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A link between Depression and Alzheimer's disease

A role for TNFα signaling and IDO?

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Contents

1 Introduction

Major depression is a state of physiologic pain and is often seen as more painful than any physical pain someone can have (Myint Kim 2003). Psychological stress is long thought to be one of the causes of depression. However more and more studies suggest depression can also be a result of a dysfunctional immune system and chronic inflammation together with the increase of cytokines. Furthermore several neurodegenerative diseases like Alzheimer's disease (AD) show an increased prevalence of developing major depression. AD is a severe, incurable, neurodegenerative disease with symptoms like memory loss, cognitive deficits and changes in behavior. Because AD is seen mostly in people above the age of 65, the occurrence of this disease is seriously growing with people getting older every day. Several theories are proposed to explain the cause of depression as seen in AD.

In the early stage of AD it was thought that the psychological stress of having a severe incurable disease may be a cause of developing depression. But psychological stress is, as stated above, shown to be no longer the only cause of depression. AD also causes an increase in the inflammatory response and thereby also an increase of pro-inflammatory cytokines, which are also associated with major depression. TNFα is one of these cytokines found upregulated in both AD and major depression. TNFα has a neurotoxic effect by stimulating production of aggregated beta-amyloid (Ab), a major mark for AD (Knezevic-Cuca, Stansberry et al. 2000). In addition higher levels of TNFα seem to be involved in the progression of major depression, likewise lower levels of TNFα is shown to correlate with improvement of major depression (Lanquillon, Krieg et al. 2000). The effect of TNFα is however influenced by its two receptors, the TNFα receptor 1 (TNFR1) and the TNFα receptor 2 (TNFR2). The signaling via these receptors has different effects on the cellular response. In general TNFR1 signaling is thought to be neurotoxic, whereas binding to the TNFR2 is thought to have mainly neuroprotective effects (Mccoy and Tansey 2008). This suggests a different role for the two receptors in the cause of major depression in AD. Another explanation for depression can be found in the metabolism of tryptophan via the kynurenine- or serotonin pathway. Indoleamine 2,3-dioxygenase (IDO) is the rate-limiting enzyme for tryptophan metabolism via the kynurenine pathway in the brain. IDO activity is found increased in AD (Heyes, Saito et al. 1993). The activation of the kynurenine pathway through IDO could play a role in depression. It leaves less tryptophan available for serotonin production and several metabolites produced in the kynurenine pathway are known to be neurotoxic.

Thus, several theories could explain the correlation between depression and AD. Besides, depression seems to be a prelude of AD. People with mild depression have a doubled risk of developing AD later in life. This suggests that depression may be a risk factor of developing AD.

In conclusion depression and AD seem to be connected to each other, but it is not clear what this connection is precisely. Is depression a cause or a consequence of AD? And what is the role of IDO and TNF signaling in AD and depression? It may also be that the two disorders both have the same causes.

2.1 Alzheimer's disease

AD is a progressive and fatal brain disease. It was first described by the German Alois Alzheimer in 1906. A lot of research has been done after AD since than, but there is still no cure against this life destructing disease. AD destroys the brain through synaptic loss, reactive astrogliosis and neuronal cell death in parts of the brain that are essential for learning and memory like the hippocampus, basal forebrain, amygdala, frontal cortex and entorhinal cortex (Yankner 1996). AD is recognized through three major markers which can do damage to the brain, found in brains from AD patients. The first hallmark is called neuritic senile plaques. Plaques are extracellular deposits of a protein fragment called beta-amyloid. These fragments of protein build up between nerve cells. Plaques are assumed to cause problems in communication and nutrition of these cells and to induce the inflammatory response. Neurofibrillary tangles in neurons are the second major marker in AD. Tangles are twisted fibers of the protein 'tau' located inside damaged nerve cells. Another marker for AD is the loss in neuronal cells. There are a lot of healthy

people aging who develop these plaques and tangles. However, people with AD tend to develop far more of these structures. The neuronal damage in AD causes serious memory loss, problems with thinking and behavior which are severe enough to change someone's social life drastically.
AD is also associated with the occurrence of depression. In the Western society more people tend to reach the age of 65 up than elsewhere in the world. The age of 65 is the main onset of developing AD. Consequently AD is an illness mainly seen in this part of the world. Moreover, people are getting older every day all over the world and thereby there is also a great increase seen of people developing AD. The European Collaboration on Dementia made a prognosis for the number of demented in Europe until 2030 as seen in figure 1, there is a great increase of dementia expected in Europe. 50 to 80 percent of dementia is caused by AD. Thus, AD is a fast growing severe illness, especially in the Western world (AD Association, 2010a)

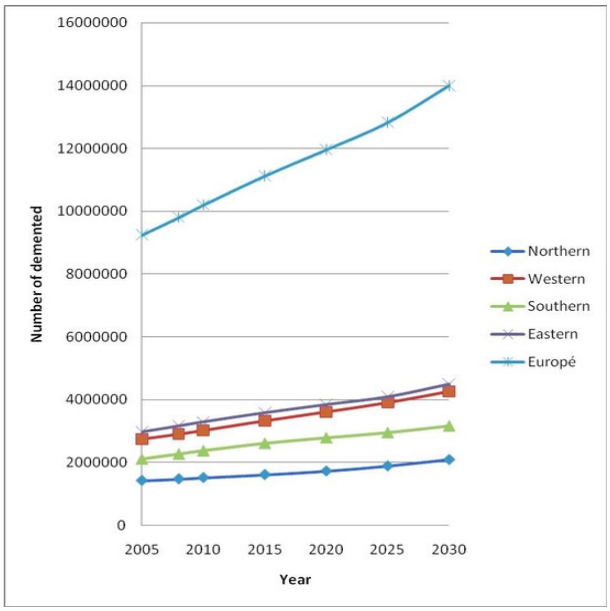

Figure 1. Prognosis for the number of demented in Europe until 2030 (Alzheimer's Association, 2010a). The number of demented people is a dramatically increasing in Europe. 50 to 80 percent of these dementia cases are caused by Alzheimer's disease.

