BACHELOR'S THESIS

The Importance of the Periphery in Depression

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Summary

Depression is a common mental disorder that is characterized by a low mood and the inability to experience pleasure. The disease is currently the leading cause of disability worldwide and its prevalence is still increasing. Depression is caused by a depletion in serotonin levels. Current treatment methods aim to increase serotonin levels in the brain. Most of the serotonin in our body is actually produced in the periphery and not in the brain. It has been established that the periphery and the brain interact with each other via the gut-brain axis. Depressive patients often show gut problems and conversely, individuals with gut problems show often depressive-like symptoms. The gut microbiota plays a key role in this bidirectional communication system. Dysbiosis in the gut has been associated with several mental disorders including depression. Diet seems to be an important factor in the development of dysbiosis and thereby in the development of depression. Future research should look beyond treatments that aim to directly increase serotonin levels in the brain and should give attention to the periphery instead. Novel treatments that seem to be effective in restoring the gut microbiota are fecal microbial transplantations, probiotics and changing the diet of depressed patients.

Introduction: Depression is a problem!

Depression is a serious mental disorder and a leading cause of disability worldwide *(WHO, 2021).* The disease affects people in multiple ways and can cause a wide range of symptoms including a low mood, inability to experience pleasure and feelings of sadness. The damage caused by depression can be long-lasting and has a huge effect on the quality of life.

The pathophysiology of depression is caused by low levels of neurotransmitters, especially serotonin *(Hasler, 2010)*. Currently, antidepressants such as SSRIs are used as a treatment because they act by increasing serotonin levels in the brain *(Harmer et al., 2017)*.

There are actually two problems that arise when antidepressants are used as a treatment. Firstly, this method aims to relieve depressive symptoms, but it is no cure for depression. Secondly, antidepressants are often accompanied by side effects. These medications may help in some cases of depression, but not in all *(Institute for Quality and Efficiency in Health Care (IQWiG), 2020)*.

Recently, there has been increasing interest in the interaction between the gut and the central nervous system through the gut-brain axis. It could be that the gut-brain axis is involved in depression because this system interacts with brain function and neurotransmitter content. The hypothesis for this thesis states, "We should look into the importance of the periphery in the development of depression."

Chapter 1: From the Brain to the Gut

Depression is a common mental disorder which causes low mood, feelings of sadness, decreased energy, anhedonia and changes in appetite. It affects over 300 million people worldwide and this prevalence is still increasing *(WHO, 2021).* The condition limits the ability to perform daily activities enormously and increases the risk of suicidal behaviour which results in increased mortality *(WHO, 2021)*. Despite major research that is done, the pathophysiology of the psychiatric disorder is not known yet as many factors contribute to the development of depression.

Depression can be caused by genetic and environmental factors such as childhood experiences, medication, gender, age and (mental) health problems *(Bruce, 2008)*. There are several hypotheses about what the cause of depression is. The monoamine theory hypothesizes that the depletion in the neurotransmitter serotonin (5-HT) is the primary cause of depression *(Mulinari, 2012)*. This seems a reliable hypothesis as low levels of 5-HT have been associated with a low mood, which is a key characteristic in depression *(Young & Leyton, 2002)*. Antidepressants are currently used as treatment and aim to increase 5-HT levels in the brain. This medication is actually not working efficiently enough, which could be due to the fact that other processes, besides depleted 5-HT levels, are involved in the development of depression as well. Research suggests that these other relevant processes are mainly disturbances in the gut but also neuroinflammation *(Carlessi et al., 2021)*.

There is a growing body of research on how depression influences peripheral components. It is notable that a lot of depressive patients display poor eating habits and experience gut-related problems *(Adibi et al., 2022) (Garcia et al., 2020)*. These features have a direct influence on peripheral health.

Research has shown that depressed individuals perform uncontrolled and emotional eating more frequently *(Paans et al., 2018)*. It is notable that depressed females are four times more likely to develop an eating disorder *(Garcia et al., 2020)*.

It is important to realize that serotonin does not only influence mood, but it also influences peripheral components. Low levels of serotonin can lead to slow movement of particles through the GI tract, resulting in constipation *(Israelyan et al., 2019)*. Research indicates that depressed patients are more likely to experience constipation and other bowel difficulties compared to healthy individuals *(Ballou et al., 2019) (Adibi et al., 2022)*.

While it is now established that depression can impact peripheral health, is it also true that the gut has an impact on mental health?

Chapter 2: From the Gut to the Brain

The gut plays a vital role in human physiological processes such as metabolism, food absorption and digestion and immunity *(Crane et al., 2015) (Rogers et al., 2016)*. This explains why disruptions in gut health can cause a wide range of issues *(Bischoff, 2011)*. Figure 1 illustrates how imbalances in the gut are associated with the onset of various pathologies *(Munawar et al., 2021)*.

