BRAIN-GUT AXIS

EXPLORING THE POWER OF PROBIOTICS

New frontiers in research

TRUST YOUR GUT

Recent research advances on the microbiome–gut–brain axis

USING PSYCHOBIOTICS

to defeat depression-like symptoms?

THE CURRENT STAGE

of research, the ongoing research on psychobiotics

LALLEMAND

EDITOR'S NOTE

Since our last publication in November 2016, there have been significant advances in scientific research on bidirectional communication between the brain, the gut and the gut microbiome. This new research has revealed the importance of the trillions of bacteria living in our digestive system. Bacteria play a critical role in our gut health, but also in our immune system, endocrine stress response and central nervous system.

Have you ever experienced intestinal discomfort from stress? Most of us have, but why? Scientists have discovered that this is due to the "brain–gut axis" (BGA); that is, the bidirectional communication pathway that takes place between our brain and gut. Over the past decade, neurobiologists and microbiologists have paid increasing attention to the concept of a brain-gut axis. Recent research have identified the scientifically crucial role of the microbiota, making it more relevant now to talk about the "microbiome-gut-brain axis" rather than the "brain-gut axis" **[Wood 2007; Cryan 2011]**. But how did this concept originate? It seems intuitive that the brain and psychological stress have a direct impact on our gut, but isn't it fascinating to learn that these effects are bidirectional?

In this issue, we take a careful look at the nature of the BGA and provide an update on the most recent research and insights emerging from these advances. We review the relationship between BGA and stress, as well as the role of probiotics. We examine probiotics and their general benefits, probiotics for maintenance of health, and probiotics for treating conditions, particularly stress-related conditions. Finally, we look at promising new research on the BGA and its effects on specific conditions and disorders.

Lallemand Health Solutions remains at the forefront of knowledge, research and development on the BGA. For 85 years Lallemand's research center, the Rosell Institute for Microbiome and Probiotics (RIMaP), has been a pioneer in BGA studies, and we remain focused on the scientific, preclinical and clinical documentation of probiotic formulations to benefit health. Lallemand is also a sponsor of the international Mind, Mood and Microbes (MMM) conference, which brings together academics, health professionals and health related industries to help accelerate and improve research.

Lucie Lingrand

PSYCHOBIOTIC SPECIALIST
AT LALLEMAND HEALTH SOLUTIONS

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TRUST YOUR GUT:

recent research advances on the microbiome-gut-brain axis

In the 1880s, scientists and clinicians began to examine the relationship between our brain and our gut, along with the gut's resident bacteria. We now call this the brain–gut axis (BGA) or microbiome-gut–brain axis. Over time, advances in research have revealed additional evidence that bidirectional communication takes place between these structures, and that it intensifies in times of stress.

The gut is sometimes referred to as our "second brain", due to its hosting the enteric nervous system (ENS), a neural network that allows the gut to work without instructions from the brain **[Liang 2018].** The ENS maintains control of our digestive system; it plays an important role in peristalsis, secretion and pain perception.

The gut is not only home to the ENS, but it also provides food and shelter for commensal microorganisms: the gut microbiome. The evolution of laboratory techniques and omics over the past decade has allowed us to gain a better understanding of these microorganisms. There is now evidence that the gut and its microbiome work together to affect immunity, endocrine functions, gut functions and neurotransmission.

Humans are superorganisms living in symbiosis with trillions of microbes distributed throughout the body. More than 90% of our cells are from microorganisms. But due to our modern lifestyle – excessive hygiene and changing diets – we have begun to lose diversity. Recent research suggests that a high-fat diet, for example, may have a negative influence on both the gut microbiome and the brain. A diet rich in saturated fatty acids can have detrimental effects, not only on the gut microbiome –characterized by lower diversity in gut microbial species– but also on brain function, inducing depression-like behavior **[MyNewGut project].**

In the field of psychology, researchers and practitioners have increasingly come to recognize patients as superorganisms, and to consider the microbiome as a way to identify disease (biomarkers), as well as a way to stratify and even treat those in their care. Unlocking the secrets of the microbiome could therefore give us access to a treasure trove of personalized nutrition and treatment resources.

The BGA is mainly composed of three pathways: the neural pathway (ENS and the vagus nerve), the neuroendocrine

MORE THAN
1,400

different bacteria species have been identified in the intestines.

LESS THAN
50 clinical studies
have been published on psychobiotics. We expect this number **to double soon** as more than 60 have been initiated in the past 2 years.

Brain and gut communicate through a vast network of
500 million

neurons innervating the gut: THE ENTERIC NERVOUS SYSTEM (ENS).

BETWEEN 2004 AND 2019, over
2.300
SCIENTIFIC PUBLICATIONS AND REVIEWS have been published on the Brain-Gut axis. This is a research boom.

> **HUMANS ARE SUPERORGANISMS LIVING IN SYMBIOSIS WITH TRILLIONS OF MICROBES DISTRIBUTED THROUGHOUT THE BODY.**

pathway and the immune pathway. So what happens to us in times of stress, and how does the brain react to stressful situations?