2.2 Depression

Twenty percent of all people experiences a major depression at least once in their life, this makes major depression the most common psychiatric disorder (Andrade, Caraveo-Anduaga et al. 2003). Depression is an illness of the mind and can be caused by continues stress. The term stress is introduced by Hans Syle in 1936 and means actually any condition that interrupts the physiological or psychological homeostasis of an organism. Stress is necessary to stay alive. Stress gives organisms the motivation to get back to their homeostasis. For example, the stress condition 'hunger' will make an organism go look for food and eat. However, continues stress could be a risk factor of developing major depression. People with major depression can experience a widespread of symptoms. It can cause physiological symptoms like anhedonia, depressed mood, feelings of worthlessness or guilt and recurrent thought of death or suicide. But depression can also cause physical symptoms like a disturbed appetite and or weight, tiredness and difficulties in concentrating. These symptoms can be caused by neuroendocrine and or neuroanatomical changes (Sierksma, van den Hove et al. 2010). Furthermore major depression can cause less well-known cognitive deficits in memory, list learning, recall, verbal and visual memory, executive function, attention and verbal fluency (Sierksma, van den Hove et al. 2010). A major role of developing depression is long thought to be in psychological stress, however more recent studies also suggest a major role for physical stress in the process of developing depression (Leonard 2007). One explanation for the development of depression can be found in the alteration of the hypothalamus–pituitary–adrenal axis (HPA-axis) and the serotonergic system in major depression.

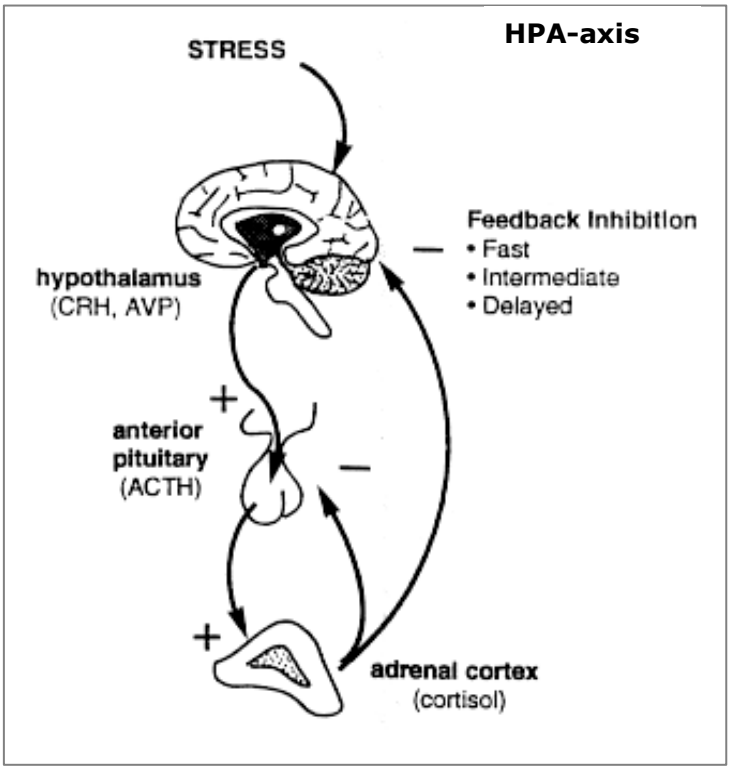

Figure 2. The HPA-axis. In conditions of stress the production of CRH in the hypothalamus is activated. This in turn activates the production of ACTH in the anterior pituitary. ACTH causes the adrenal cortex to produce cortisol. Cortisol serves as a negative feedback on the anterior pituitary and hypothalamus.

In situations of stress an organism reacts via the HPA-axis (Figure 2) to prepare the body and brain to the stressor. The HPA-axis causes the secretion of certain stress hormones, which in turn causes a change in the energy metabolism and immunity. The regulation of the stress response via the HPA-axis starts in the paraventricular nucleus of the hypothalamus (PVN). The parvocellular neurons synthesize and secrete the stress hormone corticotrophin-releasing hormone (CRH) into the pituitary portal system, in response the anterior pituitary secretes the adrenocorticotropic hormone (ACTH). ACTH is secreted into the bloodstream. It stimulates the adrenal glands to produce and release glucocorticoids. These glucocorticoids change the energy metabolism and immunity in the body. More energy is made available for activation of the sympathic nervous system. Elevated CRH levels also cause an increase in immunoreactivity, this is also seen in depressed suicide people in the raphe nuclei of the midbrain (Austin, Janosky et al. 2003). Glucocorticoids also serve as a negative feedback to the hypothalamus and pituitary by inhibiting the release of CRH and ACTH. The glucocorticoids are signaled by two types of receptors. The first one is the high-affinity mineralcorticoid receptor found almost exclusively in the hippocampus. This receptor is almost completely occupied with psychological basal levels of circadian glucocorticoids, which gives a negative feedback to the HPA-axis under normal conditions. In stress situations there is a second, low-affinity, glucocorticoid receptor which will then cause the negative feedback (Joels 2006). The glucocorticoid receptor is found throughout the entire brain, but is most dense in the hippocampus, cortex, thalamus, PVN and the dorsal raphe nucleus (Harfstrand, Fuxe et al. 1986; Reul and Dekloet 1986). In case of major depression it is thought that the negative feedback is deficient. Patients with major depression have a higher basal level of the stress hormones cortisol and ACTH. It is thought that this is caused by the elevated level of CRH found in patients suffering from major depression. However a decreased level of CRH levels is found in suicide victims. This suggests that the secretion of CRH is downregulated in depressed patients as a consequence of earlier CRH hypersecretion (Nemeroff, Owens et al. 1988). This is explained by the theory called the 'glucocorticoid cascade hypothesis of MD'. It says that the long term exposure to glucocorticoids in major depression causes a downregulation of the glucocorticoid receptors. Due to this downregulation the negative feedback on the HPA-axis will be less effective, more glucocorticoids are needed to result the same level of negative feedback.