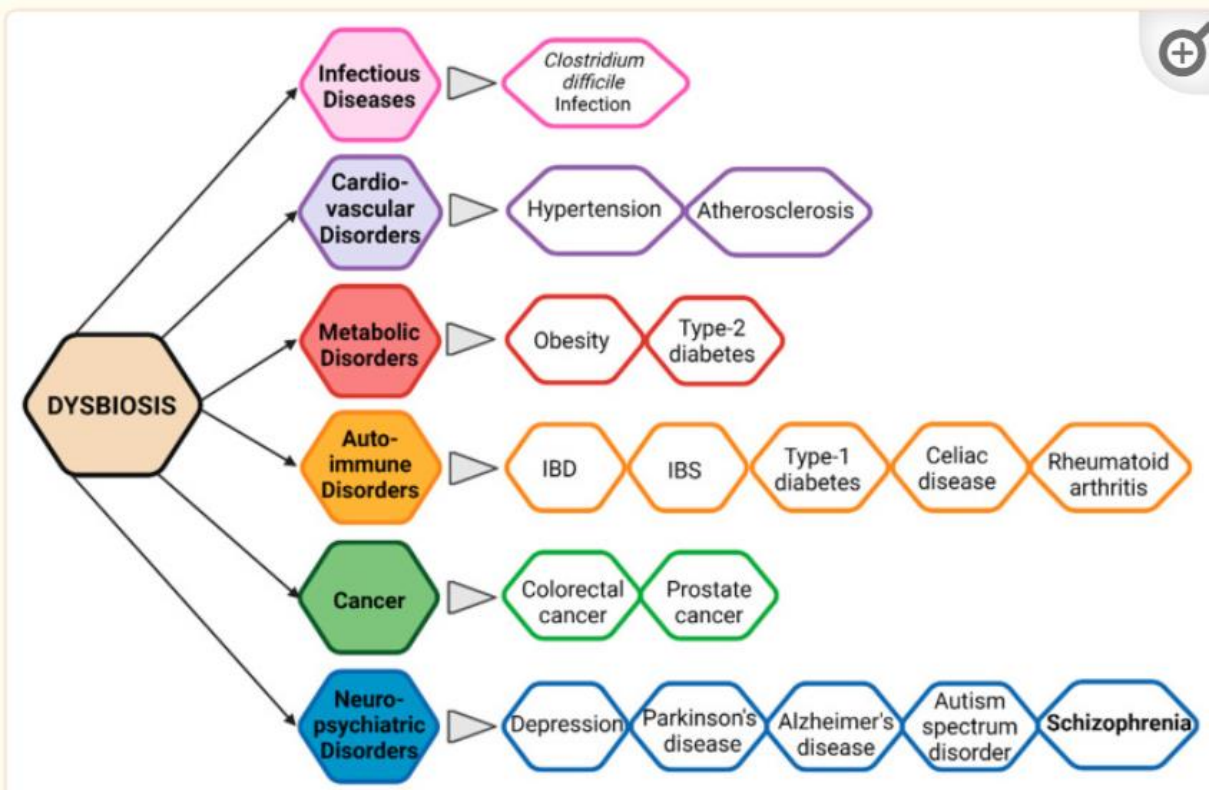

Figure 1. Diseases that are accompanied by dysbiosis.

This chapter focuses on how the gut affects brain mechanisms. There is growing interest in the communication between the gut and the brain due to the frequent co-occurrence of psychiatric illnesses and metabolic or gastrointestinal disorders *(Kennedy et al., 2014) (Luo et al., 2021)*.

Various studies imply that gastrointestinal symptoms such as digestive diseases increase the risk of developing depression and also increase depressive-like symptoms *(Yan et al., 2021) (Byrne et al., 2017)*. Figure 2 shows that patients suffering from inflammatory bowel disease (IBD) have an increased risk to develop anxiety or depression *(Byrne et al., 2017)*.

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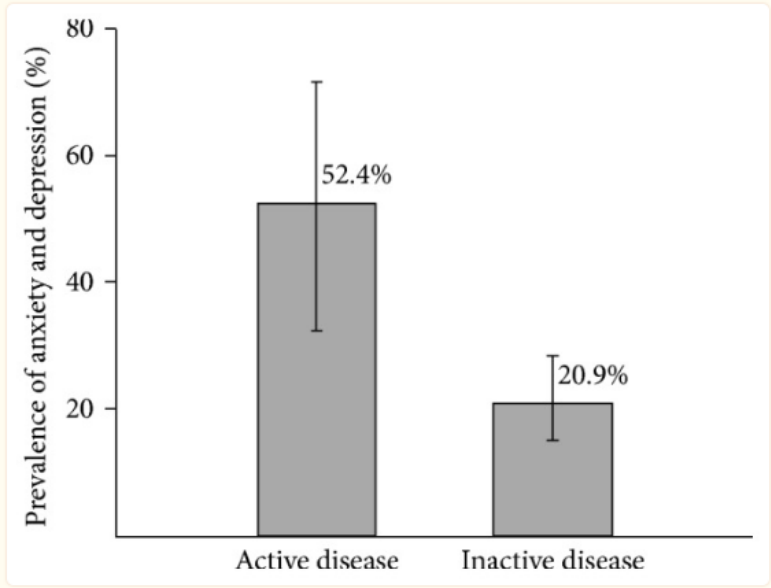

Figure 2. The risk of developing depression and anxiety is associated with inflammatory bowel disease (IBD). In active IBD a significant increase in prevalence was seen compared to inactive IBD.

Findings from studies and the National Institute of Mental Health (NIMH) indicate that obesity, cancer and eating disorders are accompanied by increased risk of developing depression, as shown in figure 3 *(Luppino et al., 2010) (Eating Disorders, z.d.).* Various types of cancer have different probabilities to develop depression. For example, patients with digestive tract cancer are more likely to develop depression than those with lung cancer *(Krebber et al., 2014)*. This highlights again that the gut plays a crucial role in the development of mental disorders.

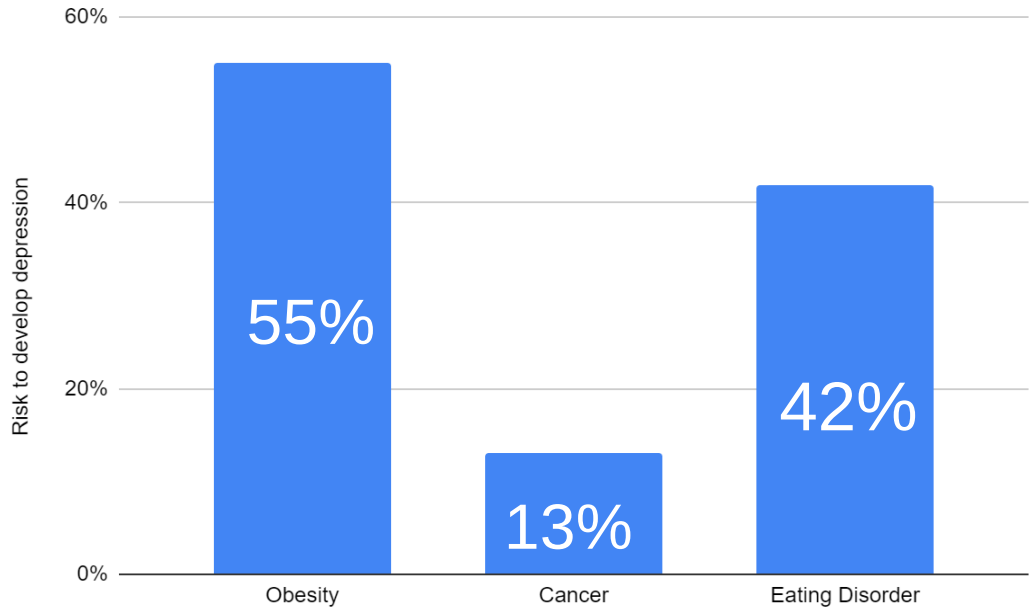

Figure 3. Risk percentages for obesity, cancer and eating disorders to develop depression. Cancer shows the average value for all cancer types. Eating disorders contain Anorexia Nervosa, Binge Eating Disorder and Bulimia Nervosa *(Luppino et al., 2010) (Eating Disorders, z.d.)*.

