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Mental Health and the Gut Microbiome

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Center for Victims of Torture

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I. Executive Summary:

The Center for Victims of Torture (CVT) is a non-for-profit organization that provides care and support to survivors of torture. The CVT works both within the US and internationally to prevent torture and treat victims, conducts research into best healing practices for survivors, and advocates for an end to torture worldwide. The CVT's mission is to heal wounds of torture survivors, their families, and communities. The purpose of this project was to research the link between the gut microbiome and mental health to inform nutritional recommendations for patients suffering from severe mental trauma. In conjunction with medication, these recommendations may be used by nurse practitioners and physicians at CVT to help relieve symptoms of chronic depression, PTSD, anxiety, and fear that their patients are experiencing.

II. Abstract:

In recent decades, mental illness and its complications have been on the rise. Many view this increase in mental illness as a consequence of modernization. Specifically, economic changes, urbanization, dietary changes, sedentary lifestyles, lack of adequate sunlight, and decreases in social support are all believed to contribute to this increase [1]. Although it is hard to pinpoint the exact cause of the increased prevalence of mental illness as it is most likely a combination of many factors, recent evidence has suggested that the gut microbiome plays a key role in the development and sustainability of mental disorders through multiple mechanisms. Additionally, dietary changes that specifically target and cultivate beneficial microbial populations in the gut may be an effective way to treat and prevent mental illness. This literature review explores the evidence linking the gut microbiome to brain diseases and how changing one's diet may help mitigate symptoms of mental disorders.

III. **Background:**

The prevalence of mental illness has been increasing in recent decades. According to the National Alliance on Mental Illness (NAMI), 1 in 5 US adults experience a mood disorder in any given year and mental illness is listed as a leading cause of disability in the US [2]. This increase in mental illness also correlates with increases in other chronic diseases, such as obesity, cardiovascular disease, type 2 diabetes, irritable bowel syndrome (IBS), autism spectrum disorder (ASD), Parkinson's Disease, and cancer [1]. Many suspect that the rise of chronic diseases in the US can be attributed to changes in lifestyle, such as sedentary behaviors, urbanization, increased social media and decreased offline social support, dietary habits, processed foods, decreased sunlight exposure, and more [1]. Additionally, these chronic diseases are often accompanied by mental illness which motivated researchers to explore how these diseases are linked and how modernization has influenced health status in contemporary society.

One area that is of particular interest involves the human gut microbiome and its influence on brain development, the stress response system, and development of chronic diseases. The human gut microbiome is a community of nearly 100 trillion bacteria and their genetic and metabolic material living in the gut, usually thriving on the mucosal surfaces of stomach and intestinal epithelial cells [3]. In normal situations, these bacteria live symbiotically with their human host and contribute to proper metabolic functioning, educate the immune system, protect the gut against pathogens, and influence basic physiological functions[4]. More recently, the gut microbiome has been shown to dramatically affect the functioning of the central nervous system and brain development. Additionally, a state of imbalance within the gut microbiome, known as dysbiosis, has been implicated in the development of chronic diseases through promotion of systemic inflammatory responses [5]. These discoveries have led to an increased awareness of how our microflora profoundly impacts our general state of wellbeing

and targeted treatments and interventions that may reverse the harmful effects of a state of long term dysbiosis.

In the following review, we will examine the gut-brain axis, the role of the microbiome in mental illness and other chronic disease, and specific dietary and lifestyle changes that can reverse dysbiosis and, potentially, alleviate symptoms of mental illness.

IV. The Gut-Brain Axis

The gut-brain axis (GBA) is a complex, bidirectional communication network between the central nervous system (CNS), the autonomic nervous system (ANS), the enteric nervous system (ENS), the hypothalamic pituitary adrenal (HPA) axis, and the gut microbiome. Research in this area has indicated that the role of this complex GBA is to monitor and integrate gut functions to emotional and cognitive centers of the brain [6]. Therefore, both the gut and the brain can be impacted by environmental, emotional, and genetic factors and a defect in one system can have profound effects on the other.

Interest in the gut-brain connection was sparked in the early 2000s when studies with germ-free mice (mice raised in a sterile environment) showed intriguing changes in their stress responses compared to mice with normal microflora. Notably, these germ-free (GF) mice showed an exaggerated HPA response to stress as compared to normal mice, indicating that bacteria may play a role in regulating the set-point of the stress response [7]. Interestingly, the anxious-like behavior was reversed when these mice were given *Bifidobacterium* species in their diet and anxious-like behavior could be transferred to non-anxious mice through a fecal microbiome transplant [8–10]. Additionally, other rodent studies utilizing probiotic treatment were able to replicate these findings as well as show decreased depression ratings, decreased stress response, and other signs of improved mental health [11–14].