As a consequence more glucocorticoids will cause further downregulation of the receptors and so result in a vicious cycle of further downregulation and a deficient negative feedback (Sapolsky, Krey et al. 1986). The elevated levels of glucocorticoids are related to the cognitive deficits seen in patients with major depression (Van Londen, Goekoop et al. 1998).
Another explanation for the cause of major depression can be found in the 'Serotonin Hypothesis of Major Depression'. This theory states that depression is a result of a decreased level of serotonin (5-HT) in the brain. In periods of stress, more 5-HT is needed to cope with the stress. However, patients with major depression have a decreased level of brain serotonin. The shortage of serotonin in the brain can be caused by a diminished availability of L-tryptophan (L-TRP), impaired 5-HT synthesis, release, reuptake, or metabolism, or by changes in the 5-HT postsynaptic receptor. Serotonin is synthesizes out of the precursor L-tryptophan in the serotonergic neurons in the raphe nuclei, located in the brain stem. Thus depletion of L-tryptophan will eventually evolve also in a depletion of serotonin in the brain. Conflicting result are found for the role of L-tryptophan in depression. Maes et al found lower levels of available L-tryptophan in patients with major depression than in healthy controls or patients with minor depression. Because L-tryptophan has to be taken in dietary, low L-tryptophan levels in patients with major depression could be a result of low dietary intake (Maes, 2000). It could also be a result in a shift towards another pathway that metabolizes L-tryptophan, the kynurenine pathway. This pathway will be explained later. It should be taken in account though that there are also other studies that can not find these results.
From the brain stem, serotonin is transported throughout the brain, with highest fiber densities in the hippocampus, hypothalamus and amygdala (Sierksma, van den Hove et al. 2010). The serotonin is transported by the 5-HT transporter (5-HTT). If this transport does not work efficiently, this will end up in low levels of active serotonin in the brain, the finding of reduced mRNA levels of 5-HTT depressed suicide victims confirmed this view, although the expression per neuron was upregulated (Arango 2001).
Finally the serotonin has to be taken up by the 5-HT receptors. In times of stress the serotonin receptor 5-HT2 is upregulated, which causes an increase in serotonin levels in the brain to compensate for the increased need of serotonin. However, when the stress is chronic this compensation does not seem to be sufficient and major depression will occur. The 5-HT autoreceptors, 5-HT1B-, 5-HT1D- and 5-HT1A receptors, are also known to play a role in major depression. Blocking these autoreceptors can result in an increase of extracellular serotonin and so be antidepressant (Myint and Kim 2003).
In summary psychological stress might be a cause of depression, but depression may also be a result of increased glucocorticoid levels as explained in 'the glucocorticoid cascade hypothesis of MD'. Another theory suggests that decreased serotonin levels in the brain are the cause of depression; this theory is called 'The Serotonin Hypothesis of Major Depression'.

2.3 Depression and Alzheimer's disease

AD is often correlated with depression. Because AD is a very severe incurable illness, it could be that patients in the early stage of AD get depressed because of the psychological stress of having AD. However, depression seems to be a prelude to dementia in later life. Patients with mild cognitive impairment associated with depression have more than twice the risk of developing dementia than patients who are not depressed (Jost and Grossberg, 1996) (Figure 3). Furthermore, there are common pathological features found in major depression, which are also seen in dementia. These features are increased neurodegeneration, reduced neuroprotection and neuronal repair (Leonard 2007). Studies on the effect of chronic stress found that chronic inflammatory changes, which are known to occur in major depression followed by chronic stress, are often associated with cardiac disease, hypertension, diabetes and different types of autoimmune disease. A possible explanation could be that the chronic low grade inflammation seen in depression, causes changes in brain structure and function, which could be a prelude of developing AD (Leonard 2007). Still, in stead of depression being the prelude of AD, the neuroinflammation in AD could also be a cause of depression.

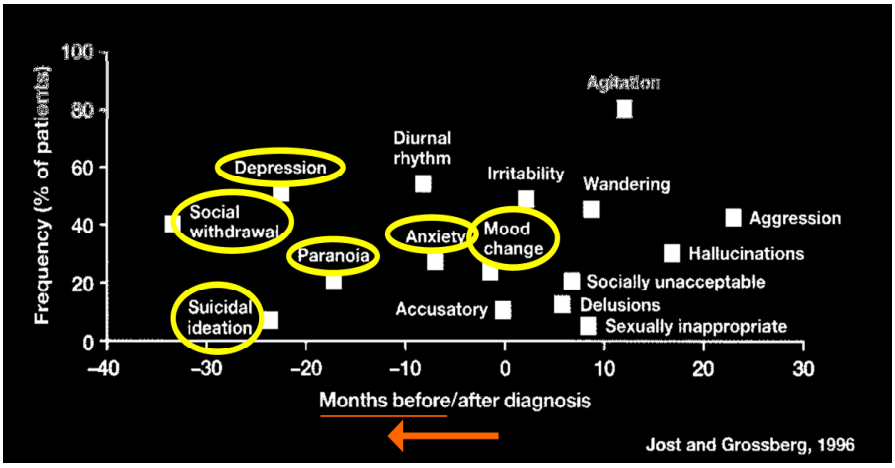

Figure 3. Peak frequency of behavioural symptoms as Alzheimer's disease progresses (Jost and Grossberg, 1996). Depression seems to be a prelude of developing Alzheimer's disease. Patients with mild cognitive impairment associated with depression have more than twice the risk of developing dementia than patients who are not depressed.

3.1 Cytokines

Cytokines are peptides that play a major role in communication within and between cells. They are secreted and released from one cell after the growth or activity of another cell. Cytokines released by macrophages have a major role in the immune response by creating the inflammatory response, called the pro-inflammatory cytokines. In the brain, most cytokines are secreted by astrocytes and microglia and, under certain conditions, neurons can also produce cytokines (Myint and Kim 2003). Astrocytes and microglia are both brain cells, known to play a crucial role in the cerebral immune response (Ting, Brew et al. 2007). The pro-inflammatory cytokines promote the inflammatory response by attracting other cytokines, increasing the capillary permeability, and causing fever. The cytokines can be transported through the circulation to serve as a long distance signal and communicate both with the nervous and endocrine system to gather information from all over the body in order to coordinate the inflammatory response. Interleukins are a major group of cytokines involved in the immune response. Interleukin-1 (IL-1) for instance, is secreted by activated macrophages and other immune cells and modulates the immune response by (1) altering blood vessel endothelium and so allowing more white blood cells and proteins to pass during inflammation (2) stimulating the production of acute-phase proteins by the liver, which will cover the pathogens to make them targets for immune cells (3) inducing fever and (4) stimulating cytokine and endocrine secretion in other cells (Silverthorn, 2007).
There are also cytokines that specifically act upon viral infections; a major group of these cytokines is called interferons. They react on a viral infection by interfering in the viral replication. Interferon-alpha and interferon-beta do this by activating pathways to prevent viral replication in uninfected cells, while interferon-gamma produced by macrophages and other immune cells interferes in the infection.

