune pathways, mostly by hallmarks of NDDs such as misfolded proteins or aggregated substances, could be an early cause rather than a consequence of neurodegeneration. This is supported by findings that have reported a correlation between severe infections and accelerated cognitive decline in AD, which is linked to increased levels of peripheral tumor necrosis factor alpha (TNF-α) and the beneficial role of non-steroidal anti-inflammatory drugs in lowering the disease risk. Furthermore, genetic analyses have identified the specific genes associated with innate immune pathways and microglial cells, suggesting the pathogenic role of neuroinflammation in AD. These include genes coding for complement receptor 1 (CR1), myeloid cell-expressed membrane-spanning 4-domains subfamily A member 4E (MS4A4E), and CD33, which is involved in suppressing pro-inflammatory cytokines and amyloid-β clearance by microglial cells. FTD, the second most common dementia type after AD, also involves neuroinflammation, evidenced by elevated TNF-α and Transforming growth factor beta (TGF-β) levels in cerebrospinal fluid and increased microglial activation. FTD is linked to mutations in the *GRN* gene that result in reduced levels of progranulin. Progranulin deficiency leads to an imbalanced inflammatory response, suggesting that neuroinflammation is not merely a secondary effect but integral to disease pathogenesis [48]. PD is the second most common NDD overall after AD [49]. Activated microglia play a key role in the progression of PD by contributing to neuroinflammation. Research has shown that in PD brains, microglia are abnormally activated, resulting in high levels of HLA-DR expression in affected brain areas. These HLA-DR molecules facilitate the presentation of antigens to CD4+ T lymphocytes. This process, along with the secretion of inflammatory mediators, leads to the degeneration of dopaminergic neurons [50]. In line with these reports, studies on ALS/FTD pathologies have highlighted the early and prominent role of microglia and astrocyte activation in pathogenesis. Key observations come from patient autopsies, showing characteristic neuronal inclusions and cell loss alongside glial activation. Human imaging studies and animal model research have further confirmed that neuroinflammation occurs early in the disease process, with microglial activation closely tied to disease progression [51].

It is becoming increasingly evident that the gut microbiota plays a pivotal role in immune regulation, inflammation, and the pathophysiology of NDDs. Emerging research elucidates how the gut microbiota directly impacts the immune system by facilitating interactions between bacterial molecules (e.g., lipopolysaccharides, peptidoglycans) and immune cells (e.g., dendritic cells, macrophages), thereby modulating immune responses [52], and indirectly, by producing various metabolites such as polyamines and SCFAs [53]. Such biomolecules modulate immune responses, both locally within the gut and systemically by

influencing the proliferation and function of Treg cells, as well as the production of anti-inflammatory cytokines. This modulation is crucial for maintaining immune homeostasis and preventing overactive immune responses that can lead to chronic inflammation. While a balanced gut microbiota plays a crucial role in controlling inflammation and maintaining a healthy gut barrier, on the contrary, dysbiosis has been linked to altered immune responses, increased intestinal permeability, and the disruption of the blood–brain barrier (BBB). In germ-free mice, a significant reduction in both occludin and claudin-5 (but not ZO-1) expression has been identified in the frontal cortex, hippocampus and striatum, compared with pathogen-free mice [54]. This facilitates the entry of pro-inflammatory cytokines into the CNS, promotes neuroinflammation, and subsequently contributes to the progression of neuronal damage and degeneration [55]. In a preclinical study, the authors reported that the gut microbiota is essential for the maturation and function of microglia. Indeed, germ-free mice exhibited microglia with defects that impaired the innate immune responses; however, reintroducing a complex microbiota or SCFAs partially restored microglia functionality [56]. Another study also found that the presence of the gut microbiota is crucial for microglial activation and is necessary for the full development of the motor deficit phenotype in mice models of synucleinopathies, such as PD. Notably, the activation of the neuroimmune response was partially attributed to SCFAs, which induced microglial activation. Moreover, mice with α-synuclein overexpression showed increased physical impairments when colonized with microbiota from PD patients compared to those from healthy donors, suggesting that human microbiome alterations could be a risk factor for PD [57].