THE VICIOUS CIRCLE OF INFLAMMATION

When we experience a stressful event, an area of the brain that controls our emotions, the amygdala, sends a distress signal to the hypothalamus, the brain's command center. The hypothalamus then sends out an alert through our nervous system, which responds by releasing a flood of stress hormones, including adrenaline and cortisol. In turn, these hormones prepare our body for emergency action, known as the fight-or-flight response. Common physical symptoms of stress include a pounding heart, tightening of muscles, a rise in blood pressure and rapid breathing. These physical changes increase our strength and stamina, improve our reaction time and enhance our focus, preparing us to either fight or escape in response to the stressful situation. When the stress response is sustained, however, it can have a negative effect on parts of the body, including the digestive system.

When the body is repeatedly exposed to stress, it can initiate a vicious cycle of inflammation. This inflammation, and the action of the pathogens, can lead to increased barrier permeability, allowing bacterial translocation and inflammation signaling from the gut to the brain through the vagus nerve. The brain interprets this inflammation signal as a new stressor. If the trend continues, the combination of said stressor and the external stressor will lead, after some time, to psychological, physiological and behavioral symptoms.

The findings of Maes *et al.* published in 2012, suggest that "translocated" gut commensal bacteria activate immune cells to elicit IgA and IgM (antibodies) responses; this phenomenon may play a role in the pathophysiology of (chronic) depression through the progressive amplification of immune pathways.

THE ROLE OF THE MICROBIOME

What role does the microbiome play in all of this? Researchers have observed significant differences in gut microbiome between healthy people and sick patients; this is just the first step toward assessing what constitutes a healthy microflora. Based on available research, diversity seems to be essential, as is a relative abundance of *Firmicutes and Bifidobacteria.* Germ-free animal models demonstrate that neither the brain nor behavior can develop fully or normally without a gut microbiome **[Luczynski 2016].**

Although this area of research is still in its infancy, these observations offer new hope to many nutritionists and neuropsychiatrists who may now be able to stratify patients based on microflora. This will potentially enhance patient response to medical drugs based on individual microbiotal identity ■

HISTORICAL OVERVIEW

of advances in the study of the brain-gut axis

2018

CEREBIOME® is shown to be beneficial as adjunctive therapy in depressive patients.

2013

The term "psychobiotics" is coined.

2010

Messaoudi publishes the first study showing that CEREBIOME® can reduce psychological symptoms in healthy adults.

2008

Desbonnet measures for the first time the direct brain-level effect of long-term probiotic intake, in a forced-swim model of stress in rats.

2006

Zareie demonstrates that the probiotic supplement Lacidofil® is effective in preventing stress-induced intestinal abnormalities such as bacterial adhesion and translocation.

2004

Sudo demonstrates in a fundamental study that postnatal microbial colonization programs the hypothalamic–pituitary–adrenal (HPA) system for stress response in germ-free mice.

1998

Lyte demonstrates a direct activation of neural pathways by gut microorganisms in mice, with consequences for their behavior, especially.

1970

Bähr observes behavioral changes in sterile piglets compared to piglets with a microbiome.

