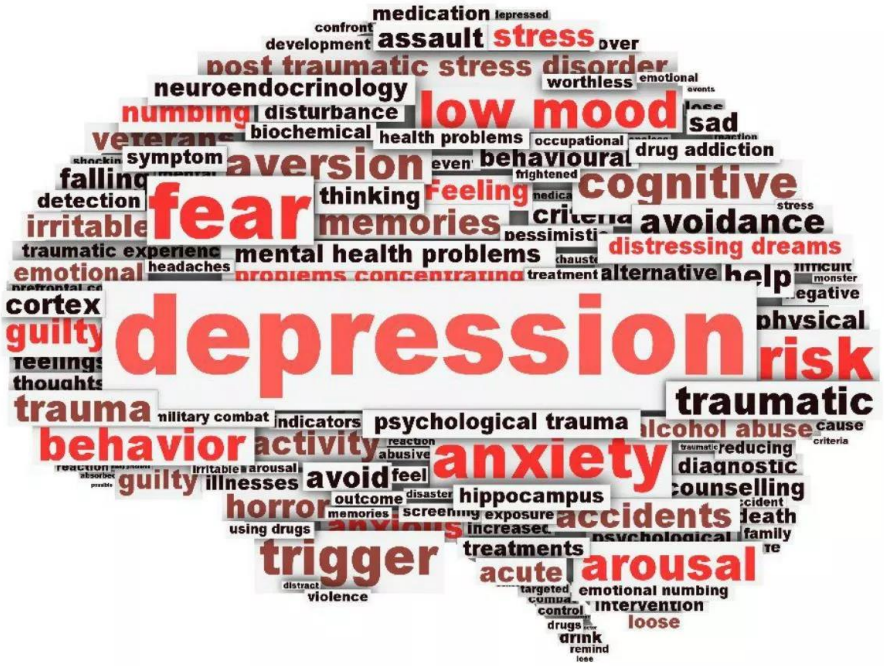
# The role of neuro-inflammation in Major Depressive Disorder

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## Abstract

Major depression is one of the biggest global health threats worldwide, affecting up to 300 million people each year. Moreover, depression is the leading cause of death among young people between 15-29 years old. Besides that, untreated depression poses a huge economic burden on society. As up to 30-50% of the patients do not respond to commonly used antidepressants, it is of vital importance a more suitable treatment is found. Perhaps a new view on depression is needed, one similar to other inflammatory diseases. During depression a process called neuro-inflammation takes place where pro-inflammatory cytokines are released, together with other inflammatory mediators, by activated microglia. Pro-inflammatory cytokines cause sickness behaviour which has many similarities with symptoms of depression; including social withdrawal, fatigue and loss of appetite. Furthermore inflammatory mediators affect serotonin and dopamine levels and have other neurotoxic effects. Prolonged activation of microglia is linked to progression of neurodegenerative diseases such as Alzheimer and Parkinson. Thus, it is vital to stop these processes. Commonly used antidepressants mostly decrease pro-inflammatory cytokine levels and increase anti-inflammatory cytokine levels. However, some will work in reverse, increasing pro-inflammatory cytokine levels while decreasing the other. By using anti-inflammatory drugs, therapy can be enhanced and a large group of non-responders will go into remission. However, caution is needed when using anti-inflammatory drugs as a treatment for depression as NSAIDs can have serious side effects.

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## 1. Introduction

Major Depressive Disorder (MDD) is a serious mental health condition that affects at least 300 million people each year. In the Netherlands up to 18.7% of the population under 65 years have suffered from depression at least once in their life [1]. Depression can be classified as either depressive episodes or recurrent depression and symptoms vary from mild to moderate or severe. When untreated, depression can lead to suicide, especially among young people (15-29 years old) where depression is the second leading cause of death. [2]
Besides accounting for the highest fatal disease burden in the world [3], MDD also poses an important non-fatal disease burden on both the individual- and population level. The impact of depression on an individual's life is highest when they suffer from longer depressive episodes, while on a population level the burden is highest for recurrent depression. [4]. Moreover, MDD poses a great economic burden for society, costing society $210.5 billion in the U.S alone [5]. Thus, discovering an effective treatment for MDD that also lowers the economic burden is of great importance.