These benefits were also found in humans. In a UCLA study, women were randomly assigned to a probiotic yogurt, a placebo dairy product, or nothing for four weeks. At the end of

the four weeks, the women who ate the probiotic yogurt showed decreased brain activity associated with anxiety and emotional reactivity to emotional stimuli as compared to the other two groups [15]. These findings suggested that certain bacterial species in the gut may impact how the brain responds to external stimuli, in turn impacting the mental state and wellbeing of an individual.

There are many proposed hypotheses that seek to explain how the microbiome influences the brain and contributes to disease states. Increased levels of inflammatory cytokines, increased oxidative stress, decreased cortisol sensitivity, and decreased levels of serotonin have been linked to adverse mental and chronic health outcomes. Interestingly, most, if not all, of these symptoms can be explained by gut dysbiosis within patients.

In individuals experiencing stressful life events, the stress response system may be over activated, leading to changes within the intestinal mucosa via the vagus nerve. Specifically, the intestinal permeability may increase in these individuals. When intestinal permeability increases, the gut becomes “leaky,” allowing bacteria in the gut to translocate across the intestinal barrier and access immune cells and the nervous system [1]. This results in systemic inflammation, which has been implicated in chronic diseases, such as mental illness, diabetes, and obesity [1].

In the next section, we will discuss how systemic inflammation might occur in depressed individuals and how the gut can modulate this response.

V. The Role of the Microbiome in Mental Health

Patients with mental illness, such as depression, anxiety, and PTSD, all tend to have one factor in common: increased systemic inflammation. This can be both a cause and an effect of these mental illnesses. During stressful life events, microglia, or immune cells in the brain, become activated [16]. Once activated, these cells produce inflammatory cytokines which, in turn, activate more immune cells throughout the body [17]. This chain of events results in chronic inflammation and oxidative stress if the stressor is not removed. Furthermore, this systemic

inflammation could result in increased gut permeability, thus exposing gut immune cells to increased levels of gut bacteria. This interaction has been found to increase the inflammatory state of the body and potentially prolonging the state of depression even after the stressor is removed [18].

One way researchers have been able to mimic the effect of systemic inflammation in rodents is through chronic administration of low doses of lipopolysaccharide (LPS). LPS is a surface molecule on many gram-negative bacteria typically found in the gut or on pathogens. When mice were exposed to low systemic doses of LPS, they showed signs of increased anxiety, depression, cognitive defects, and increased visceral pain sensitivity [19]. In humans, a higher circulating LPS level is positively associated with obesity, diabetes, CVD, and higher cholesterol [20,21]. Additionally, higher levels of LPS has been linked to decreased tryptophan and enhanced kynurenine availability, which compromises serotonin levels in the blood [14]. This research suggests that increased levels of LPS in the systemic circulation of individuals may exacerbate symptoms of depressive illness by causing increased inflammation, decreased antioxidant functioning, and decreased availability of serotonin.

One way patients may experience increased LPS levels in the blood is through a compromised intestinal barrier. Compromised intestinal barriers have been known to occur under conditions of stress, such as athletic exercise. It has also been shown, in a recent study, to be linked to both psychological and physical stress in humans undergoing combat-training. In this study, the researchers enrolled male soldiers who participated in a 6-week combat training followed by a rest period. During both time points, the researchers collected anxiety and depression scores, stress and bowel function, blood and urine samples, and assessed intestinal permeability through tests of urinary excretion of orally ingested sugar probes. The researchers found that the soldiers showed higher anxiety and depression scores, increased GI symptoms, increased inflammatory blood markers, and increased intestinal permeability during combat

training than at rest. This study further indicates that intestinal permeability and inflammation are linked to physical and mental stress and are accompanied by GI distress. [22]

Additionally, some investigators have shown signs of increased permeability in depressed patients as compared to their non-depressed counterparts. Notably, one study showed that depression in alcohol-dependent adults was linked to an increased intestinal permeability (IP) as compared to their less depressed alcohol-dependent counterparts [23]. Interestingly, increases in IP were also associated with changes in gut microflora composition and metabolic profiles of these bacteria. In order to assess these changes, the researchers enrolled adults who were undergoing a 3 week rehab for alcohol-dependency and investigated changes in IP, depressive symptoms, gut microflora composition, and gut microflora metabolic profile before and after rehab. The researchers found many interesting associations between these factors, including:

- A linear association between psychological status before and after rehab and IP (higher IP was always associated with higher depression scores)
    - Those with high IP at start and saw decreased IP at end had best positive changes in depression scores than any other group.
- These changes in IP were ascribed to changes in microbial composition and activity during the 3 week trial
- The high IP group had a different microbial composition and profile than both the low IP and the controls (low IP was not statistically significant from controls)
    - Total amount of bacteria significantly lower in high IP group than low IP and controls
    - Metabolic profiles differed between these groups: protein fermentation was different in these groups
        - Higher production of toxic metabolites and lower production of indolic compounds in high IP group

        - Linked to types of bacteria that were most or least abundant as compared to the control group
    - Short term alcohol withdrawal increased the number of total bacteria significantly, but high IP group never fully recovered (or reached same bacterial composition as low IP and controls)
        - Long lasting dysbiosis which could not be recovered through withdrawal alone

[23]

This mirrored the findings of other studies involving clinically depressed patients. Specifically, this study and others researching dysbiosis in depression have found increased bacterial diversity in the gut, lower overall numbers of gut bacteria, increased levels of anti-inflammatory cytokines, and increased gut permeability. Moreover, these studies have identified similar increases and decreases in specific bacterial species in the gut of depressed individuals as compared to controls. Overall, they have found an increased abundance of *Alistipes* (associated with decreased tryptophan production and availability) and *Proteobacterium* (inflammatory pathogens) and decreases in *Faecalibacterium (*anti-inflammatory)*,* *Ruminococcaceae* (carbohydrate metabolism)*,* and *Oscillibacter* (produces GABA homolog).[5,24]

Researchers and authors Justin and Erica Sonnenberg also have shown that intestinal permeability is increased if certain dietary needs are not met. Many beneficial bacteria in the gut metabolize compounds known as microbial accessible carbohydrates (MACs). MACs are carbohydrates in the diet that are not readily digested by the human host, but can be fermented by microbial species within the gut. As such, these are commonly referred to as “prebiotics” and include fiber from fruits and vegetables and legumes. The fermentation of MACs by microbes in the gut can lead to the production of beneficial compounds, such as short chain fatty acids. Diets with high levels of plant-based fiber have been shown to modify both the microbial populations within the gut and what these bacteria utilize as food sources. For example, the

microbiome of individuals who consume high levels of MACs daily are more diverse than the microbiome of individuals who consume low levels of MACs daily. Additionally, a low MAC diet may contribute to intestinal permeability, as the microbes that ferment MACs will also ferment mucus produced by the intestinal lining if MACs are not provided daily. Therefore, by "starving" the microbial populations in the gut, one is increasing the risk of intestinal permeability and, therefore, mental illness.[25]

Epidemiological evidence linking dietary fiber intake and depressive outcomes is scarce in the human population. Notable studies include Miki et al. 2016 and Woo et al. 2006. These studies provide strong evidence for a negative correlation between dietary fiber intake and depressive symptoms. Specifically, Miki et al. reported a statistically significant inverse relationship between dietary fiber intake from fruits and vegetables and depressive symptoms in Japanese employees aged 19-69 years [26]. Similarly, Woo et al. also reported an inverse relationship between dietary fiber and depressive symptoms in a population of elderly Chinese individuals [27]. These studies provide insight into how dietary fiber intake may affect depressive outcomes. However, these studies were cross sectional in design, thus a causal relationship cannot be established.

Additionally, several studies have implicated the gut microbiome in the production and storage and serotonin in the body independently of LPS levels. Recently, research has shown that approximately 95% of the serotonin produced in our body is actually produced and stored by the gut and most of this is made via signals that come from the gut microbiota [28]. Specifically, metabolites from gut bacterial populations signal to nearby intestinal epithelial cells to produce and store serotonin. Whether or not this has an impact on effectiveness of selective serotonin reuptake inhibitors (SSRIs) and mental illness is unknown, but further implicates diet and the microbiome in the development and sustainability of depression.