1910

J. George Porter Phillips hypothesizes for the first time that the use of live bacteria could treat melancholy.

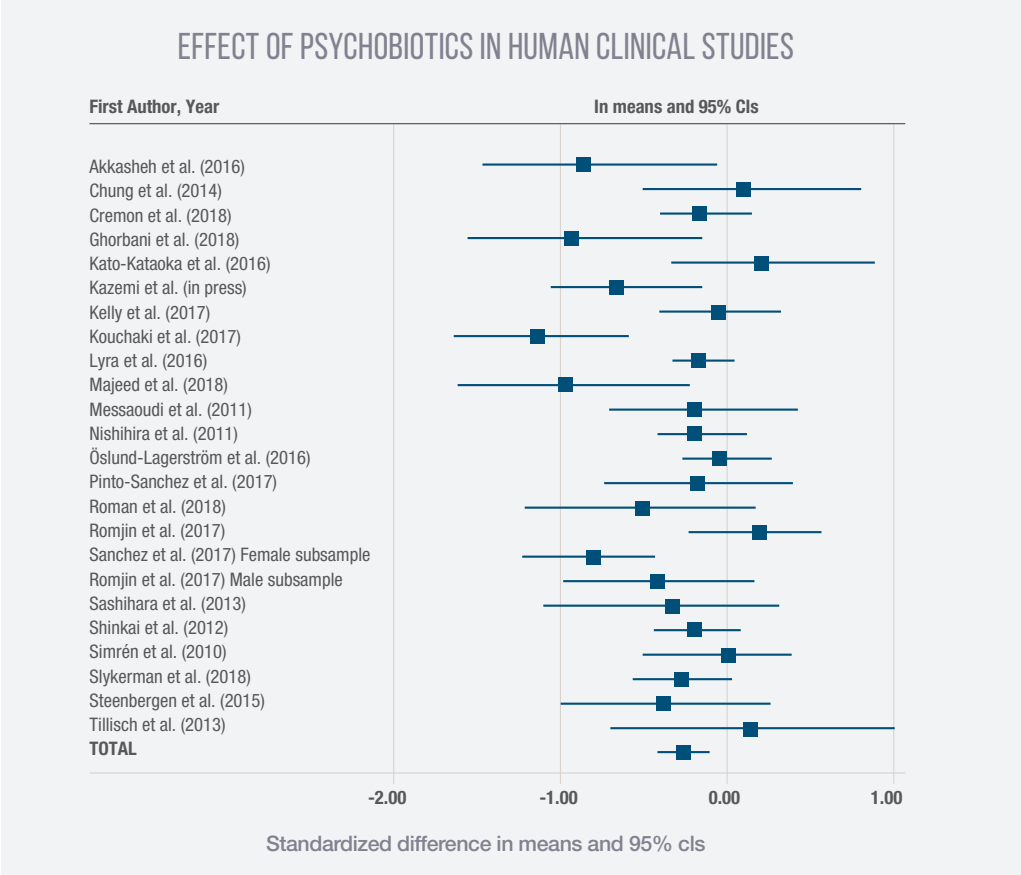
1880

W. James and C. Lange suggest that physiological stimuli can trigger emotional responses.

PROBIOTICS
for a healthier life

Probiotics are live microorganisms, and are safe and natural ingredients that can be taken as dietary/food supplements. Probiotics are known for their beneficial impact on the host's immune system and gut functions. The idea of using probiotics to improve psychological wellbeing through the BGA first appeared in 1880, but it was not until 2006 that this idea was tested in preclinical studies.

The benefits of probiotics for the BGA are described in several studies and meta-analyses. A recently published meta-analysis looked at 27 probiotic or symbiotic interventions and showed a significant improvement in depression and anxiety **[Liu 2019]**. It is important to note that the benefits are not homogeneous for all the probiotics tested, but are strain-dependent, which is the case for most of the beneficial effects of probiotics.



> **THE USE OF PROBIOTICS TO ADDRESS STRESS IS GAINING ACCEPTANCE AND SUPPORT.**

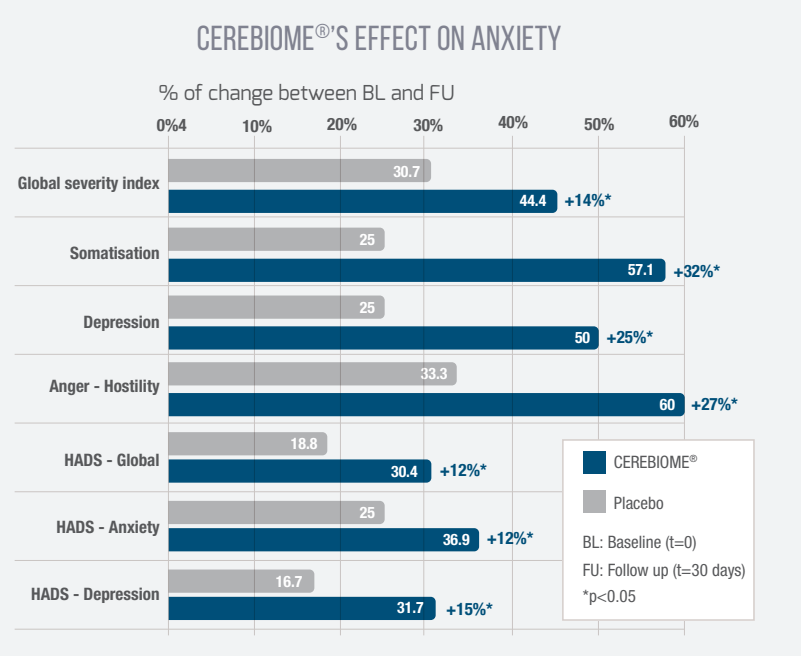
The beneficial effects of probiotics are commonly and mistakenly associated with modulation of the gut microbiome. However, research shows probiotics have their own direct effect on the host and that their benefits are not necessarily driven by modulation of gut flora **[Liu 2019].** For instance, prebiotics, mostly fibers, are known to be very effective in modulating the microbiome, but in their meta-analysis, Liu *et al.* conclude that probiotics show a beneficial impact on general anxiety and depression behaviors that prebiotics do not.
So while the microbiome is key, its modulation is not necessarily the most important mechanism to consider in investigations of the BGA and other areas.

Research conducted to date has been heterogeneous because of differences in protocols used, the different strains studied, and differences in measured outcomes. This is the case for both clinical and preclinical research; thus, preclinical studies are the best way to explore the potential effects of probiotics on the BGA. The specific probiotic combination of *Lactobacillus helveticus* Rosell®-52 and *Bifidobacterium longum* Rosell®-175 (a formula known as CEREBIOME®), a Lallemand Health Solutions proprietary formula, is the best documented probiotic on the BGA. This formula, CEREBIOME®, is now supported by five clinical and nine preclinical studies showing its beneficial impact on bidirectional communication between the brain and the gut through different pathways. Such consistency of results is rare in this innovative field and much has been learned about the BGA by investigating the same probiotic formula through various research studies.