MDD is characterized by various symptoms such as fatigue, withdrawal from social environment, a fragmented sleep and overall malaise. Notably, these symptoms show many similarities with sickness behaviour caused by viral infections or other, more chronic, illnesses [6]. Sickness behaviour is caused by the release of anti- and pro-inflammatory cytokines [7]. The similarity between sickness behaviour and MDD symptoms suggests that a similar process happens during depression. Meaning that as a result of increased release of pro-inflammatory cytokines, neuro-inflammation is induced which contributes to the development of MDD. Indeed, several studies have noticed that chronically ill individuals developed MDD, as a result of the production of pro-inflammatory cytokines [8]. In turn, patients suffering from MDD have a bigger risk of developing various illnesses such as epilepsy, cancer and Ischemic heart disease [9]. Interestingly, healthy individuals suffering from MDD also exhibit activated inflammatory pathways, including an increase in pro-inflammatory cytokines and acute-phase proteins [8.]
With so many people suffering from MDD, it is no wonder that the use of anti-depressants has shown an increase the last 20 years. In Europe an overall increase of 19,83% per year was seen between 2000-2010 while in the United States an even bigger increase of 64% was noted between 1999-2014 [10] [11].

Anti-depressants are a commonly used treatment for MDD, in America 12.7% of the population takes anti-depressants [11], however 1/3 of patients suffering from MDD do not respond to regularly used antidepressants, classifying them as 'non-responders' [12]. It has been suggested that the level of neuro-inflammation has an effect on the working of anti-depressants. Various studies found that the levels of pro-inflammatory cytokines are higher in non-responders compared to cytokine levels of patients that went into remission [13] [14]. For instance, Lanquillon et al showed that IL-6 levels were elevated pre-treatment in patients that showed to be non-responders, while post-treatment IL-6 levels were similar in both groups. This was the opposite for TNF-α, where pre-treatment levels were similar in both groups, but remained higher in non-responders after the treatment. [14]
Similarly, Fitzgerald et al found higher levels of IL-6 and TNF-α in MDD patients, compared to a group of healthy individuals [13]. These findings again suggest that cytokines might play an important role in the development of depression, as well as the severity of it.

In this literature review the role of pro-inflammatory cytokines on the development of MDD in humans will be assessed. First the communication pathways between the immune system and the brain will be assessed and how via this pathway neuro-inflammation can be induced. To further elucidate which pro-inflammatory cytokines possibly contribute to MDD and sickness behaviour, various studies of depression cases in chronically-ill individuals and healthy individuals will be compared.

## 2. Brain-immune communication pathways and neuro-inflammation

It has been well established that the brain and immune system are able to communicate via different pathways. Interestingly, in the 1980's it was thought that the brain was an immunological privileged site, thus inaccessible for the immune system [15]. However, this motion was quickly tossed aside when similar ligands and receptors were observed in the immune and nervous systems [16]. For example, the same cytokines that are expressed in the periphery are present in the brain as well and are known to cause sickness behaviour. Cytokines that induce sickness behaviour include TNF-α, IL-6 and IL-1(α and β) [17]. Moreover, certain immune cells are present in the Central Nervous System (CNS) as well. One important immune cell type in the CNS are parenchymal macrophages, also called microglia [6]. Microglia have similar functions as peripheral macrophages and function as the phagocytes of the CSN [18].

### 2.1 Pro-inflammatory cytokine enter the CNS via various pathways

Pro-inflammatory cytokines can interact with the brain via different pathway; the cellular pathway, the humoral pathway and the neural pathway [19].

