Effect of a vegetarian diet on the gut microbiome and major depressive disorder

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Abstract

Major depressive disorder (MDD) is one of the leading contributors to global disease burden. There are several mechanisms that might affect MDD. First of all, several neurotransmitters are involved in MDD; reduced levels of serotonin, dopamine noradrenaline, norepinephrine, epinephrine and GABA are associated with MDD. Contrarily, excessive levels of glutamate can aggravate depressive symptoms. Besides neurotransmitters, levels of brain-derived neurotrophic factor (BDNF) are reduced in MDD patients. Furthermore, MDD is characterized by a hyperactive hypothalamic-pituitary-adrenal (HPA) axis. Lastly, inflammation seems to aggravate depressive symptoms. The gut-brain axis has been demonstrated to be involved in the pathogenesis of depression. First of all, gut microbes can regulate the synthesis of neurotransmitters, which can signal the vagus nerve or enter the blood circulatory system. Furthermore, the gut can produce metabolites that affect the brain, most prominently short-chain fatty acids (SCFAs). Lastly, gut microbes can have (anti-)inflammatory effects on the host. Although gut microbes can affect the brain via the gut-brain axis, there is no clear shift in the microbiome composition of MDD patients, as literature reports are conflicting. Nonetheless, probiotic studies indicate that *Lactobacillus* and *Bifidobacterium* can alleviate depressive symptoms. A vegetarian diet decreased *Bifidobacterium* species and *Lactobacillus amylovorus,* suggesting a disadvantageous effect of a vegetarian diet on MDD. Meat consumption enhances serotonin and tryptophan (serotonin precursor) levels in the gut. However, this does not necessarily enhance serotonergic neurotransmission in the brain. Besides serotonin, tryptophan is also a precursor for kynurenine. Kynurenine can induce a neurotoxic effect. Meat consumption may inhibit kynurenine pathway by increasing *Lactobacillus*. However, meat-induced inflammation may upregulate the neurotoxic pathway of kynurenine. Besides tryptophan, tyrosine might also affect MDD. Tyrosine is a precursor for dopamine, epinephrine and norepinephrine. Tyrosine is synthesized in the gut. However, dietary tyrosine did not induce antidepressant effects. Thus, the effect of tyrosine metabolism on MDD remains unclear. Vitamins might affect MDD as well. Both vitamins abundant in a vegetarian diet (folate) as well as in an omnivorous diet (B12) could enhance monoaminergic neurotransmission. Moreover, meat, which is high in sulfide and zinc, seems to stimulate GABAergic neurotransmission and inhibit glutamergic neurotransmission. D-amino acids, which are abundant in a vegetarian diet, may stimulate glutamatergic neurotransmission, whilst folate seems to reduce it. Moreover, both a vegetarian and omnivorous diet can result in metabolites that enhance BDNF levels. Lastly, it is important to emphasize that an omnivorous diet induces inflammation, which could aggravate MDD. Hence, through different metabolites, a vegetarian and omnivorous diet are able to either positively or negatively impact MDD. The conflicting results might suggest there is no direct relation between a vegetarian diet and MDD. Nonetheless, ambiguous results might also suggest the need for additional research, as the relation between diet, the gut microbiome and cognitive functioning is very complex.

Keywords: major depressive disorder, vegetarian diet, gut-brain axis, short-chain fatty acids, *Lactobacillus, Bifidobacterium,* tryptophan, tyrosine

Layman's summary

Major depressive disorder (MDD) is one of the leading contributors to global disease burden. There are several mechanisms that might affect MDD. First of all, several neurotransmitters are involved; reduced levels of serotonin, dopamine noradrenaline, norepinephrine, epinephrine and GABA are associated with MDD. Contrarily, excessive levels of glutamate can aggravate depressive symptoms. Besides neurotransmitters, several neuroprotective peptides and proteins are reduced in MDD patients. The most important one being brain-derived neurotrophic factor (BDNF). Furthermore, MDD is often elicited or exacerbated by chronic stress. The hypothalamic-pituitary-adrenal (HPA) axis, the primary stress system in humans, seems to be hyperactive in MDD patients. Lastly, inflammation seems to aggravate depressive symptoms. Microbes in the gut might impact MDD by communicating with the central nervous system. This communication is also known as the gut-brain axis. Gut microbes can regulate the synthesis of neurotransmitters, which can then signal to the brain. Besides neurotransmitters, gut microbes can produce other compounds that might affect brain functioning. The most important one of these compounds are short-chain fatty acids (SCFAs). Lastly, gut microbes can also have (anti-)inflammatory effects on the host. Although gut microbes can affect the brain via the gut-brain axis, there is no clear shift in the microbiome composition of MDD patients, as literature reports are conflicting. However, ingestion of certain microbes does seem to affect MDD; *Lactobacillus* and *Bifidobacterium* are bacterial species that alleviate depressive symptoms. A vegetarian diet decreased *Bifidobacterium* species and *Lactobacillus amylovorus.* This suggests a disadvantageous effect of a vegetarian diet on MDD. Furthermore, the effects of the macro- and micronutrients in a vegetarian or omnivorous diet are discussed. Gut microbes can metabolize tryptophan to serotonin. Meat consumption can enhance tryptophan and serotonin levels in the gut. However, this does not necessarily mean serotonin levels in the brain are enhanced. Besides serotonin, tryptophan can also be metabolized into kynurenine. Enhanced kynurenine levels may have a neurotoxic effect. Meat protein may reduce kynurenine levels by increasing *Lactobacillus* species. Conversely, meat can also induce inflammation, which might enhance kynurenine levels. Besides tryptophan, tyrosine might also affect MDD. Tyrosine can be metabolized into dopamine, epinephrine and norepinephrine. Gut microbes can synthesize tyrosine. However, dietary tyrosine did not induce antidepressant effects. Thus, the effect of tyrosine metabolism on MDD remains unclear. Vitamins might affect MDD as well. Both vitamins abundant in a vegetarian diet (folate) as well as in an omnivorous diet (B12) could enhance neurotransmitters that might alleviate depressive symptoms. Moreover, both a vegetarian and omnivorous diet can result in metabolites that enhance BDNF. Lastly, it is important to emphasize that a meat-based diet generally seems to induce more inflammation, which could negatively impact depressive symptoms. Hence, through different metabolites, a vegetarian and omnivorous diet seem to be able to either positively or negatively impact MDD. The conflicting results might suggest there is no direct relation between a vegetarian diet and MDD. Nonetheless, ambiguous results might also suggest the need for additional research, as the relation between diet, the gut microbiome and cognitive functioning is very complex.

Introduction

Major depressive disorder (MDD) is a leading contributor to global disease burden. The WHO ranks depressive disorders as the single largest contributor to non-fatal health loss globally [1]. In 2020, the global prevalence of MDD was estimated at approximately 3153 cases per 100.000 population. During the COVID-19 pandemic, a major increase in disease prevalence could be observed. A systemic literature review and meta-analysis of 46 studies estimated an increase of approximately 28% [2]. Patients with MDD are dying 5 to 10 years earlier; due to maladaptive health risk behaviors patients often develop medical disorders such as vascular disease, diabetes, chronic obstructive pulmonary disease and cancer [3–5]. MDD is characterized by a depressed mood, loss of interest or pleasure (anhedonia), feeling of worthlessness, indecisiveness, significant weight or appetite alteration, insomnia or hyposomnia, psychomotor agitation or retardation, fatigue, diminished ability to concentrate and suicidality [6]. To be classified as MDD, five or more symptoms are requires to be present during a two-week period and should cause impairment of functioning [7].

The underlying pathophysiological mechanisms of MDD remains somewhat elusive. Evidence suggests depression is caused by a cumulative effect of environmental stress and genetics [8,9]. Nonetheless, as this review focuses on diet, genetics are disregarded. Chronic stress can lead to dysfunctions in monoaminergic systems, neurotrophic factors, synaptic plasticity and the hypothalamus-pituitary-adrenal axis (HPA axis). These dysfunctions induce neuronal atrophy in several regions of the brain, most notably the hippocampus and prefrontal cortex [10]. Nonetheless, the heterogeneity of MDD makes it difficult to clarify the exact pathophysiology. Diagnosis of MDD is not etiologically derived but based solely on symptoms. Hence, it is proposed depression might result from multiple pathogeneses, making it difficult to illuminate the definite mechanisms involved [11].

Nonetheless, there is accumulating evidence that the gut microbiome can modulate brain activity and is involved in development of neuropsychiatric disorders, including MDD. The gut microbiome has a bidirectional communication with the central nervous system; the gut-brain axis [12]. Gut microbes might be involved in the pathophysiology of MDD through neural, endocrine or immune pathways. Dietary patterns substantially impact the gut microbiota. Hence, dietary patterns might exacerbate or alleviate the risk of developing MDD. As food components in a vegetarian diet generally differ from that of an omnivorous diet, it is proposed there might be an effect on the development of depressive symptoms [13]. Hence, this leads to the question: what is the effect of a vegetarian diet compared to an omnivorous diet on the gut microbiome and the pathophysiology of major depressive disorder? This thesis will discuss several contemporary theories on the pathophysiology of MDD, mechanisms of the gut-brain axis, differences in gut microbiome composition and the effect of metabolites of an omnivorous or vegetarian diet on cognitive functioning.

Chapter 1: Etiology of major depressive disorder

The exact etiology of MDD is still unclear. However, literature reports several hypotheses. The most relevant include: 1) the monoaminergic hypothesis, 2) the neuroplasticity hypothesis, 3) disruption of the stress response in the HPA axis and 4) cytokine hypothesis. The following chapter will briefly explain these theories.