INVESTIGATING HEALTHY ADULTS

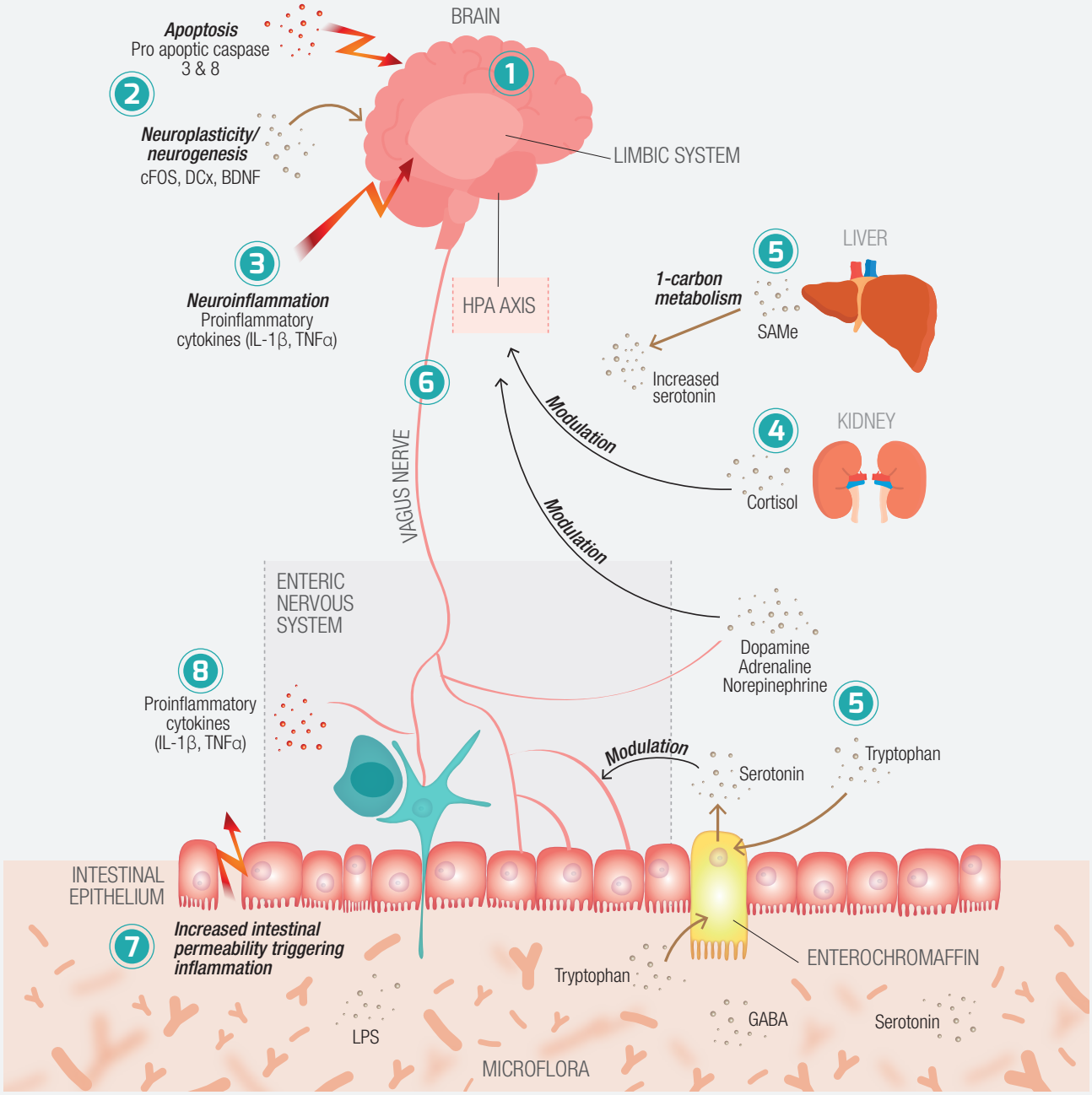
The first-ever human clinical study involving healthy stressed adults and probiotic intake was published in 2008 by Diop *et al.* This double-blind, placebo-controlled and randomized clinical trial involved healthy adults who were frequently exposed to stress, and whose symptoms were evaluated using a self-assessment visual analog scale (VAS). Over a three-week period, the subjects received a daily dose of either CEREBIOME® or a placebo. Results after three weeks confirmed that the group receiving the probiotic showed a 49% reduction in stress-induced gastrointestinal symptoms. These symptoms included abdominal pain and nausea, with some subjects also reporting a decrease in bloating and flatulence.

Two years later, Messaoudi *et al.* conducted a clinical study on chronically stressed healthy adults to look at improvement in psychological stress. In this double-blind, controlled, randomized clinical trial, Messaoudi sought to determine whether oral intake of probiotics had a beneficial effect on psychological stress. Healthy participants were evaluated using a range of validated psychological assessment scales for anxiety, depression and stress, but they were also subjected to a stress biomarker sampling using a 24-hour urinary free cortisol test (UFC). Participants in the probiotic group received a 30-day supply of the probiotic preparation, and the control group received a placebo. After one month, the data indicated that a daily dose of CEREBIOME® significantly alleviated psychological distress and had a beneficial effect on general feelings of anxiety and depression; more specifically on somatization and depression. This provided clinical proof that the BGA is characterized by bidirectional communication.



The use of probiotics to address stress is gaining acceptance and support. This is evident in the Canadian health authorities' approval of Lallemand Health Solutions' claims that CEREBIOME® "helps to moderate general feelings of anxiety" **[Claim NPN 80021343]**

CEREBIOME® modes of action



1. it **reduces** depression-like behavior, as shown in rodent models with the normalization of burying time which is associated with anxiety and back-to-normal social interaction, as well as swimming and learning time;
2. it can help to **preserve** normal neuroplasticity and neurogenesis, as measured by caspase and BDNF biomarkers in rats;
3. it can **prevent** occasional neuroinflammation in the limbic system, the brain region responsible for stress response;
4. it helps **maintain** healthy cortisol levels in humans and in animals;
5. it helps to normalize blood dopamine and norepinephrine levels in rats and **increase** neurotransmitter precursors in rats and humans;
6. it also reduces apoptosis in the brain (normally-occurring death of cells as part of growth), a process which depends on an intact vagus nerve;
7. it helps to **improve** intestinal permeability and decrease visceral pain;
8. it **reduces** intestinal inflammation due to stress, as measured through the use of biomarkers.

