Open access • Journal Article • DOI:10.1097/FBP.0000000000000478

Stress and the gut microbiota-brain axis — Source link

Guadalupe Molina-Torres, Miguel Rodriguez-Arrastia, Pablo Roman, Nuria Sánchez-Labraca ...+1 more authors

Institutions: University of Almería

Published on: 01 Apr 2019 - Behavioural Pharmacology (Behav Pharmacol)

Topics: Gut flora

TITLE

ROLE OF MICROBIOTA GUT-BRAIN AXIS ON STRESS

RUNNING HEAD

STRESS AND GUT-BRAIN AXIS

AUTHORS

Molina-Torres, Guadalupe[1]; Rodriguez-Arrastia, Miguel[1]; Roman, Pablo[1*]; Sanchez-Labraca, Nuria[1]; Cardona, Diana[1].

AFFILIATIONS

1. Department of Nursing Science, Physiotherapy and Medicine, University of Almería, Almería (Spain)

CORRESPONDING AUTHOR

Dr. Pablo Román López

Edificio de Ciencias de la Salud, Universidad de Almería

Ctra. Sacramento s/n, 04120 La Cañada de San Urbano (Almería, Spain)

Telephone: (+34) 950 214 563 Email address: pablo.roman@ual.es

CONFLICTS OF INTEREST AND SOURCE OF FUNDING

The authors declare no conflict of interests.

ABSTRACT

Stress is a nonspecific response of the body to any demand imposed upon it, disrupting the body homeostasis and that manifests with symptoms such as anxiety, depression or even headache. Response, which is quite frequent in the present competitive world. The aim of this review is to explore the impact of stress on gut-microbiota. Firstly, we summarize evidences in which the microbiota composition has changed as response of a stress situation, thus microbiota impact by stress-response. Likewise, we summarize the different interventions that can modulate microbiota and so then could modulate the stress according to the underlying mechanisms that involved the gut-brain axis on the stress. Finally, we show evidence through the gut modulation impact on stress, both preclinical and clinical studies. In conclusion, the influence of stress on gut-microbiota and gut-microbiota on stress modulation is clear through different stressors, although the preclinical evidence is so extended, the clinical evidence is more limited. A better understanding of the mechanism underlying the stress modulation through the microbiota may open new avenues for the design of therapeutics that could enhance the clinical benefits pursued. Not only on stress, but also on stress-related disorders such as anxiety and depression, both in healthy subjects and in different populations.

KEYWORDS

Gut; microbiota; gut-brain; gastrointestinal microbiome; stress; stress disorders; anxiety; diet; probiotics; faecal transplantation.

1. INTRODUCTION

Stress is a nonspecific response of the body to any demand imposed upon it (Selye, 1985). This demand can be induced by a psychological, environmental, or physiologic stressor, that disrupts homeostasis (Jafari et al., 2014; Moloney et al., 2016), and it is manifested with symptoms such as anxiety, depression or even headache. Thus, the stress can be classified in relation to the duration of the stress as acute psychological stress (surgical operation or examination) and chronic psychological stress (anxiety about family conflicts, financial problems, etc.) (L. Yang et al., 2015). Early life stress has been implicated in many psychiatric disorders such as depression or anxiety (O'Mahony et al., 2011). Exposure to stress affects sleep negatively and the sleep/wake cycle; for example, experiencing work-related stressors, having low social support (Mellman & Hipolito, 2006), or exposure to trauma/combat (Rothbaum & Foa, 2002) can all disrupt sleep and the sleep/wake cycle.

Nevertheless, stress can be hardly avoided in the present competitive world, and also important for people's rapid reaction to threats; however chronic stress is associated with detrimental effects on physical health and adverse implications on the immune, neuroendocrine and central nervous systems (Le et al., 2016). Over time, the number and frequency of diagnoses of stress-related disorders, such as depression and anxiety, have indeed grown. Due in part to greater awareness of manifestations of disease symptoms, but also because of the pace of modern life, inclusion of society, diet, and stress in association with urbanization, industrialization, westernization, and resulting changes in agriculture and food processing (revised in Schnorr & Bachner, 2016).

On the other hand, chronic stress is a considerable health concern for society, associated with various disease states including an increased risk for neuropsychiatric disorders like

depression and anxiety (L. Yang, 2015). More than 25% of individuals are affected by these disorders (Househam et al., 2017), as well as the chronic stress are related with gastrointestinal (GI) disorders such as irritable bowel syndrome (IBS) (Moloney, 2016).

Both chronic and psychological stress can have an impact on the developmental trajectory of the intestinal barrier (Lennon et al., 2013; Smith et al., 2010) and have been associated with an increase in gut permeability (Söderholm et al., 2002). Indeed, the effects of stress on intestinal permeability are complex and likely involve both the gut and the brain (Kelly et al., 2015). Additionally, psychological stress is an important factor for the development of IBS. More and more clinical and experimental evidence showed that IBS is a combination of irritable bowel and irritable brain (Qin, 2014), and is well-known that psychological stress causes bowel dysfunction like nausea, vomiting, abdominal pain and alteration in bowel habits.

The pathways through the stress influence in IBS include the following: (a) activation of mast cells and the sympathetic nervous system, (b) vagus nerve inhibition on inflammatory pathways, (c) the prefrontal cortex and amygdala control over the hypothalamic pituitary axis (HPA), (d) the hypothalamic-corticotropin releasing factor (CRF)-ergic system, (e) the peripheral CRF-ergic system, (f) the effect of early life events on colitis (the HPA axis is programmed by early life events, and neonatal inflammatory stimuli exert long-term changes in HPA activity), (g) the impact of depression on exacerbating colitis possibly through shared proinflammatory cytokines, and (h) the intestinal microbiota-brain axis (Bernstein, 2017).

Individuals suffering from chronic daily-life stressors such as loss, financial problems, unemployment, etc., are predisposed to disease in the GI tract (Mayer, 2000), e.g. exacerbations of IBS (Bennett et al., 1998), ulcerative colitis or gastroesophageal reflux

disease (Naliboff et al., 2004). Current evidence suggests that the stress-induced gut mucosal response is primarily mediated by neuroimmune interactions between the autonomic and enteric nervous systems and the intestinal immune system, and many studies have identified that chronic stress is associated with a decrease in systemic immune function (McEwen, 2003).

Stress has profound effects on the GI tract including but not limited to alterations in intestinal motility (Venkova et al., 2010), mucosal transport, gut barrier function (Hyland, 2014), and visceral perception (Moloney et al., 2012). In addition, recently, the role of the gut microbiota in the bidirectional communication along the gut–brain axis (GBA), and subsequent changes in behavior, has emerged (Cryan & Dinan, 2012), suggesting that stress can lead to long-term changes in the gut microbiota. The GBA is a bidirectional communication network between the gut and brain, in which communication occurs through three different pathways: (a) neural via, mainly by the vagus nerve and the enteric nervous system, (b) endocrine via, through glucocorticoids, such as cortisol, as well the (c) immunological pathway, through the modulation of cytokines (Bercik & Collins, 2014; De Palma et al., 2014; Mayer et al., 2015; Sherwin et al., 2016).

Nonetheless, the importance of the gut microbiota and their role in visceral sensation and nociception remains to be further explored (Moloney, 2016). Chronic stress can induce dysbiosis and enhance bacterial wall adherence, while the interaction between host and microbiota can modulate the neuro-immune-endocrine systems (Aguilera et al., 2013). Thus, the aim of this review is to explore the impact of stress on gut-microbiota and to underlying the mechanisms that involved the gut-brain axis on the stress. Finally, we show evidence through the gut modulation impact on stress, both preclinical and clinical studies.

2. Microbiota: new insight on stress disorders

Stress impact on microbiota composition

The gut microbiota has recently emerged as one of the most fascinating entities in modern biomedical research (Cryan & Dinan, 2012). The gut microbiome has been implicated in a whole host of physiological functions from energy metabolism to psychiatric well-being (Moloney, 2016). There is evidence linking various gut-related biological pathways and mechanisms to the etiology of depressive and anxiety disorders (Penninx et al., 2013). Many of these are related to the gut, such as inflammation associated with increased intestinal permeability, microbial dysbiosis (Zheng et al., 2016), HPA axis dysfunction, neuroactive substances and dietary deficiencies (Petridou et al., 2016).

Mammalian microbial colonization begins at birth, although this colonization could begin during the pregnancy given that a diverse range of microbes has been found in amniotic fluid, the placenta, umbilical cord blood, and the fetal membranes. Following parturition, the gut microbiota is refined and modified until adult-like communities reach homeostasis in its diversity around 2 years old (Ohland & Jobin, 2015).

Human GI tract is dominated by two phyla: *Firmicutes* and *Bacteroidetes*, together with members of *Actinobacteria*, *Verrucomicrobia*, *Proteobacteria*, *Fusobacteria*, and *Cyanobacteria* phyla (Lach et al., 2018; Moloney, 2016). This relative abundance of microbial population remains stable throughout adult life, but can be altered. Thus, the composition of the core bacteria harbored throughout adult life is shaped by a number of factors including mode of delivery (vaginal or cesarean section), breastfeeding or bottle-feeding, diet, some medication (specially, antibiotics), exposure to viral or bacterial infections, stress and others such as smoking (Kochhar & Martin, 2015; Martin et al., 2009; Mountzouris et al., 2015; Rea et al., 2017; Savin et al., 2018; Sukoh et al., 1998).

Concerning to the stress and the impact on microbiota, its impact begins from prenatal stress. Psychological stressors can change the intestinal microbial community and these perturbations can contribute to stressor-induced changes in immune function, neurodevelopment, and behavioral deficits (A.R. Mackos et al., 2016). Pre-clinical data shows long-lasting alterations in intestinal microbiota composition where lactobacilli was decreased. On top of that, early-life stress impact on GI microbiota, host health, and behavior, such as increased plasma corticosterone, behavioral deficits, decreased noradrenaline in the brain, increased visceral sensitivity, and increased immune response. Furthermore, early-life stress has shown results both in composition and diversity of gut-microbiota (Wiley et al., 2017). Moreover, maternal stress and the microbiota have been linked to birth outcomes, such as prematurity, and neurodevelopment (Gur et al., 2015). In fact, gastrointestinal microbial communities were different in adult females born from stressed pregnancies and adult female offspring also shows alterations in cognition and anxiety (Gur et al., 2017).

However, the early-life stress impacts on the microbiota and social stress has also shown to reduce microbial diversity whereby the relative abundance of *Bacteroides* and *Lactobacillus* spp. decreased whilst bacteria in the genus *Clostridium* increased, even having an impact on behavior mediated by microbiota. Other type of stress, evaluated in adulthood such as restraint stress, has altered the relative abundance of various groups of bacteria (i.e., a reduction in the *Lactobacillus* genus in colonic mucosa). Also, the genus *Oscillospira, Lactobacillus, Akkermansia* and *Anaeroplasma* are affected in rodent exposed to a model of post traumatic disorder stress (Gautam et al., 2018). Prolonged restraint stressor exposure also reduced short chain fatty acids SCFAs but increase in infectious mice (Maltz et al., 2018). Although human studies are more limited, results are

shown as similar than in preclinical studies concerning to the impact of stress on microbiota diversity (Wiley, 2017).

As for stressors and their impact on microbiota, not only would physical and psychological stressors affect the composition and metabolic activity of the gut microbiota, but it is also suggested that the intestinal microbiome affects the brain by the humoral and neuronal mechanisms with particular attention to the vagus nerve, one of the pathways of GBA. Signals from the brain may influence sensory, motor, and secretory modalities of the GI tract, and signals from the GI tract influence brain functions, despite its exact mechanisms are not well understood (revised in Grochowska et al., 2018).

In this connection, most researches working in the area of gut-microbiota-brain (GMB) axis agree on the importance of the stress to analyse the changes of microbiota composition (Foster et al., 2017; Mayer, 2015; Rea, 2017). Nevertheless, although there is no consensus as to which symptoms or biomarkers define stress, some common signs that are widely accepted in the scientific literature include clinical, hormonal indicators and other symptoms associated with fatigue, performance decline, insomnia, change in appetite, weight loss and mood disturbances such as irritability, anxiousness, as well as inflammation and immunosuppression.

Mechanisms underlying the gut-brain axis on stress

Stress physiology includes processes across the autonomic nervous system, the immune system, and even over the gut microbiota (Househam, 2017). The cumulative physiological effect of stressors causes the dysregulation of multiple host systems due to allostatic overload (Bharwani et al., 2017).