Furthermore, gut health can be affected by external factors such as diet. Poor nutrition can directly affect gut health and has been associated with the promotion of metabolic and mental disorders *(Ruusunen et al., 2014)*. It is notable that the dietary intake pattern of common populations in several countries show a lack of nutrients, this might be due to the increased consumption of a western diet *(Cordain et al., 2005) (Rao et al., 2008)*. The western diet is characterized by containing high fat, refined carbohydrates and a low fiber content *(López-Taboada et al., 2020)*. Studies imply that the western diet is related to a decline in cognitive functions later in life *(Kanoski & Davidson, 2011) (Jacka et al., 2010)* and has been linked to the increased prevalence of mental disorders, including depression *(World Health Organization: WHO, 2019)*,

Now it is known that the gut influences mental health and contributes to the development of depression. In order to continue, it is important to examine the components that are important in this process.

Chapter 3: The Gut-Brain Axis and Microbiota

It is now established that serotonin is an important factor in depression. It is important to realize that 95% of 5-HT is actually produced in the periphery *(Appleton, 2018)*. This raises interest in pathways that are involved in the translocation of this neurotransmitter to the brain.

The gut-brain axis is the bidirectional signaling network that allows communication between the enteric nervous system and the central nervous system. This network involves multiple components such as the gut microbiota, the immune system, the hypothalamic-pituitary axis (HPA) and the tryptophan metabolism *(Carabotti, 2015)*. The gut is sometimes referred to as the "second brain" as it influences the brain by the secretion of various compounds.

The gastrointestinal tract is colonized by all kinds of microbes such as bacteria, viruses and fungi *(Ferranti et al., 2014)*. Previously, it was thought that these microorganisms were not involved in mental processes, but they seem to be key players in signaling to the brain by the production of their metabolites *(Perino et al., 2021)*. They influence the gut-brain axis via the regulation of the immune system, HPA axis and via the digestion of food *(Gensollen et al., 2016) (Baümler & Sperancio, 2016) (Thursby et al., 2017) (Rosin et al., 2021)*. Communication via the microbiome is established by the neuroactive compounds that they produce via their metabolites. One of these compounds is 5-HT and acts on 5-HT receptors that are present on immune, epithelial and nerve cells *(Averina et al., 2020)*. Serotonin is in the gut produced by enterochromaffin cells and in the brain by serotonergic neurons *(Walther & Bader, 2003)*. There are in total 18 serotonin receptors which are expressed in CNS and/or in the GI tract. Serotonin regulates various cognitive processes such as memory and emotional well-being, but has also an influence on gut motility as mentioned in chapter 1 *(Israelyan et al., 2019) (Averina et al., 2020) (Mawe and Hoffman, 2013)*.

When the composition of the microbiota gets altered, this results in dysbiosis. Dysbiosis is defined as the imbalance in the microbial composition which could be due to the gain or loss of community members *(Messer & Chang, 2018)*. It is established that dysbiosis contributes to the onset of multiple diseases such as obesity, inflammatory bowel disease, Alzheimer's disease and depression as illustrated in figure 1 from chapter 2 *(Munawar et al., 2021) (Tagliabue & Elli, 2013) (Liu et al., 2022)*. A microbiome with a high alpha diversity, which means a rich functional community of microorganisms, is essential for maintaining gastrointestinal (GI) homeostasis and cognitive functions *(Li et al., 2022)*. There are many factors that contribute to the richness of our microbiome such as diet, mode of delivery during birth and environmental factors. The contribution of these many features explains that there are interindividual differences in the diversity of microbiomes among people. A healthy microbiome is characterized by high diversity in species and is dominated by anaerobic bacteria *(Rinninella et al., 2019)*. Phyla that consist of these bacteria are Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria. Despite interindividual differences within the microbiome, these phyla were consequently found in healthy human microbiomes. The Bacteroidetes and Firmicutes phyla seem to represent 90% of the microbiome *(Arumugam et al., 2011)*.

The dominant species in the microbiota result in adult life mainly from our diet. A diverse diet based on plants has been associated with greater alpha diversity in the gut *(Johnson et al., 2019) (Miao et al., 2022)*. Furthermore, the proportion of macronutrient intake is an important determinant for the composition of the microbiota. Diets that are high in fat and low in fiber, commonly referred to as “the western diet” in chapter 2, have been linked to dysbiosis and an increased risk of developing mental, metabolic and inflammatory diseases *(Munawar et al., 2021)*. Figure 4 shows that the consumption of a high fat diet results in a decrease in Bacteroidetes and Bifidobacterium, and an increase in both Firmicutes and Proteobacteria *(Zhang et al., 2012)*. A diet with increased carbohydrate intake shows decreased abundance of Firmicutes in the gut *(Averina et al., 2020)* and diets high in proteins are associated with a Bacteroidetes enterotype *(Huttenhower et al., 2012)*. It is thus important to acknowledge that changes in diet can cause alterations in the microbiome composition, regardless of factors such as age, BMI and gender *(Caporaso et al., 2011)*.