1.1 Monoaminergic hypothesis

The monoaminergic hypothesis is one of the oldest hypotheses on the development of MDD. Abnormalities of monoamines have long been recognized in the pathophysiology of MDD. These monoamines include noradrenaline, serotonin, norepinephrine and dopamine [14]. Most contemporary antidepressants are still using mechanisms to increase these monoamines at the synapse, either by inhibiting neuronal uptake or by increasing their release [15]. Possible involvement of all neurotransmitters in development of MDD will be briefly discussed.

Noradrenaline

Noradrenaline is involved in several physiological processes in the brain, including learning and memory, sleep, arousal and adaptation [16]. Even before the monoaminergic hypothesis, the catecholamine hypothesis suggested major symptoms of depression arise due to noradrenaline deficiency [17]. The role of noradrenaline in MDD has been confirmed in animal studies with tyrosine hydroxylase, a rate-limiting enzyme in the biosynthesis of noradrenaline. In knockout mice without a tyrosine hydroxylase gene, noradrenaline levels decreased significantly in several brain regions. These mice displayed depressive-like behavior comapred to healthy controls, suggesting involvement of noradrenaline is MDD development [18]. As its importance has been recognized for some time, there are alreadye several antidepressants that have a stimulating effect on noradrenaline concentrations [19]. Nonetheless, the catecholamine hypothesis has been revised over time, as the importance of serotonin became more apparent. Hence, the hypothesis changed into the monoaminergic theory of depression.

Serotonin

The involvement of serotonin in the etiology of MDD has long been recognized. The link between lowered serotonin levels and depression was first suggested in 1960 [20]. Mice with impaired hippocampal serotonin receptor expression showed more depressive behavior [21]. The serotonergic system may be more involved in aspects of behavior; modulating sexual function, appetite, and impulsiveness. At both the brain level and the spinal cord level, serotonin is involved in the etiology of some physical and emotional symptoms of depression [14,22]. Serotoninergic stimulation is also associated with neurogenesis, synaptic plasticity and can induce dopamine release [22,23].

Norepinephrine

The noradrenergic system may be involved in motivation; modulating energy, interest, and concentration. At both the brain level and the spinal cord level, these neurotransmitter systems are involved in the etiology of some physical and emotional symptoms of depression [14,22]. Moreover, norepinephrine is involved in neurogenesis and synaptic plasticity [22].

Dopamine

Depression is characterized by an increase of negative emotions and a reduce ability to experience pleasure. Dopamine is involved in the latter. Dopamine is one of the major neurotransmitters that is involved in reward-motivated behavior [24][25]. Depressed patients often display a reduced ability to experience pleasure, also known as anhedonia. Anhedonia has been linked to dysfunctions in the dopamine system [26,27]. Chronic stress can interfere with dopamine functioning [27]. The role of dopamine in MDD remains somewhat elusive as the field has mostly focused on serotonergic and noradrenergic mechanism [28]. There are some reports of antidepressants altering dopaminergic transmission [29,30]. The role of

dopaminergic transmission has also been receiving more attention in development of new antidepressants, including ketamine, which interferes with dopamine dysfunction [30]. In animal models, dopamine transporter knockout mice chronically elevated extracellular dopamine levels. Remarkably, dopamine knockout animal models displayed more depressive symptoms than serotonin or norepinephrine knockouts, suggesting a prominent role of dopamine in the pathophysiology of MDD [31].

1.2 Neuroplasticity hypothesis

So far, the majority of MDD research and antidepressant development has focused on the monoaminergic hypothesis. However, currently only 50-60% of patients directly respond to antidepressant treatment [32]. Moreover, the currently used antidepressants take several weeks to achieve their therapeutic effects. This is remarkable, as the antidepressants have an effect on the monoamine availability within hours [33]. Hence, this indicates other mechanisms also come into play in the pathophysiology of MDD. More recently, a new hypothesis has evolved; the neuroplasticity hypothesis. This hypothesis entails that mood disorders can be elicited by maladaptive neuroplasticity [34]. This hypothesis was supported by animal studies, where maladaptive plasticity in the hippocampus was reversed by antidepressants [35,36]. Glutamate, the main excitatory neurotransmitter in the brain, is present in very high concentrations in synaptic vesicles, suggesting an important role in neuroplasticity [34,37]. Hence this hypothesis focusses mainly on the balance of the main excicitory neurotransmitter glutamate and the main inhibitory neurotransmitter GABA. Both will be discussed in this section. Moreover, neuroplasticity is impacted by neurotrophic factors, a protein family involved in synapse formation, neuronal growth, differentiation, maturarion and survival [38,39].

Glutamate

Glutamergic transmission is very important in synaptic plasticity and there are implications that MDD is associated with abnormal glutamatergic transmission. The glutamate hypothesis was first proposed in 1990, when it was found an antagonist of the glutamate receptor N-methyl-D-aspartate (NMDA) had an antidepressant effect [40]. Glutamergic excess can contribute to cell damage or even cell death [41]. Stress can enhance glutamate levels in the prefrontal cortex and hippocampus [42]. Expression of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, another glutamate receptor, is elevated after exposure to stress as well [43].

GABA

Γ-aminobutyric acid (GABA) is the principal inhibiting neurotransmitter in the brain MDD [44]. GABAergic transmission seems to be downregulated in MDD patients [45–49]. It is suggested GABA may facilitate monoaminergic transmission, in particular serotonergic transmission, which can suppress depressive symptoms [50,51]. Chronic stress can reduce abundance and function of GABA receptors in the cerebral cortex and hippocampus [52–54]. Inactivation of a GABA receptor subunit in animal models resulted in reduced hippocampal neurogenesis, which is associated with depressive behavior [55]. Suppressed neurogenesis is associated with an increased HPA-axis response after exposure to stress, thus creating a positive feedback loop [56]. This was confirmed in animal models, where deficits in GABA receptors caused hyperactivity of the HPA axis [57].

Neurotrophic factors

Impaired neuroplasticity can be a result of reduced levels of neurotrophic factors. The neurotrophic factor that has been most prominent in MDD studies is brain-derived neurotrophic factor (BDNF). Reduced BDNF levels have been associated with MDD patients [58–60].

BDNF seems to elicit a neuroprotective effect; it promotes neuroplasticity and survival and differentiation of neurons [38,39]. The neuroprotective abilities of BDNF result from its activation of the mTOR pathway [61–63]. BDNF binds to tyrosine kinase B (TrkB) receptors,

which enhances the mTOR signaling pathway. Activation of this pathway can promote neurogenesis and neuroplasticity [64,65]. Besides its neuroprotective effects, BDNF can also enhance serotonin and GABA neurotransmission [66–68].

Besides BDNF, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor signaling can also induce activation of the mTOR pathway [61–63]. Activation of the NMDA receptor inhibits the mTOR signaling pathway (figure 1) [63].

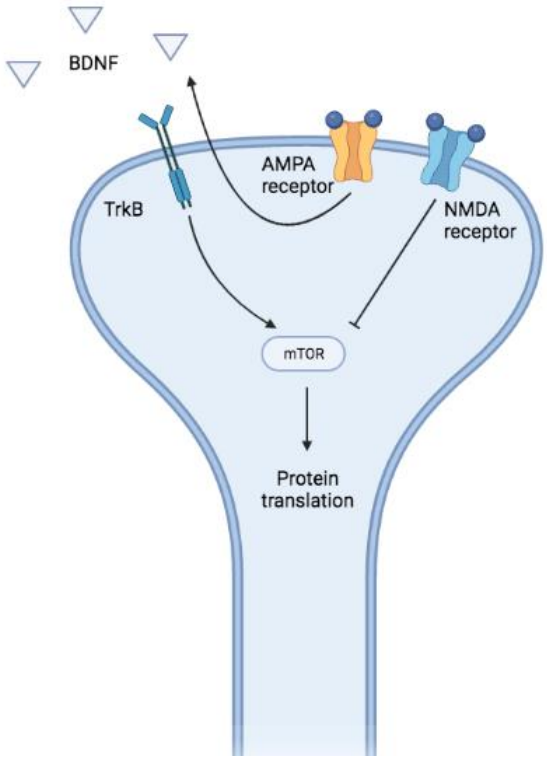

Figure 1. Simplified neuronal mTOR signaling pathway. Synaptic brain-derived neurotrophic factor (BDNF) activates tyrosine receptor kinase B, leading to mTOR activation and hence protein translation. The N-methyl-D-aspartate (NMDA) receptor inhibits mTOR activation.

1.3 Glucocorticoid hypothesis

Mood disorders are often elicited or exacerbated by acute or chronic stress [69]. The HPA axis is one of the primary stress systems in humans [70]. An environmental stressor stimulates corticotropic-releasing hormone (CRH) in the hypothalamus. This results in the pituitary releasing adrenocorticotropic hormone (ACTH). When ACTH reaches the adrenal, cortisol (or corticosterone in animals) is released. This system is regulated by a negative feedback loop; when cortisol is transported back to the hypothalamus and pituitary, it acts as a suppressor. It binds to glucocorticoid and mineralocorticoid receptors (GRs and MRs). These receptors result in down-regulation of CRH and ACTH until a state of homeostasis is reached (figure 2) [70]. However, long-term stress and elevation of cortisol levels, has been suggested to result in GR resistance, due to decreased sensitivity and decreased number of GRs [71,72]. This leads to consistently elevated cortisol levels, associated with fatigue, a bad mood and impaired cognitive functioning [72,73]. However, some discrepancies in literature arise; both elevated and blunted cortisol levels have been described in MDD patients [74,75]. Hyperactivation of the HPA axis can result in its inability to adequately respond to subsequent stressors, going from a hyper- to a hypo-responsive system [76].

