The role of inflammatory processes in the development of depression and Alzheimer's disease

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Abstract

Studies have suggested a link between experiencing episodes of depression and the subsequent development of dementia later in life. Evidence of this link consists of neuroanatomical similarities, including a decrease in hippocampal volume, as well as the epidemiological finding that the risk of dementia increases with 13-14% for every depressive episode. However, information on the cellular and molecular mechanism underlying the link between these disorders is limited. Inflammation is known to play an important role in both diseases, and is suggested as a candidate system involved in the link between both diseases. More specifically, it was recently suggested that the enzyme indoleamine 2,3-dioxygenose (IDO) may be an important player in the association between depression and dementia. IDO is the rate-limiting enzyme in the kynurenine pathway for tryptophan metabolism and is activated by pro-inflammatory cytokines. The aim of this thesis is to review evidence for a causal the link between both diseases and to test the plausibility of inflammation, and more specifically IDO, as a mechanistic factor. There is both qualitative and quantitative evidence that supports the hypothesis that IDO contributes to the symptoms of major depression as well as to the cognitive symptoms of Alzheimer's disease. IDO exhibits this detrimental effect in close collaboration with the immune system and the hypothalamus-pituitary-adrenal (HPA)-axis. Therapeutic options based on alleviating IDO levels are suggested, but not proven irrefutably yet.

Layman summary

Depression and dementia are usually seen as two distinct psychiatric disorders. However, it is shown that people with depression have a higher risk to develop Alzheimer's disease, the most common form of dementia, when they age. People who experienced episodes of depression more often, have the highest risk to indeed develop Alzheimer's disease. In addition, changes in certain brain areas are seen in both diseases, but not in healthy people. These findings indicate that some of the problems in depression and Alzheimer's disease are caused by the same factor.

It is thought that this common factor might be inflammation. Inflammation normally occurs when an intruder (e.g. bacterium or virus) tries to enter the body. An inflammatory response activates several mechanisms that will kill the intruder, but might at the same time be harmful for the own body. Normally, inflammation will only take place for a few days in order to kill the intruder, which will cause no serious problems for the own tissue. However, in depression and Alzheimer's disease, the inflammation will last much longer and can therefore damage the tissue. One of the enzymes that plays a role in inflammation is indoleamine 2,3-dioxygenase (IDO). This enzyme plays a role in starving bacteria, but at the same time produces a substance that is toxic for neurons. These toxic substances are thought to be the cause of the changes in the brain areas that are seen in both diseases. The aim of this thesis is to study if previous research indeed indicates that IDO is the factor that is responsible for the similarities between depression and Alzheimer's disease. The conclusion is that IDO indeed plays a role in causing these similarities, but that it does not do this on its own. IDO collaborates with other factors of the immune system, as well as with the system that is activated in response to stress, which is called the hypothalamus-pituitary-adrenal (HPA) axis. It is suggested that after extensive follow-up research, IDO might be an interesting target for new treatments.

Contents

1 Introduction

Depression and dementia are both highly prevalent disorders, which have a large social, medical and economic impact (Hermida, McDonald, Steenland, & Levey, 2012). It becomes increasingly apparent that there may be similarities in the etiology of these two disorders (Hermida et al., 2012), whereby some researchers even postulate that depression might be a prelude to dementia (Leonard & Myint, 2009). Initial indications for a causal link between depression and dementia came from clinical evidence and epidemiological findings (Hermida et al., 2012; Leonard & Myint, 2006a). Several epidemiological studies showed that depression is an important predisposing factor for dementia, particularly in Alzheimer's disease (Leonard & Myint, 2006a). However, the role of depression as a risk factor for the development of dementia later in life is still controversial (Hermida et al., 2012). Much research is currently aimed at elucidating the exact mechanisms that may explain the mechanism of action that links between both disorders.

An important line of neurobiological research focuses on the involvement of immune reactions in the pathophysiology of depression, and more recently this research has been extended to include dementia. This research forms one of the branches of the larger field of psychoneuroimmunology (PNI), which studies the interactions between the nervous, immune and endocrine system in psychiatric disorders (Leonard & Myint, 2009). The first paper to suggest involvement of immune activation in the pathophysiology of depression was published in Lancet as early as 1969 (Lapin & Oxenkrug, 1969; Oxenkrug, 2010). In this paper it was proposed that disturbances in the kynurenine pathway for tryptophan metabolism in the brain, of which indoleamine 2,3-dioxygenase (IDO) is the rate-limiting enzyme, contributes to the development of depression. Since upregulation of this pathway was later shown to occur during infection (Duleu et al., 2010), the paper by Lapin and colleagues can be seen as the first to link depression and inflammation. The Lancet paper resulted in more than 40 years of subsequent research, aiming to further clarify the role of the immune system, and IDO in particular, in the etiology of depression.