Given the emerging evidence highlighting the role of the gut microbiota in regulating the immune system and neuroimmune responses, and the link to various neurological disorders, including NDDs, it becomes increasingly intuitive to consider psychobiotics as potential modulators within this context. While studies evaluating the direct effects of psychobiotics on neuroinflammation are limited, some studies have tested specific strains and partially linked their beneficial effects to immune modulation. For example, the administration of *Lactobacillus plantarum* PS128 has been shown to significantly reduce neuroinflammation, by preventing gliosis, and improve cognitive function in animal models of AD [58]. Another study focused on inflammation, insulin and lipid-related genes in peripheral blood mononuclear cells (PBMCs) in PD patients. It reported that a probiotic blend containing *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *L. reuteri*, and *Lactobacillus fermentum* significantly decreased the expression of the pro-inflammatory genes IL-1, IL-8, and TNF-α, while increasing the expression of TGF-β, a regulatory cytokine, and PPAR-γ, which is associated with anti-inflammatory processes [59]. Furthermore, in another AD mice model, the administration of a SLAB51 probiotic formulation resulted in an increase in *Bifidobacterium* spp., known for its anti-inflammatory properties, and a decrease in Campylobacterales, which are associated with pro-inflammatory effects. This shift in the composition of the gut microbiota led to reduced plasma levels of pro-inflammatory cytokines, indicating the probiotic's potential to modulate inflammatory pathways. Additionally, treated AD mice showed increased levels of G-CSF, a cytokine involved in systemic immune response modulation [60]. The oral supplementation of LPS-treated rats with a combination of *L. helveticus* R0052 and *B. longum* R0175 (development of AD-associated mechanisms) significantly decreased the elevation of both circulating and hippocampal levels of proinflammatory cytokines and attenuated the decremental effect of LPS on memory through BDNF protein expression [61]. Another interesting probiotic effect on BBB permeability was reported in germ-free mice monocolonized with a single bacterial strain, either *Clostridium tyrobutyricum*, a butyrate producer, or with *Bacteroides thetaiotaomicron*, an acetate and propionate producer. Indeed, after 3 days of oral gavage, the analysis performed after Evans blue perfusion demonstrated that both probiotic strains and also the sodium butyrate treatment decreased BBB permeability; this was associated with an increase in tight-junction protein expression and may be also linked to an increase in histone acetylation after sodium butyrate or *C. tyrobutyricum* treatments [54].

Despite these promising findings, the mechanisms through which psychobiotics exert their effects on the immune system and inflammation within the MGBA remain to be fully elucidated and confirmed in randomized placebo-controlled clinical trials. The complexity of microbial communities, coupled with the diversity of immune responses and neural effects, presents a challenge in delineating causal relationships. This challenge is even more important when one considers the comorbidities that are related to dysregulated or low-grade, chronic inflammation such as metabolic syndrome, obesity and diabetes.

5. Eating Behaviors, Metabolic Health, and NDDs

The multidirectional interactions existing between the brain and the GI tract suggest that diet might impact mental health and vice versa, and that dietary patterns might be altered in individuals suffering from neurological disorders. It is now widely recognized that both the CNS and ENS play a significant role in regulating food intake [62]. Food itself plays a major role in regulating appetite. Some nutrients, but also probiotics and prebiotics, might interact with the sensor neurons present in the GI tract, modulating the feeling of hunger (or satiety) and inflammatory processes. These nutrients or dietary supplements may also modulate the composition and functions of the intestinal microbiome, which in turn impact the production of metabolites of interest. For example, ingesting polyphenols modifies the microbiota, but the microbiota also enhances the effects of polyphenols and modifies them by producing metabolites that may improve the prognosis of NDDs [63,64].