Firstly, pro-inflammatory cytokines can be directly released in the brain by microglia, via the so called cellular pathway [19].
Secondly, pro-inflammatory cytokines can be produced in the periphery and are then required to cross the Blood-Brain barrier (BBB) to enter the brain. This pathway is also called the humoral pathway [19]. However, cytokines are large, hydrophilic molecules which makes it hard for them to cross the BBB. This suggests that they need other intermediate molecules to act on the brain [17]. Multiple studies have looked at possible mechanisms for cytokine transportation via the BBB [20]. For example, Herkenham et al demonstrated that IL-1β-induced markers are activated at the BBB. IL-1β activity was measured through the amount of *c-fos* mRNA induced by IL-1β activity. At 0.5 hours after injection, *c-fos* mRNA was detected in the outer cells of the BBB. After 3 hours *c-fos* mRNA was measured at the parenchymal site of the BBB mainly in astrocytes and other glial cells. Furthermore they saw that IL-1β diffusion occurred mostly in the circumventricular organs (CVO) where the BBB is more leaky [21]. Another, earlier study, showed that injections with LPS induced IL-1β mRNA in different parts of the brain [22].
Thirdly, cytokines are able to enter the brain via the neural pathway. Here cytokine messages are transported to the brain via the nerves vages by afferent pathways. This initial neural message is then transformed into an immunological message, by which cytokines for example alter the activity of neurons. However, this hypothesis is in contradiction with various studies [17] [19].
Finally, cytokines can reach the different parts of the brain through diffusion, which happens via the Cerebrospinal Fluid (CSF). As mentioned before, diffusion of IL-1β occurs mostly in the CVO where the BBB is more leaky. Here it is easier for bigger molecules, such as cytokines, to enter the CSF [23]. Once the cytokines have entered the CSF, diffusion to other parts of the brain takes place via a natural flow that is the result of constant CSF production. Through this natural flow, cytokines are able to diffuse over long distances within a couple of hours. [21]

### 2.2 Pro-inflammatory cytokines activate inflammatory pathways in the CNS

Once pro-inflammatory cytokines have entered the brain, they can induce neuro-inflammation via several mechanisms. For instance, peripheral cytokines that are the result of stress or infection can stimulate microglia that in turn will produce pro-inflammatory cytokines in the brain. [24].
Chronic release of pro-inflammatory cytokines have numerous consequences. These consequences include decreased neurogenesis, dysregulation of cognitive function, increased oxidative stress and increased uptake of important monoamine neurotransmitters [25]. Furthermore activated microglia and endothelial cells will stimulate the production of other pro-

inflammatory mediators such as Prostaglandin 2 (PGE2), cyclooxygenase-2 (COX-2), nitric oxide (NO), chemokines and Indoleamine-2,3-dioxygenase (IDO) [26]. Activation of the COX enzymes will result in a chain-reaction that leads to the production of prostaglandins, and particularly PGE2 that is important in the process of fever and pain. During these reactions Reactive Oxygen Species (ROS) will also be produced, contributing to cell damage [24].
Prolonged activation of microglia can be harmful as they mediate the production of these pro-inflammatory mediators and prolonged neuro-inflammation is known to play a role in the development of neurodegenerative diseases [27]. Besides the harmful effects of neuro-inflammation, the presence of cytokines in the CNS disturbs the catabolism of the important neurotransmitters serotonin and dopamine. [26] For example, IDO reduces tryptophan levels through tryptophan metabolism via the kynurenine pathway, which in turn affects serotonin synthesis. Namely, it will lead to serotonin depletion. Moreover, end products of the tryptophan catabolism include neurotoxins such as quinolinic acid (QUIN) and 3-hydroxykynurenine (3-HK) of which the latter induces apoptosis in neurons [28].
Another important inflammatory pathway that can be activated by cytokines is the NF-kB pathway. This pathway leads to production of the transcription factor NF-kB, which promotes transcription of a wide range of immunological compounds including cytokines, acute-phase proteins and immunoreceptors [29].

### 2.3 Stress and cytokines cause hyperactivity of the HPA axis

Besides the direct communication between the CNS and the immune system via cytokines, the Hypothalamic-pituitary-adrenal (HPA) axis is another important communication pathway. Normally the HPA axis stimulates the release of anti-inflammatory substances, such as glucocorticoid cortisol. Through the release of these anti-inflammatory substances, the HPA axis suppresses pro-inflammatory and anti-viral responses. For example, the glucocorticoid receptor can suppress pro-inflammatory gene transcription or it can stimulate transcription of anti-inflammatory genes that inhibit the NF-kB pathway. [30]
However under certain conditions, such as chronic or acute stress, this system can get dysregulated. This happens when immune cells develop glucocorticoid resistance due to high cortisol concentrations, resulting in an increased release of pro-inflammatory cytokines in the body. [30]
Besides stress, cytokines can also have a major influence on the HPA axis. It has been observed that acute administration of pro-inflammatory cytokines will result in an increased production of corticotropin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH) and cortisol. The sudden release of these hormones via cytokine administration leads to hyperactivity of the HPA axis, which has been shown to lead to depression later on. [25] Interestingly, hyperactivity of the HPA axis later on in life is correlated with early childhood trauma. Subjects that suffered from such traumas responded more intensely to acute stress; they exhibited higher heart rates and ACTH concentrations. They also had the highest ACTH- and cortisol concentration during depression. [31]
Capuron et al showed that acute administration of the pro-inflammatory cytokine IFN-α resulted in an increased susceptibility to develop MDD in patients that later on received IFN-α therapy. They also found that the patients that developed MDD after this therapy had higher concentrations of cortisol and ACTH after the initial IFN-α administration. However, when IFN-α was chronically administered no elevated hormonal responses were found [32]. Indeed, other studies confirm that chronic immune activation does not necessarily result in elevated levels of CRH or cortisol [25]. For example, Raison et al found that chronic administration of IFN-α resulted in flattening of ACTH and cortisol concentrations during the day. However, higher cortisol concentrations were witnessed in the evening which was correlated with an increase in fatigue and depression. Besides measuring IFN-α concentrations, they also measured different immunological compounds namely TNF-α and its receptor. Notably, no significant correlation was found between the immunological measurements and alterations in the HPA axis. Thus, the effect of chronic cytokine administration on the HPA axis remains partly unclear. [33]