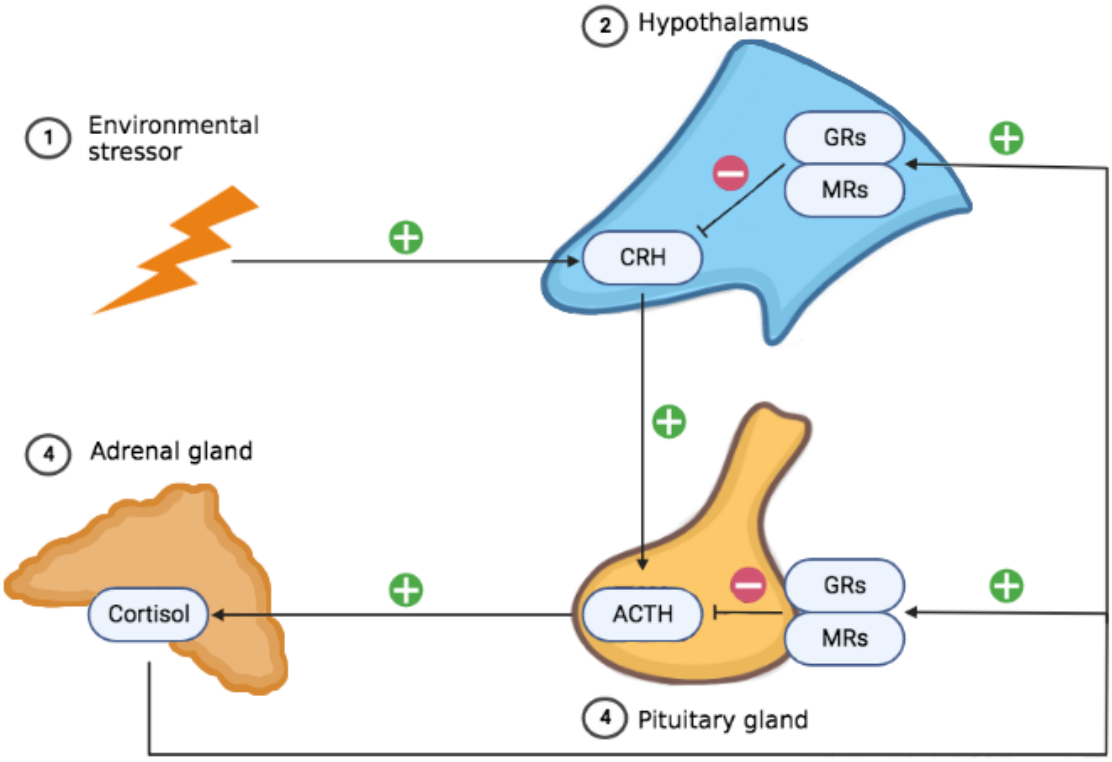

Figure 2. Stress response in the HPA axis of healthy individuals. Stress stimulates corticotropin-releasing hormone (CRH), which stimulates adrenocorticotropic hormone (ACTH). ACTH stimulates the release of cortisol. Cortisol inhibits glucocorticoid and mineralocorticoid receptors (GRs and MRs), creating a negative feedback loop.

Moreover, the HPA axis affects other systems involved in the etiology of MDD, including the monoaminergic system. Chronic stress decreased serotonin receptor expression and affected binding of serotonin to its receptor [77]. Inhibition of serotoninergic transmission decreases GR and MR gene expression in the hippocampus. Moreover, serotonin caused release of ACTH and corticosteroids. Hence the relation between serotonin and the HPA axis seems bidirectional [78]. HPA axis activation is also associated with BDNF dysfunction as well. GRs and MRs can regulate transcription of neurotrophic factors, including BDNF [79].

1.4 Neuroinflammation hypothesis

Inflammation has been implicated in the pathophysiology of depression. MDD patients exhibit increased serum levels of pro-inflammatory cytokines compared to healthy controls [80–83]. There are several implications of the involvement of inflammatory responses in the etiology of MDD. These will be briefly discussed.

Inflammation and tryptophan metabolization

Tryptophan can be metabolized into serotonin, but it can also be synthesized into kynurenine [23,84,85]. The kynurenine pathway can be dysregulated by pro-inflammatory cytokines, resulting in neurotoxicity and less availability of tryptophan for serotonin synthesis [86–90]. More details on the kynurenine pathway can be found in section 2.1.

Inflammation and neuroplasticity

Pro-inflammatory cytokines can enhance glutamate release, but also inhibit glutamate uptake [91,92]. This exxagerated glutamate release and failed synaptic clearance can result in synaptic dysfunction [93]. Besides glutamate, BDNF plays an important role in neuroplasticity as well [38]. Inflammation results in decreased levels of BDNF in several brain regions, including the hippocampus [94].

Inflammation and the HPA axis

The immunosuppressive effects of glucocorticoids have long been recognized [95]. However, there are implications this interaction is bidirectional, as glucocorticoids can also elicit a pro-inflammatory response [96]. Moreover, the interaction seems bidirectional. Pro-inflammatory cytokines can stimulate the HPA axis by increasing glucocorticoid or ACTH levels [97].

The effect of inflammation on mood disorders is a highly complex proces. Further details are beyond the scope of this thesis. For an extensive review see Loftis *et al*. [11]

Chapter 2: The gut-brain axis

Gut microbiota are receiving increasing emphasis in the pathophysiology of MDD. The importance of gut microbes is evident from animal studies; germ-free mice show less depressive symptoms than controls [98]. The gut microbiome has a bidirectional communication with the central nervous system; the gut-brain axis [12]. Disruptions of the gut microbiome have been associated with several neuropsychiatric disorder, including MDD. This chapter will focus on the mechanism of this gut-brain axis and how these might be involved in the pathophysiology of MDD. Gut microbes can affect cognitive functioning in several ways. First of all, gut microbes can regulate the synthesis of neurotransmitters, which can signal the vagus nerve or can enter the blood circulatory system. Furthermore, the gut can produce metabolites that affect the brain, most prominently SCFAs. Lastly, gut microbes can have inflammatory or immunosuppressive effects on the host, which is also regulated by the HPA axis (figure 3).

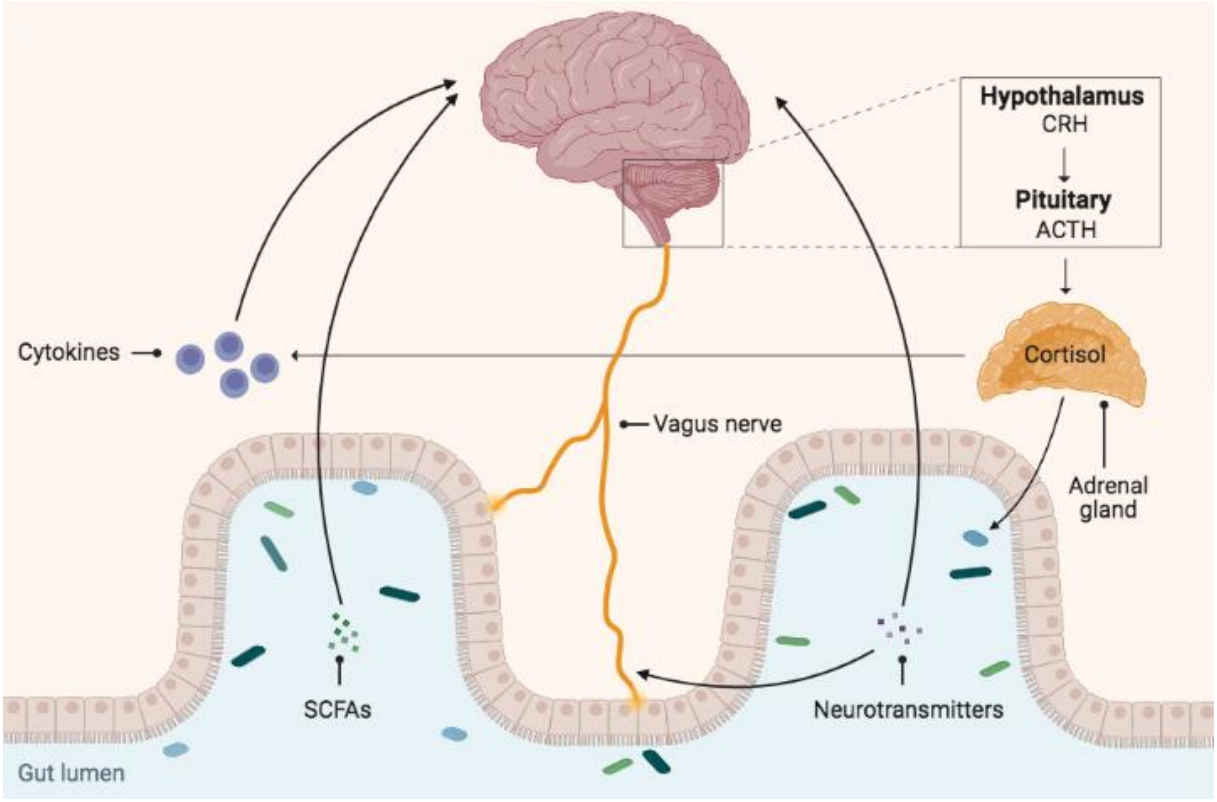

Figure 3. The gut-brain axis. Gut microbiota can be involved in the pathophysiology of MDD through neural, endocrine and immune pathways. Gut microbes produce neurotransmitters and SCFAs, which regulate cognitive functioning though vagus nerve stimulation or via the blood circulatory system. Gut microbes can induce an (anti-) inflammatory response as well, affecting brain functioning as well. The HPA axis can regulate an inflammatory response.

2.1 Neurotransmitter modulation

Gut bacteria are able to produce a range of mammalian neurotransmitters. A summary is provided in table 1. These neurotransmitters can signal the vagus nerve, which provides a connection to the central nervous system [99]. Fibers of the vagus nerve do not cross the epithelial layer, so they are not directly in contact with the gut luminal microbiota [100]. Hence, these fibers of can only sense signals from the microbiome through diffusion of bacterial metabolites or neurotransmitters [101]. Vagus nerve activation can modify serotonin, norepinephrine, GABA and glutamate concentrations in the brain [102–105]. Hence, dysregulation of the nerve can cause neurodegenerative disorders [106].