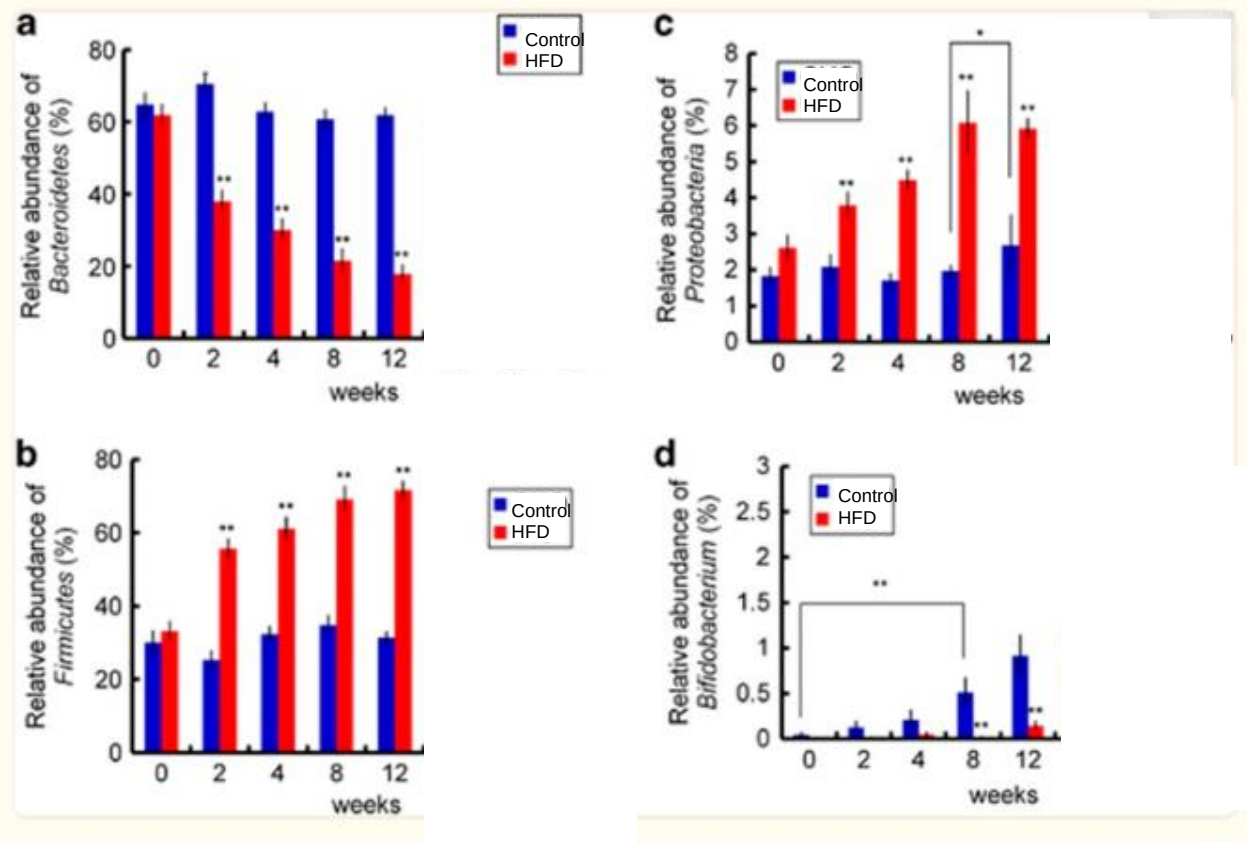

Figure 4. The effect of a high fat diet (HFD) on the prevalence of a. Bacteroidetes, b. Firmicutes, c. Proteobacteria and d. Bifidobacteria compared to a control group.

The fermentation of nutrients by the microbiome results in the production of metabolic compounds that play major roles in the gut-brain axis *(Vernocchi et al., 2020)*. The so-called postbiotics that seem to have big influences are short-chain fatty acids (SCFAs), bile acids (BAs), branched-chain amino acids (BCAAs) and vitamins *(Agus et al., 2021)*. These metabolic compounds have the ability to produce neurotransmitters, such as serotonin *(Carlessi et al.,*

2021). Although these components are synthesized in the periphery they impact the levels in the brain as well *(Gao et al., 2019) (Frost et al., 2014)*.

Short-chain fatty acids (SCFAs), namely acetate, propionate and butyrate, are generated through the fermentation of dietary fibers *(Ranaivo et al., 2022) (Fu et al., 2015)*. In the periphery, SCFAs promote the conversion from tryptophan to serotonin via tryptophan hydroxylase (TRPH1) *(Layunta et al., 2021)*. Tryptophan is an essential amino acid and the precursor of serotonin *(Capuron et al., 2002)*. Figure 5 shows that increasing levels of SCFAs butyrate and acetate enhances the production of 5-HT by the stimulation of TRPH1 *(Reigstad et al., 2015)*. 5-HT produced from the periphery can signal to the CNS by activating afferent nerve endings.

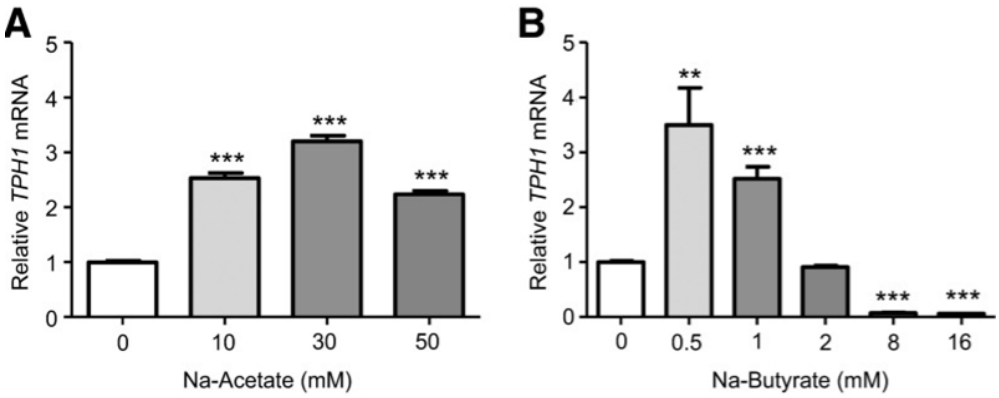

Figure 5. Increasing levels of Acetate (A) and Butyrate (B) both result in increased tryptophan hydroxylase (TPH1) mRNA.

It is possible to increase the SCFA abundance either by increasing fiber intake or consuming probiotics. The intake of dietary fiber has been positively associated with a diverse microbiota *(Ranaivo et al., 2022)*. Besides this, research found that fiber intake has been positively linked to the increase of the butyrate producing bacteria F. Prausnitzii and the increase in the abundance of Bifidobacterium which can be seen in figure 6 *(Ramirez-Farias et al., 2008).*