As mentioned previously, stress usually influences the depression and anxiety disorders. Both disorders are stress-related and the common mechanism between them are the HPA

axis, mediating the biological effect of stress on the host. The HPA and sympathomedullary axes are the two stress response pathways in mammals. The HPA axis is slower-acting and adaptive, encompassing a network of anatomical constituents located both in the central nervous system and in the periphery. The crucial components are the paraventricular nucleus of the hypothalamus, the pituitary gland (anterior lobe) and the adrenal gland (Smith et al., 2006).

The HPA axis appears to be the most important stress response system, with CRF as mediator, since stress-induced release CRF can also lead to bowel dysfunction by acting directly on the bowel itself and also through the central nervous system (Armario, 2006). The HPA mediates the microbiota through the glucocorticoids released from adrenal cortex, cortisol in humans and corticosterone in rodents. Thus, the administration of *Lactobacillus* during the early stress period has been found to normalize basal corticosterone levels. Furthermore, the immune via of communication in the GBA can be mediated by the stress; the microbiota can influence the central nervous system via the immune system and enteric nervous system in the presence of stress (Foster & McVey Neufeld, 2013). In addition, glucocorticoids can also induce non-neuronal catecholamine enzymes which may add to the multiple signalling mechanisms of chronic stress exposure (Holzer et al., 2017).

Other pathway is the influence of microbiota on central nervous system functions directly through neuronal activation of stress circuits; specifically some food-borne pathogens have shown an activation of vagal pathways. Likewise, sensory neurons of the myenteric plexus in the enteric nervous system are the first point of contact for the intestinal microbiota residing in the gut lumen. These sensory neurons synapse on enteric motor neurons controlling gut motility. Moreover, there is anatomical evidence of closing, synaptic-like connections with vagal nerve endings in the gut (Foster, 2013).

The major response to stress is releasing glucocorticoid hormones, as mentioned, that leads to a range of biological effects, including immune modulation and energy metabolism. Permanently increased glucocorticoid levels are associated with reduced hippocampal volume and impairments in cognitive domains, such as memory, perception, and attention. Even, chronic stress has been found to induce alteration in various neurotransmitter systems and affect inflammatory cytokine expression (Wiley, 2017)

The immunological pathway is other via through the stress can modulate the microbiota from, since psychological stressors cause formation of proinflammatory cytokines. Hence, a clinical evidence is found in stress-related psychiatric disorders as patients with treatment-resistant major depression display highly elevated serum levels of IL-6 (Holzer, 2017).

Restoring the microbiota

Current research seems to indicate that it is possible to interact with this axis, even modulate the stress throughout the intestinal microbiota using probiotics, prebiotics, symbiotics and parabiotics, among others (Fond et al., 2015).

Probiotics

Probiotic is defined as a live bacterium which when administered in adequate amounts confers a health benefit on the host (WHO, 2001). Among the most commonly used are *Lactobacilli*, *Bifidobacteria* and *Saccharomyces boulardii*. The action mechanism supports the idea that these bacteria can compete against pathogen bacteria to join the host epithelial cells, thus improving its barrier function by inhibiting the pathogen growth and secreting antimicrobial peptides (Hardy et al., 2013).

Despite previous probiotic health claims have been exaggerated (Hoffmann et al., 2013; Sanders, 2016; Shanahan, 2002), it is particularly interesting to consider the possibility

that probiotics can affect emotion in health and disease by modulating the GMB and confer a health benefit in the host (Dinan et al., 2013). Therewith, animal studies have demonstrated that the administration of probiotics maintains mucosal barrier function under stressful situations and mitigates stress-induces glucocorticoid and inflammatory cytokine responses in association with a reduction of depression and anxiety-related behavior (Eutamene & Bueno, 2007; Kelly, 2015; Logan & Katzman, 2005; Mennigen & Bruewer, 2009).

Probiotics have also been shown to reduce the mRNA expression of the GABA receptor and c-Fos in the brain, possibly by modulating the GMB via vagal pathways. Same studies noted that probiotics have beneficial effects by alleviating psychological distress in healthy subjects and normalizing the stress-induced reduction of natural killer cell numbers and gastrointestinal symptoms (Akito Kato-Kataoka, Nishida, Takada, Kawai, et al., 2016). In this sense, some studies have shown that some probiotics can increase tryptophan levels in plasma, serotonin precursor, a neurotransmitter which modules brain functions such as emotion, cognition, motor function and pain process, as well as neuroendocrine functions such as food ingestion, circadian rhythms and reproductive activity (Desbonnet et al., 2008; Martinowich & Lu, 2008). Furthermore, probiotics have a catalytic activity over oligosaccharides, increasing short-chain fatty acids, which are capable of trespassing the hematoencephalic barrier, affecting the central nervous system and therefore the mood and behavior (Dinan, 2013; Macfabe, 2012; Ohland et al., 2013). To sum up, not only will it have positive effects in mental health but it will also increase the immune response or intestinal flora, reduce fecal enzymes related to cancer initiation, diarrhea, controlling colitis caused by rotavirus or *Clostridium* spp. and prevent ulcers related to *Helicobacter pylori* spp. (Kaur et al., 2002; Khoder et al., 2016).

Tillisch et al. (2013) investigated the effects of probiotics on brain function in healthy female participants on a 4-week chronic probiotic treatment, including *Bifidobacterium animalis* subspecies *Lactis*, *Streptococcus thermophiles*, *Lactobacillus bulgaricus*, and *Lactococcus lactis* subspecies *Lactis*. Reduced brain response to the emotional faces attention task, particularly in sensory and interoceptive regions, was evident in participants who ingested the probiotic. Besides, probiotic ingestion was also associated with changes in mid-brain connectivity, although no differences in mood were observed between the treatment groups (Malan-Muller et al., 2017; Tillisch et al., 2013).

Continuing with the gut microbiota structure, a number of studies have found that one approach used to alleviate the negative effects of stressor exposure on its structure is through prophylactic administration of probiotics. Certain probiotics, such as *Lactobacilli* spp. and *Bifidobacteria* spp. can modulate brain function and stress responses (Burokas et al., 2015; Dash et al., 2015; Forsythe & Kunze, 2013; G. R. Gibson & Roberfroid, 1995; Galland, 2014; Monteagudo-Mera et al., 2016; Neuman et al., 2015; Saulnier et al., 2013; Takada et al., 2016a; Zhou & Foster, 2015). In humans, for example, consumption of *Lactobacillus* spp. and *Bifidobacteria* spp. significantly reduced self-reported cognitive reactivity to sad mood in depressed individuals, thus alleviating stress-induced symptoms (Steenbergen et al., 2015). In addition, *Lactobacillus reuteri* administered to infants reduced colic and colic-associated maternal depression (Mi et al., 2018). Similarly, *Lactobacillus rhamnosus* reduced anxiety and depressive-like behavior and exaggerated HPA axis activation in rodent models (Bravo et al., 2011). On the other hand, *Lactobacillus farciminis* attenuated stress-evoked HPA responses (Afifa Ait-Belgnaoui et al., 2012; Rea et al., 2016; Sudo, 2014) and *Lactobacillus plantarum* attenuated early-life stress-induced depressive behavior (Liu et al., 2016). Finally, *Bifidobacterium*

longum was also reported to reduce anxiety-like behavior in the innately anxious BALBc mice (Savignac et al., 2014).

Prebiotics

Another approach that may yield long-term benefits to the gut microbiota structure is to administer prebiotics in the diet, specifically staring early in life (Schmidt et al., 2015). Prebiotics are defined as non-viable food components that confer a health benefit on the host associated with modulation of the microbiota (Glenn R. Gibson, 2008; Glenn R. Gibson et al., 2010; Hoseinifar et al., 2014; Roberfroid et al., 2010). Compounds that can enhance the growth of administered or commensal probiotic microbes are typically identified as prebiotics. For example, human milk oligosaccharides can be considered prebiotics, because they have been demonstrated to play a significant role in the growth of specific bacteria including probiotic members of the genus *Bifidobacterium* and *Lactobacillus* (Bindels et al., 2015; Coppa et al., 2006). Moreover, *Bifidobacterium* and *Lactobacillus* spp. strongly affect the GMB (Dinan, 2013; Zhou, 2015). Prebiotic-induced enhancement of these beneficial microbes is thought to have multiple beneficial effects on host immunity and physiology (Vandenplas et al., 2015). After ingestion, human milk oligosaccharides pass mainly unabsorbed through the small intestine into the colon, where they are fermented to short-chain fatty acids and lactic acids. These fatty acids act on G-protein-coupled receptors located along the GI tract to regulate energy homeostasis via the stimulation of leptin production in adipocytes, and the secretion of gut peptides from colonic enteroendocrine cells (Caporaso et al., 2011; Lach, 2018; Martín-Sosa et al., 2003; Ogawa et al., 1992; Witaicenis et al., 2010).

Conversely, additional dietary components lactoferrin and milk fat globule membrane can also affect the gut microbiota. A recent study reported an association between the concentration of human milk lactoferrin, which has antimicrobial properties, and the

abundance of *Bifidobacteria* and *Lactobacilli* in breast-fed infants (Mastromarino et al., 2014). Thus, lactoferrin may also help promote the growth of beneficial bacteria in the host, specifically in early-life. Furthermore, milk fat globule membrane also provides a variety of important nutritional, antimicrobial and cognitive benefits (Chatterton et al., 2013; Dewettinck et al., 2008; Timby et al., 2014). In this sense, some studies suggest that dietary prebiotic such these can have a positive influence in the gut microbiota and potentially promote stress resistance (Kelly, 2015; Sarao & Arora, 2017; Thompson et al., 2017).

Evidence also suggest that prebiotic galacto-oligosaccharides can improve intestinal barrier function in rats (Zhong et al., 2015). Moreover, mice treated with prebiotics exhibit improvements in intestinal permeability, tight junction integrity decreased plasma Lipopolysaccharides and cytokine levels in addition to decreased hepatic expression of inflammatory and oxidative stress markers (Cani et al., 2009).

Para-probiotics or ghost probiotics

Para-probiotics or ghost probiotics are non-living probiotic strains, resulting from exposure to high temperatures or irradiation, or some probiotic fractions (Taverniti & Guglielmetti, 2011). Fermentation is a biochemical process involving microorganisms being deliberately added to foods or occurring naturally in foods. The two main types of fermenting processes are alcoholic and lactic acid fermentation, which includes genera such as *Lactobacillus*, *Streptococcus*, *Enterococcus*, *Lactococcus*, *Bifidobacterium*, and *Leuconostoc*. Due to the fermentation process, fermented foods – such as sauerkraut, kichi, miso, soy sauce, tempeh, kombucha, kefir, cheese and yoghurt – contain three main functional components that may be present in varying amounts: functional microorganisms (probiotics), prebiotics and biogenics –metabolites that make fermented foods functionally active. Some or all of these components can influence the gut

microbiome composition and function, alter macronutrient breakdown and absorption, change gut permeability, and stimulate immune cells in the gut. Fermented foods have also been reported to have direct anti-inflammatory, immunomodulatory, and brain modulatory effects. For this reason, fermented foods may have the potential to modify depression and anxiety by altering the underlying pathways involved in the etiology of these common mental disorders (Aslam et al., 2018).

3. STRESS MODULATION THROUGH MICROBIOTA INTERVENTIONS

According to the relationship between microbiota and stress aforementioned, there are certain researches showing the modulation of stress through microbiota interventions, mainly with probiotics in both pre-clinical and clinical studies.

Preclinical evidence

The effects of microbiota interventions have been widely studied on emotional disorders, mainly on anxiety and depression disorders and on stress. Numerous studies have evaluated the effects of probiotics on emotional disorders (revised in Roman, Abalo et al., 2018). Others microbiota interventions, such as diet, prebiotics or fecal transplant have been less explored and the evidence is scant. The mainly preclinical evidence about the microbiota interventions on stress is summarized in Table 1.

INSERT TABLE 1 AROUND HERE

Probiotics

One of the first studies was carry out by Zareie et al. (2006) with rats exposed to a chronic stress in a model of chronic water avoidance stress (WAS) during 10 days. Probiotic treatment (*L. helveticus* and *L. rhamnosus* combination*)* reduced luminal bacterial adherence and translocation to the mesenteric lymph nodes after this chronic stress.