Table 1. Neurotransmitter producing bacteria in the gut.
The majority of this table was adapted from [107].

Neurotransmitter	Bacterial strain
Dopamine	*Bacillus cereus* [108] *Bacillus mycoides* [108] *Bacillus subtilis* [108] *Escherichia coli* [108] *Escherichia coli* (K-12) [109] *Hafnia alvei* (NCIMB, 11999) [110] *Klebsiella pneumoniae* (NCIMB, 673) [110] *Morganella morganii* (NCIMB, 10466) [110] *Proteus vulgaris* [108] *Serratia marcescens* [108] *Staphylococcus aureus* [108]
Norepinephrine	*Bacillus mycoides* [108] *Escherichia coli* (K-12) [109] *Proteus vulgaris* [108] *Serratia marcescens* [108]
Serotonin	*Escherichia coli* (K-12) [109] *Hafnia alvei* (NCIMB, 11999) [110] *Klebsiella pneumoniae* (NCIMB, 673) [110] *Lactobacillus plantarum* (FI8595) [111] *Lactococcus lactis subsp. cremoris* (MG 1363) [111] *Morganella morganii* (NCIMB, 10466) [110] *Streptococcus thermophilus* (NCFB2392) [111]
GABA	*Bifidobacterium adolescentis* (DPC6044) [112] *Bifidobacterium angulatum* (ATCC27535) [113] *Bifidobacterium dentium* (DPC6333) [112] *Bifidobacterium infantis* (UCC35624) [112] *Lactobacillus brevis* (DPC6108) [112] *Lactobacillus buchneri* (MS) [114] *Lactobacillus paracasei* (NFRI) (7415) [115] *Lactobacillus plantarum* (ATCC14917) [116] *Lactobacillus reuteri* (100–23) [113] *Lactobacillus rhamnosus* (YS9) [116] *Lactobacillus. delbrueckiisubsp. bulgaricus* (PR1) [116] *Monascus purpureus* (CCRC 31615) [117] *Streptococcus salivarius subsp. thermophilus* (Y2) [118]

Tryptophan metabolism

Tryptophan is the precursor for serotonin. It is an essential amino acid that cannot be produced by the host [119,120]. Approximately 95% of the body's serotonin is synthesized in the gut [121]. Low concentrations of tryptophan were found to be correlated with more severe depressive symptoms [122,123]. Synthesis of serotonin is mediated via SCFAs; acetate, propionate and butyrate signal to enterochromaffin cells to produce serotonin [124–126].

Besides serotonin, tryptophan can also be synthesized into kynurenine, which is also regulated by gut microbes. This reduces the availability of tryptophan for serotonin synthesis [23,84,85]. Kynurenine is metabolized into a glutamate NMDA receptor agonist, which increases glutamate neurotransmission and has a neurotoxic effect. However, kynurenine can also be metabolized into an NMDA receptor antagonist, which inhibits glutamergic transmission and has a neuroprotective effect [127]. Upregulation of the kynurenine pathway has been reported in MDD patients and animal studies [86,123,128]. The kynurenine pathway is significantly upregulated in response to inflammation, thus decreasing tryptophan availability for serotonin synthsis [86][87][88][89]. Moreover, inflammation enhances the neurotoxic pathway of

kynurenine as well, resulting in a higher synthesis of NMDA receptor agonists [89].

Moreover, tryptophan is also metabolized to skatole and indole by gut microbes [129]. Low host indole levels were also correlated with more severe depressive symptoms [122]. Indoles are proposed to demonstrate an anti-inflammatory effect; in obese patients, high levels of indoles were negatively correlated with inflammatory markers [130]. Skatole, on the other hand, may induce an inflammatory effect [131].

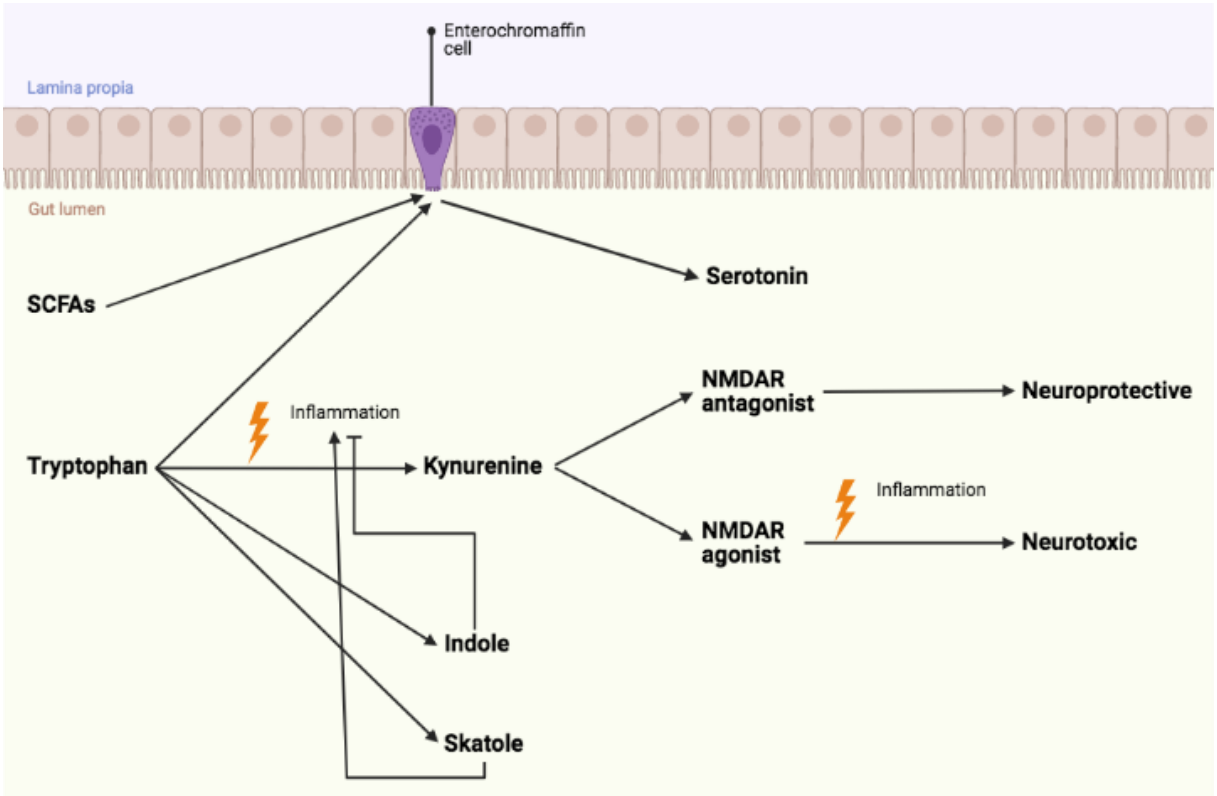

Figure 4. Overview of tryptophan metabolism pathways in the gut. Tryptophan can be metabolized into serotonin, kynurenine, indole and skatole. Serotonin synthesis is regulated through enterochromaffin cells in the gut. The kynurenine pathway can cause either a neuroprotective or neurotoxic effect through modulation of glutamergic transmission.

Tyrosine metabolism

Tyrosine is the precursor for dopamine, epinephrine and norepinephrine. However, tyrosine is not an essential amino acid and can also be produced by the host *in vivo* [132]. Tyrosine biosynthesis is also regulated by gut microbes. *Dialister invisus* seems to be a main driver in this synthesis [133]. Literature on the effect dietary tyrosine on MDD is conflicting. Some studies suggest dietary tyrosine elicits an antidepressant effect and it can raise dopamine and norepinephrine levels in the brain [134–136]. However, other studies observe no significant effect [137–140]. Thus, it is ambiguous if the gut microbiome is imperative in regulating host tyrosine levels.

Norepinephrine is produced as a quorum sensing molecule by gut microbes [141]. *Escherichia coli* O157:H7, *Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter cloacae, Shigella sonnei*, and *Staphylococcus aureus* have an improved growth rate in the presence of norepinephrine [142,143]. In *vitro*, it was found that *E. coli, Proteus vulgaris, Serratia marcescens*, *Bacillus subtilis*, and *Bacillus mycoides* have relatively high levels of norepinephrine in their biomass [108].

Mainly *Bifidobacteria* and *Lactobacilli* are able to produce GABA (table 1). GABA has also been found to be consumed by several bacteria, as they use it as an energy source [144].

Germ free mice have substantially reduced luminal and serum levels of GABA. However, the cerebral levels of GABA were not substantially reduced [145].

Germ free mice also display decreased dopamine levels [146]. Dopamine is mainly produced by several *Proteobacteria* or *Firmicutes* species (table 1). However, the incentive of dopamine production for the gut microbes undetermined [107].

However, elevated neurotransmitter levels in the gut do not automatically implicate elevated host levels. Nevertheless, in *vivo* it was also found the gut microbiome influences host norepinephrine levels; in germ free animals substantially reduced levels of norepinephrine were found in the lumen as well as the brain [146,147]. Hence, the microbiome influences norepinephrine levels. This effect on the monoaminergic levels of the host was also confirmed with GABA, as probiotics with *Lactobacillus rhamnosus* were able to elevate brain GABAergic transmission [148].

2.2 Short chain fatty acid regulation

Short-chain fatty acids (SCFAs) are fatty acids derived from fermentation in the gut [149,150]. There are several types of SCFAs, but in this thesis the main focus will mainly be on butyrate, propionate, acetate, pyruvate and valerate. SCFAs have a pivotal part in gut-brain communication, as they can cross the blood-brain barrier [151]. SCFAs have been associated with the pathophysiology of MDD. Butyrate, propionate, pyruvate and valerate seem to be negatively associated with depressive symptoms, whilst acetate showed a positive association [152–154]. SCFAs can stimulate vagus nerve signaling or reach the brain by entering the blood circulatory system [155,156].