The regulation of eating behaviors is complex and results from the modulation of both intrinsic factors, such as genetics, hormones and neural signals, and extrinsic factors, including the environment. This regulation is even more complex in humans than in other mammals due to hedonic food or social contexts. Moreover, it is important to consider that individuals are not always rational regarding food consumption. Some people act as emotional eaters, consuming food in response to a (positive or) negative stimulus, including stress, rather than as a response to a physiological need. Ultimately, if it becomes a habit, this behavior might lead to the development of pathological issues such as overeating episodes or binge-eating disorders (BEDs), for instance [65]. A recent stratification of the Food4Gut cohort (ancillary study) revealed that individuals with obesity suffering from BED had slight but significant differences in their gut microbiota composition and metabolomic profile compared to individuals with obesity but without BED [66].

In the context of obesity, it has been reported that the proinflammatory molecules produced by adipose tissue expansion could reach the hypothalamus from the vagus nerve, thus promoting the production of neural proinflammatory mediators via the activation of endothelial and glial cells [67]. Several studies have reported that the low-grade proinflammatory status reported in obesity and its related metabolic disorders has the potential to affect the brain negatively, increasing local inflammation and altering plasticity or the brain structure [68]. In patients with type 2 diabetes, insulin resistance has also been reported in the hippocampus, which is associated with alterations in learning and memory capacities [69]. In the aging population, individuals with obesity or diabetes are at a high risk of AD. Another interesting mechanism in this vast network of molecules linking energy metabolism and mental health is the dual role of ghrelin. Ghrelin—a well-documented orexigenic hormone—induces, among others, feelings of hunger and energy intake through the stimulation of orexigenic neurons of the central nervous system. Growing evidence also suggests that ghrelin has a key role in improving neuroplasticity, neuroprotection and cognitive functions, particularly in AD and PD, potentially through the indirect inhibition of microglia activation [70,71]. Further experiments remain necessary to demonstrate these ghrelin-signaling-dependent pathways [70].

Moreover, depression reflects a negative emotion but can be subdivided into atypical depression, mainly characterized by an increase in appetite and highly palatable food consumption, and melancholic depression, typically characterized by appetite loss and a decrease in body weight. In MDDs, the “loss of pleasure” or anhedonia is an intriguing symptom associated with reward-associated disorders [72]. In the pathophysiology of

depression, several signaling pathways and molecular alteration hypotheses have been investigated, including decreases in monoamines brain levels or GABAergic neurons, for instance. Recent studies have also highlighted the potential role of the endocannabinoid (eCB) system in the regulation of a plethora of metabolic and NDDs, since cannabinoid receptors (i.e., CB1 and CB2 subtypes) are widely expressed in the body [72]. The endocannabinoidome has been described as a large family of lipid mediators produced from ubiquitous lipid precursors that is involved in metabolism, inflammation, and behavior; it is thus involved in eating disorders, as explained more recently [73]. Growing evidence has also demonstrated that the neuroprotective, anti-inflammatory and antioxidant properties of the Mediterranean diet could be partly explained by beneficial modulations of the eCB system [74]. The MIND diet, meaning Mediterranean-DASH Intervention for Neurodegenerative Delay, has been proposed to specifically focus on brain health and thus reduce the dementia and cognitive decline that occur as people get older. Clinical trials are currently being conducted to demonstrate its efficiency, and some studies have already reported improvements in cognitive function [75–77].

These examples demonstrate that mental and metabolic health are interconnected, and that some regulatory mechanisms share similar origins, targets and signaling pathways. Eating behavior alterations could be both the cause and the consequence depending on the origin of the pathology. Many preclinical experiments carried out in rodents have reported that drug or dietary treatments impacting either mental or metabolic health also have significant effects on the other. However, clinical trials considering both aspects are still underrepresented in the literature, especially in mild mental disorders and neurodegenerative pathologies. These missing connections between mental and metabolic health in humans should be evaluated in future clinical trials by involving experts from both areas of health from the start of the project. It is of the utmost interest to demonstrate that the use of treatment to prevent or decrease symptoms of cognitive decline and NDDs could also have a beneficial effect on body composition, the quality and quantity of food intake and possibly on the regulation of the proinflammatory status of the adipose tissue.