### 2.4 Evidence of neuro-inflammation in Major Depressive Disorder

Various meta-analyses have been performed that looked at the presence of inflammatory markers in MDD. For instance, Haapakoski et al performed a meta-analysis of in total 58 studies that looked at C-reactive protein (CRP), TNF-α, IL1-β and IL-6. They found significant higher mean levels of CRP and IL6 in patients suffering from MDD, however no clear association was found for the other markers [34]. Interestingly, another meta-analysis did find significant higher levels of TNF-α in MDD patients together with significant higher levels of IL6 [35]. Even though these meta-analyses find significant higher levels for different inflammatory markers, we can say that this is clear evidence that inflammation occurs in MDD patients. Acute and chronic administration of cytokines, will lead to sickness-behaviour which has many similarities with symptoms of MDD. For instance, IL6 and activation of the NF-kB pathway is associated with sleep dysregulation and sleep deprivation in MDD patients. [25]

Chronic hyperactivity of the HPA axis has also been associated with several mental health conditions, including MDD. This lead to overall higher cortisol levels, which was partly explained by a difference in glucocorticoid sensitivity. [30]

Certain viral infections cause neuro-inflammation, which can in turn cause depressive-like symptoms [36]. For instance, the human roseoloviruses (HHV-6A and HHV-6B) can be found in the CNS both during latent or active infection and can lead to behavioural alterations, quite similar to depressive symptoms. Prusty et al have studied this phenomenon and found that in many cases of patients suffering from MDD and Bipolar Disorder (BP) viral DNA of HHV-6A or HHV-6B was found in the cerebellum. Meaning that active infection of HHV-6A and HHV-6B occurs more often in MDD and BD patients and can be the cause of depressive and bipolar symptoms. [36]

## 3. Animal models for inflammatory-related depression

Numerous studies have been performed that induce depressive-like behaviour in animals This is either done by exposing them to stress or direct administration of immunogenic compounds such as LPS or even cytokines that induce inflammation. In this section findings derived from animal studies will be discussed. These studies all contribute greatly in elucidating the role of cytokines in the development of MDD.

Various forms of stress can be used to induce depression in rodents. Firstly, early-life stress can be induced by separating young pups from their mother, a process called maternal separation. Secondly, chronic mild stress is a commonly used animal model in which animals are exposed to unpredictable, mild stressors. Such mild stressors can be water/food deprivation, disruption of light/dark cycle and keeping them restrained for a period of time. Finally, social stress is another realistic model, in rodents social stress can be formed by social defeat. During this process an intruder is transferred to another resident's cage, which causes stress for the resident. This method is also called the resident-intruder paradigm. [37]