3.2 Cytokines in depression

In patients with major depression there are raised pro-inflammatory cytokine levels found for interleukin-6 (IL-6), IL-1 and tumor necrosis factor alpha (TNFα) (Leonard 2007). There is also a decreased level of the anti-inflammatory cytokines IL-4 and IL-10 observed in these patients (Maes 1999). The increase in pro-inflammatory cytokines can be explained through the role of CRH in the HPA-axes. In depressed patients there is a reduced threshold to stress. In situations of stress the hypothalamus produces CRH, which activates the anterior pituitary in the production of ACTH. ACTH goes to the adrenal gland where it activates the production of cortisol, the mean stress hormone. It seems that CRH has a major role in the increase of the cytokines in depressed patients. Several structures that produce cytokines like T helper, T memory and activated T-cells, macrophages and monocytes are also found increased in patients with major depression. One explanation for these observations is 'the macrophage theory of depression' suggested by Smith (Smith 1991). This theory states that, in depressed patients, there is an imbalance between the inflammatory and anti-inflammatory arms of the cellular

immune system in which the inflammatory cytokines are predominant over the anti-inflammatory cytokines. This is also found in patients with various types of cancer, or hepatitis. These patients were treated with IFN that can induce other pro-inflammatory cytokines like Il-6, TNFα and IL-1. This treatment caused a depressed mood, anxiety, sleep disturbance, loss of libido, lack of motivation and deficits in short term memory (Wichers, Koek et al. 2005). These symptoms are also typical for major depression. This supports the theory that there is a connection between inflammation and depression. Furthermore, these symptoms were attenuated by chronic treatment with antidepressant (Leonard 2007).
It should be noted thought that there are also studies that failed in finding a correlation between the depression's severity and the level of cytokines. These contradictory findings suggests that there is a major role in the pathogenesis of major depression for cytokines, but that there are probably also other important factors in the occurrence of major depression (Leonard 2007).

3.3 Cytokines and Alzheimer's disease

Cytokines do not only play a role in depression, but also seem to influence the neurodegeneration in AD. There are several pro-inflammatory cytokines upregulated in AD patients. They are thought to cause serious brain damage through the direct or indirect release of neurotoxins; the reduction in neuronal repair due to the decrease in neurotrophic factors and by the stimulation of the tryptophan-kynurenine pathway. In depressed patients there are also neuropathological changes found in the brain. The pro-inflammatory cytokines are thought to cause neuronal damage in major depression (Leonard 2007). IL-1, IL-6 and TNFα are three of these cytokines that are also known to cause brain damage in AD. IL-1 is found up regulated in both AD and in major depression (Leonard 2007). This cytokine can do damage to brain by inducing expression of nitric oxide synthase (iNOS). iNOS in turn causes neurotoxicity through NMDA-induced neurotoxicity (Hewett, Csernansky et al. 1994). Administer of IL-1 also demonstrated a decrease of the anti-inflammatory cytokine IL-10 (Song, Horrobin et al. 2006), thereby shifting the balance between the anti-inflammatory effects and the inflammatory effects even more to the inflammatory side. This could mean that IL-1 has a neurotoxic effect by inhibiting the anti-inflammatory response in the brain. Furthermore IL-1 is shown to increase cognitive deficit and depressive and anxiety-like behavior in rats, which suggests a link between AD and depression (Song, Horrobin et al. 2006).
A second cytokine found up regulated in both AD and major depression is IL-6 (Vandenabeele and Fiers 1991). The level of IL-6 is positively associated with the occurrence of neurotic plaques, a major mark for AD (Leonard 2007). It is thought that IL-6 does not directly damage the brain. IL-6 stimulates the expression of other inflammatory cytokines, which can cause neuronal damage (Vandenabeele and Fiers 1991). There are also studies that showed that IL-6 enhances NMDA-induced neurotoxicity, probably via promoting an increase in the calcium-influx (Qui 1998).
Another cytokine found increased in both AD and depression is TNFα (Vandenabeele and Fiers 1991). TNFα production is probably stimulated by aggregated beta-amyloid (Ab) (Knezevic-Cuca, Stansberry et al. 2000), which is also a major mark of AD. The combination of TNFα and IFN in turn seem to increase the synthesis of this beta-amyloid (Blasko, Marx et al. 1999). Thereby causes a vicious cycle in the occurrence of Ab and the cytokine TNFα. The Ab plaques are known to cause brain damage. And so, via the stimulation of Ab, TNFα has a neurotoxic effect in AD.
In conclusion pro-inflammatory cytokines that are up-regulated in AD seem to have several neurotoxic effects, either directly or indirectly.

3.4 Tumor Necrosis Factor α, a cytokine out lighted

The pro-inflammatory cytokine TNFα is of special interest for its role in depression and AD because it is shown that improvement of major depression correlates with lower levels of TNFα (Lanquillon, Krieg et al. 2000). It is a member of a large cytokine family, the TNF ligand family. TNF stands for Tumor Necrosis Factor. This name was based on its first discovered antitumoral activity in mouse tumor models. TNF was first described

about 30 years ago. It was identified to be produced upon activation by the immune system, able to exert significant cytotoxicity on many tumor cell lines and to cause tumor necrosis in certain animal models systems (Wajant, Pfizenmaier et al. 2003).
TNF works via two receptors, the TNF receptor 1 (TNFR1) and the TNF receptor 2 (TNFR2). TNFR1 is activated by binding to both soluble TNF (sTNF) and membrane-integrated TNF (memTNF), whereas TNFR2 can only be activated through memTNF. They differ in their expression profiles, ligand affinity, cytoplastic tail structure and the downstream signaling pathway activation (Mccoy and Tansey 2008). These differences influence in the activation of a number of intracellular signaling pathways which in turn influence the cellular response in terms of inflammation, proliferation, cell migration, apoptosis and necrosis (Mccoy and Tansey 2008). In general TNFR1 is thought to be neurotoxic, whereas TNFR2 is thought to have mainly neuroprotective effects (Mccoy and Tansey 2008). However, TNFR1 activation can also have protective effects as TNFR2 can have destructive effects. There is also much crosstalk between the two TNFα receptors (Wajant, Pfizenmaier et al. 2003).
Thus there may also be a role for the two different receptors in depression and AD, but their precise effects on neurotoxicity and neuroprotection are complex due to numerous pathways and crosstalk between the two receptors.