Histone deacetylase regulation

Histone deacetylase can regulate gene expression by epigenetic modulation. SCFAs can inhibit histone deacetylase, thus altering epigenetic gene expression and increasing accessibility for DNA transcription factors [157–160]. Inhibition of histone deacetylase has been suggested as a therapeutic target for depressive symptoms [161]. Histone deacetylase seems involved in serotonin and BDNF expression as inhibition of the enzyme decreased depressive symptoms, serotonin levels and BDNF expression [162,163]. Butyrate seems to be the most potent inhibitor, but propionate and pyruvate also affect histone deacetylase [157,159,164]. It is suggested *Firmicutes* and *Actinobacteria* might positively effect BDNF expression through SCFA regulation, whilst *γ-proteobacteria* and *Bacteroidetes* might reduce BDNF expression [165].

2.3 Immune regulation

As discussed in chapter 1, there are several ways an inflammatory response might affect cognitive functioning. Gut microbes can either have an immunosuppressive or inflammatory effect. These will be briefly discussed.

MAMPs

All microbes possess a specific microbe-associated-molecular pattern (MAMP) [166]. Pattern-recognition receptors in the lumen can register these MAMPs. These receptors signal to the enteric nervous system and transmit information about the microbial environment to the host, which could enable a specific immunological host response [167]. Microbes can either trigger an inflammatory or anti-inflammatory response. For example, mutualistic bacteria, like *Bifidobacterium infantis,* can enhance secretion of anti-inflammatory cytokines by triggering pattern-recognition receptors [168]. Other species, like *Coprococcus*, *Pseudobutyrivibrio*, *Dorea and Trichuris muris*, seem to be associated with a pro-inflammatory response [169] [170,171]. In the *Enterobacteriacea* family are several inflammogenic species as well [172,173].

Gut epithelium integrity

A defect in the epithelial barrier, results in a leaky gut and inflammation [174]. Gut microbes can have a protective effect on the epithelial barrier but can also induce an inflammatory response. A leaky gut can be exacerbated by a hyperactive HPA axis. First implications on the effect the gut microbiome has on the HPA axis arise from studies of germ-free mice. In germ-free mice, exposure to stress induced an excessive ACTH and corticosterone release compared to controls [175]. Elevated cortisol levels, as found in MDD patients, can dysregulate the integrity of the gut epithelium, which triggers an inflammatory immune response [172,174,176]. Some microbial species are able to restore the integrity of the gut epithelium; several *Lactobacillus* species, including *L. helveticus, L. rhamnosus* and *L. farciminus,* could supress stress-induced hyperpermeability and inflammation [170,177]. Moreover, *Akkermansia mucinphila* and *Bifidobacterium longum* elicit an anti-inflammatory as well [178].

Chapter 3: Microbiome composition and biomarkers

The gut microbiome composition of MDD patients seems to be different from that of healthy controls. Chapter 2 focused on the mechanisms of the gut-brain axis and its involvement in the pathophysiology of MDD. This chapter will focus on the microbiome composition of MDD patients. Moreover, this chapter will also focus on the gut microbiome composition of vegetarians compared to omnivores.

3.1 Gut microbiome composition of MDD patients

Shifts in the gut microbiome composition of MDD patients are summarized in table 2 and 3. Remarkably, literature reports seem to be contradictory. Especially at phylum level variations are difficult to differentiate. For example, some seem to report an increase in in *Bacteroidetes* [179–181], whilst others report a decrease [182–185]. At family level results are less conflicting. Several species in the phylum of *Actinobacteria* seem to be higher in abundance in MDD patients [182,184]. In the *Bacteroidetes* phylum only *Porphyromonadaceae* seems increased [180]. In the *Firmicutes* phylum, *Eubacteriaceae*, *Fusobacterium, Streptococcaceae* and *Thermoanaerobacteraceae* are increased [180,181,184]. In the *Bacteroidetes* phylum, a decrease of *Chitinophagaceae, Marinilabiliaceae* and *Prevotellaceae* is established [180,182,186,187]. In the *Firmicutes* phylum, *Oscillospiraceae* and *Veillonellaceae* are decreased [180,182,184,187]. Of the *Proteobacteria,* only *Sutterellaceae* is decreased [182,184,187]. However, as literature seems to be conflicting on the gut microbiome shift of MDD patients, the accuracy of the observations depicted in table 2 and 3 could be debatable.

Table 2. Higher abundance of bacterial taxa in MDD patients compared to healthy controls

This table was partially adapted from [187]**.**

Phylum	Family	Genus
Actinobacteria [182,184,185] [1]	*Actinomycetaceae* [182,184]	
	Coriobacteriaceae [184]	*Eggerthella* [186]
	Nocardiaceae [182]	
	Streptomycetaceae [182]	
Bacteroidetes [179–181] [1]	*Bacteroidaceae* [180] [1]	*Bacteroides* [179,180] [1]
		Prevotella [179,183] [1] *Paraprevotella* [179,186,187]
	Porphyromonadaceae [180]	
	Rikenellaceae [180] [1]	*Alistipes* [180][181] [1]
		Parabacteroides [169,180] [1]
Firmicutes [182][183][183] [1]	*Acidaminococcaceae* [180] [1]	*Phascolarctobacterium* [180]
	Clostridiaceae [182] [1]	*Candidatus Arthromitus* [188]
		Clostridium [169,180,183,184] [1]
	Erysipelotrichaceae [182,184] [1]	*Bulleidia* [189]
	Eubacteriaceae [184]	
	Fusobacterium [180]	
	Lachnospiraceae [185] [1]	*Anaerostipes* [183] *Blautia* [180,184] [1] *Lactobacillus* [184,188] [1]

		Roseburia [180] [1] *Unidentified genera* [180] [1] *Dorea* [184] [1] *Anaerofilum* [186] *Oscillibacter* [180,181] *Peptostreptococcus* [189]
	Ruminococcaceae [182,184] [1]	
	Streptococcaceae [184]	*Streptococcus* [183]
	Thermoanaerobacteraceae [181]	*Gelria* [186] *Megamonas* [186] [1] *Parvimonas* [184,189] *Dialister* [179] [1] *Veillonella* [179] *Gemella* [189] *Holdemania* [186] *Turicibacter* [186]
Proteobacteria [180] [1]	*Enterobacteriaceae* [180] [1]	*Klebsiella* [183] *Parasutterella* [180] *Haemophilus* [179] *Oxalobacter* [189] *Pseudomonas* [189]
Fusobacteria [180]		

1. Results in literature are conflicting; other studies also report a decrease of these species in MDD patients (see table 3).

Table 3. Lower abundance of bacterial taxa in MDD patients compared to healthy controls

This table was partially adapted from [187].

Phylum	Family	Genus
Actinobacteria [180] [1]		*Bifidobacterium* [179,187,190]
Bacteroidetes [182–185] [1]	*Bacteroidaceae* [180,184] [1]	*Bacteroides* [169,180] [1]
		Barnesiella [179]
		Butyricimonas [179]
	Chitinophagaceae [182]	
	Marinilabiliaceae [182]	
		Odoribacter [179]
		Parabacteroides [179]
	Prevotellaceae [180,182,186,187]	*Prevotella* [180,186] [1]
	Rikenellaceae [184] [1]	*Alistipes* [179,184] [1]
Firmicutes [189][179][180] [1]	*Acidaminococcaceae* [184] [1]	*Phascolarctobacterium* [184]
	Clostridiaceae [189] [1]	*Clostridium* [179,184] *Faecalibacterium* [180,187,189] Unidentified species [188]
	Erysipelotrichaceae [180] [1]	
		Anaerovorax [188] *Christensenella* [188]
	Lachnospiraceae [180,181,189] [1]	*Blautia* [189][179] [1] *Coprococcus* [179,184,187,188,191] *Dorea* [189] [1] *Lactobacillus* [188,190] [1] *Marvinbryantia* [188] *Roseburia* [179,184] [1]
	Oscillospiraceae [182]	*Oscillibacter* [179]
	Ruminococcaceae [180,189] [1]	*Acetivibrio* [179] *Ruminococcus* [179,180,187,189]
		Megamonas [179,184] [1] *Mitsuokella* [179]
	Veillonellaceae [180,184,187]	*Dialister* [180,186] [1]
		Faecalibacterium [179,180,184,189]
Proteobacteria [182] [1]	*Enterobacteriaceae* [182] [1]	*Escherichia* [179,180,187]
	Sutterellaceae [182,184,187]	*Sutterella* [179]
		Comamonas [179]
		Psychrobacter [188]

	Gemmiger [179]
	Vampirovibrio [179]
Fusobacteria	*Fusobacterium* [179]

1. Results in literature are conflicting; other studies also report an increase of these species in MDD patients (see table 2).

Probiotics

As results of studies on gut microbiome composition are inconsistent, probiotics might provide further insights on species involved in the pathophysiology of MDD. There are implications probiotics can have potential applications for mood disorders.

Probiotics positively affecting MDD mainly contained *Lactobacillus* or *Bifidobacterium* species. In animal studies, administration of probiotics containing *Lactobacillus helveticus, Lactobacillus rhamnosus, Bifidobacterium longum* or *Mycobacterium vaccea* reversed depressive symptoms [148,171,192–196]. In human studies, probiotics have been reported to induce mood changes as well. Several *Lactobacillus* species, including *Lactobacillus helveticus, Lactobacillus acidophilus, Lactobacillus brevis, Lactobacillus casei, Lactobacillus salivarius, Lactobacillus lactis, Lactobacillus casei Shirota* and *Lactobacillus gasseri* substantially reduced depressive symptoms compared to controls receiving a placebo [192,197–199]. Furthermore, *Bifidobacterium* species, including *Bifidobacterium longum, Bifidobacterium bifidum* and *Bifidobacterium lactis,* also improved depressive symptoms [192,197].