USING PSYCHOBIOTICS

to defeat depression-like symptoms?

In 2013, Cryan *et al.* published their research paper, "Psychobiotics: a novel class of psychotropic." In this paper, the term psychobiotics referred to live microorganisms that, when ingested in adequate amounts, produced a health benefit in patients suffering from psychiatric illness. The term "psychobiotics" has since been widely adopted by neuroscientists conducting research on neurodegenerative diseases and depressive disorders, in order to describe the use of probiotics to tackle depression, stress, anxiety, and other mental health complaints through the BGA.

Depression is a common and serious medical condition that negatively affects how people feel, think and act. Though there are many different types of depression, all of them cause feelings of sadness and/or a lack of interest in activities, also known as anhedonia (the incapacity to experience positive feelings). Treatment options for depression include antidepressant medications, cognitive behavioral therapy, interpersonal therapy, and psychodynamic therapy.

Several cross-sectional studies have been conducted using a nutritional modification approach to evaluate the association between diet, the gut microbiome and mental health. These studies have linked psychiatric disorders such as depression to changes in the microbiome of the GI tract, making it a potential target for novel antidepressant treatments. Probiotics are central to this research.

There is considerable evidence that this is a viable solution, as probiotics have shown the ability to change behavior and improve mood, anxiety and cognition in rodent models. These preclinical results have now been corroborated in at least 10 psychobiotic clinical studies involving depressed patients. This research has evolved since Messaoudi's first study in 2010 on probiotics and psychological stress in healthy adults, addressing more serious conditions in recent years. In 2015, a study looked at probiotic effects on cognitive reactivity associated with sadness (an established marker of vulnerability to depression in healthy people) **[Steenbergen 2015].** In the same year, probiotic studies looked at academic stress in healthy students, as well as stress in petrochemical workers.

Are there bacteria in our brain?

In 2019, a research group focused on understanding Alzheimer's disease published an exciting paper demonstrating the presence of bacteria in the brain. Is Alzheimer's due to a brain infection? Or are the bacteria just another symptom?

Of course, correlation is not the same as causation and experts in sampling and sequencing warn that the group's findings may be due to contamination. At the same time, some neuroscientists argue that these findings make sense, considering that the brain has a structurally distinct immune system. To date, however, these research findings remain unconfirmed.

Another intriguing study was presented by Rosalinda Roberts at the latest Society for Neuroscience meeting **[November 2018].** Using electron microscopy, Roberts and colleagues at the University of Alabama unexpectedly found bacterial forms penetrating and inhabiting tissue samples from healthy human brains. Similar evidence was found in samples from patients with schizophrenia, the disease they were actually studying.

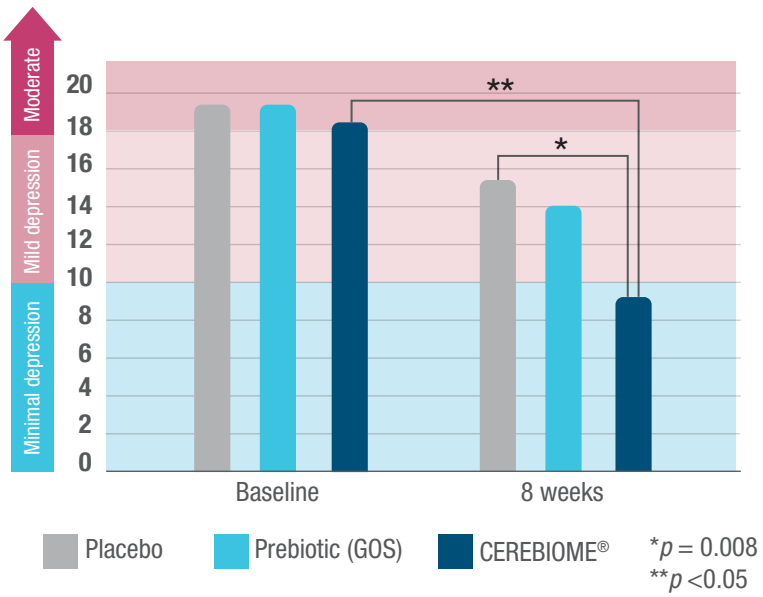
In 2017, Slykerman looked at women suffering from postnatal depression, as well as links to eczema in offspring as a primary outcome.

SIGNIFICANT RESULTS WITH CEREBIOME®

Interestingly, in 2017, a randomized, double-blind, placebo-controlled study was published by Romijn that studied patients suffering from depression who were not being treated with antidepressants. Results indicated that the probiotic product CEREBIOME® significantly decreased dry mouth and sleep disruption ($p<0.05$). In 2018, the results of another randomized, double-blind and placebo-controlled study using CEREBIOME® were published. Here, the research included 110 patients suffering from mild to moderate depression that were receiving antidepressant treatment **[Kazemi 2018].** The probiotic was used as an adjunct therapy to conventional antidepressant treatment and showed a significant decrease in Beck Inventory Depression (BDI) scores, from 18 down to 9 on average. These results are clinically significant, showing the patients were now categorized with "minimal depression" according to the validated assessment scale. Specifically, the CEREBIOME® group showed a decrease in the blood kynurenine/tryptophan ratio, which suggests that tryptophan was diverted toward the synthesis of serotonin and away from the inflammatory pathway ($p<0.05$).