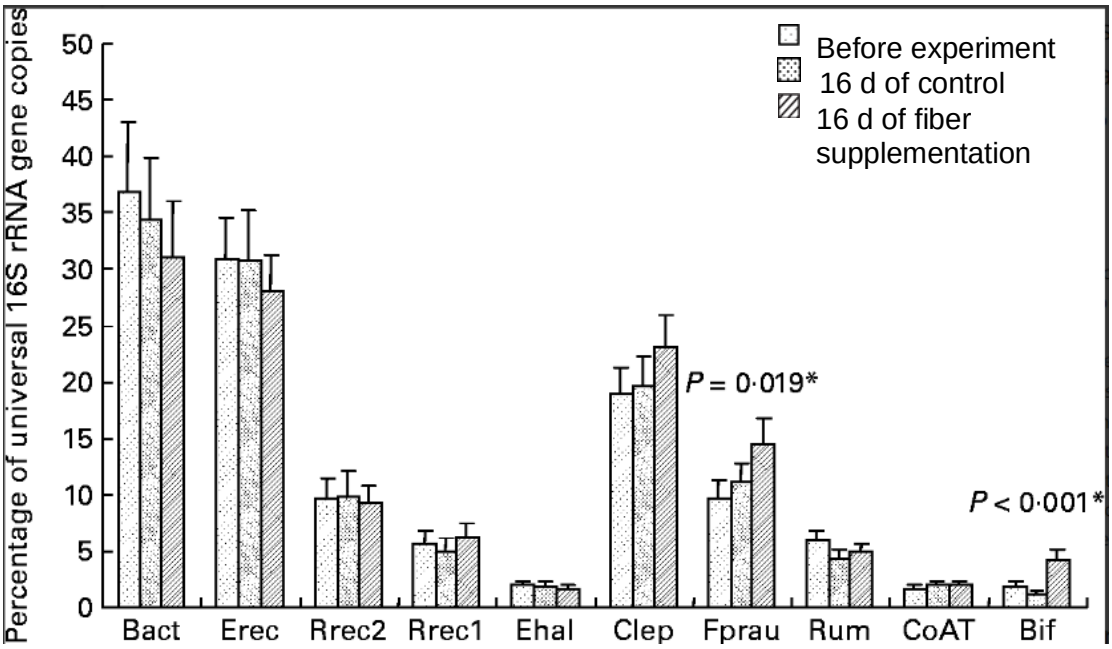

Figure 6. Dietary fiber consumption results in a significant increase in the abundance of F. Prausnitzii (Fprau) and Bifidobacterium (Bif) after 16 days of fiber consumption compared to controls that were not supplemented with fiber..

Besides our diet, antibiotics have been demonstrated to affect the microbial composition resulting in reduced diversity *(Dubourg et al., 2014)*. They affect the metabolite production which alters the neurotransmitter secretion in both the brain and the periphery *(Carlessi et al., 2021)*. Studies show that short-term administration of antibiotics already results in significant long-term alterations in the microbiota *(Jernberg et al., 2007).* On the other hand, probiotics - living microorganisms that offer health advantages upon consumption - may enhance diversity in the microbiota by the suppression of pathogens, promoting the differentiation of the intestinal barrier and exerting immunomodulation *(Thomas & Versalovic, 2010)*.

The current understanding about how the gut and the brain interact with each other allows for further exploration of the role of the periphery in depression.

Chapter 4: The Gut-Brain axis and Depression

The gut-brain axis serves as a major communication system between the brain and the periphery. Growing evidence points towards its involvement in the development of mental disorders such as depression *(Mayer et al., 2014)*. The microbiota is a key component in this communication system and it is believed that this component exerts a significant influence on the development of depression. A study showed for example that the transplantation of fecal microbiota of depressed humans into germ free rats increased depressive symptoms *(Kelly et al., 2016)*. Research obtained that depression is linked to dysbiosis and decreased alpha diversity as can be seen in figure 7 *(Sherwin et al., 2016) (Li et al., 2022).*

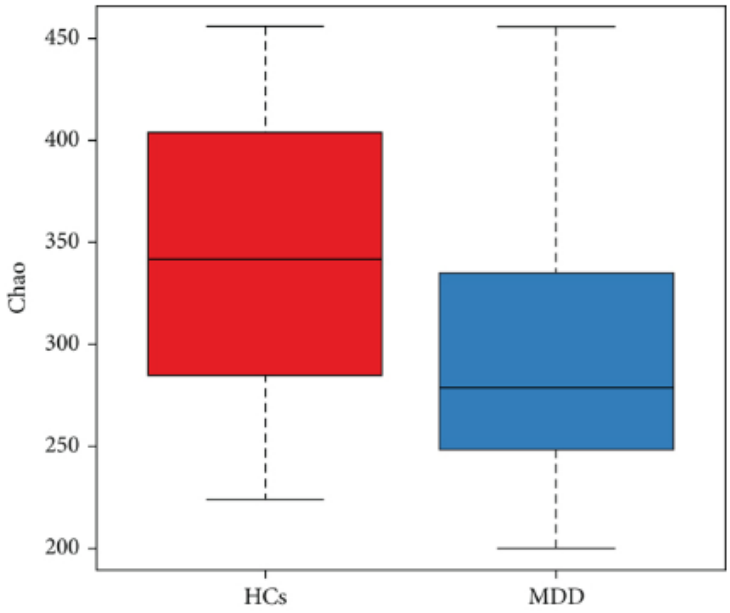

Figure 7. Differences in alpha diversity between healthy controls (HCs) and major depressive disorder (MDD) patients. The box chart displays lower diversity in MDD compared to HCs (Li et al., 2022).

As previously discussed in chapter 2, dysbiosis has been identified as an important contributing factor in the development of several mental disorders, including depression *(Munawar et al., 2021)*. The current treatment methods for depression are antidepressants which act by boosting serotonin levels as mentioned in chapter 1. This medication works actually counterproductive as antidepressants such as SSRIs have antibiotic effects, thereby influencing the gut microbiome by the stimulation of dysbiosis *(Lukic et al., 2019)*. This might even contribute to an increase in depressive-like symptoms in some patients *(Sjöstedt et al., 2021).*

It is established that the microbiome of depressed individuals is altered as different studies demonstrate that the disorder accompanies decreased levels of Bifidobacterium, Lactobacillus, Firmicutes and Faecalibacterium *(Aizawa et al., 2016) (Zheng et al., 2016) (Heym et al., 2019)*. On the other hand, a higher abundance of inflammatory phyla such as Bacteroides, Ruminococcaceae and Prevotella have been found in depressed patients *(Liu et al., 2016)*. The observation of increased Ruminococcaceae in depression could explain the prevalence of

constipation in depressed individuals, as discussed in chapter 1, as an increased abundance of this species accompanies slow transit time *(Raes et al., 2016) (Liu et al., 2016)*. Furthermore, the abundance of Eggerthella seems positively linked to incidence of anxiety and depression according to a microbiome-wide association study *(Radjabzadeh et al., 2022)*. This species induces inflammation by the activation of Th17 cells and displays increased abundance in inflammatory bowel disease (IBD) *(Davami et al., 2016) (Alexander et al., 2022) (Kostić et al., 2017)*.