3.2 Gut microbiome composition of vegetarians and omnivores

Literature on the effects of a vegetarian on the gut microbiome composition diet seems less contradictory. A vegetarian diet seems to decrease diversity of the gut microbiome. Several *Veillonella*, *Haemophilus* and *Aggregatibacter* species seem to increase in a vegetarian diet compared to an omnivorous diet [200]. A vegetarian diet decreases the relative abundance of several *Bacteroides, Prevotella, Clostridium* and *Desulfovibrio* species (table 4 and 5) [200–203].

Table 4. Higher abundance of bacterial taxa in a vegetarian diet compared to an omnivorous diet.

This table was adapted from [204].

Phylum	Family	Genus	Species
Bacteroidetes [205,206]	*Bacteroidaceae* [206] [1]	*Bacteroides* [201] [1] *Prevotella* [201,202] *Capnocytophaga* [200] *Porphyromonas* [200]	*Prevotella copri* [202]
Firmicutes [207]		*Faecalibacterium* [207] *Lachnospira* [205] *Peptoniphilus* [200] *Roseburia* [207] *Staphylococcus* [200] [1] *Veillonella* [200]	*Blautia hydrogenotrophica* [200] *Clostridium ramosum* [200] *Clostridium symbiosum* [200] *Peptoniphilus duerdenii* [200] *Streptococcus peroris* [200] *Veillonella dispar* [200] *Veillonella parvula* [200] *Veillonella atypica* [200]
Actinobacteria		*Actinobacillus* [200] *Atopobium* [200] *Actinoplanes* [200] *Cryptobacterium* [200] *Micrococcus* [200]	*Micrococcus luteus* [200]
Proteobacteria		*Aggregatibacter* [200] *Aeromonas /Pseudomonas* [201] *Haemophilus* [200] *Neisseria* [200]	*Aggregatibacter segnis* [200] *Aggregatibacter actinomycetemcomitans* [200] *Campylobacter concisus* [200] *Haemophilus haemolyticus* [200] *Haemophilus influenzae* [200] *Haemophilus parainfluenzae* [200] *Klebsiella pneumoniae* [202] *Neisseria mucosa* [200]

1. Results in literature are conflicting; other studies also report a decrease of these species in a vegetarian diet (see table 5).

Table 5. Lower abundance of bacterial taxa in a vegetarian diet compared to an omnivorous diet

This table was adapted from [204].

Phylum	Family	Genus	Species
Bacteroidetes	*Bacteroidaceae* [202] [1]		
	Rikenellaceae [202]	*Alistipes* [202]	
		Bacteroides [202,208,209] [1]	*Bacteroides vulgatus* [202] *Bacteroides fragilis* [201] *Bacteroides dorei* [202] *Bacteroides thetaiotaomicron* [202] *Bacteroides uniformis* [202] *Bacteroides finegoldii* [200] *Bacteroides stercoris* [200]
	Porphyromonadaceae [202]		*Porphyromonas gingivalis* [200]
		Parabacteroides [202]	*Parabacteroides distasonis* [202] *Prevotella buccalis* [200] *Prevotella oris* [200] *Prevotella tannerae* [200]
Firmicutes	*Bacillaceae* [207]	*Acetobacterium* [200]	
			Anaerostipes caccae [200]
		Bulleidia [200]	
			Blautia hansenii [200]
		Caldanaerobacter [200]	
			Clostridium Clostridioforme [202] *Clostridium kluyveri* [200] *Clostridium coccoides-E. rectale* [210]
			Clostridium innocuum [203]
			Clostridium paraputrificum [203]
		Desulfitobacterium [200]	
		Dialister [200]	*Dialister invisus* [200]
		Dorea [200,207]	*Dorea longicatena* [200]
			Enterococcus faecium [200]
			Finegoldia magna [200]
		Holdemania [200]	
		Phascolarctobacterium [200]	*Lactobacillus amylovorus* [200] *Phascolarctobacterium succinatutens* [200]
	Planococcaceae [207]	*Peptostreptococcus* [203] *Streptococcus* [211]	
	Ruminococcaceae [207]	*Ruminococcus* [205]	*Ruminococcus torques* [200]
			Roseburia Eubacterium rectale [210]
		Staphylococcus [212] [1]	
			Thermoanaerobacter pseudo ethanolicus [200]
Actinobacteria		*Bifidobacterium* [208]	
		Corynebacterium [212]	
			Parascardovia denticolens [200]
		Eggerthella [200]	
		Mobiluncus [200]	*Mobiluncus curtisii*
Proteobacteria			*Acinetobacter baumannii* [200]
		Bilophila [200]	*Bilophila wadsworthia* [200]

		Campylobacter [200]	
	Comamonadaceae [207]		
		Desulfovibrio [200]	*Desulfovibrio piger* [200] *Desulfovibrio alaskensis* [200] *Desulfovibrio aespoeensis* [200]
			Edwardsiella ictaluri/ tarda [200]
		Escherichia	*Escherichia hermannii* [202]
		Halomas [207]	
		Oxalobacter [200]	
		Ralstonia [200]	
		Ruegeria [200]	
		Succinivibrio [207]	
		Syntrophobacter [200]	*Syntrophobacter fumaroxidans* [200]
		Taylorella [200]	
Euryarchaeota		*Methanosphaera* [200]	*Methanosphaera stadtmanae* [200]
Chloroflexi		*Dehalogenimona* [200]	*Dehalogenimona lykanthroporepellens* [200]
Fusobacteria		*Streptobacillus* [200]	*Fusobacterium ulcerans* [200]
Verrucomicrobia	*Verrucomicrobiaceae* [202]	*Akkermansia* [202]	

1. Results in literature are conflicting; other studies also report a decrease of these species in a vegetarian diet (see table 4).

Lactobacillus and *Bifidobacterium* species appear to positively affect depressive symptoms, as was suggested in the probiotic studies. The abundance of *Bifidobacterium* is decreased in a vegetarian diet [208]. Moreover, one *Lactobacillus species (Lactobacillus amylovorus)* is decreased in a vegetarian diet as well [200]. This suggests a meat-based diet might be beneficial in averting or alleviating depressive symptoms. However, in MDD an increase of *Porphyromonadaceae* and *Streptococcaceae* is observed as well [180,184]. The abundance of *Porphyromonadaceae* appears to be reduced in vegetarians [202]. Nevertheless, within the *Porphyromonadaceae* family, an increase in the *Porphyromonas* genus is observed in vegetarians [200]. Of the *Streptococcaceae* family, the genus *Streptococcus* is decreased in vegetarians [211]. Abundance of *Prevotellaceae* and *Veillonellaceae* species is reduced in MDD patients [180,182,184,186,187]. Several *Prevotella* species are relatively lower in abundance in vegetarians than in omnivores [200]. However, several *Veillonella* species are higher in abundance in vegetarians [200]. Hence, as some species associated with MDD patients are in relative higher abundance in vegetarians, but others are decreased in abundance, there seems to be no clear association between a vegetarian diet and the microbiome composition of MDD patients.

Moreover, as the gut-brain axis is bidirectional, it cannot be concluded these species have a causative role in the pathophysiology of MDD. Hence, the next chapter will establish the impact of a vegetarian or omnivorous diet on metabolic pathways of the gut microbiome that might impact the etiology of MDD.

Chapter 4: Effect of metabolites in of omnivorous and vegetarian diet

There is emerging evidence of the impact of dietary patterns on the risk of developing MDD. However, findings on the relation of meat consumption to MDD are inconsistent. Some studies report that vegetarians are depressed more often than non-vegetarians [213–215]. Nonetheless, other meta-analyses indicate meat consumption is associated with higher risk of MDD [216,217]. Hence, findings are inconclusive and the relation still remains very complex as it is affected by many confounding factors. Moreover, it is not clear if the relation between a vegetarian diet and MDD is causative, as other factors might influence mental health status as well. Thus, this chapter attempts to further elucidate the mechanisms behind meat consumption and MDD. The chapter will discuss the effect of: 1) animal-based proteins compared to plant-based proteins, 2) fatty acids in omnivorous diets compared to vegetarian diets 3) dietary fibers and 4) vitamins and minerals. This thesis will not report on the specific effects of fish and seafood, but will focus on red meat and poultry.

4.1 Protein and gut microbiome composition

Animal-based diets are higher in total protein intake [13]. The amount, but also type of protein consumption can affect the gut microbiome composition and metabolism, which in turn might affect cognitive function. The most important effects of meat consumption on protein metabolism will be briefly discussed.

Tryptophan metabolism

Meat protein seems to increases serotonin levels in the gut compared to a diet containing soy protein [125]. There are several ways dietary protein may affect tryptophan metabolism and serotonin production.

First of all, dietary proteins can affect the gut microbial composition, which changes SCFA production [125]. Acetate, propionate and butyrate can induce production and secretion of serotonin from enterochromaffin cells [125,126]. SCFA production was significantly elevated in mice fed with pork protein compared to mice fed with soy protein. Pork protein increased butyrate, isovalerate and valerate levels by promoting *Odoribacter* growth or by inhibiting *Romboutsia* and *Turicibacter* growth. The soy protein diet decreased propionate, valerate and isobutyrate levels by promoting growth of *Prevotellaceae* Ga6A1 and *Escherichia Shigella* [125]. Secondly, meat protein is high in tryptophan levels [125,129]. Tryptophan is a precursor for serotonin and it is an essential amino acid that cannot be produced by the host *in vivo* [119,120]. Hence, tryptophan is essential in serotonin production. However, although meat may generate high levels of tryptophan and serotonin in the gut, the tryptophan and serotonin in the brain not necessarily correspond. To cross the blood-brain barrier, a carrier protein must transport tryptophan. Tryptophan is in competition with other amino acids to bind the carrier protein. As meat is very abundant in several amino acids, there is more competition to bind the carrier protein [218]. This is confirmed by several studies, where a protein rich diet decreased brain tryptophan levels [219–221].