VI. Recommendations: Dietary Changes for Individuals Experiencing Mental Distress Accompanied by Gastrointestinal Issues

"Let food be thy medicine and medicine be thy food"

-Hippocrates

There have been numerous human studies (cross-sectional and prospective) that indicate diet can have an impact on risk for depression and other mental illnesses, like Alzheimer's disease and dementia. For example, multiple studies have found a correlation between adherence to the Mediterranean style diet and risk for mental illness [29–31]. Specifically, an increased adherence to the Mediterranean style diet was associated with decreased risk of mental illness. However, this may not be evidence for the therapeutic benefit of a Mediterranean style diet for people with existing mental illness.

With that said, there have been studies suggesting that diets higher in fat and low-fiber carbohydrates are linked to elevated LPS in the blood. Similarly, simple sugars, such as fructose found in high-fructose corn syrup, were linked to higher circulating LPS. By contrast, switching to a more Mediterranean style diet was linked to a decrease in blood LPS and reduced fasting blood glucose. These studies may indicate that diet is directly related to intestinal permeability and, therefore, the amount of circulating LPS and subsequent inflammation a person might experience. Therefore, it may be beneficial for those experiencing depressive and anxiety-like symptoms to adhere to a better diet and take probiotic supplements (either from fermented dairy products or as a pill). It may not eliminate symptoms, but it may help reduce inflammation associated with mental illness. [1]

There have been some anecdotal evidence suggesting a direct correlation between dietary changes and a reversal of symptoms related to autism spectrum disorder, depression,

schizophrenia, and other mental disorders. This evidence comes mainly from people adhering to the gut and psychology syndrome (GAPS) diet developed by Dr. Natasha Campbell-McBride. Namely, the diet is gluten, sugar and dairy-free, high in veggies and fruits, eliminates processed foods from the diet, and encourages people to consume probiotics (homemade yogurt and sauerkraut) and cook their own meals. By doing so, she claims the proper balance of beneficial gut microbes are restored and can prosper, restoring proper brain function and reversing symptoms of many mental disorders. Several parents have claimed their child's ASD symptoms decreased as a result of this diet, but little evidence has been indicated in the diet's effectiveness to treat major depression and anxiety. [32]

Dr. Campbell-McBride also states in her book that medication should not be stopped during the dietary changing process until after the diet has reversed most of their symptoms or when a physician or healthcare provider supports it. She also suggests to slowly introduce dietary changes over the course of a few years due to potential side effects of changing the microbiome too rapidly. For example, she states that many of her patients experience bad side effects after taking prescribed probiotics. She attributes this to a "die off" of less beneficial bacteria in the gut when beneficial probiotic bacteria are introduced to the gut. This die off causes inflammation in your body, leading to flu-like symptoms. Therefore, she suggests that one should start with small doses of probiotics and slowly increase the dose over a series of months. Little scientific evidence supports this theory, but many have claimed they experienced these symptoms when taking a probiotic or starting a new diet. [32]

Although there isn't direct scientific evidence supporting her claims, there are numerous studies that do show a relationship between diet and improved mental status. In a cross sectional and prospective studies on adolescents, researchers have found a dose-response relationship between eating a healthier diet and having better mental status, even after adjustment for gender and physical activity levels [31]. However, no randomized clinical trial has been developed to test if changing diet will increase mental health status.

According to research with healthy individuals and rodents, here are some recommendations for those experiencing mental illness:

- Grain and dairy-free diet
- Low sugar diet
- No processed foods
- Cold pressed oils: olive oil, fish oil, nuts and seed
- Fermented foods (yogurt, sauerkraut, kombucha, kimchi, pickles)
- Probiotics
- herbs/spices, onions and garlic
- Homegrown or locally produced and organic fruits/veggies
- Eliminating animal fat from processed foods and substituting for wild caught/free range/grass-fed animal products
- Eliminating additives
- Avoiding extreme diets (extremely low calorie, no carb, etc)
- Avoiding mass produced and processed foods (artificial sweeteners, fast foods, etc)
- Avoiding foods that use antibiotics or pesticides
- Avoid eating when stressed/anxious/depressed and eat meals with family members or friends

Again, these dietary recommendations have yet to be formally tested on a group of patients experiencing mental illness. Most studies have been cross-sectional or prospective studies looking at the links between diet and risk of depression/anxiety. Further research, specifically clinical trials, needs to be conducted in order to assess the efficacy of nutritional changes as a treatment for mental health. Nonetheless, the evidence in this literature review suggests that nutrition may be a helpful option for those experiencing depression and anxiety.

VII. References

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