Besides decreased levels of Faecalibacterium, other butyrate-producing bacteria such as Coprococcus, Subdoligranulum and Dialister also seem to be reduced in depressed individuals *(Noriega et al., 2016)*. As explained in chapter 3, butyrate is a type of short-chain fatty acid that stimulates the secretion of 5-HT. Additionally, this SCFA has major anti-inflammatory effects and is important in the prevention of excessive immune responses *(Zhang et al., 2022).*

Chapter 1 highlighted the significance of neuroinflammation in depression *(Carlessi et al., 2021)*. It is important to realize that 70% of the immune system is located in the gut. This explains that the microbiota has a huge influence on the immune system *(Wiertsema et al., 2021)*. The immune system functions as an important regulator in the gut-brain axis as emphasized in chapter 3. Dysbiosis alters the permeability of the gut and blood-brain barrier which enables various bacteria and metabolic compounds to cross these barriers and activate immune responses via the release of pro-inflammatory cytokines *(Kiliaan et al., 1998) (Carlessi et al., 2021)*. This clarifies the observed high levels of pro-inflammatory cytokines such as IL-6 and TNF-a in depressed individuals *(Maes, 1999) (Myint et al., 2005) (Peruga et al., 2011)*. The increase in pro-inflammatory cytokines and excessive immune responses in depressive patients could also be explained by the observed rise of inflammation-stimulating bacteria and the reduction in SCFA-producing bacteria in the gut *(Rathour et al., 2022)*.

The immune system influences the serotonergic system by altering 5-HT signaling and receptor activity *(Shajib & Khan, 2015)*. Inflammatory conditions such as IBD and colitis have been associated with high serotonin availability but low serotonin uptake due to reduced sensitivity for the receptors *(Linden et al., 2003)*. High levels of inflammation also trigger the degradation of tryptophan via the kynurenine pathway *(Rogers et al., 2016)*. As previously mentioned, tryptophan is an essential amino acid and the precursor of serotonin *(Capuron et al., 2002)*. In high inflammatory conditions, kynurenic and quinolinic acid are made at the expense of serotonin *(Maes et al., 2001) (Savitz, 2016)*. Depressive patients have increased degradation of tryptophan via the kynurenine pathway, leading to high levels of kynurenic and quinolinic acid, which causes inflammation *(Maes et al., 2001) (Savitz, 2016) (Oxenkrug, 2013)*. It is established that the restoration of a diverse microbiome normalizes kynurenine and tryptophan levels which is positively associated with reduced anxiety *(Clarke et al., 2013)*. Bifidobacterium is able to increase the levels of tryptophan and restore serotonin levels via the regulation of quinolinic acid and GABA levels *(Desbonnet et al., 2008) (Desbonnet et al., 2010) (Qingmin et al., 2022)*. Therefore, increasing Bifidobacterium by consumption of probiotics may be advantageous for individuals who suffer from depression.

It is already known that depression is characterized by low levels of serotonin which is directly linked to a low mood *(Lukić et al., 2022)*. The microbiota is capable of producing neurotransmitters such as serotonin via their metabolites as mentioned in chapter 3 *(Lener et al., 2017)*. Consequently, the production of metabolites is affected by dysbiosis. According to research, the onset of depression is associated with a decrease in the abundance of fecal metabolites, which also contributes to the alteration of 5-HT levels *(Jianguo et al., 2019)*.

Dysbiosis has thus an effect on the metabolites that were mentioned in chapter 3. Bile acid (BA) is a metabolite that regulates intestinal homeostasis by the absorption of lipids and the uptake of cholesterol. Primary BAs originate from cholesterol and are produced by the liver. Primary BAs are in the intestine converted into secondary BAs by the microbiome *(Ridlon et al., 2016)*. Due to decreased levels of gram-positive bacteria such as Bifidobacteria and Lactobacillus in depressive patients, the microbiome is incapable of metabolizing primary BAs into secondary BAs *(Ridlon et al., 2006)*. This results in an accumulation of primary BAs which might contribute to the observed low-grade intestinal inflammation in depression as secondary BAs act as anti-inflammatory agents *(Duboc et al., 2013) (MahmoudianDehkordi et al., 2022)*. Increasing the content of gram-positive bacteria by consuming probiotics might be beneficial in decreasing the observed low-grade inflammation.

Low levels of the branched-chain amino acids (BCAAs) are also observed in depressed patients *(Baranyi et al. , 2016)*. This observed reduction could be attributed to the severe nutrient deficiency in their diet leading to dysbiosis, as discussed in chapter 3 *(Rao et al., 2008)*. Dietary intake of BCAAs may be associated with lower odds of depression and may be beneficial in its treatment. Although a recent study supports this claim, more research is required to validate these findings *(Koochakpoor et al., 2021)*.

As mentioned in chapter 1, depression is currently treated with antidepressants which act by boosting serotonin levels. This medication works counterproductive as it also influences the gut microbiome by stimulating dysbiosis *(Lukic et al., 2019)*. This might even contribute to an increase in depressive-like symptoms in some patients (BRON!!!).

It has become clear how the gut-brain axis influences depression via the gut microbiota. Before diving into treatment options, it might be interesting to look into external factors that influence the microbial composition thereby initiating depression.

Chapter 5: Diet, microbiome and depression

The composition of the gut microbiota can be altered by external factors. Diet exerts major influence on the composition and metabolism of the microbiota and is thereby a main contributor to dysbiosis *(Ruusunen et al., 2014)*.

Chapter 2 demonstrated that the proportion of daily macronutrient intake influences the composition of the microbiota. Studies show that an increase in the proportion of protein intake in the total calorie consumption is associated with a decreased prevalence of depression *(Journel et al., 2012) (Oh et al., 2020) (Wolfe et al., 2011)*. This might be because the consumption of protein rich meals blocks 5-HT secretion in the brain but activates the secretion in the periphery *(Wurtman et al., 2003)*. Besides this, an increase in protein intake has been positively linked to an increased BCAA-content. As discussed in chapter 4, an adequate BCAA content seems to be associated with a lower risk to develop depression *(Koochakpoor et al., 2021)*. The aforementioned western diet, which contains high saturated fat, high refined carbohydrates, low fiber and high processed foods, is on the other hand associated with increased odds to develop anxiety and depression *(Akbaraly et al., 2009) (Jacka et al., 2011) (Le Port et al., 2012)*. This might be due to its contribution to dysbiosis *(Martinez et al., 2017)*. Contrary to meals high in proteins, carbohydrate rich meals increase levels of tryptophan in the brain *(Wurtman et al., 2003)*.

Several studies have reported increased refined carbohydrate and saturated fat intake together with less frequent fruit and vegetable consumption in depressed individuals *(Mikolajczyk et al., 2009) (C. Liu et al., 2007) (Paans et al., 2019)*. Depressive patients tend to increase their carbohydrate and fat intake as these macronutrients are able to directly increase serotonin levels which should stimulate their mood. Increased consumption of these macronutrients actually results in the opposite as a too high secretion of 5-HT is accompanied by 5-HT receptor insensitivity which results in an even lower mood *(Wurtman & Wurtman, 1995) (Hryhorczuk et al., 2016)*. Insensitivity results in lower activity of the serotonergic system which is seen in depression *(Drevets et al., 2007)*. Making these poor nutritional choices contributes to the onset but also to the severity of depression *(Rao et al., 2008)*.