3.4.1 TNFR1
TNFR1 (Figure 4) is expressed in most cell types and binds primarily to sTNF (Grell, Wajant et al. 1998). There are two main subgroups of the TNF-R family, the death domain-containing receptors and the TRAF-interacting receptors. TNFR1 belongs, with its TNF receptor associated death domain (TRADD), to the first group (Tartaglia, Ayres et al. 1993). The binding with TRADD can induce cell-death via recruitment with other proteins and caspase activation. Furthermore, binding of TNF to TNFR1 can lead to renewal of the pro-caspase 8 and the formation of the death-inducing signal complex. This will activate the executioner capsases that will lead to apoptosis (Micheau and Tschopp 2003; Schneider-Brachert, Tchikov et al. 2004).

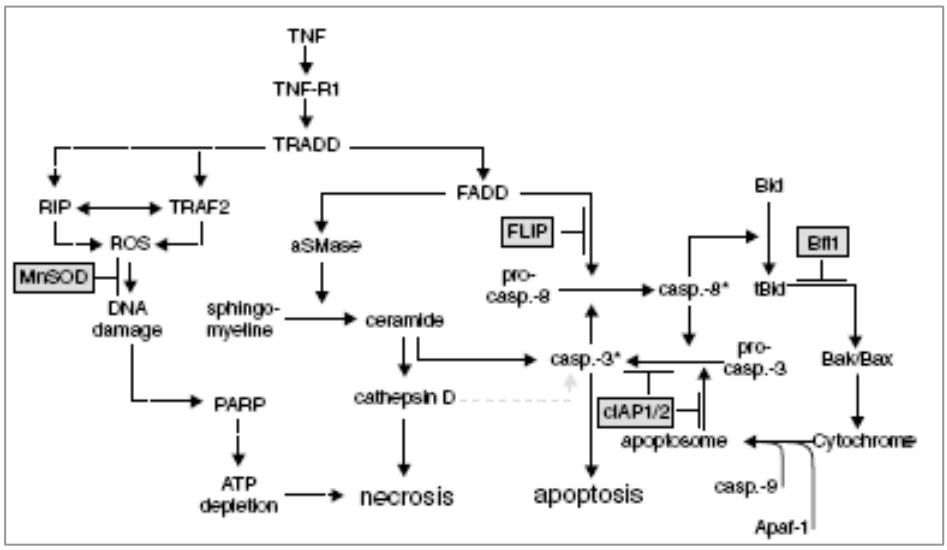

Figure 4. The TNFα signalling pathway by TNFR1 (Wajant, Pfizenmaier et al. 2003). The bindin of TNF with TNFR1 is thought to be mainly destructive. However activation of TNFR1 causes a complex activation of different pathways, which allows also other outcomes for the binding with TNFR1.

However, the binding with TNFR1 can also activate the NF-κB pathway, known to initiate pro-survival signaling and cellular proliferation (Mccoy and Tansey 2008). Additionally activation of the NF-κB pathway can lead to activation of JNK, which is cytoprotective. Yet sustained JNK activation will also lead to apoptosis (Tobiume, Matsuzawa et al. 2001).
Conclusively, the activation of TNFR1 is associated with tissue destruction (Wajant, Pfizenmaier et al. 2003), but it may also have pro-survival outcomes due to complex signaling pathways.

3.4.2 TNFR2

Expression of TNFR2 (Figure 5) is highly regulated and mostly found in cells of the immune system. TNFR2 seems to play a major role in the lymphoid system. It can only be fully activated by memTNF and not by sTNF (Grell 1996). It seems that activation of TNFR2 primarily initiates pro-inflammatory and pro-survival pathways (Mccoy and Tansey 2008). One pro-survival pathway of TNFR2 is seen the activation of the NF-κB pathway (Mccoy and Tansey 2008), where NF-κB is protective by targeting a variety of anti-apoptotic genes (Wajant, Pfizenmaier et al. 2003). Furthermore, TNFR2 binding has been shown to activate the so called phosphatidylinositol 3-kinase-dependent signaling, which promotes neuron survival (Marchetti, Klein et al. 2004). TNFR2 can also inhibit apoptosis by activation of TNF receptor associated factor 1 (TRAF1) and TNF receptor associated factor 2 (TRAF2). TRAF1 and TRAF2 in turn, interfere with TNFR1 induced apoptosis and activation of caspase-8 (Wang, Mayo et al. 1998). In addition, though the TNFR2 does not contain a DD, TNFR2 can enhance the binding between solTNF and the TNFR1, hereby indirectly inducing the apoptotic pathway via TNFR1 DD by promotion of the this receptor (Tartaglia, Pennica et al. 1993). It should be noted however, that the role of TNFR2 may be underestimated, because detect TNFR2 can only be fully activated by memTNF and memTNF is hard to.

Thus the direct effects of TNFR2 seem to be protective; however the crosstalk between TNFR1 and TNFR2 also allows apoptotic activation via TNFR2.

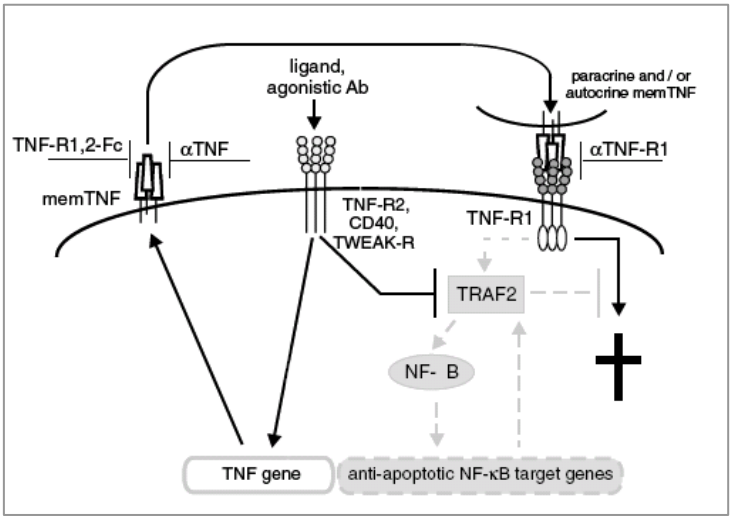

Figure 5. The TNFα signaling pathway by TNFR2. The TNFR2 can induce apoptosis indirectly by stimulating TNFR1.