### 3.1 Activation of the NF-kB pathway leads to sickness behaviour

In a study performed by Madrigal et al they induced inflammation via acute stress. During this study acute stress was induced by restraining the rodents for six hours. After this short period of acute stress, TNF-α levels in the cortex and NF-kB activation were measured [38]. TNF-α is an important pro-inflammatory cytokine that is known to induce sickness behaviour [17]. After 30 minutes, an increase in Tumor Necrosis Factor-α Converting Enzyme (TACE) was seen in the cortex, consequently followed by increased TNF-α levels after one hour. [38] Furthermore they studied the role of TNF-α on activation of the NF-kB system. They found that TACE inhibitors blocked complete activation of the NF-kB pathway by inhibiting the translocation of NF-kB to the nucleus. These findings suggest that TNF-α plays an important role in NF-kB activation. NF-kB activation will lead to expression of iNOS, which is an important inflammatory

mediator as it produces NO which contributes to neurotoxic damage [26] [38]. Thus as expected, TACE-inhibitors also blocked the expression of iNOS [38].
Though this study does not focus on the effects of stress on the behaviour of the rats, it does show elevated levels of a known pro-inflammatory cytokine and that it causes an activation cascade of inflammatory mediators, which could contribute to the development of MDD. Thus this study has important implications for further research in the field.
Namely, another study shows that inactivation of the cerebral NF-kB pathway inhibits sickness behaviour in rodents. In this study they did not induce sickness behaviour through stress, but through peripheral administration of IL-1β [39]. IL-1β is another inflammatory cytokine known to induce sickness behaviour by activating the NF-kB pathway [29]. In this study they showed that, by using an NF-kB inhibitor, the cerebral response to IL-1β was inhibited as well as the sickness behaviour that would have been caused by this response. This indicates that NF-kB activation, especially at the BBB, is of major importance in inducing sickness behaviour [39].

### 3.2 Peripheral immune challenges increase inflammatory responses in microglia

Another immunological component in the brain that is interesting to study are the microglia, as they produce pro-inflammatory mediators when they are activated [26]. One study performed by Wohleb et al have looked at the consequence of peripheral immune activation on microglia. They activated the immune system by peripheral administration of LPS, both in control and socially defeated mice. Administration of a saline solution was used as a control for both groups. They found that in both groups that were treated with LPS, but especially in the socially defeated mice, depressive-like behaviour occurred in the form of increased weight loss and social withdrawal. They also found an increase in IL-1β, TNF-α, and iNOS levels in socially defeated mice, together with an increase in activated macrophages in different regions of the brain and an increased inflammatory response of microglia. Socially defeated mice also had a prolonged sickness response compared to the control group, which was associated with the presence of IL-1β in the brain. [40]
This study is especially interesting, as increased and prolonged microglial activity is associated with the development and progression of neurodegenerative diseases [27]. If the same process occurs during depression this could implicate that patients suffering from MDD might have an increased risk at developing neurodegenerative diseases. Indeed, a meta-analysis performed by Ownby et al showed that patients suffering from MDD had an increased risk of developing Alzheimer Disease later on [41]. Another meta-analysis enhances this hypothesis, as they showed that depression was correlated with a 2.2 fold increased risk of developing Parkinson Disease [42].

### 3.3 IDO mediates depressive-like behaviour by activating tryptophan metabolism

As discussed before, activated microglia will produce pro-inflammatory mediators [26]. One of these inflammatory mediator is IDO which contributes greatly to neuro-inflammation. It does so by activating tryptophan metabolism via the kynurenine pathway. This pathway has neurotoxic end products and at the same time serotonin levels are reduced [28]. Thus, it would be interesting to study IDO as a potential drug target for antidepressants.
An early study of Lestage et al found that peripheral administration of LPS or a superantigen (SEB) in mice caused elevated levels of IFN-γ, which was later followed by a two-fold increase in IDO activity [43]. Thus the pro-inflammatory cytokine IFN-γ mediates tryptophan catabolism.
A more recent study performed by Dobos et al in mice also shows an increase in IDO activity after an intracerebroventricular injection with LPS. Interestingly, the LPS injection was followed by depressive-like behaviour in a forced swim test. Here immobility time is used as a measure for depressive-like behaviour, an increase in immobility time indicates an increase in depressive behaviour. Besides the increased immobility time, a reduced body weight was witnessed in mice that were injected with LPS. This study also confirms the role of IDO in depressive-like behaviour, as this behaviour was blocked by inhibiting IDO. [44]
What is interesting to note here is that this study distinguished between cytokine-induced sickness and depressive-like behaviour, not only by monitoring the innate cerebral immune

response, but also by performing behavioural tests after the peak in neuro-inflammation. For instance, the swimming test was performed on the 4th day after injection when neuro-inflammation was almost gone. Even though neuro-inflammation was subsided, the LPS injected mice still showed depressive-like behaviour. Suggesting that depressive-like behaviour lasts even after the initial neuroinflammatory response and can be distinguished from the initial cytokine-induced sickness behaviour. [44]