However, the probiotic supplementation has no effect in behavior. Another probiotic formulation, in this case of *L. helveticus* and *B. longum,* prevent abnormal brain plasticity and reduction in neurogenesis and attenuated the HPA response to chronic stress induced by WAS (A. Ait-Belgnaoui et al., 2014), whereas the administration of one of them alone is less effective to reduce this chronic stress (Afifa Ait-Belgnaoui et al., 2018). Similar results over HPA response have been observed after *L. casei*, which suppresses the increase in plasma corticosterone and the number of CRF-expressing cells (Takada et al., 2016b). Also, a symbiotic treatment has been found useful to reduce the effect observed in the intestinal morphology and permeability after acute stress (Takadanohara et al., 2012). *L. rhamnosus* as well *L. helveticus* have demonstrate its efficacy in other stress related disorders such as anxiety and depression (Bravo, 2011; Liang et al., 2015). Likewise, the ability of other *Lactobacillus* strain, *farciminis,* to prevent WAS-induced epithelial barrier impairment and visceral hypersensitivity has been proved (Silva et al., 2014).

The stress modulation through microbiota has been evaluated too in animals exposed to a protocol of early life stress, maternal separation (MS). This model also has been considered a model of depression where efficacy of probiotics to reversed the depressive phenotype has been demonstrated (Desbonnet et al., 2010). MS is an excellent model of brain-gut axis dysfunction for the study of disorders such as IBS, anxiety or depression (O'Mahony, 2011). García-Ródenas and co-workers (2006) evaluated if an adapted diet with prebiotic and probiotics could attenuate the negative effects of early stress. According to their results, the adapted diet was able to normalize gut permeability and further restore growth rate that had been impaired after early stress. In the same line, the administration of a mixture of two strains of *Lactobacillus* species normalised gut physiology and prevented bacterial attachment into the mucosa. Moreover, it was able to

revert the enhanced level of circulating corticosterone induced by MS (Gareau et al., 2007). Furthermore, a multispecies formulation (*L. rhamnosus* and *L. helveticus*) prevents accelerated emotional development in MS infants (C S M Cowan et al., 2016), as well prevents the precocious physical maturation observed in stressed females (Caitlin S M Cowan & Richardson, 2018). *L. rhamnosus* seems to be able to revert the effects of maternal stress in memory that are transmitted to the new generation (Callaghan et al., 2016). Another *Lactobacillus, L. fermentum,* increased exploratory behavior in an elevated plus maze, and reduced permeability in the small intestine and stress-induced by WAS and MS model (Vanhaecke et al., 2017). It is also interesting to note that probiotics seems to be a sex depended effect due to reduced WAS-induced colonic microinflammation in female rates but not in male rats (Lee et al., 2017).

Other stress models such as restraint and passive avoidance are employed to evaluated stress in adulthood and are associated with gut hypersensitivity in response to rectal distension in rats (Gué et al., 1997). Also, chronic stress in adulthood induced, gut-derived, pro-inflammatory milieu exacerbates the Parkinson disease via a dysfunctional microbiota-gut-brain axis (Dodiya et al., 2018). The colorectal distension induced by acute stress is reduced by *L. farciminis* (ait-belgnaoui et al., 2009) and prevented HPA axis stress response and increased hypothalamic expression of pro-inflammatory cytokines (Afifa Ait-Belgnaoui, 2012). Another probiotic, *Escherichia coli Nissle*, protects gastric mucosa against restraint stress due to antiinflammatory and vasodilatory actions involving heat-shock protein, prostaglandins and sensory afferent neurons (Konturek et al., 2009). Visceral sensitivity was analysed in rats subjected to partial restraint stress pre-treatment with fermented milk containing *Bifidobacterium lactis.* Probiotic product prevented the increase in intestinal permeability and restored colonic occluding (Agostini et al., 2012). Another *Bifidobacterium*, *pseudocatenulatum CECT*

7765, ameliorate the exaggerated HPA mediated stress response to acute physical and social stress observed in obese mice exposed to restraint (Agusti et al., 2018). Additionally, exposure to prolonged restraint significantly enhanced *C. rodentium* induced infectious colitis in resistant mice that is ameliorate by *L. reuteri* treatment although it did not reduce all the effects caused by the stress (Amy R. Mackos et al., 2013). *L. rhamnosus* also attenuates peripherally and centrally induced visceral hypersensitivity produced by restraint that is similar to IBS symptoms (Darbaky et al., 2017). Similar effects were observed after administration of *L. Reuteri* in mice exposed to prolonged restraint. This probiotic significantly attenuated the effects of stressor exposure on *C. Rodentium* exposed mice reducing colonic inflammation (A R Mackos et al., 2016) but not microbial community composition in a model of social disruption stress (Galley et al., 2017). One possibility could be that stressor affect in the same line that infection, so future studies should be evaluated the similarities in the composition of the microbiota between between stressor-induced and inflammation-induced (Galley, 2017). In the same line, the effects of a combination of several stressors, include restrain, are alleviated by a mixture of three probiotic strains (*L. helveticus R0052, L. plantarum R1012, and B. longum R0175*), reversing changes in microbiota composition caused by stress (Li et al., 2018). Nevertheless, the strains should be considered in future studies due to a reduction in stress reactivity following treatment with *L. rhamnosus* was observed in BALB/c but no in Swiss Webster mice (McVey Neufeld et al., 2018).

Recently, the forced swim test (FST) has been employed to evaluate the effect of ADR-159, a heat-killed fermentate generated by two *Lactobacillus* strains, on the acute stress in mice (Warda et al., 2019). Their results show that ADR-169 fed animals has lowers levels resting stress levels, showing a reduction in baseline corticosterone levels. Also, this sedative effects is associate with a little change in the composition of the microbiota,

characterized by a reduction of both *Alistipes* and *Odoribacter,* as well an increase of *Prevotella,* a similar pattern was observed in other researches about anxiety and microbiota (Bangsgaard Bendtsen et al., 2012).

Other microbiota interventions

The modulation of stress trough microbiota manipulations such as prebiotic, diet or fecal transplant have been less evaluated. In this sense, prebiotic composed by an enzyme-treated rice fiber has been shown efficacy reducing hypersensitivity induced by WAS (Larauche et al., 2012). IMO, a prebiotic that promote the growth of *Lactobacillus* and *Bifidobacterium*, is able to repairing stress injury on the ultrastructure of intestinal mucosal epithelial cells induced by WAS (Wang et al., 2017). In addition, the effects of prebiotics on consequences of chronic unpredictable social stress have been also evaluated. Specifically, a prebiotic combination of fructo-oligosaccharides and galacto-oligosaccharides protect to reduced social isolate caused by chronic stress (Burokas et al., 2017).

Tarr and co-workers evaluate the effect of two probiotics (3′SL and 6′SL) over modulation of social stressor in mice. Their results showed that the disruption in the composition of the intestinal microbiota associated to an stressor exposure (Bailey et al., 2010) is not observed in mice fed 6′SL or 3′SL (Tarr et al., 2015).

An early life supplementation of two prebiotics (galactooligosaccharide and polydextrose), and the glycoprotein lactoferrin suggested a differential effect of each diet, although all diets studied attenuate the effects on learned helplessness induced by stress, also alter gene expression in brain circuits implicated (Mika et al., 2017). A combination of prebiotic (polydextrose), probiotic (*L. rhamnosus*) and galactooligosaccharide, reduce the effects of MS in anxiety and memory (McVey Neufeld et al., 2017). Moreover, effects

of chronic stress could be potentiated by a high-fat-high-fructose diet, both promoted changes in intestinal proteins and increases in insulin resistance and plasma cholesterol (de Sousa Rodrigues et al., 2017).

On the other hand, SCFAs supplementation alleviates selective and long-lasting alterations induced by repeated psychosocial stress in mice. However, chronic stress-induced alterations in body weight gain, faecal SCFAs and the gene expression of the SCFA receptors remained unaffected by SCFA supplementation (van de Wouw et al., 2018). Similary, dietary manipulations with n-3 polyunsaturated fatty acids have behavioural effects in control but not early-life stressed rats (Pusceddu et al., 2015).

Finally, it is necessary to highlight that faecal transplantation might be a useful tool to treat different effects of chronic stress, preventing the elevation of plasma KC and IL-6 induced by stress, among others (Langgartner et al., 2018). Once said that, it is also necessary to explore in more detail this recent intervention.

Clinical evidence

Despite the widely evidence on preclinical studies, little is known about the clinical. As for preclinical evidence, the most used study intervention is the probiotic administration. Table 2 shows the clinical evidence about the different interventions on stress measures.

INSERT TABLE 2 AROUND HERE

Probiotics

As said, probiotics is the most used intervention exploring the microbiota modulation on stress. Diop and co-workers (2008) explored the effects of a probiotic preparation (Probio-Stick; *L. acidophilus and B. longum*) during 3 weeks on stress-induced symptoms in volunteers affected by daily stress with at least two symptoms induced by stress

(anxiety, nervousness, irritability, sleeping problems, gastrointestinal disturbances) during the last month. Results show that the probiotic used provided a beneficial effect on the gastrointestinal symptoms experienced by individuals affected by chronic stress.

In the double-blind, placebo-controlled, and parallel-group clinical trial conducted by (Kato-Kataoka, 2016a), the daily administration of a fermented milk, containing *L. casei* strain Shirota during 8 weeks in medical students previous to the exposition of a brief naturalistic stressor (academic examination), preserved the diversity of the gut microbiota and relieved the stress-associated psychological, physiological, and physical stress responses to prevent the onset of common abdominal dysfunction. In addition, *L. casei* strain Shirota may exert beneficial effects preventing the onset of physical symptoms in healthy subjects exposed to stressful situations (Kato-Kataoka et al., 2016b). In other clinical trial performed by Takada and coworkers (2016) in a large sample, the same intervention (*L. casei* strain Shirota, during 8 weeks) prevented hypersecretion of cortisol and physical symptoms under an academic exam, compared with placebo administration.

The treatment with *B. longum 1714* strain ameliorate both the physiological and psychological response to an acute stressor, as well as longer-term daily self-reported psychological stress, in healthy human adults exposed to the *cold pressor test* (Allen et al., 2016). However, the treatment with *L. Rhamnosus* has no a differential effect in the same model (Kelly et al., 2017). Recently, Papalini and co-workers have observed that the group treated with a multispecies probiotic showed an increased buffer against the negative effects of stress on working memory (Papalini et al., 2019).

On another population, patients scheduled for laryngectomy, probiotic administration (*Clostridium butyricum*) has shown to ameliorate the clinical anxiety and biochemical features of stress in compared with placebo administration (H. Yang et al., 2016). So

probiotics could be an effective anxiolytic previous a surgery intervention, although more research is required to understand this effect.

Other trials have not shown howbeit a positive effect of probiotics in the stress-modulation. Thus, the daily administration of a multistrain and multispecies probiotics probiotic ((*B. breve, B.longum, B. infantis, L. acidophilus, L. plantarum, L. paracasei, L. bulgaricus, and S. thermophilus)*) during 2 weeks have not shown an influence on psychological reactions to acute psychological stress during post stress recovery in young adults (Möller et al., 2017).

Other interventions

There is a scarce of evidence of other interventions and, for our knowledge, only a few studies have performed diet interventions and their impact on stress through the gut or microbiota modulation. The administration of dark chocolate (40g) during 2 weeks modifies the metabolism of free living and healthy human subjects, as per variation of both host and gut microbial metabolism. Specifically, dark chocolate reduced the urinary excretion of the stress hormone cortisol and catecholamines and partially normalized stress-related differences in energy metabolism (glycine, citrate, *trans*-aconitate, proline, alanine) and gut microbial activities (hippurate and *p*-cresol sulfate) (Martin, 2009). Curiously, the p-cresol is related with autism, which has been recently revised (Roman, Rueda-Ruzafa, et al., 2018).

Conclusions

This study sought to explore the impact of stress on gut-microbiota. According to the evidence, both clinical and preclinical, we can conclude that the influence of stress on gut-microbiota and gut-microbiota on stress modulation is clear through different stressors like a surgical intervention, academic examination or military training among

others (H. Yang, 2016; Karl et al., 2017; Kato-Kataoka, 2016a; Takada, 2016). Although the preclinical evidence is so extended, the clinical evidence is more limited and the actual challenge is translating the promising preclinical studies to healthy human participants with different stressors or different stress situations.

As specified, there are different microbiota modulation interventions. Notwithstanding, one of the most considerable interventions could be probiotics, given that the cumulative evidence. Future studies must consider aspects such as study design, intervention, adherence, safety assessment, strain specificity, bacterial quantification and microbial metabolites (Shane et al., 2010; Welch et al., 2011).

Lastly, a better understanding of the mechanism is needed, underlying the stress modulation through the microbiota. It may open new avenues for the design of therapeutics that could enhance the clinical benefits pursued, on stress and stress-related disorders such as anxiety and depression, both in healthy subjects and in different populations.