3.5 TNFα and its receptors in depression in Alzheimer's disease.

Pro-inflammatory cytokines like IL-1, IL-6 and TNFα are upregulated in patients with major depression. TNFα is suggested to have a special role in major depression, because the levels of TNFα correlate with the severity of the depression (Lanquillon, Krieg et al. 2000). Levels of TNFα are also found elevated in the amyloidogenic plaques of AD brains (Dickson 1997). The severity of AD seems to correlate with the level of TNFα as well. In patients with severe AD elevated levels of serum TNFα are found compared to patients with mild-to-moderate AD (Paganelli, Di Iorio et al. 2002). Other evidence was found for contribution of inflammation and in the progression and onset of AD. This was found in a study in mice with three familial AD-linked mutations, which cause the aggregation of intraneural amyloid immunoreactivity in certain regions in the cortex. In the same regions an increase in TNFα mRNA level was observed, which correlated with the onset of cognitive deficits in the mice (Janelsins 2005; Billings, Oddo et al. 2005). In addition, a clinical study showed improvements in cognitive performance after treatment with anti-TNFα biologic etanercept in patients with AD compared to the placebo group (Tobinick 2006). These findings suggest a possible connection between the depression seen in AD and the elevated levels of TNFα. Thought it should be noted that there are also studies that do not find differences in TNFα levels in severe- and mild AD patient (Mccoy and Tansey 2008).

However it is noteworthy that TNFα acts via two receptors that both influence the progression and development of major depression and AD. Theories about different functions of the two TNF receptors suggest that the neurotoxic effects of TNFα could be mainly caused through signaling via the TNFR1, whereas the TNFR2 is thought to have mainly neuroprotective effects. The neurotoxic effects could result in a progression of AD. Evidence for a link between TNF receptors and AD is found in a study that showed mice with a deletion of the TNFR1 had reduced amyloid β pathology, microglia activation, neuron loss and memory deficits compared to mice with normal TNFR1 levels (He, Zhong et al. 2007). Thought this study shows a role for the TNFR1 in AD, it does not show the differences between the two TNF receptors. A study by Simen et al. shows different outcomes for TNFα signaling via the TNFR1 or TNFR2 in depression. However these differences are only based on different magnitude of depressive behavior (Simen, Duman et al. 2006). This suggests that there is indeed a difference in TNFα signaling via TNRF1 and TNFR2. But to unravel the exact differences between these two receptors and their role in depression, more research has to be done.
Thus TNFα signaling through TNFR1 is thought to be mainly neurotoxic and thereby be involved in both inducing depression as AD. On the other hand, signaling through the TNFR2 is thought to have mainly neuroprotective effects. However, there seems to be a lot of crosstalk between TNFR1 and TNFR2. This way both receptors could also have counteracting effects then the ones stated above. But still too little is known about these receptors to get a clear picture of TNFα signaling through TNFR1 and TNFR2. So, more research is needed.

4.1 Indoleamine 2,3-dioxygenase

Tryptophan is an essential amino acid and the precursor for serotonin. However, the main part of tryptophan is oxidatively degraded by the kynurenine pathway into quinolinic acid. There are two rate-limiting enzymes in the kynurenine pathway; tryptophan dioxygenase (TDO) and Indoleamine 2,3-dioxygenase (IDO). TDO is primarily expressed in the liver and catabolizes the main part of the tryptophan. Outside of the liver IDO, first described by Higuchi et al (Higuchi 1963), represents the rate-limiting enzyme of the kynurenine pathway (Kwidzinski and Bechmann 2007).
IDO is expressed in all organs including the brain in immune cells like macrophages and dendrite cells. In the brain IDO is mainly expressed by microglia cells. Thought IDO activation in normal conditions is negligible, its activation is highly increased in inflammatory condition through induction by pro-inflammatory cytokines including TNFα (Dantzer, O'Connor et al. 2008). Activation of IDO in the peripheral tissues can suppress the proliferation of infectious parasites like Chlamydia trachomatis (Nettelnbreker, Zeidler et al. 1998) and Toxoplasma gondii (Pfefferkorn 1984). In the brain, activation of IDO has been shown to downmodulate the neuroinflammation during experimental autoimmune encephalomyelitis (Kwidzinski and Bechmann 2007). But activation of IDO also induces the kynurenine pathway and several metabolites of this pathway are known to be neurotoxic (Whetsell and Schwarcz 1983). Furthermore blocking IDO has also been shown to reduce depression-like behavior (Dantzer, O'Connor et al. 2008). These contradictionary findings suggest a role for IDO in neuroinflammation, neurodegeneration and depression, but what this role precisely contains is not yet clear.

4.2 IDO in depression

4.2.1 Depression and the serotonin pathway

Activation of IDO could influence the development of depression by reducing the plasma levels of tryptophan for serotonin metabolism. There are two major pathways for the degradation of tryptophan: the kynurenine pathway and the serotonin pathway (Figure 6). IDO degrades tryptophan via the kynurenine pathway, thereby leaving less tryptophan available for the serotonin pathway.

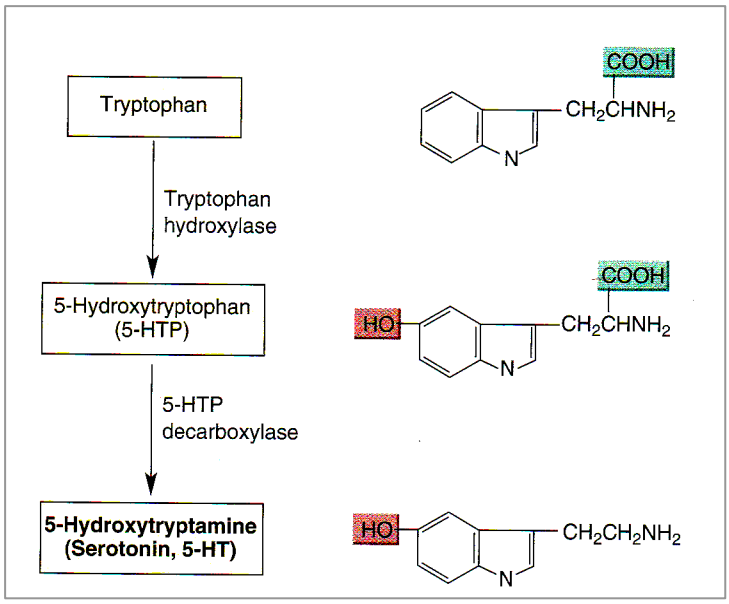

Figure 6. The synthesis of serotonin from tryptophan in the serotonin pathway (Bear 2007). Tryptophan is synthesized into serotonin by the serotonin pathway. Tryptophan is converted by tryptophan hydroxylase into 5-hydroxytryptophan. 5-Hydroxytryptophan is further converted into serotonin by 5-HTP decarboxylase.