## 4. Chronic illness and depression

### 4.1 Elevated cytokine levels mediates depression in chronically-ill patients

It is well known that chronically-ill patients have a higher chance of developing MDD, as a result of the chronic inflammation associated with their illness [8] [30]. Even more interesting is that it also occurs in patients who have never suffered from depression or other mental disorders before their chronic illness [6]. It has been established that peripheral immune challenges induce neuro-inflammation via several pathways, including the release of pro-inflammatory cytokines [40] [43] [44]. As chronic illness is associated with chronic inflammation and thus chronic release of cytokines, the high prevalence of MDD in chronically-ill patients could be explained by peripheral cytokines that enter the CSN and induce neuro-inflammation. Indeed, one study performed in elderly diabetic patients that showed depressive symptoms/ mild cognitive impairment (MCI) concluded that all subjects suffering from MCI and/or depressive symptoms had higher levels of the pro-inflammatory mediators TNF-α, CRP and IL-6 compared to controls. All inflammatory markers were positively correlated with the depressive symptoms, as measured by a GDS-30 score. [45]

### 4.2 Cancer-related depression is mediated by pro-inflammatory cytokines and leads to a poorer prognosis

Depression is often witnessed in cancer patients and has been correlated with a worse prognosis [46]. In women suffering from breast cancer an increase in depression was associated with shorter survival times, compared to women whose depression improved over time [47]. It has also been established that depression in cancer patients is not only caused by stress of the diagnosis, but that pro-inflammatory cytokines are of importance as well [46]. For instance, increased cytokine levels were found in patients with acute myeloid leukaemia or myelodysplastic syndrome. Elevated levels of IL-6 were correlated with poorer executive function as well as increased fatigue. The increased levels of TNF-α and IL-1RA were also correlated with increased fatigue [48]. Another study has studied the effects of TNF-α inhibition by etanercept in cancer patients undergoing chemotherapy. TNF-α can induce the NF-kB pathway and together these pro-inflammatory mediators result in fatigue and loss off appetite in cancer patients. By blocking TNF-α these symptoms were reversed and, interestingly, antitumor activity was witnessed. [49]

The efficacy of antidepressants in relieving the depressive symptoms in cancer patients has been studied in a meta-analysis that compared 19 studies. They found that especially Selective Serotonin Uptake Inhibitors (SSRI) and the Tetracyclic antidepressant mianserin were efficient in relieving depression and other cancer-related distressing symptoms [50]. As depression is correlated with a poor prognosis [46], antidepressants could be used to improve prognosis in cancer patients.

### 4.3 IFN-α therapy causes depressive symptoms via IDO activation

Another reason why prevalence of MDD is witnessed more often in chronically-ill patients is because of the use of certain immunotherapies. For instance, IFN-α therapy can be used for the treatment of certain cancers and hepatitis C as it enhances the immune response to eliminate tumours that are resistant to chemotherapy or to clear viruses [6]. The therapy requires patients to inject themselves with IFN-α subcutaneous for months up to years. [51]