REFERENCES

Agostini, S., Goubern, M., Tondereau, V., Salvador-Cartier, C., Bezirard, V., Lévèque, M., … Eutamene, H. (2012). A marketed fermented dairy product containing Bifidobacterium lactis CNCM I-2494 suppresses gut hypersensitivity and colonic barrier disruption induced by acute stress in rats. *Neurogastroenterology & Motility*, *24*(4), 376-e172. https://doi.org/10.1111/j.1365-2982.2011.01865.x

Aguilera, M., Vergara, P., & Martínez, V. (2013). Stress and antibiotics alter luminal and wall-adhered microbiota and enhance the local expression of visceral sensory-related systems in mice. *Neurogastroenterology and Motility*, *25*(8), 515–529. https://doi.org/10.1111/nmo.12154

Agusti, A., Moya-Pérez, A., Campillo, I., Montserrat-de la Paz, S., Cerrudo, V., Perez-Villalba, A., & Sanz, Y. (2018). Bifidobacterium pseudocatenulatum CECT 7765 Ameliorates Neuroendocrine Alterations Associated with an Exaggerated Stress Response and Anhedonia in Obese Mice. *Molecular Neurobiology*, *55*(6), 5337–5352. https://doi.org/10.1007/s12035-017-0768-z

Ait-Belgnaoui, A., Colom, A., Braniste, V., Ramalho, L., Marrot, A., Cartier, C., … Tompkins, T. (2014). Probiotic gut effect prevents the chronic psychological stress-induced brain activity abnormality in mice. *Neurogastroenterology & Motility*, *26*(4), 510–520. https://doi.org/10.1111/nmo.12295

Ait-Belgnaoui, A., Durand, H., Cartier, C., Chaumaz, G., Eutamene, H., Ferrier, L., … Theodorou, V. (2012). Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. *Psychoneuroendocrinology*, *37*(11), 1885–1895. https://doi.org/10.1016/j.psyneuen.2012.03.024

Ait-Belgnaoui, A., Payard, I., Rolland, C., Harkat, C., Braniste, V., Théodorou, V., & Tompkins, T. A. (2018). Bifidobacterium longum and Lactobacillus helveticus Synergistically Suppress Stress-related Visceral Hypersensitivity Through Hypothalamic-Pituitary-Adrenal Axis Modulation. *Journal of Neurogastroenterology and Motility*, *24*(1), 138–146. https://doi.org/10.5056/jnm16167

ait-belgnaoui, a., eutamene, h., houdeau, e., bueno, l., fioramonti, j., & theodorou, v. (2009). *Lactobacillus farciminis* treatment attenuates stress-induced overexpression of Fos protein in spinal and supraspinal sites after colorectal distension in rats. *Neurogastroenterology & Motility*, *21*(5), 567-e19. https://doi.org/10.1111/j.1365-2982.2009.01280.x

Allen, A. P., Hutch, W., Borre, Y. E., Kennedy, P. J., Temko, A., Boylan, G., … Clarke, G. (2016). Bifidobacterium longum 1714 as a translational psychobiotic: modulation of stress, electrophysiology and neurocognition in healthy volunteers. *Translational Psychiatry*, *6*(11), e939. https://doi.org/10.1038/tp.2016.191

Armario, A. (2006). The hypothalamic-pituitary-adrenal axis: what can it tell us about stressors? *CNS & Neurological Disorders Drug Targets*, *5*(5), 485–501.

Aslam, H., Green, J., Jacka, F. N., Collier, F., Berk, M., Pasco, J., & Dawson, S. L. (2018). Fermented foods, the gut and mental health: a mechanistic overview with

implications for depression and anxiety. *Nutritional Neuroscience*, *0*(0), 1–13. https://doi.org/10.1080/1028415X.2018.1544332

Bailey, M. T., Dowd, S. E., Parry, N. M. A., Galley, J. D., Schauer, D. B., & Lyte, M. (2010). Stressor Exposure Disrupts Commensal Microbial Populations in the Intestines and Leads to Increased Colonization by Citrobacter rodentium. *Infection and Immunity*, *78*(4), 1509–1519. https://doi.org/10.1128/IAI.00862-09

Bangsgaard Bendtsen, K. M., Krych, L., Sørensen, D. B., Pang, W., Nielsen, D. S., Josefsen, K., … Hansen, A. K. (2012). Gut Microbiota Composition Is Correlated to Grid Floor Induced Stress and Behavior in the BALB/c Mouse. *PLoS ONE*, *7*(10), e46231. https://doi.org/10.1371/journal.pone.0046231

Bennett et al. (1998). Level of chronic life stress predicts clinical outcome in irritable bowel syndrome. *Gut*, *43*(2), 256–261. https://doi.org/10.1136/gut.43.2.256

Bercik, P., & Collins, S. M. (2014). The effects of inflammation, infection and antibiotics on the microbiota-gut-brain axis. *Advances in Experimental Medicine and Biology*, *817*, 279–289. https://doi.org/10.1007/978-1-4939-0897-4_13

Bernstein, C. N. (2017). The Brain-Gut Axis and Stress in Inflammatory Bowel Disease. *Gastroenterology Clinics of North America*, *46*(4), 839–846. https://doi.org/10.1016/j.gtc.2017.08.006

Bharwani, A., Mian, M. F., Surette, M. G., Bienenstock, J., Forsythe, P., & Bharwani et al. (2017). Oral treatment with Lactobacillus rhamnosus attenuates behavioural deficits and immune changes in chronic social stress. *BMC Medicine*, *15*(1), 1–14. https://doi.org/10.1186/s12916-016-0771-7

Bindels, L. B., Delzenne, N. M., Cani, P. D., & Walter, J. (2015). Towards a more comprehensive concept for prebiotics. *Nature Reviews. Gastroenterology & Hepatology*, *12*(5), 303–310. https://doi.org/10.1038/nrgastro.2015.47

Bravo, J. A., Forsythe, P., Chew, M. V, Escaravage, E., Savignac, H. M., Dinan, T. G., … Cryan, J. F. (2011). Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(38), 16050–16055. https://doi.org/10.1073/pnas.1102999108

Burokas, A., Arboleya, S., Moloney, R. D., Peterson, V. L., Murphy, K., Clarke, G., … Cryan, J. F. (2017). Targeting the Microbiota-Gut-Brain Axis: Prebiotics Have Anxiolytic and Antidepressant-like Effects and Reverse the Impact of Chronic Stress in Mice. *Biological Psychiatry*, *82*(7), 472–487. https://doi.org/10.1016/j.biopsych.2016.12.031

Burokas, A., Moloney, R. D., Dinan, T. G., & Cryan, J. F. (2015). Microbiota regulation of the Mammalian gut-brain axis. *Advances in Applied Microbiology*, *91*, 1–62. https://doi.org/10.1016/bs.aambs.2015.02.001

Callaghan, B. L., Cowan, C. S. M., & Richardson, R. (2016). Treating Generational Stress. *Psychological Science*, *27*(9), 1171–1180. https://doi.org/10.1177/0956797616653103

Cani, P. D., Possemiers, S., Van de Wiele, T., Guiot, Y., Everard, A., Rottier, O., … Delzenne, N. M. (2009). Changes in gut microbiota control inflammation in obese

mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut*, *58*(8), 1091–1103. https://doi.org/10.1136/gut.2008.165886

Caporaso, J. G., Lauber, C. L., Costello, E. K., Berg-Lyons, D., Gonzalez, A., Stombaugh, J., … Knight, R. (2011). Moving pictures of the human microbiome. *Genome Biology*, *12*(5), R50. https://doi.org/10.1186/gb-2011-12-5-r50

Chatterton, D. E. W., Nguyen, D. N., Bering, S. B., & Sangild, P. T. (2013). Anti-inflammatory mechanisms of bioactive milk proteins in the intestine of newborns. *The International Journal of Biochemistry & Cell Biology*, *45*(8), 1730–1747. https://doi.org/10.1016/j.biocel.2013.04.028

Coppa, G. V., Zampini, L., Galeazzi, T., & Gabrielli, O. (2006). Prebiotics in human milk: a review. *Digestive and Liver Disease: Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*, *38 Suppl 2*, S291-294. https://doi.org/10.1016/S1590-8658(07)60013-9

Cowan, C. S. M., Callaghan, B. L., & Richardson, R. (2016). The effects of a probiotic formulation (Lactobacillus rhamnosus and L. helveticus) on developmental trajectories of emotional learning in stressed infant rats. *Translational Psychiatry*, *6*(5), e823–e823. https://doi.org/10.1038/tp.2016.94

Cowan, C. S. M., & Richardson, R. (2018). Early-life stress leads to sex-dependent changes in pubertal timing in rats that are reversed by a probiotic formulation. *Developmental Psychobiology*. https://doi.org/10.1002/dev.21765

Cryan & Dinan. (2012). Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. *Nature Reviews Neuroscience*, *13*(10), 701–712. https://doi.org/10.1038/nrn3346

Darbaky, Y., Evrard, B., Patrier, S., Falenta, J., Garcin, S., Tridon, A., … Diop, L. (2017). Oral probiotic treatment of *Lactobacillus rhamnosus* Lcr35 ® prevents visceral hypersensitivity to a colonic inflammation and an acute psychological stress. *Journal of Applied Microbiology*, *122*(1), 188–200. https://doi.org/10.1111/jam.13320

Dash, S., Clarke, G., Berk, M., & Jacka, F. N. (2015). The gut microbiome and diet in psychiatry: focus on depression. *Current Opinion in Psychiatry*, *28*(1), 1–6. https://doi.org/10.1097/YCO.0000000000000117

De Palma, G., Collins, S. M., Bercik, P., & Verdu, E. F. (2014). The microbiota-gut-brain axis in gastrointestinal disorders: stressed bugs, stressed brain or both? *The Journal of Physiology*, *592*(14), 2989–2997. https://doi.org/10.1113/jphysiol.2014.273995

de Sousa Rodrigues, M. E., Bekhbat, M., Houser, M. C., Chang, J., Walker, D. I., Jones, D. P., … Tansey, M. G. (2017). Chronic psychological stress and high-fat high-fructose diet disrupt metabolic and inflammatory gene networks in the brain, liver, and gut and promote behavioral deficits in mice. *Brain, Behavior, and Immunity*, *59*, 158–172. https://doi.org/10.1016/j.bbi.2016.08.021

Desbonnet, L., Garrett, L., Clarke, G., Bienenstock, J., & Dinan, T. G. (2008). The probiotic Bifidobacteria infantis: An assessment of potential antidepressant properties in the rat. *Journal of Psychiatric Research*, *43*(2), 164–174. https://doi.org/10.1016/j.jpsychires.2008.03.009

Desbonnet, L., Garrett, L., Clarke, G., Kiely, B., Cryan, J. F., & Dinan, T. G. (2010). Effects of the probiotic Bifidobacterium infantis in the maternal separation model of depression. *Neuroscience*, *170*(4), 1179–1188. https://doi.org/10.1016/j.neuroscience.2010.08.005

Dewettinck, K., Van Bockstaele, F., Kühne, B., Van de Walle, D., Courtens, T., & Gellynck, X. (2008). Nutritional value of bread: influence of processing, food interaction and consumer perception. *JOURNAL OF CEREAL SCIENCE*, *48*(2), 243–257. https://doi.org/http://dx.doi.org/10.1016/j.jcs.2008.01.003

Dinan, T. G., Stanton, C., & Cryan, J. F. (2013). Psychobiotics: a novel class of psychotropic. *Biological Psychiatry*, *74*(10), 720–726. https://doi.org/10.1016/j.biopsych.2013.05.001

Diop, L., Guillou, S., & Durand, H. (2008). Probiotic food supplement reduces stress-induced gastrointestinal symptoms in volunteers: a double-blind, placebo-controlled, randomized trial. *Nutrition Research*, *28*(1), 1–5. https://doi.org/10.1016/j.nutres.2007.10.001

Dodiya, H. B., Forsyth, C. B., Voigt, R. M., Engen, P. A., Patel, J., Shaikh, M., … Keshavarzian, A. (2018). Chronic stress-induced gut dysfunction exacerbates Parkinson's disease phenotype and pathology in a rotenone-induced mouse model of Parkinson's disease. *Neurobiology of Disease*. https://doi.org/10.1016/j.nbd.2018.12.012

Eutamene, H., & Bueno, L. (2007). Role of probiotics in correcting abnormalities of colonic flora induced by stress. *Gut*, *56*(11), 1495–1497. https://doi.org/10.1136/gut.2007.124040

Fond, G., Boukouaci, W., Chevalier, G., Regnault, A., Eberl, G., Hamdani, N., … Leboyer, M. (2015). The "psychomicrobiotic": Targeting microbiota in major psychiatric disorders: A systematic review. *Pathologie Biologie*, *63*(1), 35–42. https://doi.org/10.1016/j.patbio.2014.10.003