A 2018 open-label study by Wallace and Milev found that in treatment-naïve patients, CEREBIOME® had a positive effect on mood, anxiety, anhedonia, and perceived stress, lasting up to eight weeks after treatment ■

A SIGNIFICANT REDUCTION OF DEPRESSION SCORE



PREVENTING
the domino effect

Clinical studies have found that the establishment of the gut microbiome between birth and three years of age is vital to the development of the brain, as the two organs co-develop during this phase **[Jasarevic 2016]**. Subtle alterations in microbiome acquisition or maintenance in early life may constitute a vulnerability, impacting the (neuro-) endocrine and (neuro-) immune signaling pathways of the microbiome–brain–gut axis. As they co-develop in early childhood, any disruption in the gut or brain may subsequently predispose children to stress-related disorders in adulthood; this was shown in a study by Borre *et al.* (2014), who described the relationship as a "domino effect" that could induce mental disease and a higher stress response later in life.

Lacidofil®, a Lallemand Health Solutions proprietary probiotic formula combining *Lactobacillus rhamnosus* Rosell®-11 and *Lactobacillus helveticus* Rosell®-52, has been studied since 2006 for its effects on the BGA and early life stress (ELS). These 9 preclinical studies provide evidence that this probiotic supplement may be effective in preventing stress-induced intestinal abnormalities, and they indicate that it has an impact on the brain–gut axis in mammals.

THE CONFIRMED BENEFITS OF LACIDOFIL®

In 2016, Cowan et al. published an innovative preclinical study in *Nature* that addressed developmental trajectories of emotional learning in ELS infant rats. They concluded that Lacidofil® acted as an effective and non-invasive treatment to restore normal developmental trajectories of emotion-related behaviors in infant rats. These results provided promising evidence that probiotics could reduce the risk of mental health problems. That same year, Callaghan *et al.* published a study on generational paternal stress in rats and its impact on the development of memory and stress response in their offspring. The study demonstrated for the first time the normalization of emotion-related behavior (especially fear) in the offspring (F1 generation) of rats exposed to maternal separation (F0 generation), compared with the offspring of rats not exposed to maternal separation. Interestingly, these generational effects were reversed by probiotic supplementation, which was effective in normalizing emotion-related behavior as both an active treatment when administered to infant F1 rats and as a prophylactic when administered to F0 fathers prior to conception (i.e., during the fathers' infancy). These findings have high clinical relevance in the identification of early

emerging putative risk phenotypes across generations, and of potential therapies to ameliorate such generational effects. The beneficial effect of Lacidofil® has been corroborated in two other recent studies in animals. The Peng et al. 2019 study confirmed that this probiotic combination can prevent abnormalities in fear-related behavior, decrease anxiety-like behavior, and restore normal developmental trajectories in the same model of ELS.

Now that we understand the domino effect from ELS, it is interesting to look at longer-lasting effects later in life.

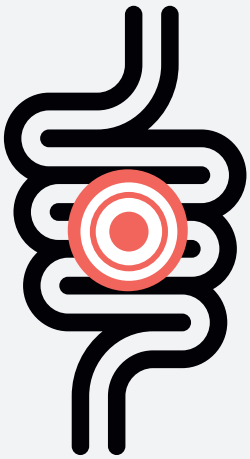
THE LONGER-LASTING EFFECTS OF ELS LATER IN LIFE

Puberty is another important yet stressful period of change. How stress is handled during the transition to adulthood can be critical for mental health and wellness. In 2018, Cowan et al. published a preclinical study on the same probiotic formula, showing the sex-specific effects of early life maternal separation stress on the timing of puberty onset. Stressed female rats exhibited earlier pubertal onset compared to standard-reared females, and stressed males matured later than their standard-reared counterparts. It was demonstrated that a probiotic treatment could restore the normative timing of puberty in both sexes. These results are in line with previous findings that probiotics can reverse stress-induced changes in learned fear behaviors and stress hormone levels, highlighting the remarkable and diverse restorative effects of probiotics in the context of ELS **[Gareau 2007].**

In addition, the effects of Lacidofil® on the gut barrier and its anti-inflammatory properties have now been extensively documented in 26 clinical trials mainly focusing on gut health in children and adults (AAD, acute diarrhea in children and adults, IBS). This could pave the way for preventing modern disorders induced by stress ■

Multidisciplinary R&D

A shift in neuroscience: targeting the gut to reach the brain



Until recently, there was no biomarker for mental disorders, and diagnostics were based on validated questionnaires. Because of research on the BGA, the microbiome is now viewed as a potential biomarker for stratification and a predictive model for treatment resistance. Dedicated congresses and conferences, such as MMM, bring experts together to share research insights in this field. Research on the BGA is improving with the increasing use of validated questionnaires, biomarkers and objective measures of the brain through imaging.
Neuropsychiatrists and neuroscientists are now working with nutritionists and microbiologists to explore the BGA. They plan to hijack its bidirectional communication to support overall health with natural solutions involving probiotics.
A perfect example of this multidisciplinary work is the ongoing study by C. Wallace at the Center of Neuroscience Studies, Department of Psychiatry, at Queen's University in Canada. Here, the goal is to assess the effects of probiotics on depression. The outcomes measured include seven validated questionnaires for depression and associated symptoms, polysomnography in order to assess sleep quality, neuroimaging, and molecular analysis of blood, urine and fecal samples. To successfully conduct this study, the neuropsychobiology team is collaborating with microbiology specialists from Lallemand's Rosell Institute for Microbiome and Probiotics.