Dietary protein might affect the kynurenine pathway as well. Probiotics can effect kynurenine synthesis. Several probiotics with Lactobacillus species, including *Lactobacillus Plantarum, Lactobacillus johnsonii* and *Lactobacillus helveticus,* and *Bifidobacterium longum* decreased kynurenine levels and improved depressive symptoms [222–224]. The abundance of *Lactobacillus* species was increased in rats fed with a meat protein diet compared to rats fed with a soy protein diet [225,226]. However, it is not evident if the abundance of these specific *Lactobacillus* species are enhanced after meat consumption or if other *Lactobacillus* species might affect kynurenine synthesis and depressive symptoms.

Besides serotonin, tryptophan is also metabolized to skatole and indole by gut microbes [129]. Diets high in pork and chicken protein elevated *Lactobacillus* and *Desulfovibrio* abundance, which are presumed to be involved in production of indole and skatole [129]. Indoles are

proposed to be anti-inflammatory, whilst skatoles are proposed to be inflammatory [130,131]. In general meat is presumed to induce inflammation [129,200,227–230], although there are also some reports meat is not associated with inflammation [231,232]. Hence, the anti-inflammatory effect of indole might be nullified by other components of meat products.

Tyrosine metabolism

Dialister invisus is a main driver in of tyrosine biosynthesis [133]. *Dialister* species are less abundant in vegetarians [200]. Moreover, a vegetarian diet decreased serum tyrosine levels as well [233]. Hence, it is suggested meat might enhance tyrosine levels. However, as literature is conflicting on the antidepressant effect of dietary tyrosine, it is not certain meat consumption can affect the pathophysiology of MDD through tyrosine metabolism [137–140].

D-amino acids

Amino acids can exist in two stereoisomeric forms: the L-form and the D-form. L-amino acids serve as building blocks for polypeptides and are usually higher in abundance. However, in the gut, D-amino acids are more evident as microbes are a substantial source of D-amino acid synthesis [234]. D-serine and D-aspartate stimulate NMDA receptor-mediated neurotransmission, which could suggest a part in neurotoxicity and neuronal cell death [235,236]. Plant-based diets generally contain higher levels of D-amino acids than meat-based diets [237]. However, when D-amino acids are orally administered, they are immediately metabolized, thus declining its bioavailability [238]. Nonetheless, administration of a prebiotic with soluble fiber resulted in higher levels of hippocampal D-serine [239]. Thus, direct administration might not elevate D-amino acid levels in the brain, but through microbial synthesis these levels can be elevated, although the exact mechanisms remain unclear. As vegetarian diets are usually high in fiber (see section 4.3), this might suggest a stimulating effect on D-amino acid production. D-amino acids are mainly produced by *Acetobacter*, *Lactobacillus*, *Micrococcus* and *Streptococcus* [211]. *Micrococcus* prevalence seems higher in a vegetarian diet than an omnivorous diet [200]. On *Streptococcus* literature reports mixed results [183,211]. Literature reports associating D-amino acids with cognitive functioning are limited. However, D-amino acids could be of considerable significance in the pathophysiology of MDD. Hence, additional research could provide further insights into the impact of dietary mediation on D-amino acids and development of depressive symptoms.

Carnitine

Carnitine is an amino acid derivative and can be metabolized from the amino acids lysine and methionine [240,241]. However, although the ammonium compound can be produced *in vivo*, diet still remains an important source. Carnitine is mostly abundant in meat. The compound can be metabolized into trimethylamine-N-oxide (TMAO). Vegetarians indeed were shown to produce less TMAO than meat-consumers [242]. Serum TMAO levels are positively correlated with depressive symptoms [243]. TMAO can contribute to neurodegeneration by causing inflammation and increasing oxidative stress [244]. Gut microbiota regulate TMAO metabolism. A positive association with TMAO levels and the family *Lachnospiraceae,* the order *Clostridiales* and the genus *Ruminococcus* was found [245].

Sulfur-containing amino acids

Meat contains an abundance of sulfur-containing amino acids and taurine, which can be metabolized to hydrogen sulfide. In a controlled feeding study in humans, significantly higher levels of sulfide generation by gut bacteria were found in the group consuming a meat-rich diet compared to a control group [246]. The genus of *Desulfovibrio* bacteria are main fermenters of sulfur-containing amino acids. In animal studies, hydrogen sulfide seems to exhibit an antidepressant effect, which might be due to its ability to upregulate BDNF expression and GABAergic neurotransmission and the ability to protect neurons from oxidative stress [247–250].

4.2 Lipids and gut microbiome composition

In an animal-based diet total fat intake is substantially higher than in a vegetarian diet [13]. The type of fatty acids can affect gut microbiome composition and have an impact on neuropsychiatric disorders, mainly through inflammatory pathways.

Saturated and unsaturated fatty acids

A diet high in saturated fat can cause inflammation [251]. Moreover, a diet high in saturated fat reduces BDNF expression and impairs neurogenesis [252,253]. Conversely, unsaturated fatty acids can alleviate inflammation [254]. An animal-based diet contains mainly saturated fatty acids, whilst a plant-based diet contains mainly unsaturated fatty acids [211]. High intake of saturated fatty acids is associated with an increase in *Clostridium bolteae* and *Blautia.* Monounsaturated fatty acids are associated with an increase in *Parabacteroides*, *Prevotella, Turucibacter, Enterobacteriaceae* and *Blautia* as well. A diet high in polyunsaturated fatty acids increased *Tenericutes* [255]. A diet supplemented with polyunsaturated fatty acids decreased abundance of *Streptococcus* and *Clostridium.* Moreover, the diet decreased genera within the *Enterobacteriaceae* family, including *Escherichia, Pantoea, Serratia* and *Citrobacter* [256].

Most fatty acids can be produced *in vivo*, but n-3 polyunsaturated fatty acids are essential fatty acids [257]. Red meat is considered an important source of n-3 polyunsaturated fatty acid [257]. Around 43% of adult n-3 PUFA intake comes from beef, poultry and game. 48% comes from fish and seafood [258]. There is a positive correlation between n-3 PUFA intake and BDNF levels [259,260].

Bile

An animal-based diet, which is high in fat intake, causes more bile acids to be secreted [261]. This increases the abundance of several bile-tolerant microbes, including *Alistipes putredinis, Bilophila wadsworthia* and *Bacteroides* species [13]. Abundant bile acid levels decrease the levels of several *Firmicutes* species that mainly metabolize dietary plant polysaccharides, including *Roseburia, Eubacterium rectale* and *Ruminococcus bromii* [13]. Moreover, it decreases an unidentified *Peptostreptococcaceae* species as well [188]. Bile acid metabolism seems hyperactive during development of depression, as some bile-tolerant species cause intestinal inflammation [188,262].

4.3 Dietary fiber and gut microbiome composition

Humans lack the enzymes to degrade the majority of dietary fibers. Hence, these fibers pass through the gastrointestinal tract to the cecum and large intestine, where they are fermented by anaerobic microbiota, resulting in synthesis of SCFAs [149,150]. Fiber can have an antidepressant effect. A prebiotic containing soluble fiber increased BDNF expression, reduced cortisol levels and depressive symptoms [239,263].

In a diet exclusively based on protein, animal proteins stimulated SCFA synthesis more than a soy-protein diet [125]. However, in a fully balanced vegetarian SCFA was enhanced compared to an omnivorous diet [200,264]. This is due to the high fiber intake of a vegetarian diet compared to an animal-based diet [13]. A prebiotic containing soluble fiber increased BDNF expression, reduced cortisol levels and depressive symptoms [239,263]. Species that are associated with fiber fermentation are several *Firmicutes* species, including *Lachnospiraceae, Ruminococcaceae, Veinellaceae, Veillonellaceae, Clostridiaceae* and an unidentified *Clostridiales* species. Moreover, *Prevotella, Treponema* and an unidentified species of *Bacteroidetes* were also associated with fiber fermentation [265].

4,4 Vitamins, minerals and food contaminants

There are several differences in the vitamin and mineral content of an omnivorous compared to a vegetarian diet. The most important differences will be discussed here.

Zinc

Meat is an important source of zinc, hence vegetarians are at higher risk of zinc deficiency [266,267]. Chronic deficiency in zinc, an essential trace mineral, is associated with MDD [268]. It has been shown to exhibit antidepressant activity in animal studies [269]. Zinc deficiency can excacerbate excessive glutamergic neurotransmission by modulating AMPA and NMDA receptors and it can impair GABAergic neurotransmission [270,271]. Moreover, activation of the zinc receptor can elevate BDNF levels [272,273]. Gut microbiota seem to play a role in regulating host zinc levels. Germ-free mice required nearly twice as little zinc as normal controls [274]. However, the exact involvement of the gut microbiome in zinc deficiency remains ambiguous. Nontheless, it suggested the gut microbiome might be able to contribute to host zinc deficiency. At species level, *Ruminococcus lactaris,* an unclassified *Enterococcus* species, *Clostridium lactatifermentans* and *Clostridium clostridioforme* seem to increase zinc serum levels of the host. *Clostridium indolis* and an unclassified member of *Bacteroidales* seems to negatively impact serum zinc levels of the host [275]. However, the exact involvement of the gut microbiome regulation of zinc levels in relation to MDD remains somewhat elusive.