Forsythe, P., & Kunze, W. A. (2013). Voices from within: gut microbes and the CNS. *Cellular and Molecular Life Sciences: CMLS*, *70*(1), 55–69. https://doi.org/10.1007/s00018-012-1028-z

Foster, J. A., & McVey Neufeld, K.-A. (2013). Gut–brain axis: how the microbiome influences anxiety and depression. *Trends in Neurosciences*, *36*(5), 305–312. https://doi.org/10.1016/j.tins.2013.01.005

Foster, J. A., Rinaman, L., & Cryan, J. F. (2017). Stress & the gut-brain axis: Regulation by the microbiome. *Neurobiology of Stress*, *7*, 124–136. https://doi.org/10.1016/j.ynstr.2017.03.001

Galland, L. (2014). The gut microbiome and the brain. *Journal of Medicinal Food*, *17*(12), 1261–1272. https://doi.org/10.1089/jmf.2014.7000

Galley, J. D., Mackos, A. R., Varaljay, V. A., & Bailey, M. T. (2017). Stressor exposure has prolonged effects on colonic microbial community structure in Citrobacter rodentium-challenged mice. *Scientific Reports*, *7*, 45012. https://doi.org/10.1038/srep45012

Garc??a-R??denas, C. L., Bergonzelli, G. E., Nutten, S., Schumann, A., Cherbut, C.,

Turini, M., … Corth??sy-Theulaz, I. (2006). Nutritional Approach to Restore Impaired Intestinal Barrier Function and Growth After Neonatal Stress in Rats. *Journal of Pediatric Gastroenterology and Nutrition*, *43*(1), 16–24. https://doi.org/10.1097/01.mpg.0000226376.95623.9f

Gareau, M. G., Jury, J., MacQueen, G., Sherman, P. M., & Perdue, M. H. (2007). Probiotic treatment of rat pups normalises corticosterone release and ameliorates colonic dysfunction induced by maternal separation. *Gut*, *56*(11), 1522–1528. https://doi.org/10.1136/gut.2006.117176

Gautam, A., Kumar, R., Chakraborty, N., Muhie, S., Hoke, A., Hammamieh, R., & Jett, M. (2018). Altered fecal microbiota composition in all male aggressor-exposed rodent model simulating features of post-traumatic stress disorder. *Journal of Neuroscience Research*, *96*(7), 1311–1323. https://doi.org/10.1002/jnr.24229

Gibson, G. R. (2008). Prebiotics as gut microflora management tools. *Journal of Clinical Gastroenterology*, *42 Suppl 2*, S75-79. https://doi.org/10.1097/MCG.0b013e31815ed097

Gibson, G. R., & Roberfroid, M. B. (1995). Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *The Journal of Nutrition*, *125*(6), 1401–1412. https://doi.org/10.1093/jn/125.6.1401

Gibson, G. R., Scott, K. P., Rastall, R. A., Tuohy, K. M., Hotchkiss, A., Dubert-Ferrandon, A., … Buddington, R. (2010). Dietary prebiotics: current status and new definition. *Food Science and Technology Bulletin: Functional Foods*, *7*, 1–19.

Grochowska, M., Wojnar, M., & Radkowski, M. (2018). The gut microbiota in neuropsychiatric disorders. *Acta Neurobiologiae Experimentalis*, *78*(2), 69–81.

Gué, M., Del Rio-Lacheze, C., Eutamene, H., Théodorou, V., Fioramonti, J., & Buéno, L. (1997). Stress-induced visceral hypersensitivity to rectal distension in rats: role of CRF and mast cells. *Neurogastroenterology and Motility : The Official Journal of the European Gastrointestinal Motility Society*, *9*(4), 271–279. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9430796

Gur, T. L., Shay, L., Palkar, A. V., Fisher, S., Varaljay, V. A., Dowd, S., & Bailey, M. T. (2017). Prenatal stress affects placental cytokines and neurotrophins, commensal microbes, and anxiety-like behavior in adult female offspring. *Brain, Behavior, and Immunity*, *64*, 50–58. https://doi.org/10.1016/j.bbi.2016.12.021

Gur, T. L., Worly, B. L., & Bailey, M. T. (2015). Stress and the Commensal Microbiota: Importance in Parturition and Infant Neurodevelopment. *Frontiers in Psychiatry*, *6*, 5. https://doi.org/10.3389/fpsyt.2015.00005

Hardy, H., Harris, J., Lyon, E., Beal, J., & Foey, A. D. (2013). Probiotics, prebiotics and immunomodulation of gut mucosal defences: homeostasis and immunopathology. *Nutrients*, *5*(6), 1869–1912. https://doi.org/10.3390/nu5061869

Hoffmann, C., Dollive, S., Grunberg, S., Chen, J., Li, H., Wu, G. D., … Bushman, F. D. (2013). Archaea and fungi of the human gut microbiome: correlations with diet and bacterial residents. *PloS One*, *8*(6), e66019. https://doi.org/10.1371/journal.pone.0066019

Holzer, P., Farzi, A., Hassan, A. M., Zenz, G., Jačan, A., & Reichmann, F. (2017).

Visceral Inflammation and Immune Activation Stress the Brain. *Frontiers in Immunology*, *8*, 1613. https://doi.org/10.3389/fimmu.2017.01613

Hoseinifar, S. H., Soleimani, N., & Ringø, E. (2014). Effects of dietary fructo-oligosaccharide supplementation on the growth performance, haemato-immunological parameters, gut microbiota and stress resistance of common carp (Cyprinus carpio) fry. *British Journal of Nutrition*, *112*(8), 1296–1302. https://doi.org/10.1017/S0007114514002037

Househam, A. M., Peterson, C. T., Mills, P. J., Chopra, D., & Househam et al. (2017). The Effects of Stress and Meditation on the Immune System, Human Microbiota, and Epigenetics. *Advances in Mind-Body Medicine*, *31*(4), 10–25.

Hyland. (2014). Microbiota-host interactions in irritable bowel syndrome: Epithelial barrier, immune regulation and brain-gut interactions. *World Journal of Gastroenterology*, *20*(27), 8859–8866. https://doi.org/10.3748/wjg.v20.i27.8859

Jafari, M., Salehi, M., Zardooz, H., & Rostamkhani, F. (2014). Response of liver antioxidant defense system to acute and chronic physical and psychological stresses in male rats. *EXCLI Journal*, *13*, 161–171.

Karl, J. P., Margolis, L. M., Madslien, E. H., Murphy, N. E., Castellani, J. W., Gundersen, Y., … Pasiakos, S. M. (2017). Changes in intestinal microbiota composition and metabolism coincide with increased intestinal permeability in young adults under prolonged physiological stress. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, *312*(6), G559–G571. https://doi.org/10.1152/ajpgi.00066.2017

Kato-Kataoka, A., Nishida, K., Takada, M., Kawai, M., Kikuchi-Hayakawa, H., Suda, K., … Rokutan, K. (2016). Fermented Milk Containing Lactobacillus casei Strain Shirota Preserves the Diversity of the Gut Microbiota and Relieves Abdominal Dysfunction in Healthy Medical Students Exposed to Academic Stress. *Applied and Environmental Microbiology*, *82*(12), 3649–3658. https://doi.org/10.1128/AEM.04134-15

Kato-Kataoka, A., Nishida, K., Takada, M., Suda, K., Kawai, M., Shimizu, K., … Rokutan, K. (2016). Fermented milk containing Lactobacillus casei strain Shirota prevents the onset of physical symptoms in medical students under academic examination stress. *Beneficial Microbes*, *7*(2), 153–156. https://doi.org/10.3920/BM2015.0100

Kato-Kataoka, A., Nishida, K., Takada, M., Suda, K., Kawai, M., Shimizu, K., … Rokutan, K. (2016). Fermented milk containing *Lactobacillus casei* strain Shirota prevents the onset of physical symptoms in medical students under academic examination stress. *Beneficial Microbes*, *7*(2), 153–156. https://doi.org/10.3920/BM2015.0100

Kaur, I. P., Chopra, K., & Saini, A. (2002). Probiotics: potential pharmaceutical applications. *Eur J Pharm Sci.*, *15*(1), 1–9.

Kelly, J. R., Allen, A. P., Temko, A., Hutch, W., Kennedy, P. J., Farid, N., … Dinan, T. G. (2017). Lost in translation? The potential psychobiotic Lactobacillus rhamnosus (JB-1) fails to modulate stress or cognitive performance in healthy male subjects. *Brain, Behavior, and Immunity*, *61*, 50–59.

https://doi.org/10.1016/j.bbi.2016.11.018

Kelly, J. R., Kennedy, P. J., Cryan, J. F., Dinan, T. G., Clarke, G., & Hyland, N. P. (2015). Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Frontiers in Cellular Neuroscience*, *9*, 392. https://doi.org/10.3389/fncel.2015.00392

Khoder, G., Al-Menhali, A. A., Al-Yassir, F., & Karam, S. M. (2016). Potential role of probiotics in the management of gastric ulcer. *Experimental and Therapeutic Medicine*, *12*(1), 3–17. https://doi.org/10.3892/etm.2016.3293

Kochhar, S., & Martin, F.-P. (2015). *Metabonomics and Gut Microbiota in Nutrition and Disease* (1st ed.). Springer Publishing Company.

Konturek, P. C., Sliwowski, Z., Koziel, J., Ptak-Belowska, A., Burnat, G., Brzozowski, T., & Konturek, S. J. (2009). Probiotic bacteria Escherichia coli strain Nissle 1917 attenuates acute gastric lesions induced by stress. *Journal of Physiology and Pharmacology : An Official Journal of the Polish Physiological Society*, *60 Suppl 6*, 41–48. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20224150

Lach, G., Schellekens, H., Dinan, T. G., & Cryan, J. F. (2018). Anxiety, Depression, and the Microbiome: A Role for Gut Peptides. *Neurotherapeutics*, *15*(1), 36–59. https://doi.org/10.1007/s13311-017-0585-0

Langgartner, D., Vaihinger, C. A., Haffner-Luntzer, M., Kunze, J. F., Weiss, A.-L. J., Foertsch, S., … Reber, S. O. (2018). The Role of the Intestinal Microbiome in Chronic Psychosocial Stress-Induced Pathologies in Male Mice. *Frontiers in Behavioral Neuroscience*, *12*, 252. https://doi.org/10.3389/fnbeh.2018.00252

Larauche, M., Mulak, A., Yuan, P.-Q., Kanauchi, O., & Taché, Y. (2012). Stress-induced visceral analgesia assessed non-invasively in rats is enhanced by prebiotic diet. *World Journal of Gastroenterology*, *18*(3), 225. https://doi.org/10.3748/wjg.v18.i3.225

Le, C. P., Nowell, C. J., Kim-Fuchs, C., Botteri, E., Hiller, J. G., Ismail, H., … Sloan, E. K. (2016). Chronic stress in mice remodels lymph vasculature to promote tumour cell dissemination. *Nature Communications*, *7*. https://doi.org/10.1038/ncomms10634

Lee, J. Y., Kim, N., Nam, R. H., Sohn, S. H., Lee, S. M., Choi, D., … Lee, D. H. (2017). Probiotics reduce repeated water avoidance stress-induced colonic microinflammation in Wistar rats in a sex-specific manner. *PLOS ONE*, *12*(12), e0188992. https://doi.org/10.1371/journal.pone.0188992

Lennon, E. M., Maharshak, N., Elloumi, H., Borst, L., Plevy, S. E., & Moeser, A. J. (2013). Early life stress triggers persistent colonic barrier dysfunction and exacerbates colitis in adult IL-10-/-Mice. *Inflammatory Bowel Diseases*, *19*(4), 712–719. https://doi.org/10.1097/MIB.0b013e3182802a4e

Li, N., Wang, Q., Wang, Y., Sun, A., Lin, Y., Jin, Y., & Li, X. (2018). Oral Probiotics Ameliorate the Behavioral Deficits Induced by Chronic Mild Stress in Mice via the Gut Microbiota-Inflammation Axis. *Frontiers in Behavioral Neuroscience*, *12*, 266. https://doi.org/10.3389/fnbeh.2018.00266

Liang, S., Wang, T., Hu, X., Luo, J., Li, W., Wu, X., … Jin, F. (2015). Administration of

Lactobacillus helveticus NS8 improves behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress. *Neuroscience*, *310*, 561–577. https://doi.org/10.1016/j.neuroscience.2015.09.033