Although available evidence shows that probiotics can modulate the immune system and exert anti-inflammatory effects, alter the gut microbiota, produce neuroactive substances, and influence gut barrier function, these mechanisms are not well defined at the molecular level and likely vary across different probiotic strains and individual hosts. Indeed, mechanisms involving specific metabolic or cellular pathways should be explored. Finally, the matrix or environmental factors to which the strain is exposed during production could significantly affect the end outcomes if the mechanisms are proven to depend on the presence of specific substrates for a given metabolic reaction to occur [78]. The consistent quality of probiotic sourcing for clinical trials and afterwards should be considered early and included among the key factors during the development of clinical trial protocols to limit downstream changes in therapeutic formulations. To achieve personalized clinical trials, future research should first focus on conducting studies with more rigorous designs and well-documented and diversified outcome measures, with a greater emphasis on unraveling the mechanisms of action. This would help bridge the gap between the preventive and therapeutic applications of psychobiotics to finally unravel their full potential in managing mental and neurological disorders. But how do we move away from traditional study designs towards more innovative designs that could allow causality to be proven?

6. Psychobiotics as Prevention versus Treatment

There is a clear dichotomy between the use of probiotics as therapeutic agents and their use as preventive or adjunctive agents in the context of mental and neuropsychiatric disorders. Traditionally, probiotics have been studied in a “clinical” context or disease situation, where animal models modified to express a certain pathological phenotype are administered probiotics. In humans, probiotics are primarily perceived as a supportive food supplement rather than treatment, with their main goal being to improve general wellbeing,

enhance individuals' quality of life and prevent disease occurrence or progression. A recent systematic review and meta-analysis reported that out of 54 clinical trials in humans, only 13 studies (24.1%) recruited participants with diagnosed psychiatric disorders such as MDD and schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), whereas 41 studies presented data for healthy participants with no diagnosed psychiatric disorder [79]. The discrepancies between studies conducted in healthy or stressed versus medically diagnosed individuals leave a gap in our understanding and ability to exploit probiotics to their full potential. The inconsistency in available data may also be attributed to the high variability in trial designs, including significant variations in the strains, doses, timelines, and clinical assessment tools used and outcome measures taken [27]. Other challenges that can influence the effectiveness of psychobiotics as LBPs include the timing of administration (with respect to age or disease onset), regional diet differences, and for some strains, the matrix in which they are delivered.

Some psychobiotics have demonstrated anxiolytic and antidepressant effects in both preclinical and clinical studies, while other studies have suggested that probiotics could enhance the efficacy of conventional drugs. A recent study showed that in adults diagnosed with MDD and with an incomplete response to prescription antidepressants, supplementation with a 14-strain blend probiotic resulted in a greater improvement compared to those on placebo [80]. Given the expanding horizon of probiotic research, it is crucial to distinguish probiotics used as food supplements from live biotherapeutic products (LBPs) that are to be used in patients [78,81]. As evidence grows supporting the role of probiotics in treating, not just preventing, specific CNS diseases, the conversation around using bacteria in medicines rather than as a preventive measure gains even more relevance. Furthermore, interindividual variability in the composition of the gut microbiota underscores the benefits of developing panels or cocktails of probiotic strains tailored to individual or subgroups' needs, a concept that aligns with the principles of personalized medicine or stratified approaches [82]. The list of key variables to take into consideration while designing clinical trials is long, and it is becoming clearer that a 'one size fits all' approach may not be sufficient in the context of using psychobiotics as LBPs.