What is the current state
OF RESEARCH?

The clinical research on BGA is very heterogeneous, given that stress is a risk factor and a consequence of many modern diseases. This heterogeneity is why research is conducted on a variety of people: healthy people as well as people suffering from depression, chronic diseases or neurodegenerative diseases, and on ageing people. Some conditions, such as Parkinson's disease, have promising preclinical data but no clinical study results at present.

THE CONDITIONS STUDIED TO DATE INCLUDE

Condition	*Number of clinical studies*
Alzheimer's disease (cognitive functions)	2
Autism	1
Bipolar disorder	1
Chronic fatigue	2
IBS (anxiety and depression associated)	2
Laryngeal cancer (anxiety associated)	2
Major depression	4
Migraine (open label)	1
Neurodevelopment in NEC	1
Psychological scores in obese patients	1

We present an overview of those published studies on next page as well as an overview of registered clinical studies in this field, paving the way for future publications and discoveries. Among published studies, 46% considered biomarkers and only 44% showed a positive effect on the measured biomarker, representing 18% of the total research on BGA and probiotics. In addition, 36% of published clinical trials on probiotics for BGA focused on non-healthy populations.

There is, of course, no magic remedy for treating or preventing psychological and neuronal disorders. However, current research suggests that targeting the BGA and the gut microbiome represents a promising avenue for neuroscience, psychology and psychiatry. It may soon be possible to improve a patient's quality of life using non-invasive and natural methods such as probiotics, prebiotics and adjustments to diet. In addition, this new area of research can help provide guidance for healthy people on how to maintain their cognitive health, achieve healthy sleep patterns, and improve stress resistance ■

Research on psychobiotics

an overview

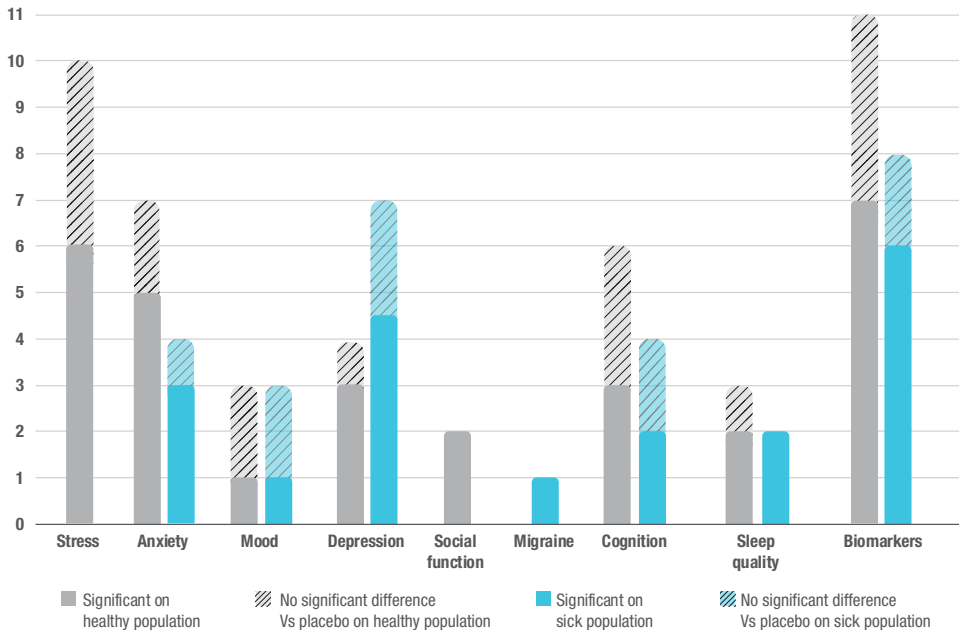
PUBLISHED

CLINICAL STUDIES

The following graph presents an overview of the outcomes measured in all of the clinical studies (29 in total) published on BGA as of January 2019. To get a better overview, we focused on outcomes, rather than conditions; for example, anxiety is an outcome that was measured in depressed patients, students or even people suffering from chronic diseases such as IBS. Of these 29 studies, 70% were published after 2014 and **60% were significant based on primary outcomes** ■

OVERVIEW OF CLINICAL OUTCOMES ON PROBIOTICS IN BGA

(WHO database: 2012 - January 2019)