A downside to this therapy is that it is known to cause depressive-like side effects in up to 40% of the patients. However, severity of the side effects can be dose-dependent. Side effects of IFN-α therapy include anxiety, social withdrawal, fatigue and anorexia. In worst cases IFN-α therapy can even lead to suicidal ideations. Severe side effects can be a reason for dose reduction or for discontinuing the treatment which, especially in the case of cancer, can be lethal. [51]
Why IFN-α therapy induces depression can be explained by its effect on serotonin. Namely, IFN-α is one of the cytokines that directly activates IDO, which metabolises the pre-cursor of serotonin; tryptophan. Another way IFN-α disturbs serotonin uptake is by decreasing the serotonin receptor 1A. [6] Moreover, IFN-α induces pro-inflammatory cytokines IL-6, IL-1β and TNF-α that induce neuro-inflammation [8].
Interestingly, the side effects of IFN-α therapy can be treated by commonly used antidepressants. Indeed, a study performed by Musselman et al studied the effects of pre-treatment with the antidepressant paroxetine, which is a serotonin-reuptake inhibitor. The subjects were patients suffering from malignant melanoma, who would get a high dose treatment with IFN-α in two weeks. They found that pre-treatment with paroxetine lowered the incidence of depressive-like side effects induced by IFN-α therapy. 2 out of 18 subjects that were treated with paroxetine developed depression, compared to 9 out of 20 patients in the placebo group. [52] Similarly, a second study, performed by Kraus et al, showed positive effects of paroxetine treatment as well. Here the subjects were patients with chronic hepatitis C. Paroxetine treatment was initiated after the start of IFN-α therapy, only when patients developed psychological problems. In 78.6% of the patients that were given paroxetine as treatment for their depression, improvement was seen in their depression and patients were well enough to complete their therapy. [53]
Studies show a definite correlation between IFN-α treatment and the development of depressive-like side effects [8] [51]. However, the occurrence of side effects differs greatly per study [51]. A possible explanation can be found if we look at the genetics of the serotonin transporter. Genetic differences in this receptor have an effect on the response to IFN-α therapy. The serotonin reuptake transporter promotor (5-HTTLPR) of non-depressed patients suffering from hepatitis C was genotyped. They found that the S/S genotype was most susceptible to developing depression during IFN-α therapy, while the $L_A/L_A$ genotype was most resilient to the effects of IFN-α therapy. [54] The findings of this study are especially important to improve IFN-α therapy. With this information genotyping of the serotonin transporter can be performed pre-treatment and susceptible patients can be put on antidepressants before they develop depressive-like side effects.

## 5. Different treatments for MDD and their effectiveness

### 5.1 Regular antidepressant treatment affect pro- and anti-inflammatory cytokine levels

There are multiple classes of antidepressants that are commonly used for treating MDD. These include Selective Serotonin Reuptake Inhibitors (SSRIs), Selective Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs) and Monoamine Oxidase Inhibitors (MAOIs) [55]. Antidepressants can have an influence on cytokine release, however the exact mechanism behind this remains unclear [56]. Interestingly, some SSRIs are able to block production of TNF-α and NO from microglia, when used in high doses [56].
Many studies have looked at the effect of different antidepressant treatments on cytokine levels and have found diverging, and sometimes even contradicting, results [56] [57] [58]. In a review by Kenis et al an overall decrease in levels of pro-inflammatory cytokines such as TNF-α, IFN-α was seen after treatment with various antidepressants. More specifically, treatment with fluoxetine, a SSRI, decreased levels of IL-6 and IFN-γ. Besides the decrease in pro-inflammatory cytokines, an overall increase of the anti-inflammatory cytokine IL-10 was shown.

More specifically, TCAs, SSRIs and SNRIs all reduced the IFN-v/IL-10 ratio by decreasing IFN-γ production and increasing IL-10 production. [57]
Contradicting to the results of the review by Kenis et al, a more recent meta-analysis found an overall decrease in IL-10 [58]. However, this study included 45 studies, while the review only looked at a small amount of studies, rendering the meta-analysis as more reliable. Furthermore, this meta-analysis did find a decrease in TNF-α as well, together with a decrease in IL-6 and the chemokine CCL-2 [58]. However, a high degree in heterogeneity was found during this meta-analysis, which could be explained by the fact that cytokine levels vary much between patients and are correlated with severity of their depression [14].