7. Towards Mechanisms of Action: New Technologies for Preclinical and Clinical Investigations

A main challenge in the study of psychobiotics as biotherapeutics is the lack of a clear understanding of their full mechanisms of action. This gap in the knowledge not only impose limitations on current research, but also creates resistance toward the use of probiotics by patients and health care providers. This is particularly relevant in the context of mental and neurological disorders such as NDD. To this day, most NDDs are lifelong with no curative treatment. Thus, patients being presented with psychobiotics as a potential management modality would expect to at least know the primary mechanism through which the psychobiotics are acting. In addition, awareness of the detailed mechanisms of action will greatly improve our understanding of probiotic–host interactions, which will subsequently improve strain selection for future research and help tailor our supplementation to specific disease phenotypes. Key mechanisms could involve metabolites such as SCFAs and neurotransmitters, as already proposed, but it is highly possible that other factors are involved. As we eliminate certain possibilities, we will move closer to understanding how psychobiotics function. To achieve this, a systematic approach is needed, and although probiotics and psychobiotics may work through multiple mechanisms biologically, which is a fascinating possibility, it is beneficial for both the industry and clinicians to identify a primary mechanism. Similar to drugs, a useful starting point would be to develop a comprehensive strain collection that is suitable for high-throughput screening (HTS) via fast, automated, or AI-assisted processes [83,84]. This can be coupled with genomics, especially whole-genome sequencing and genetic modification techniques. Such approaches could help pinpoint the key genes involved in certain probiotic effects,

potentially facilitate the validation of probiotic activity, and even lead to the discovery of new mechanisms and therapeutic interventions.

Utilizing emerging monitoring technologies could also provide valuable insights in this pursuit. Smart devices, like watches, urinary metabolite monitors, stool sampling and consistency monitoring devices, and sleep quality and respiratory activity monitors, offer new ways to track health parameters in healthy, at-risk, or diseased populations during observational and clinical studies [85–87]. These technologies, paired with tailored questionnaires and the collection of blood, saliva, and stool samples using protocols suited to metagenomic and metabolomic analyses, would yield rich datasets. However, maintaining compliance can pose challenges if the clinical protocols become overly complex. Therefore, balancing thoroughness and simplicity is key.

8. Conclusions

The study of psychobiotics has come a long way already, but the road ahead is still winding; we need to reshape the ways in which we study the applications of probiotics in human health. While the use of some psychobiotic formulations like Cerebiome® is well established and supported by several trials in participants with depression [27], it is important to remember that not all probiotics are psychobiotics. Further clinical trials are needed and should take into account the high inter-individual variability, as well as the specific formulations and dose. Mental health-related diseases have been associated with pleiotropic alterations along the MGBA, including in the composition and functions of the gut microbiota, and also in overall and local immunity.

Our understanding of how communities of commensal microorganisms function and interact with their hosts is improving all the time. This is largely due to the development of investigation technologies, which are increasingly precise and accessible, combined with ever-greater data analysis and integration capabilities. Advances in our knowledge are leading to a better understanding of the activity of well-known probiotic strains, but also to the development of new strains that target specific mechanisms of action that have recently been highlighted. Among the many possible applications, MGBA-based interventions could help to prevent and/or treat a multitude of conditions, the prevalence of which is constantly increasing throughout the world. However, these subjects remain extremely complex and difficult to understand in their entirety; the activity of the strains, interactions with the host, production on an industrial scale, etc., all require specific specialist knowledge.

Collaborations and partnerships between various academic, public and industrial bodies sharing their know-how and expertise will therefore undoubtedly be essential for accelerating the development and rapid availability of new 'psychobiotic' solutions. While we have everything at hand, it is a matter of uniting the right teams with the right tools and methods and asking the right research questions.

Author Contributions: Conceptualization, all authors; writing—original draft preparation, U.H.I., O.K., M.L.B. and A.T.; writing—review and editing, all authors. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Not applicable.

Conflicts of Interest: Authors Sylvie Binda, Annie Tremblay, Umar Haris Iqbal, Ola Kassem, Mélanie Le Barz, Vincent Thomas and Stéphane Bronner are employed by Lallemand Health Solutions, a company that researches, develops, manufactures, markets, and sells probiotics to business clients but not directly to consumers. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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