In the serotonin pathway tryptophan is synthesized into serotonin by the serotonergic neurons. The synthesis of serotonin occurs in two steps. The first step is converting of tryptophan into 5-Hydroxytryptophan by tryptophan hydroxylase. In the second step 5-hydroxytryptophan is converted into serotonin by 5-HTP decarboxylase. The synthesis of serotonin is limited by the available tryptophan in the extracellular fluid in which the neurons are located. Tryptophan is transported out of the blood into the brain. Tryptophan has to be taken in by diet to reach the blood. So a deficiency in the dietary intake of tryptophan can result in a depletion of serotonin in the brain. A lack of serotonin in the brain has been associated with an increase in aggression, a decrease in food-intake and major depression (Coppen, Shaw et al. 1967; Myint and Kim 2003; Bear 2007). Thus activation of IDO could cause depression by decreasing available tryptophan levels for serotonin metabolism. This theory is supported by the finding that reduction in plasma levels of tryptophan correlate with patients depression score three week after immunotherapy treatment (Capuron, Ravaud et al. 2002), still it is unclear if this is a consequence of their psychiatric symptoms (Dantzer, O'Connor et al. 2008).

4.2.2 Depression and the kynurenine pathway

As noted before, IDO degrades tryptophan into kynurenine (KYN) via the kynurenine pathway (Figure 7). This is the main pathway for tryptophan metabolism. It converts tryptophan into kynurenine, which in turn has several metabolites. The kynurenine pathway is active in both the liver and the brain. In the brain the rate limiting enzyme is IDO. In the liver the rate limiting enzyme is TDO (Kwidzinski and Bechmann 2007).

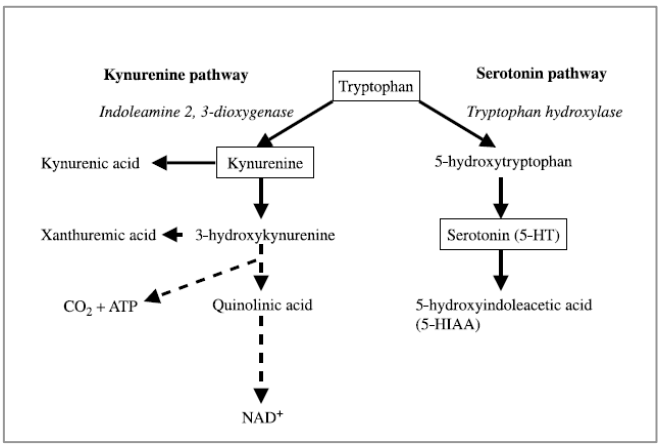

Figure 7. The kynurenine pathway and serotonin pathway (Miura, Ozaki et al. 2008). In the kynurenine pathway tryptophan is converted by IDO into kynurenine. Further down the kynurenine pathway several metabolites are produced. Of these metabolites kynurenic acid is thought to be neuroprotective, whereas 3-hydroxykynurenine and quinolinic acid are thought to be neurotoxic. In the serotonin pathway tryptophan is converted into serotonin.

In the kynurenine pathway in the brain tryptophan is first degraded by IDO to kynurenine (KYN) and further to kynurenine acid (KYNA). KYN is metabolized into 3-hydroxykynurenine (3-OH KYN). 3-OH KYN is further converted into quinolinic acid (QUIN). One of the main functions of the kynurenine pathway is the production of nicotinamide adenine dinucleotide (NAD^+) from QUIN. NAD^+ serves a lot of functions inside the cell like control of the energy metabolism, DNA repair and transcription (Ting, Brew et al. 2007). The kynurenine pathway is known to be upregulated in conditions of stress. The study of Pawlak et al. shows that, in rats stress in form of a footshock increases brain tryptophan, KYN, KYNA and 3-OH KYN (Pawlak, 2000). Recent data of Miura et al. shows that a 20-min novelty stress exposure of animals to a condition they have never experienced before, elevates brain kynurenine levels as well as tryptophan levels without changing the kynurenine/tryptophan ratio (Miura, Ozaki et al. 2008). The serotonin/tryptophan ratio on the other hand is increased in a situation of this novelty stress. This suggests that novelty stress causes a shift in the balance of serotonin metabolism towards the kynurenine pathway. Thereby it causes a higher level of the neurotoxic metabolite QUIN, which in turn causes extra damage to the brain (Miura, Ozaki et al. 2008). QUIN has several neurotoxic effects. First of all it acts as a NMDA agonist which, in line with previous findings, could mean that QUIN can be involved in depression. QUIN can also induce depression through activation of the glutamatergic system by causing an over release of glutamate in the striatum and in the cortex (Fedele and Foster 1993; Chen, Surmeier et al. 1999). Several studies indeed support the theory of QUIN being responsible for depression. Increase of QUIN has been strongly associated with anxiety and features of depression like decrease in reaction time and cognitive deficits (Muller 2007). Furthermore the degradation of tryptophan in patients of major depression (MD) was shown to be increased compared to the controls, however the levels of KYNA were lower in the patients with MD. This suggests that in these patients the metabolism of tryptophan is preferred into QUIN in stead of KYNA. KYNA, another metabolite of the kynurenine pathway, is thought to be neuroprotective by counteracting on this effect by acting as a NMDA receptor antagonist (Muller 2007). IDO can thus have a depressive effect by its activation of the kynurenine pathway and thereby probably decreasing serotonin levels and increasing the neurotoxic metabolites like QUIN.

4.3 IDO in Alzheimer's disease

IDO activity is found to be increased in AD (Heyes, Saito et al. 1993). The kynurenine pathway, which is activated by IDO, is also associated in several other neurodegenerative diseases like Huntington's disease, AIDS dementia complex, amyotrophic lateral sclerosis and multiple sclerosis (Ting, Brew et al. 2007). Of the kynurenine metabolites QUIN and 3-OH KYN are known to have mainly neurotoxic effects, while KYNA and NAD^+ have mostly neuroprotective effects (Miura, Ozaki et al. 2008). QUIN is among others neurotoxic through its contribution in the inflammatory response in the brain by the production of several chemokines (Guillemin, Croitoru-Lamoury et al. 2003). This response causes the release of the cytokines TNFα and IL-1β (Fiala, Zhang et al. 1998). TNFα in turn triggers the production of amyloid-beta (Aβ), which causes neuronal cell damage. IL-1β can cause the release of one other cytokine, S100β. This cytokine promotes inducible nitric oxide synthase (iNOS) followed by reactive oxygen species (ROS) and nitric oxide formation (Yasuda, Tateishi et al. 2004). This way IL-1β indirectly causes cell death or apoptosis when it is present in pathological concentrations via S100β.