Liu, Y.-W., Liu, W.-H., Wu, C.-C., Juan, Y.-C., Wu, Y.-C., Tsai, H.-P., … Tsai, Y.-C. (2016). Psychotropic effects of Lactobacillus plantarum PS128 in early life-stressed and naïve adult mice. *Brain Research*, *1631*, 1–12. https://doi.org/10.1016/j.brainres.2015.11.018

Logan, A. C., & Katzman, M. (2005). Major depressive disorder: probiotics may be an adjuvant therapy. *Medical Hypotheses*, *64*(3), 533–538. https://doi.org/10.1016/j.mehy.2004.08.019

Macfabe, D. F. (2012). Short-chain fatty acid fermentation products of the gut microbiome: implications in autism spectrum disorders. *Microbial Ecology in Health and Disease*, *23*. https://doi.org/10.3402/mehd.v23i0.19260

Mackos, A. R., Eubank, T. D., Parry, N. M. A., & Bailey, M. T. (2013). Probiotic Lactobacillus reuteri Attenuates the Stressor-Enhanced Severity of Citrobacter rodentium Infection. *Infection and Immunity*, *81*(9), 3253–3263. https://doi.org/10.1128/IAI.00278-13

Mackos, A. R., Galley, J. D., Eubank, T. D., Easterling, R. S., Parry, N. M., Fox, J. G., … Bailey, M. T. (2016). Social stress-enhanced severity of Citrobacter rodentium-induced colitis is CCL2-dependent and attenuated by probiotic Lactobacillus reuteri. *Mucosal Immunology*, *9*(2), 515–526. https://doi.org/10.1038/mi.2015.81

Mackos, A. R., Varaljay, V. A., Maltz, R., Gur, T. L., & Bailey, M. T. (2016). Role of the Intestinal Microbiota in Host Responses to Stressor Exposure. In *International review of neurobiology* (Vol. 131, pp. 1–19). https://doi.org/10.1016/bs.irn.2016.08.002

Malan-Muller, S., Valles-Colomer, M., Raes, J., Lowry, C. A., Seedat, S., & Hemmings, S. M. J. (2017). The Gut Microbiome and Mental Health: Implications for Anxiety- and Trauma-Related Disorders. *OMICS: A Journal of Integrative Biology*, *21*(0), omi.2017.0077. https://doi.org/10.1089/omi.2017.0077

Maltz, R. M., Keirsey, J., Kim, S. C., Mackos, A. R., Gharaibeh, R. Z., Moore, C. C., … Bailey, M. T. (2018). Prolonged restraint stressor exposure in outbred CD-1 mice impacts microbiota, colonic inflammation, and short chain fatty acids. *PLOS ONE*, *13*(5), e0196961. https://doi.org/10.1371/journal.pone.0196961

Martín-Sosa, S., Martín, M. J., García-Pardo, L. A., & Hueso, P. (2003). Sialyloligosaccharides in human and bovine milk and in infant formulas: variations with the progression of lactation. *Journal of Dairy Science*, *86*(1), 52–59. https://doi.org/10.3168/jds.S0022-0302(03)73583-8

Martin, F.-P. J., Rezzi, S., Peré-Trepat, E., Kamlage, B., Collino, S., Leibold, E., … Kochhar, S. (2009). Metabolic Effects of Dark Chocolate Consumption on Energy, Gut Microbiota, and Stress-Related Metabolism in Free-Living Subjects. *Journal of Proteome Research*, *8*(12), 5568–5579. https://doi.org/10.1021/pr900607v

Martinowich, K., & Lu, B. (2008). Interaction between BDNF and serotonin: role in mood disorders. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *33*(1), 73–83.

https://doi.org/10.1038/sj.npp.1301571

Mastromarino, P., Capobianco, D., Campagna, G., Laforgia, N., Drimaco, P., Dileone, A., & Baldassarre, M. E. (2014). Correlation between lactoferrin and beneficial microbiota in breast milk and infant's feces. *Biometals: An International Journal on the Role of Metal Ions in Biology, Biochemistry, and Medicine*, *27*(5), 1077–1086. https://doi.org/10.1007/s10534-014-9762-3

Mayer. (2000). Inflammatory mediators in human acute pancreatitis: Clinical and pathophysiological implications. *Gut*, *47*(4), 546–552. https://doi.org/10.1136/gut.47.4.546

Mayer, E. A., Tillisch, K., Gupta, A., Mayer, E. E. A., Rhee, S., Pothoulakis, C., … Ley, R. (2015). Gut/brain axis and the microbiota. *Journal of Clinical Investigation*, *125*(3). https://doi.org/10.1172/JCI76304

McEwen, B. S. (2003). Mood disorders and allostatic load. *Biological Psychiatry*, *54*(3), 200–207. https://doi.org/10.1016/S0006-3223(03)00177-X

McVey Neufeld, K.-A., Kay, S., & Bienenstock, J. (2018). Mouse Strain Affects Behavioral and Neuroendocrine Stress Responses Following Administration of Probiotic Lactobacillus rhamnosus JB-1 or Traditional Antidepressant Fluoxetine. *Frontiers in Neuroscience*, *12*, 294. https://doi.org/10.3389/fnins.2018.00294

McVey Neufeld, K.-A., O'Mahony, S. M., Hoban, A. E., Waworuntu, R. V., Berg, B. M., Dinan, T. G., & Cryan, J. F. (2017). Neurobehavioural effects of *Lactobacillus rhamnosus* GG alone and in combination with prebiotics polydextrose and galactooligosaccharide in male rats exposed to early-life stress. *Nutritional Neuroscience*, 1–10. https://doi.org/10.1080/1028415X.2017.1397875

Mellman, T. A., & Hipolito, M. M. S. (2006). Sleep disturbances in the aftermath of trauma and posttraumatic stress disorder. *CNS Spectrums*, *11*(8), 611–615. https://doi.org/10.1017/S1092852900013663

Mennigen, R., & Bruewer, M. (2009). Effect of probiotics on intestinal barrier function. *Annals of the New York Academy of Sciences*, *1165*, 183–189. https://doi.org/10.1111/j.1749-6632.2009.04059.x

Mi, L., Yang, B., Hu, X., Luo, Y., Liu, J., Yu, Z., & Wang, J. (2018). Comparative Analysis of the Microbiota Between Sheep Rumen and Rabbit Cecum Provides New Insight Into Their Differential Methane Production. *Frontiers in Microbiology*, *9*. https://doi.org/10.3389/fmicb.2018.00575

Mika, A., Day, H. E. W., Martinez, A., Rumian, N. L., Greenwood, B. N., Chichlowski, M., … Fleshner, M. (2017). Early life diets with prebiotics and bioactive milk fractions attenuate the impact of stress on learned helplessness behaviours and alter gene expression within neural circuits important for stress resistance. *European Journal of Neuroscience*, *45*(3), 342–357. https://doi.org/10.1111/ejn.13444

Möller, C. M., Olsa, E. J. A., Ginty, A. T., Rapelje, A. L., Tindall, C. L., Holesh, L. A., … Conklin, S. M. (2017). Influence of Acute Multispecies and Multistrain Probiotic Supplementation on Cardiovascular Function and Reactivity to Psychological Stress in Young Adults. *Psychosomatic Medicine*, *79*(8), 914–919. https://doi.org/10.1097/PSY.0000000000000489

Moloney, R. D., Johnson, A. C., O'Mahony, S. M., Dinan, T. G., Greenwood-Van Meerveld, B., & Cryan, J. F. (2016). Stress and the Microbiota-Gut-Brain Axis in Visceral PaRelevance to Irritable Bowel Syndrome. *CNS Neuroscience and Therapeutics*, *22*(2), 102–117. https://doi.org/10.1111/cns.12490

Moloney, R. D., O'Leary, O. F., Felice, D., Bettler, B., Dinan, T. G., & Cryan, J. F. (2012). Early-life stress induces visceral hypersensitivity in mice. *Neuroscience Letters*, *512*(2), 99–102. https://doi.org/10.1016/j.neulet.2012.01.066

Monteagudo-Mera, A., Arthur, J. C., Jobin, C., Keku, T., Bruno-Barcena, J. M., & Azcarate-Peril, M. . (2016). High purity galacto-oligosaccharides (GOS) enhance specific Bifidobacterium species and their metabolic activity in the mouse gut microbiome. *Beneficial Microbes*, *7*(2), 247–264. https://doi.org/10.3920/BM2015.0114

Mountzouris, K. C., Dalaka, E., Palamidi, I., Paraskeuas, V., Demey, V., Theodoropoulos, G., & Fegeros, K. (2015). Evaluation of yeast dietary supplementation in broilers challenged or not with Salmonella on growth performance, cecal microbiota composition and Salmonella in ceca, cloacae and carcass skin. *Poultry Science*, *94*(10), 2445–2455. https://doi.org/10.3382/ps/pev243

Naliboff, B. D., Mayer, M., Fass, R., Fitzgerald, L. Z., Chang, L., Bolus, R., & Mayer, E. A. (2004). The effect of life stress on symptoms of heartburn. *Psychosomatic Medicine*, *66*(3), 426–434. https://doi.org/10.1097/01.psy.0000124756.37520.84

Neuman, H., Debelius, J. W., Knight, R., & Koren, O. (2015). Microbial endocrinology: the interplay between the microbiota and the endocrine system. *FEMS Microbiology Reviews*, *39*(4), 509–521. https://doi.org/10.1093/femsre/fuu010

O'Mahony, S. M., Hyland, N. P., Dinan, T. G., & Cryan, J. F. (2011). Maternal separation as a model of brain-gut axis dysfunction. *Psychopharmacology*, *214*(1), 71–88. https://doi.org/10.1007/s00213-010-2010-9

Ogawa, K., Ben, R. A., Pons, S., de Paolo, M. I., & Bustos Fernández, L. (1992). Volatile fatty acids, lactic acid, and pH in the stools of breast-fed and bottle-fed infants. *Journal of Pediatric Gastroenterology and Nutrition*, *15*(3), 248–252.

Ohland, C. L., & Jobin, C. (2015). Microbial Activities and Intestinal Homeostasis: A Delicate Balance Between Health and Disease. *Cellular and Molecular Gastroenterology and Hepatology*, *1*(1), 28–40. https://doi.org/10.1016/j.jcmgh.2014.11.004

Ohland, C. L., Kish, L., Bell, H., Thiesen, A., Hotte, N., Pankiv, E., & Madsen, K. L. (2013). Effects of Lactobacillus helveticus on murine behavior are dependent on diet and genotype and correlate with alterations in the gut microbiome. *Psychoneuroendocrinology*, *38*(9), 1738–1747. https://doi.org/10.1016/j.psyneuen.2013.02.008

Papalini, S., Michels, F., Kohn, N., Wegman, J., van Hemert, S., Roelofs, K., … Aarts, E. (2019). Stress matters: Randomized controlled trial on the effect of probiotics on neurocognition. *Neurobiology of Stress*, *10*, 100141. https://doi.org/10.1016/J.YNSTR.2018.100141

Penninx et al. (2013). Understanding the somatic consequences of depression: Biological

mechanisms and the role of depression symptom profile. *BMC Medicine*, *11*(1), 1. https://doi.org/10.1186/1741-7015-11-129

Petridou, E. T., Kousoulis, A. A., Michelakos, T., Papathoma, P., Dessypris, N., Papadopoulos, F. C., & Stefanadis, C. (2016). Folate and B12 serum levels in association with depression in the aged: a systematic review and meta-analysis. *Aging and Mental Health*, *20*(9), 965–973. https://doi.org/10.1080/13607863.2015.1049115

Pusceddu, M. M., Kelly, P., Ariffin, N., Cryan, J. F., Clarke, G., & Dinan, T. G. (2015). n-3 PUFAs have beneficial effects on anxiety and cognition in female rats: Effects of early life stress. *Psychoneuroendocrinology*, *58*, 79–90. https://doi.org/10.1016/j.psyneuen.2015.04.015

Qin. (2014). Impact of psychological stress on irritable bowel syndrome. *World Journal of Gastroenterology*, *20*(39), 14126–14131. https://doi.org/10.3748/wjg.v20.i39.14126

Rea, K., Dinan, T. G., & Cryan, J. F. (2016). The microbiome: A key regulator of stress and neuroinflammation. *Neurobiology of Stress*, *4*, 23–33. https://doi.org/10.1016/j.ynstr.2016.03.001

Rea, K., Dinan, T. G., & Cryan, J. F. (2017). The Brain-Gut Axis Contributes to Neuroprogression in Stress-Related Disorders. *Modern Trends in Pharmacopsychiatry*, *31*, 152–161. https://doi.org/10.1159/000470813