ON-GOING

CLINICAL STUDIES

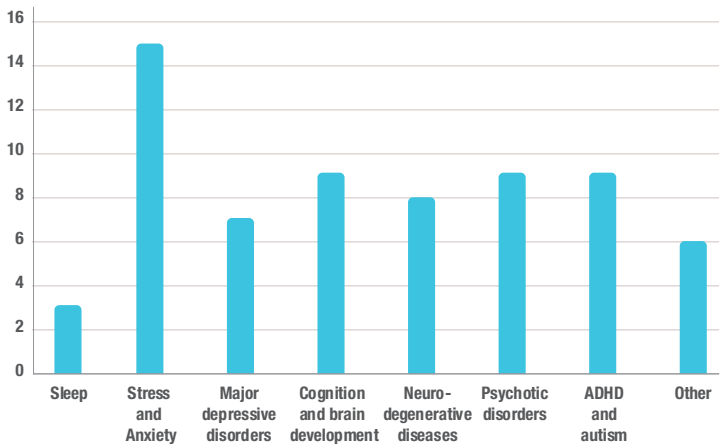
From 2017 to mid-2019, 66 clinical trials targeting the BGA with probiotics were registered. Currently, the most frequent areas studied are stress and anxiety, but other areas include severe depression, cognition, autism and Parkinson's disease. The techniques associated with these studies are also evolving. Researchers use professionally validated questionnaires and biomarkers such as cortisol, as well as brain imaging, which reveals the regions of the brain being stimulated and what this means. Research teams are also exploring ways to study the brain without using invasive techniques.

We estimate that 42% of ongoing research is funded by private companies. This shows that both academia and private industry are investing in this research and working collaboratively. The MMM conference initiative is another example of this shared commitment.

We are excited to see what ongoing and future BGA studies reveal ■

REGISTERED CLINICAL STUDIES ON PSYCHOBIOTICS

(WHO 2017- mid 2019)



Promising research
on the microbiome in serious conditions

Neurodegenerative disorders

Neurodegenerative disorders include Alzheimer's, dementia and Parkinson's disease. Patients with these conditions may suffer from gut disorders long before they are diagnosed **[Kraneveld 2019]**. This is why neuroscientists and neurology practitioners place great hope in research that looks at the gut and gut microbiome. An emerging hypothesis is that gut disturbances earlier in life represent a risk factor for developing neuro-degenerative disorders later in life. This is because an inflammatory state is induced by a leaky gut sending stress messages to the brain.

The differences in gut microbiome between healthy and neurodegenerative patients have been widely studied **[Giau 2018; Ambrosini 2019]**. It is not clear how these microbiome differences may contribute to, or provide a marker for, neurodegenerative disorders.

Jean Pierre Trezzi's team in Luxembourg is focusing on *Akkermansia* abundance and functionality with meta-bolomics analysis. There is also preclinical work being conducted which will explore links between the gut and neurogenerative disorders through the use of probiotic and dietary interventions in rodent models for brain neuro-inflammation. There is, however, no published human data yet.

Autism spectrum disorder

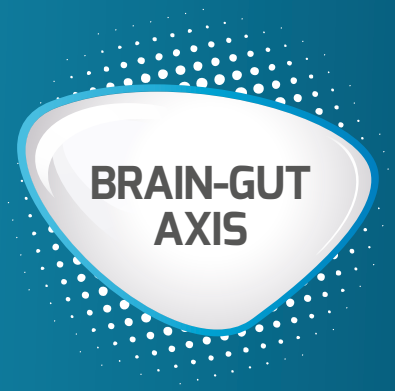
Autism spectrum disorder (ASD) refers to a group of neurodevelopmental disorders that are associated with deficits in social interactions, including verbal and non-verbal behaviors. Researchers believe that these ASD-like behaviors are the result of a complex interplay between genetic defects and environmental risk factors that cause abnormal neurodevelopment in utero and in early childhood. ASD is associated with some serious and painful gut symptoms **[Dominy 2019].** Gut dysbiosis appears to be a symptom of ASD. Analysis of fecal samples from children with ASD has revealed an imbalance in certain microbiome species, together with lower overall diversity of gut microbiome species.

Anecdotally, there have been observations of improved symptoms in children with ASD who experience changes in their gut microflora populations caused by the ingestion of either antibiotics against these bacteria or probiotics that provide the gut with more synergistic bacteria **[Kaluzna-Czaplinska 2012]**. Although these results are observations from exploratory studies, they are of interest to families who are open to information that might help their child.

Addictions

It is well known that alcohol influences behavior. It induces psychological symptoms and alcohol-seeking behavior in alcohol-dependent subjects, in a heterogeneous way. Several pathways have been studied in an effort to explain why and how (in addition to its important effect on brain and neurotransmitter equilibrium) alcohol abuse also affects peripheral organs, including the gut **[Leclerc 2017]**. Little is known about the influence of intestinal bacteria on neurobiological processes in humans with substance-use disorders, as highlighted by a systematic review **[Stadlbauer 2008]**. However, several research teams have found that chronic alcohol abuse increases intestinal permeability and alters the composition of the gut microbiome (mainly a decrease in *Bifidobacteria* and *Lactobacilli*), allowing bacterial components from the gut lumen to enter systemic circulation. There is an emerging link between inflammation, the intestine and the brain in alcohol dependence. Animal studies on germ-free models and supplementation with *Bifidobacteria* or *Lactobacilli* have shown promising results **[Leclerc 2019]**.

"These observations support the possibility that targeting the gut microbiome, by the use of probiotics or prebiotics, could restore the gut barrier function, reduce systemic inflammation and could have a beneficial effect in treating alcohol dependence and in reducing alcohol relapse." **[Leclerc 2019]**.



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