QUIN also acts as a selective *N*-methyl-D-aspartate (NMDA) receptor agonist which can cause excitotoxic lesions in the brain (Schwarcz, Whetsell et al. 1983). Furthermore, it inhibits the uptake of glutamate in the astrocytes, which causes a misbalance in the extracellular glutamate (Tavares, Tasca et al. 2002). Glutamate plays a major role in the metabolism of neurons. Glutamate is converted in astrocytes to glutamine or oxidized via the tricarboxylic acid cycle (Yu, Schousboe et al. 1982). Most metabolites that are formed in these pathways are energy substrates for the neurons (Poitry, Poitry-Yamate et al. 2000). Because of this important role of glutamate in the neurons, depletion of glutamate causes a lot of damage in the neurons.

The second neurotoxic metabolite is 3-OH KYN and can cause serious damage to the brain by metabolism of 3-hydroxyanthranillic acid (3-OH AA). 3-OH AA in turn can cause brain damage by producing reactive radical species, that induces oxidative stress and apoptosis in neurons (Kwidzinski and Bechmann 2007).
QUIN and 3-OH are also found to be toxic to astrocytes in concentrations as seen in AD. Because astrocytes are a major source of KYNA, the production of the KYNA will also be reduced. KYNA is known to be neuroprotective by counteracting the neurotoxic effect of QUIN, thus depletion of KYN will also result in an increase of neuronal damage (Leonard 2007).
To conclude, IDO can play a role in AD through the activation of the kynurenine pathway and thereby its neurotoxic metabolites (Figure 8).

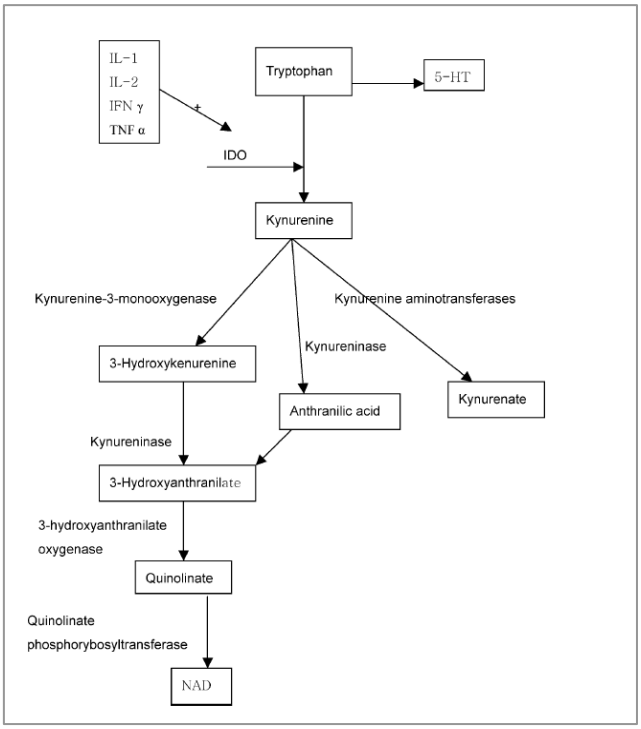

Figure 8. The role of IDO in the serotonin- and kynurenine pathway (Myint and Kim 2003). IDO induces the activation of the kynurenine pathway. This results in less tryptophan available for the serotonin pathway, which is associated with developing depression. Furthermore several neurotoxic metabolites are produces in the kynurenine pathway that could contribute in the progression of Alzheimer's disease and major depression.

5 Conclusion

AD is seen to be connected with major depression. Both diseases can have severe symptoms and the number of patients suffering from these diseases is seriously growing every day. A lot of research is going on to unravel what mechanisms connect AD and major depression. Though a lot of these connections have already been found, still much is unclear about AD and major depression.
One connection is found in the upregulation of cytokines in both diseases. A very important cytokine in this connection seems to be TNFα. TNFα stimulates the production of aggregated beta-amyloid (Ab). Ab causes damage to the brain and could thereby influence the progression of AD and depression.
However, it should be taken in account that TNFα acts via the two receptors TNFR1 and TNFR2. They are both shown to have different effects on the brain. Whereas TNFR1 seems to be mainly involved in neurotoxic effects, TNFR2 is thought to be mainly neuroprotective. But there is a lot of complex signaling and crosstalk going on between these receptors, which could also allows other outcomes in the signaling through TNFR1 and TNFR2. There is still little known about these two receptors in depression and AD, but already shown differences in depressive behavior by the two receptors are promising for further research.
Moreover TNFα is known to induce the enzyme IDO, which is also thought to have a role in depression and AD. This can be explained by the activation of the kynurenine pathway through IDO. With this activation, less tryptophan is left available for the synthesis of serotonin, which could result in a lower serotonin level in the brain. A lack of serotonin in

the brain has been associated with depression. Thus activation of the kynurenine pathway may indirectly be a risk of developing depression through depletion of serotonin levels in the brain. Furthermore, the metabolites QUIN and 3-OH KYN, produced by the kynurenine pathway, are shown to be neurotoxic and also associated with depression. These metabolites can thus be involved in the progression of AD by damaging the brain and also seem to induce depression. KYNA on the other hand, is a metabolite of the kynurenine pathway that seems to have neuroprotective effects. KYNA inhibits the neurotoxic effects of QUIN, thereby protecting the brain. But the ratio KYNA/QUIN is shown to be decreased in patients with depression. This suggests that the metabolism in depressed patients is preferred into QUIN, causing even more brain damage and inhibiting the neuroprotective effects. So depression may influence the progression of neurodegeneration and that may also induce the progression of AD.
To conclude, it seems that depression can be a risk factor of developing AD and AD in turn may promotes further developing of depression through increased pro-inflammatory cytokines and activation of the kynurenine pathway by IDO. However there are a lot of different complex mechanisms involved in depression and AD. This makes it hard to get a clear picture of the connection between major depression and AD. A lot of promising connections are already made, but still much research is needed to unravel the precise connection between AD and depression.

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