Roberfroid, M., Gibson, G. R., Hoyles, L., McCartney, A. L., Rastall, R., Rowland, I., … Meheust, A. (2010). Prebiotic effects: metabolic and health benefits. *The British Journal of Nutrition*, *104 Suppl*, S1-63. https://doi.org/10.1017/S0007114510003363

Roman, P., Abalo, R., Marco, E. M., & Cardona, D. (2018). Probiotics in digestive , emotional , and pain-related disorders. *Wolters Kluwer Health, INC*, *0*(0), 1–19. https://doi.org/10.1097/FBP.0000000000000385

Roman, P., Rueda-Ruzafa, L., Cardona, D., & Cortes-Rodríguez, A. (2018). Gut–brain axis in the executive function of austism spectrum disorder. *Behavioural Pharmacology*, *29*(7), 654–663. https://doi.org/10.1097/FBP.0000000000000428

Rothbaum & Foa. (2002). Smallpox, October 1945, *346*(17), 1329–1336. https://doi.org/10.1056/NEJM200204253461716

Sanders, M. E. (2016). Probiotics and microbiota composition. *BMC Medicine*, *14*. https://doi.org/10.1186/s12916-016-0629-z

Sarao, L. K., & Arora, M. (2017). Probiotics, prebiotics, and microencapsulation: A review. *Critical Reviews in Food Science and Nutrition*, *57*(2), 344–371. https://doi.org/10.1080/10408398.2014.887055

Saulnier, D. M., Ringel, Y., Heyman, M. B., Foster, J. A., Bercik, P., Shulman, R. J., … Guarner, F. (2013). The intestinal microbiome, probiotics and prebiotics in neurogastroenterology. *Gut Microbes*, *4*(1), 17–27. https://doi.org/10.4161/gmic.22973

Savignac, H. M., Kiely, B., Dinan, T. G., & Cryan, J. F. (2014). Bifidobacteria exert strain-specific effects on stress-related behavior and physiology in BALB/c mice.

Neurogastroenterology and Motility : The Official Journal of the European Gastrointestinal Motility Society, *26*(11), 1615–1627. https://doi.org/10.1111/nmo.12427

Savin, Z., Kivity, S., Yonath, H., & Yehuda, S. (2018). Smoking and the intestinal microbiome. *Archives of Microbiology*, *200*(5), 677–684. https://doi.org/10.1007/s00203-018-1506-2

Schmidt, K., Cowen, P. J., Harmer, C. J., Tzortzis, G., Errington, S., & Burnet, P. W. J. (2015). Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers. *Psychopharmacology*, *232*(10), 1793–1801. https://doi.org/10.1007/s00213-014-3810-0

Schnorr, S. L., & Bachner, H. A. (2016). Integrative Therapies in Anxiety Treatment. *Yale Journal of Biology and Medicine*, *89*, 397–422. https://doi.org/10.1016/0145-305X(84)90006-5

Selye, H. (1985). The nature of stress. *Basal Facts*, *7*(1), 3–11.

Shanahan, F. (2002). The host-microbe interface within the gut. *Best Practice & Research. Clinical Gastroenterology*, *16*(6), 915–931.

Shane, A. L., Cabana, M. D., Ellis, C. L., Heimbach, J. T., Hempel, S., Hummelen, R., … Vidry, S. (2010). Guide to designing, conducting, publishing, and communicating results of clinical studies involving probiotic applications in human participants. *Gut Microbes*, *1*(4), 243–253. https://doi.org/10.4161/gmic.1.4.12707

Sherwin, E., Rea, K., Dinan, T. G., & Cryan, J. F. (2016). A gut (microbiome) feeling about the brain. *Current Opinion in Gastroenterology*, *32*(2), 96–102. https://doi.org/10.1097/MOG.0000000000000244

Silva, S. Da, Robbe-Masselot, C., Ait-Belgnaoui, A., Mancuso, A., Mercade-Loubière, M., Salvador-Cartier, C., … Mercier-Bonin, M. (2014). Stress disrupts intestinal mucus barrier in rats via mucin *O* -glycosylation shift: prevention by a probiotic treatment. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, *307*(4), G420–G429. https://doi.org/10.1152/ajpgi.00290.2013

Smith, F., Clark, J. E., Overman, B. L., Tozel, C. C., Huang, J. H., Rivier, J. E. F., … Moeser, A. J. (2010). Early weaning stress impairs development of mucosal barrier function in the porcine intestine. *AJP: Gastrointestinal and Liver Physiology*, *298*(3), G352–G363. https://doi.org/10.1152/ajpgi.00081.2009

Smith et al. (2006). The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. *Dialogues in Clinical Neuroscience*, *8*(4), 383–395.

Söderholm, J. D., Yates, D. A., Gareau, M. G., Yang, P.-C., MacQueen, G., & Perdue, M. H. (2002). Neonatal maternal separation predisposes adult rats to colonic barrier dysfunction in response to mild stress. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, *283*(6), G1257–G1263. https://doi.org/10.1152/ajpgi.00314.2002

Steenbergen, L., Sellaro, R., van Hemert, S., Bosch, J. A., & Colzato, L. S. (2015). A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. *Brain, Behavior, and Immunity*, *48*, 258–264. https://doi.org/10.1016/j.bbi.2015.04.003

Sudo, N. (2014). Microbiome, HPA axis and production of endocrine hormones in the gut. *Advances in Experimental Medicine and Biology*, *817*, 177–194. https://doi.org/10.1007/978-1-4939-0897-4_8

Sukoh, N., Yamamoto, H., & Ohizumi, S. (1998). An Autopsied Case of Pulmonary Infarction Associated with Small Gastric Cancer. *Japanese Journal of Chest Diseases*, *57*(5), 413–414. https://doi.org/10.1079/BJN2002563

Takada, M., Nishida, K., Kataoka-Kato, A., Gondo, Y., Ishikawa, H., Suda, K., … Rokutan, K. (2016a). Probiotic *Lactobacillus casei* strain Shirota relieves stress-associated symptoms by modulating the gut-brain interaction in human and animal models. *Neurogastroenterology & Motility*, *28*(7), 1027–1036. https://doi.org/10.1111/nmo.12804

Takada, M., Nishida, K., Kataoka-Kato, A., Gondo, Y., Ishikawa, H., Suda, K., … Rokutan, K. (2016b). Probiotic *Lactobacillus casei* strain Shirota relieves stress-associated symptoms by modulating the gut-brain interaction in human and animal models. *Neurogastroenterology & Motility*, *28*(7), 1027–1036. https://doi.org/10.1111/nmo.12804

Takadanohara, H., Catanzaro, R., Chui, D. H., He, F., Yadav, H., Ganguli, A., … Marotta, F. (2012). Beneficial effect of a symbiotic preparation with S. boulardii lysate in mild stress-induced gut hyper-permeability. *Acta Bio-Medica : Atenei Parmensis*, *83*(3), 208–216. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23762997

Tarr, A. J., Galley, J. D., Fisher, S. E., Chichlowski, M., Berg, B. M., & Bailey, M. T. (2015). The prebiotics 3'Sialyllactose and 6'Sialyllactose diminish stressor-induced anxiety-like behavior and colonic microbiota alterations: Evidence for effects on the gut-brain axis. *Brain, Behavior, and Immunity*, *50*, 166–177. https://doi.org/10.1016/j.bbi.2015.06.025

Taverniti, V., & Guglielmetti, S. (2011). The immunomodulatory properties of probiotic microorganisms beyond their viability (ghost probiotics: proposal of paraprobiotic concept). *Genes & Nutrition*, *6*(3), 261–274. https://doi.org/10.1007/s12263-011-0218-x

Thompson, R. S., Roller, R., Mika, A., Greenwood, B. N., Knight, R., Chichlowski, M., … Fleshner, M. (2017). Dietary Prebiotics and Bioactive Milk Fractions Improve NREM Sleep, Enhance REM Sleep Rebound and Attenuate the Stress-Induced Decrease in Diurnal Temperature and Gut Microbial Alpha Diversity. *Frontiers in Behavioral Neuroscience*, *10*(January), 1–16. https://doi.org/10.3389/fnbeh.2016.00240

Tillisch, K., Labus, J., Kilpatrick, L., Jiang, Z., Stains, J., Ebrat, B., … Mayer, E. A. (2013). Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology*, *144*(7), 1394–1401, 1401-4. https://doi.org/10.1053/j.gastro.2013.02.043

Timby, N., Domellöf, E., Hernell, O., Lönnerdal, B., & Domellöf, M. (2014). Neurodevelopment, nutrition, and growth until 12 mo of age in infants fed a low-energy, low-protein formula supplemented with bovine milk fat globule membranes: a randomized controlled trial. *The American Journal of Clinical Nutrition*, *99*(4), 860–868. https://doi.org/10.3945/ajcn.113.064295

van de Wouw, M., Boehme, M., Lyte, J. M., Wiley, N., Strain, C., O'Sullivan, O., … Cryan, J. F. (2018). Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain-gut axis alterations. *The Journal of Physiology*, *596*(20), 4923–4944. https://doi.org/10.1113/JP276431

Vandenplas, Y., Abkari, A., Bellaiche, M., Benninga, M., Chouraqui, J. P., Çokura, F., … Thapar, N. (2015). Prevalence and Health Outcomes of Functional Gastrointestinal Symptoms in Infants From Birth to 12 Months of Age. *Journal of Pediatric Gastroenterology and Nutrition*, *61*(5), 531–537. https://doi.org/10.1097/MPG.0000000000000949

Vanhaecke, T., Aubert, P., Grohard, P.-A., Durand, T., Hulin, P., Paul-Gilloteaux, P., … Neunlist, M. (2017). *L. fermentum CECT 5716* prevents stress-induced intestinal barrier dysfunction in newborn rats. *Neurogastroenterology & Motility*, *29*(8), e13069. https://doi.org/10.1111/nmo.13069

Venkova et al. (2010). Exposure of the amygdala to elevated levels of corticosterone alters colonic motility in response to acute psychological stress. *Neuropharmacology*, *58*(7), 1161–1167. https://doi.org/10.1016/j.neuropharm.2010.02.012

Wang, W., Xin, H., Fang, X., Dou, H., Liu, F., Huang, D., … Ke, M. (2017). Isomalto-oligosaccharides ameliorate visceral hyperalgesia with repair damage of ileal epithelial ultrastructure in rats. *PloS One*, *12*(4), e0175276. https://doi.org/10.1371/journal.pone.0175276

Warda, A. K., Rea, K., Fitzgerald, P., Hueston, C., Gonzalez-Tortuero, E., Dinan, T. G., & Hill, C. (2019). Heat-killed lactobacilli alter both microbiota composition and behaviour. *Behavioural Brain Research*, *362*, 213–223. https://doi.org/10.1016/J.BBR.2018.12.047

Welch, R. W., Antoine, J.-M., Berta, J.-L., Bub, A., de Vries, J., Guarner, F., … Woodside, J. V. (2011). Guidelines for the design, conduct and reporting of human intervention studies to evaluate the health benefits of foods. *British Journal of Nutrition*, *106*(S2), S3–S15. https://doi.org/10.1017/S0007114511003606

WHO. (2001). *Report of the Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria, Córdoba, Argentina, 1-4 October 2001*. Food and Agriculture Organization of the United Nations.

Wiley, N. C., Dinan, T. G., Ross, R. P., Stanton, C., Clarke, G., & Cryan, J. F. (2017). The microbiota-gut-brain axis as a key regulator of neural function and the stress response: Implications for human and animal health1,2. *Journal of Animal Science*, *95*(7), 3225–3246. https://doi.org/10.2527/jas.2016.1256

Witaicenis, A., Fruet, A. C., Salem, L., & Di Stasi, L. C. (2010). Dietary polydextrose prevents inflammatory bowel disease in trinitrobenzenesulfonic acid model of rat colitis. *Journal of Medicinal Food*, *13*(6), 1391–1396. https://doi.org/10.1089/jmf.2009.0275

Yang, H., Zhao, X., Tang, S., Huang, H., Zhao, X., Ning, Z., … Zhang, C. (2016). Probiotics reduce psychological stress in patients before laryngeal cancer surgery. *Asia-Pacific Journal of Clinical Oncology*, *12*(1), e92–e96.

https://doi.org/10.1111/ajco.12120

Yang, L., Zhao, Y., Wang, Y., Liu, L., Zhang, X., Li, B., & Cui, R. (2015). The Effects of Psychological Stress on Depression. *Current Neuropharmacology*, *13*(4), 494–504. https://doi.org/10.2174/1570159X1304150831150507

Zareie, M., Johnson-Henry, K., Jury, J., Yang, P.-C., Ngan, B.-Y., McKay, D. M., … Sherman, P. M. (2006). Probiotics prevent bacterial translocation and improve intestinal barrier function in rats following chronic psychological stress. *Gut*, *55*(11), 1553–1560. https://doi.org/10.1136/gut.2005.080739

Zheng, P., Zeng, B., Zhou, C., Liu, M., Fang, Z., Xu, X., … Xie, P. (2016). Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. *Molecular Psychiatry*, *21*(6), 786–796. https://doi.org/10.1038/mp.2016.44

Zhong, Y., Marungruang, N., Fåk, F., & Nyman, M. (2015). Effects of two whole-grain barley varieties on caecal SCFA, gut microbiota and plasma inflammatory markers in rats consuming low- and high-fat diets. *British Journal of Nutrition*, *113*(10), 1558–1570. https://doi.org/10.1017/S0007114515000793

Zhou, L., & Foster, J. A. (2015). Psychobiotics and the gut–brain axis: In the pursuit of happiness. *Neuropsychiatric Disease and Treatment*, *11*, 715–723. https://doi.org/10.2147/NDT.S61997

Table 1. Effects of stress modulation through microbiota interventions: Evidence from animal models.