Vitamin B12

Meat is an important source of vitamin B12. Hence omnivores are shown to consume more of the vitamin than vegetarians [276,277]. A meta-analysis found a significantly positive association between low B12 levels and depressive symptoms. [278]. Moreover, B12 supplementation in combination with antidepressants significantly improved depressive symptoms compared to antidepressant treatment without the vitamin [279]. There are implications vitamin B12 is involved in serotonin, dopamine and norepinephrine synthesis [280]. Diet is the main source of vitamin B12, as there are not many bacterial species reported with the ability to synthesize the vitamin [281]. However, several gut microbiome species are reported to consume B12, thus might creating competition between the host and gut microbes for bioavailabilty of the vitamin. Several species from the *Firmicutes* phylum, including *Blautia, Faecalibacterium, Fusicatenibacter, Lachnospira* and *Lachnospiraceae*, were increased after administration of B12 supplementation, indicating these species as possible consumers of B12 [282]. However, this is a presumption, as there is no direct association between host serum levels of B12 and gut microbes.

Folate

Vegetarians consume more of the vitamine folate than omnivores [276,277]. A meta-analysis found a significantly positive association between low folate and depressive symptoms [278]. Folate can regulate the serotonergic and noradrenergic system [283]. Moreover, the vitamin is involved in inhibition of NMDA receptors or an increase in hippocampal BDNF levels [283]. The gut microbiome seems to be a pivotal source of folate. There are several gut commensals that are folate producers, including several *Bifidobacteria* and *Lactobacilli* [284–286]. A probiotic formula with folate-producing *Bifidobacteria* increased plasma folate levels in rats, thus confirming these species can produce the vitamin *in vivo* [287].

PAHs

Polycyclic aromatic hydrocarbons (PAHs) are food contaminants that arise by heating foods to high temperatures. Ingestion of grilled meat is one of the main sources of exposure to PAHs [288,289]. In a study comparing the gut microbiome composition of participants consuming either an animal-based or plant-based diet, only in the animal-based diet increased expression of genes of gut microbes involved in the degradatin of PAHs [13]. PAHs are associated with MDD, as they can cause oxidative stress and inflammation, enhancing neurodegeneration [290–292]. PAH exposure enhances several pro-inflammatory microbes belonging to the *Alcaligenaceae, Turibacter, Bacteroidaceae, Porphyromonadaceae Erysipelotrichaceae* or *Paraprevotellaceae* family. It reduces *Lactobacillaceae, Lachnospiraceae, Muscispirillum,*

Verrucomicrobiaceae and *Ruminococcaceae* populations [293]. This might partially explain the inflammatory effects of meat consumption.

4.5 Summary

This chapter discussed several ways the gut microbiome might affect cognitive functioning. A summary of the main effects of a vegetarian or omnivorous diet is provided in table 6.

Table 6. The effect of gut microbiome metabolites in a vegetarian and omnivorous diet on MDD pathophysiology

Meat-based diet	Metabolite	Effect	Vegetarian diet	Metabolite	Effect
Odoribacter	SCFAs	+ Serotonin [1]	*Acetobacter* *Lactobacillus* *Micrococcus* *Streptococcus*	D-amino acids	+ Glutamergic transmission
Bifidobacterium longum *Lactobacillus helveticus* *Lactobacillus johnsonii* *Lactobacillus Plantarum*	- Kynurenine	- Kynurenine + Serotonin - Glutamergic transmission	*Blautia* *Enterobacteriaceae* *Parabacteroides* *Prevotella* *Turucibacter* *Tenericutes*	Unsaturated fatty acids	- Inflammation
Desulfovibrio *Lactobacillus*	Indole	- Inflammation	*Bacteroidetes* spp. *Clostridiaceae* *Clostridiales* spp. *Lachnospiraceae* *Prevotella* *Ruminococcaceae* *Treponema* *Veinellaceae* *Veillonellaceae*	SCFAs	+ BDNF - Cortisol
Desulfovibrio *Lactobacillus*	Skatole	+ Inflammation	*Bifidobacteria* *Lactobacilli*	Folate	+ Serotonergic/ noradrenergic transmission - Glutamergic transmission + BDNF
Dialister invisus	Tyrosine	+ Dopaminergic/ norepinephrinergic transmission[1]			
Clostridiales *Lachnospiraceae* *Ruminococcus*	TMAO	+ Inflammation + Oxidative stress			
Desulfovibrio	Sulfide	+ BDNF + GABA receptor modulation - Oxidative stress			
Blautia *Clostridium bolteae*	Saturated fatty acids	- BDNF + Inflammation			
	n-3 polyunsaturated fatty acid	+ BDNF			
Alistipes putredinis *Bacteroides* spp. *Bilophila wadsworthia*	Bile	+ Inflammation [2]			
Clostridium clostridioforme	Zinc	- Glutamergic transmission + GABAergic			

Clostridium lactatifermentans *Enterococcus* *Ruminococcus lactaris*		transmission + BDNF	
	B12	+ Serotonin + Dopamine + Norepinephrine	
Alcaligenaceae *Bacteroidaceae* *Erysipelotrichaceae* *Paraprevotellaceae* *Porphyromonadaceae* *Turibacter*	PAHs	+ Oxidative stress + Inflammation	

1. Serotonin levels are elevated in the gut, but not in the brain.
2. Conflicting results
3. Inflammation is not an effect of bile secretion, but of bile-tolerant microbes.

Discussion

Epidemiological studies associating meat consumption with MDD are conflicting. Some studies report vegetarians to being depressed more often, whilst others report meat consumption is associated with higher incidence of MDD. As results are inconsistent, this thesis attempted to give an overview of the effects of a vegetarian diet on the gut microbiome and the pathophysiology of MDD.

Even though many studies have explored the pathophysiological mechanisms of MDD, the heterogeneity of MDD still makes it difficult to clarify the precise mechanisms involved, especially since MDD might be a result of multiple pathogeneses. This complicates determination of the impact of the gut microbiome on depressive symptoms. Literature reports on shifts in the microbiome composition of MDD patients seem to be contradictory. Inconsistencies in literature might arise from differences in methodologies in analyzing microbiome compositions. Moreover, there could be several confounding factors in these studies, like age or diet of the participants. Several of the studies reported a high risk of bias. There seems to be no clear association between the gut microbiome composition of vegetarians compared to the gut microbiome of MDD patients; some microbial species that are associated with MDD are higher in abundance in vegetarians, whilst others are lower.

Research on probiotics clarifies the effect of gut microbes to some extent. *Lactobacillus* and *Bifidobacterium* species seem to alleviate depressive symptoms. A vegetarian diet decreased *Bifidobacterium* species and *Lactobacillus amylovorus.* This suggests a disadvantageous effect of a vegetarian diet. Moreover, animal studies suggest meat-protein to enhance *Lactobacillus* abundance when compared to soy-protein. However, although this gives some first implications, additional studies are needed to substantiate the effect of meat on *Lactobacillus* and *Bifidobacterium* species.

The gut microbiome may affect cognitive functioning though several mechanisms. First of all, through the tryptophan pathway, an omnivorous diet seems to increase gut microbiome species that enhance serotonin and tryptophan levels in the gut. However, tryptophan levels in the brain are not elevated and are even suggested to decrease. Hence, via the blood circulatory system, an omnivorous diet does not seem to enhance serotonergic neurotransmission. Nonetheless, a meat-based diet may still affect serotoninergic neurons through vagus nerve stimulation. Meat consumption may inhibit the kynurenine pathway and reduce glutamergic neurotransmission, as meat protein may increase *Lactobacillus*. *Lactobacillus* species seem to reduce the kynurenine pathway. However, meat does induce inflammation, which might upregulate the neurotoxic pathway of kynurenine and enhance glutamergic neurotransmission.

Tyrosine synthesis is downregulated in vegetarians, which might affect dopamine and norepinephrine levels. However, dietary tyrosine was not found to elicit an antidepressant effect, suggesting no direct effect of meat on dopaminergic or norepinephrinergic neurotransmission. The enhanced folate consumption of vegetarians can also increase monoaminergic transmission. However, the vitamin B12 in meat products can enhance monoaminergic neurotransmission as well.

D-amino acids, which seem more abundant in a vegetarian diet, stimulate glutamergic neurotransmission. Conversely, the enhanced folate consumption of vegetarians might reduce glutamergic neurotransmission. Zinc, which is abundant in meat, can inhibit the glutamate neurotransmission pathway. Meat seems to stimulate GABAergic neurotransmission, as both sulfide and zinc seem to have a positive effect. Both a vegetarian and meat-based diet seem to result in metabolites that can enhance BDNF levels of the host. Lastly, it is important to

emphasize that a meat-based diet generally seems to induce more inflammation and oxidative stress, which could negatively impact depressive symptoms.

Hence, neither analysis of the gut microbiome composition or microbial metabolites generates conclusive results on the effect of a vegetarian or omnivorous diet on the pathogenesis of MDD. Through different pathways a vegetarian and omnivorous diet seem to be able to either positively or negatively impact MDD. The ambiguous results suggest the need for additional research on the effect of a vegetarian diet on the gut microbiome composition, as well as the impact of gut microbes in the pathogenesis of MDD. However, the conflicting results might also suggest there is no direct relation between a vegetarian or omnivorous diet and MDD.

Some limitations of this literature review should be reported. This thesis did not differentiate between beef, pork or poultry. The type of meat may substantially differ in its effect on the gut microbiome. Moreover, not all food components were considered within this thesis. Other vitamins, which were not discussed in this thesis, may affect the pathophysiological mechanisms of MDD as well.

MDD is one of the leading contributors to global disease burden and prevalence is only increasing. The gut-brain axis has been demonstrated to be involved in the pathogenesis of depression. Dietary intervention may provide a novel approach to alleviate depressive symptoms. However, contemporary literature reports on the effect of gut microbes on cognitive functioning and the effect of meat consumption on gut microbes remains undetermined, as these relations are very complex and may be affected by many confounding factors. Hence, additional research on the effect of a vegetarian diet on the gut microbiome and MDD is required.

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