### 5.2 COX-2 inhibition enhances antidepressant treatment

Neuro-inflammation clearly plays a role in the development of depression in chronically-ill patients but also in medically healthy individuals. Since this is the case, inflammatory mediators and pathways should be drug targets and anti-inflammatory drugs should be tested in MDD patients. It has been shown that severity of MDD is influenced by the levels of inflammatory cytokines [13] [14] so this most likely also influences anti-inflammatory therapy.
Raison et al have studied anti-inflammatory therapy for MDD patients by using a TNF-α antagonist; Infliximab. Infliximab was injected intravenously for 12 weeks. Even though in general no significant decrease in depressive symptoms was noticed and treatment was rendered ineffective, for the group of patients with the highest levels of CRP ( >5mg/L) treatment did seem effective. More specifically symptoms such as depressed mood, psychic anxiety, suicidal ideation and fatigue all decreased. [59]
COX genes are activated by microglia during the neuro-inflammatory process associated with MDD, thus looking at COX inhibition as a drug target for treating MDD could be interesting [24]. Indeed Müller et al have studied the effects of a COX-2 inhibitor; celecoxib (Müller et al, 2006). COX-2 is an inflammatory mediator that is also able to produce other pro-inflammatory cytokines and plays an important role in the formation of prostaglandins, especially PGE2 [26] [56]. In this study reboxetine treatment was enriched with celecoxib, reboxetine enriched with saline solution was used as a control here. Treatment was given to MDD patients once a day, over a period of 6 weeks. During this period a decrease in depressive symptoms was noticed in both groups, however this decrease was much more prominent in the celecoxib treated group. Moreover, 75% of the celecoxib group responded well to therapy, compared to 45% of the placebo group. [60] Furthermore, other studies have seen a decrease in depressive symptoms, together with a decrease in IL-6 levels, after treatment with celecoxib [24] No adverse effects of celecoxib treatment were found in these studies, but a short treatment period (6-8 weeks) could be an explanation for this.
However, whether long-term inhibition of COX2 is the right treatment for MDD is to be questioned, as it has also been shown that COX2 can have anti-inflammatory and neuroprotective properties [56]. Moreover, long term usage of Non-Steroid Anti-Inflammatory Drugs (NSAIDs), that can be used for COX-2 inhibition, is correlated with an increase in cardiovascular events [24].

## 6. Discussion

During neuro-inflammation different processes take place that can contribute to the development of MDD. Most important are the hyperactivity of the HPA axis and activation of microglia. Microglia can be activated by pro-inflammatory cytokines and once they are activated they are important for the production of other inflammatory mediators. Chronic activation of microglia is a problem as it has been associated with progression of neurodegenerative diseases such as Alzheimer and Parkinson.
This paper has discussed how neuro-inflammation, and in particular pro-inflammatory cytokines, plays a role in the pathophysiology of MDD.
Firstly, there is substantial evidence for increased levels of pro-inflammatory cytokines in MDD patients. Animal studies show that after a peripheral immune challenge or acute stress, where neuro-inflammation is induced, an increased level of pro-inflammatory cytokines occurs, which contributes to so-called sickness behaviour. Interestingly, this sickness behaviour has many similarities with behaviour during MDD.
Secondly, hyperactivity of the HPA axis leads to glucocorticoid resistance, which is caused by chronic stress but can also be induced by administration of cytokines. Moreover, hyperactivity of the HPA axis has been associated with fatigue and depressive symptoms. (source).
Thirdly, in patients with chronic inflammation and other chronic illnesses where chronic pro-inflammatory cytokine production occurs, depression has a higher prevalence compared to the normal population. Cytokines have been associated with depressive behaviour and cognitive impairment in depressed elderly and with fatigue and loss of appetite in cancer patients. Furthermore, usage of antidepressants in cancer patients caused relieve of these symptoms and improved prognosis.
Lastly, immunotherapy where IFN-ALPHA is used to enhance the immune response against a virus or tumour, induces depressive-like symptoms in a subgroup of patients. Interestingly, IFN-ALPHA induced depressive symptoms can be treated by commonly used antidepressants.

Taking all these bullet points together, it can be concluded that pro-inflammatory cytokines are important in MDD. However, there are numerous other factors that influence the likelihood of someone developing depression. For instance, multiple Single Nucleotide Polymorphisms (SNPs) have been associated with an increased risk of developing MDD. These SNPs are often located in genes that are expressed in the CNS and are associated with neurodevelopment [61]. However, one single SNP can't fully be responsible for developing MDD. Epigenetics most likely play a role in the development of MDD, thus eventually complex gene x environment interactions will determine whether someone will develop depression [62]. Besides that, it is commonly known that a higher prevalence of MDD occurs in females when compared to males. An explanation can be found on hormonal level, women have high fluctuation in their oestrogen levels which could make them more vulnerable for developing depression. It has been suggested that oestrogen has neuroprotective properties and a meta-analysis shows that women that get into menopause at a later age, thus have prolonged oestrogen production, have a lower risk of developing depression. [63].

To conclude, pro-inflammatory cytokines are involved in many processes that can eventually contribute to the development of major depression, however the pathophysiology of MDD is very complex and gene x environment interactions will determine whether someone will develop MDD or not. Furthermore, sex differences are seen in the prevalence of MDD that can be explained on a hormonal level. Since many patients do not respond well to commonly used antidepressants other treatment options should be explored. Finding a suitable treatment for MDD is of great importance as major depression is one of the biggest threats to public health all over the world.

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