The high saturated fatty acid content in western diets acts as a stressor and activates the HPA axis *(Domínguez-Vías et al., 2021)*. Chapter 4 demonstrated that the HPA axis is an important pathway in the gut-brain axis and that the microbiota exerts major influence on this pathway *(Rosin et al., 2021)*. Multiple studies suggest that saturated fatty acids contribute to a hyperactive HPA axis thereby stimulating stress and anxiety behaviors *(Sullivan et al., 2015) (Hryhorczuk et al., 2017)*. Hyperactivity of the HPA axis has continuously been observed in depressed individuals *(Holsboer, 2000) (Leonard, 2005)*. The high fat consumption elevates glucocorticoid levels - corticosterone in rats and cortisol in humans - which contributes to an altered negative feedback loop in the HPA axis as illustrated in figure 8 *(He et al., 2017)*. Glucocorticoids function in the inhibition of the immune system. However, in depressed individuals increased levels of both glucocorticoids and pro-inflammatory cytokines are visible *(Pariante, 2017)*. Chronic high levels of the glucocorticoid cortisol that are caused by the

increased saturated fatty acid intake results in the insensitivity of glucocorticoid receptors *(Gaffey et al., 2019)*. This may explain the observed coexistence . Research shows that cortisol insensitivity is associated with increased depressive symptoms *(Gaffey et al., 2019)*.

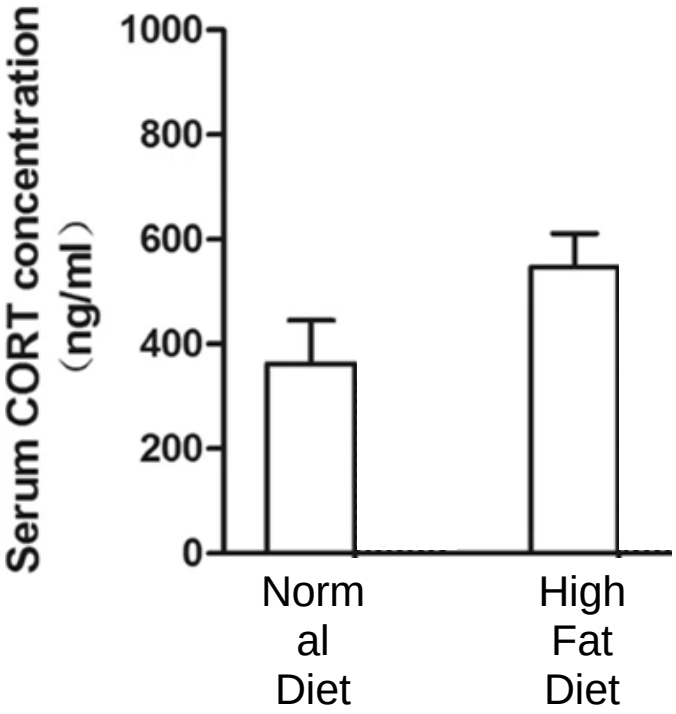

Figure 8 . High fat diets increase corticosterone (CORT) levels in rats compared to a normal diet *(He et al., 2017).*

Studies demonstrate that the restoration of a diverse gut microbiome by the consumption of probiotics Bifidobacterium and Lactobacillus reduces stressor-induced HPA reactivity *(Messaoudi et al., 2011) (De Weerth, 2017)*. Administration of these probiotics might therefore be advantageous for the treatment of depression.

By now it is known that the western diet contributes to dysbiosis in the gut, it alters the HPA axis and the serotonergic system. Furthermore, the western diet has been associated with increased inflammation *(Turnbaugh et al., 2008)*. Its high saturated fatty acid content promotes the release of bacteria-derived lipopolysaccharide (LPS) from the gut into the circulatory system *(Erridge et al., 2007) (Ghanim et al., 2009)*. LPS increases the permeability of the gut thereby triggering an inflammatory response by the release of pro-inflammatory cytokines *(Candelli et al., 2021)*. As mentioned in chapter 4, depression is associated with increased levels of pro-inflammatory cytokines and excessive immune responses *(Peruga et al., 2011)*.

The intake of dietary fiber has on the other hand been associated with decreased levels of inflammation *(Swann et al., 2020)*. A meta-analysis shows that increased fiber consumption is negatively associated with the risk of developing depression as can be seen in figure 9. Dietary fiber intake also contributes to an increased alpha diversity and SCFA production as discussed in chapter 3 *(Ranaivo et al., 2022) (Ramirez-Farias et al., 2008)*. This may be promising for the treatment of depression.

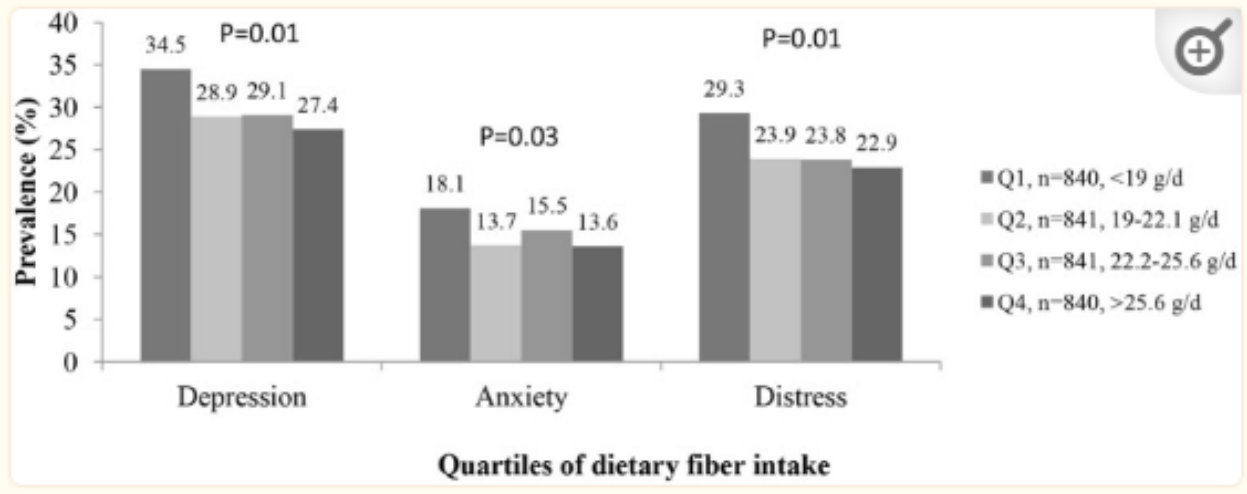

Figure 9. Prevalence of depression, anxiety and distress in people consuming different amounts of fiber per day. An increase in fiber intake was inversely associated with the prevalence of depression, anxiety and distress.