Reference	Animal model	Microbiota manipulation	Test	Main findings
		Probiotics		
(Li et al., 2018)	Male C57BL/6 mice	*L. helveticus* R0052, *L. plantarum* R1012, and *B. longum* R0175 4 weeks	Chronic mild stress (CMS)	Decreasing hippocampal levels of proinflammatory cytokines (IFN-γ and TNF-) produced by CMS
(Warda et al., 2019)	Male C57BL/6 mice	ADR-159 contains a co-fermentate of *Lactobacillus fermentum* and *Lactobacillus delbrueckii*, 3 weeks	FST	Reduction in baseline corticosterone levels in ADR-159 fed animals reducing both *Alistipes* and *Odoribacter*, as well increasing *Prevotella*
(van de Wouw et al., 2018)	Male C57Bl/6J mice	A mix of the three principal short-chain fatty acids Psychosocial stress	Stress-induced hyperthermia test	Increase in body temperature after an acute stressor in psychosocially stressed mice was restored by SCFAs SCFAs ameliorated the stress-induced corticosterone

(Pusceddu et al., 2015)	Sprague-Dawley female rats	Eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) (80% EPA, 20% DHA) n-3 PUFAs mixture 10 days	MS	n-3 PUFAs have little positive benefit in animals exposed to early life stress
(Cowan and Richardson, 2018)	Sprague Dawley female rats	*Lactobacillus rhamnosus* R0011, 95%, and *Lactobacillus helveticus* R0052, 5% 12 days	MS	Probiotic treatment prevents this precocious physical maturation in stressed females
(Agusti et al., 2018)	Male wild-type	C57BL-6 mice high-fat diet (HFD) *B. pseudocatenulatum* CECT 7765 standard diet (SD) 14 weeks	Acute restraint	Bacterial strain to reverse the anxiogenic obesity profile
(McVey Neufeld, 2018)	BALB/c and Swiss Webster mice	*L. rhamnosus* JB-1 28 days	Acute restraint	Feeding *L. rhamnosus* JB-1 to BALB/c attenuates plasma corticosterone. No effects on Swiss Webster mice

(Tarr et al., 2015)	Male C57/BL6 mice	IN-93G semi-purified laboratory mouse diet, a modified AIN-93G diet supplemented with 6′SL or a modified AIN-93G diet supplemented with 3′SL 2 weeks	Social Disruption (SDR) Stressor	Prebiotic diminish stressor-induced alterations in colonic mucosa-associated microbiota community structure
(Mackos et al., 2016)	Male CD-1 mice	*Lactobacillus reuteri* 13 days	Prolonged restraint	Probiotic attenuate the stressor-induced increases in pathogen translocation from the colon to the spleen, elevations in circulating IL-6, and anxiety-like behaviour
(Galley et al., 2017)	Male C57Bl/6 mice	*Lactobacillus reuteri* 6 days	Social disruption stress (SDR)	*L. reuteri* reduces colonic inflammation, but not microbial community composition

(Zareie et al., 2006)	Male Brown Norway rats	*Lactobacillus rhamnosus*, strain R0011 and *Lactobacillus helveticus*, strain R0052 (Lacidofil) 17 days	WAS	No changes in behaviour and no effect in intestinal barrier function. Luminal bacterial adherence and translocation to the mesenteric lymph nodes reduced.
(Garc??a-R??denas, 2006)	Female Long-Evans rats	*Lactobacillus para- casei NCC2461* combined with diet (arachidonic and docosahexaenoic acids, galacto- and fructo-oligosaccharides*)* 20 days	MS	Intestinal permeability normalized and the growth rate recovery improved and it resulted in increased villus length in small intestine. Diet does not restore intestinal mucin content or microbiota.
(Gareau, 2007)	Sprague–Dawley female rats	*Lactobacillus rhamnosus strain R0011 (95%) and L helveticus strain R0052*	MS WAS	It restores normal ion transport and macromolecular permeability in colon.

		15 days		The enhanced level of circulating corticosterone reduced.
(ait-belgnaoui, 2009)	Female Wistar rats	*Lactobacillus farciminis* 14 days	Restraint stress	Sensitivity to colorectal distension reduced.
(Konturek, 2009)	Rats	*Escherichia coli Nissle*	Restraint stress	It protects gastric mucosa.
(Agostini, 2012)	Female Wistar rats	*Bifidobacterium lactis CNCM I-2494* 15 days	Restraint stress	The increase in intestinal permeability prevented and restored, occluding and JAM-A expressions to control levels. The increase concentration of blood endotoxin abolished.

(Afifa Ait-Belgnaoui, 2012)	Female Wistar rats	*Lactobacillus farciminis* 2 weeks	Partial restraint stress	HPA axis stress response prevented and hypothalamic expression of pro-inflammatory cytokines increased.
(Takadanohara, 2012)	Sprague-Dawley rats	*Symbiotic preparation containing microbial lysates* 10 days	WAS	Enhanced intestinal permeability reduced.
(Amy R. Mackos, 2013)	Male CD-1 mice	*Lactobacillus reuteri* 12 days	Prolonged restraint	It reduces pathogen translocation from the colon to the spleen The stressor-enhanced susceptibility to *C. rodentium*-enhanced infectious colitis reduced.
(Silva, 2014)	Male Wistar rats	*Lactobacillus farciminis* 14 days	WAS	WAS-induced functional alterations prevented. It makes changes in mucin O-glycosylation and mucus physical properties and conferring epithelial and mucus barrier strengthening.

(A. Ait-Belgnaoui, 2014)	C57Bl6 mice	*Lactobacillus helveticus and Bifidobacterium longum,* 2 weeks	WAS	Plasmatic levels of corticosterone, adrenaline, and noradrenaline in stressed mice decreased. Changes in central neuronal activation and neurogenesis prevented.
(Takada, 2016b)	Male F344 rats	*Lactobacillus casei* 2 weeks	WAS	It suppresses the increase in plasma corticosterone and the number of CRF-expressing cells.
(Darbaky, 2017)	Male Sprague Dawley rats	*Lactobacillus rhamnosus* 8 days	Restraint stress	Peripherally and centrally induced visceral hypersensitivity attenuated.
(Vanhaecke, 2017)	Sprague-Dawley rats	*Lactobacillus fermentum* 15 days	WAS MS	Permeability in the ileum but not in the proximal colon reduced. Increase corticosterone reduced and exploratory behaviour increased

(Lee, 2017)	Male and female Wistar rats	*Lactobacillus farciminis* 10 days	WAS	Colonic mucosal mast cell count in females reduced. The mRNA levels of IFNR, TNFA, and IL6 in females reduced.
(Afifa Ait-Belgnaoui, 2018)	C57BL/6J male mice	*L. helveticus R0052 and B. longum R0175 (combinate and alone)* 2 weeks	WAS	Both probiotics strains combined reduce the chronic stress-induced visceral hypersensitivity, attenuated of stress hormones, and has a potential effect on GR expression. Each probiotic strain alone are less effective.
Other interventions (prebiotics, diet)				
(Larauche, 2012)	Male Wistar rats	Enzyme treated rice fiber 2 weeks	WAS	The development of hyperalgesia prevented.

(Burokas, 2017)	Male C57BL/6J mice	*fructo-oligosaccharides and galacto-oligosaccharides* 3 weeks	Chronic unpredictable social stress	Stress-induced corticosterone release reduced. Chronic stress-induced elevations in corticosterone and proinflammatory cytokine levels normalizing the effects of stress on the microbiota reduced.
(Wang, 2017)	Male Wistar rats SPF	*IMO* 14 days	WAS	Visceral hyperalgesia repaired intestinal mucosal.
(Mika, 2017)	Male Fischer 344 rats	Galactooligosaccharide, polydextrose, and the glycoprotein lactoferrin 4 weeks	Inescapable stress	Stress-induced learned helplessness attenuated. Stress-evoked cfos mRNA in the DRN attenuated stress-evoked decreases in mRNA for the 5-HT1A autoreceptor in the DRN and increased basal BDNF mRNA within the prefrontal cortex.

(de Sousa Rodrigues, 2017)	Male C57Bl/6 mice	*High-fat high-fructose* 6 weeks	Predatory stress model	Stress promoted an adaptive anti-inflammatory profile in the hippocampus that was abolished by diet treatment

Abbreviations: WAS: chronic water avoidance stress; MS: maternal separation; SPF: specific pathogen free; IMO: isomalto-oligosaccharides; DRN: dorsal raphe nucleus; GR. glucocorticoid receptors BDNF: brain-derived neutrophic factor.

Table 2. Effects of stress modulation through microbiota interventions: Evidence from clinical studies.

Reference	Population	Intervention	Stress Measures	Results
		Probiotic		
(Allen, 2016)	22 healthy male volunteers	*Bifidobacterium longum* 1714 strain 4 weeks	Cold pressor test (SECPT)	Total cortisol output was significantly affected by probiotic
(Allen, 2016)	44 healthy male volunteers	*L. Rhamnosus* 4 weeks	Cold pressor test (SECPT)	Total cortisol output was significantly affected by probiotic
(Papalini et al., 2019)	58 healthy volunteers	Ecologic barrier 28 days	Cold pressor test (SECPT)	Stress-induced working memory performance in DS (digits span) backward that was differentially affected by the probiotics

(Diop et al., 2008)	Volunteers affected by stress received a probiotic (n = 37) or a placebo (n=38)	Probio-Stick (*L. acidophilus and B. longum*) Placebo (3 weeks)	Stress-induced symptoms (VAS)	Improvement of stress-induced gastrointestinal symptoms (abdominal pain, nausea).
(Kato-Kataoka et al., 2016 a,b)	Medical students previous academic examination received probiotic intervention (n=25) or placebo (n=24)	Milk fermented with with *L. casei* strain Shirota Milk (Placebo) (8 weeks)	Feelings of stress (VAS) Abdominal dysfunction Anxiety (STAI). Salivary Cortisol Others measures indirectly stress-related	Relieve the stress-associated psychological, physiological, and physical stress responses.
(Takada, 2016b)	Medical students previous academic examination received probiotic intervention	Milk fermented with with *L. casei* strain Shirota Milk (Placebo) (8 weeks)	Physical symptoms present (abdominal, cold symptoms, etc.) Anxiety (STAI)	Physical symptoms were significantly suppressed in the LcS group

	(n=70) or placebo (n=70)		Salivary cortisol Others measures indirectly stress-related	
(H. Yang, 2016)	Laryngeal cancer patients scheduled for laryngectomy (n=20)	Probiotic *(Clostridium butyricum)* Placebo (2 weeks)	Anxiety (HAMA) CRF levels	CRF levels and heart rate did not increase before surgery. Relieved the degree of anxiety.
(Möller, 2017)	Young adults (N=105)	Multistrain and multispecies probiotics *(B. breve, B.longum, B. infantis, L. acidophilus, L. plantarum, L. paracasei, L. bulgaricus, and S. thermophilus)*	Psychological Stress *(Paced Auditory Serial Addition Test)*	Not influence measures of responsivity to psychological stress.

		Placebo (2 weeks)		
Other interventions				
(Martin, 2009)	Healthy volunteers (n=30)	Daily consumption of 40 g of dark chocolate (14 days)	Anxiety Physiological determinations	variation of both host and gut microbial metabolism.

HAMA: Hamilton Anxiety Rating Scale; STAI: State-Trait Anxiety Inventory; VAS: Visual Analogue Scale.