The western diet (high fat, high carbs) is severely obtained in depressed individuals and lacks a lot of essential nutrients such as omega-3 fatty acids, amino acid precursors and various essential vitamins *(Rao et al., 2008)*. Evidence shows that these nutrients are able to influence the gut-brain axis via the gut microbiota by increasing the alpha diversity *(Costantini et al., 2017) (Menni et al., 2017)*. Recent studies suggest that the maintenance of a healthy diet is positively linked to a diverse microbiome and thereby to a reduced risk of developing depression *(Khosravi et al., 2015) (Le Port et al., 2012)*. Observational studies have found that increased fiber intake together with fruit and fish consumption results in less depressive-like symptoms *(Swann et al., 2020)*. Consuming these compounds contributes to the restoration of essential nutrients that are lacking in depressed individuals such as omega-3 fatty acid and vitamins. The only thing that is not known yet is if diet-induced alterations in the microbiome will stand long-term and therefore more research should be conducted *(Wu et al., 2011)*.

The obtained knowledge of how various factors affect the gut microbiota, thereby influencing the gut-brain axis explains the importance of the periphery in the development of depression. With this understanding, novel therapies can be explored that might be beneficial for the treatment of depression.

Chapter 6: Therapies

It is now recognized that there are many contributors to the altered serotonin levels that are accompanied by depression. As mentioned in chapter 4, 95% of 5-HT is produced in the periphery *(Appleton, 2018).* Communication via the gut-brain axis reveals that 5-HT in the gut influences 5-HT in the brain as well. With this knowledge it might be interesting to look beyond current treatment methods that focus on the CNS and focus on microbiome-based approaches as novel treatment options.

Recent studies suggest that the maintenance of a healthy diet is positively linked to a diverse microbiome and therefore to a reduced risk of developing depression *(Khosravi et al., 2015) (Le Port et al., 2012)*. As outlined in previous chapters, depressive individuals tend to make poor dietary choices and are often observed consuming a western diet, which is characterized by high intake of saturated fat and refined carbohydrates. The western diet has been associated with dysbiosis and alters the gut-brain axis by a hyperactive HPA axis and increased activation of the immune system *(Martinez et al., 2017) (Gensollen et al., 2016) (Thursby et al., 2017)*. Improving nutrition might restore these systems by enhancing alpha diversity and might therefore contribute to decreased depressive-like symptoms *(Costantini et al., 2017) (Menni et al., 2017)*. Especially the intake of fiber, fish and vegetables seems to reduce depressive-like symptoms as consumption of these compounds increases the amount of SCFAs and essential nutrients that are lacking in depressed individuals such as omega-3 fatty acid and vitamins *(Swann et al., 2020) (Ramirez-Farias et al., 2008).*. Chapter 5 indicated that these nutrients are able to influence the gut-brain axis by increasing alpha diversity in the gut and thereby decreasing depressive-like symptoms *(Costantini et al., 2017) (Menni et al., 2017)*.

Another way to restore the microbiota is by altering the species directly via the consumption of probiotics. As discussed in previous chapters, consumption of the probiotics Bifidobacteria and Lactobacillus seemed to have beneficial effects on the restoration of the tryptophan metabolism *(Desbonnet et al., 2010)*, decreasing low-grade inflammation *(Duboc et al., 2013)*, reducing stressor-induced HPA reactivity *(Messaoudi et al., 2011)*,and increasing the SCFA content *(Ramirez-Farias et al., 2008)*, thereby improving cognition *(Dinan et al., 2013) (Liu et al., 2015)*. This might be promising in the treatment of depression. Depressed patients could also take postbiotics as these are the fermentation products of the microbiota that play a major role in the gut-brain axis and 5-HT production, which was demonstrated in chapter 3 *(Vernocchi et al., 2020) (Carlessi et al., 2021)*.

Furthermore, future research should focus on fecal microbiota transplantations (FMT). This technique promotes the repopulation of the microbiota directly in people with dysbiosis. Chapter 5 indicated that the transplantation of fecal microbiota of depressed humans into germ free rats increased depressive symptoms *(Kelly et al., 2016)*. Conversely a systematic review found that the transplantation of a healthy microbiome reduces depressive symptoms in psychiatrically ill individuals *(Meyyappan et al., 2020)*. Another study observed that fecal microbiota transplantations in patients with MDD improve depressive symptoms, the results can be seen in figure 10 *(Doll et al., 2022)*. These studies indicate that FMT might be a promising method in

treating depression. However, it is necessary to maintain this transplanted population and depressed patients are able to achieve this by changing their diet.

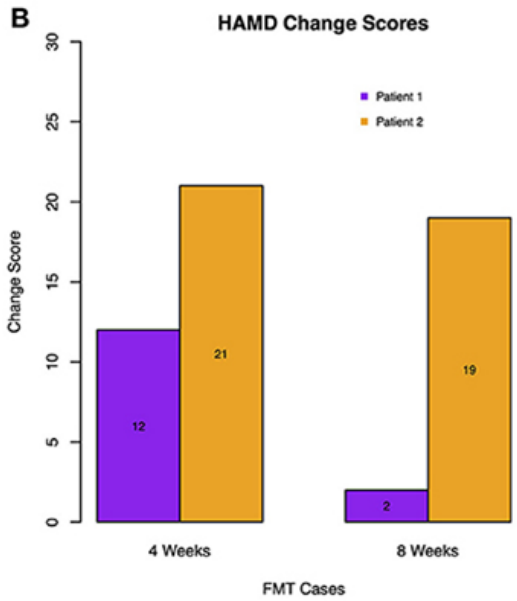

Figure 10. Depressive symptoms decreased for both patients after 4 week and 8 weeks after FMT administration .

In conclusion, it can be stated that attention should be given to the importance of periphery in the development of depression. This thesis raises the interest to look beyond current treatment methods that focus on the CNS and give attention to the periphery instead for the treatment of depression. It has been achieved that affecting 5-HT in the periphery also affects 5-HT in the brain because of the gut-brain axis that communicates between these systems. Future treatment methods should focus on changing the gut microbiota as this is a key component in this bidirectional communication system. Novel treatment methods have been devised that target the microbiota directly. These methods are fecal microbial transplantations, probiotics and changing the diet. These methods seem to be effective in restoring the microbiota of depressed patients and this is why more research has to be done in this field.

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