Importantly, in the late 1980's and early 1990's, the first studies were published suggesting that tryptophan metabolism might be involved in the development of dementia as well (Fuchs et al., 1990; Heyes, Mefford, Quearry, Dedhia, & Lackner, 1990). Both studies showed increased levels of kynurenine pathway metabolites following an human immunodeficiency virus-type 1 (HIV-1) infection, suggesting activation of IDO. Some patients with HIV-1 development symptoms of dementia, known as the acquired immune deficiency syndrome (AIDS) dementia complex (Fuchs et al., 1990). In patients with the AIDS dementia complex, levels of tryptophan were lower, while IDO activity and levels of inflammatory factors were increased compared to HIV-1 patients without dementia (Fuchs et al., 1990). These data suggest a role for IDO and inflammation in the pathological mechanism leading to dementia. After these initial studies, the main focus of the field shifted towards studying the involvement of tryptophan metabolism in patients with Alzheimer's disease (AD). However, the majority of the studies looking at the involvement of IDO in neuropsychiatric disorders focus on depression rather than dementia.

In 2006, it was proposed that IDO might be the missing link between depression and dementia (Leonard & Myint, 2006a; Leonard & Myint, 2006b). Activation of IDO upregulates the kynurenine pathway for tryptophan degradation, a pathway implicated in inflammatory responses (Duleu et al., 2010). Since IDO activity can be manipulated using medication, this would suggest that IDO might be

a promising new target for dementia treatment (Christmas, Potokar, & Davies, 2011; Sublette & Postolache, 2012).

The main hypothesis explored in this thesis, is that the pathway regulated by IDO is indeed (one of) the mechanism(s) linking depression and dementia. First, a general review on the progress of the disease is described for depression and dementia separately. Subsequently, this thesis will present the results of a literature search which evaluates the likelihood of the immune system being an important player in both diseases. Finally, the available evidence for the central hypothesis will be critically discussed, whereby strengths and limitations of the current literature, as well as potential targets for future research, will be identified.

2 Depression

2.1 General facts

Depression is an extremely common and debilitating psychiatric disorder (Christmas et al., 2011). According to the World Health Organization, it is the leading cause of years live with disability (Maj, 2012) and the fourth leading cause of disability and disease worldwide (Christmas et al., 2011; Hermida et al., 2012).

In most countries, the lifetime prevalence of major depressive disorder is reported to range between 8 and 12%, which would make it the most common mental disorder (Maj, 2012). In the USA, a study amongst elderly showed a prevalence of 11%, with a lifetime prevalence for major depressive episode of 19% (Hermida et al., 2012). The higher lifetime prevalence found by Hermida and colleagues might be explained by the fact that they look at depressive episodes, whereas Maj et al. studied depressive disorder. Since two or more depressive episodes are required for the diagnosis of depressive disorder (Center for Substance Abuse Treatment, 2008), it is plausible that the prevalence of depressive episodes (as found by Maj et al.) is higher than that of depressive disorder (studied by Hermida et al.).

2.1.1. Diagnosis

For the diagnosis of a major depressive episode, the DSM 4th edition requires 'depressed mood and/or loss of interest or pleasure in life activities for at least two weeks' (Center for Substance Abuse Treatment, 2008). Besides, five out of nine additional symptoms should be met and should cause clinically significant impairments in functioning, almost every day. These nine symptoms encompass 1) depressed mood during most of the day, 2) diminished interest or pleasure in activities, 3) unintentional weight loss or gain, 4) sleep disturbances (insomnia or sleeping too much), 5) agitation or psychomotor retardation noticed by others, 6) fatigue or loss of energy, 7) excessive guilt or feelings of worthlessness, 8) indecisiveness or reduced ability to concentrate or think, and 9) recurrent thoughts of death (Center for Substance Abuse Treatment, 2008). In addition to these requirements, the DSM-IV states that there should be no direct physiological effects of a substance or medical condition that might explain the symptoms (Center for Substance Abuse Treatment, 2008).

If not all requirements for the diagnosis of major depression as stated in the DSM-IV are met, patients can be diagnosed with minor or sub-threshold depression (Rodriguez, Nuevo, Chatterji, & Ayuso-Mateos, 2012). The 10th edition of the International Classification of Diseases (ICD-10) does

not use the terms major and minor depression, but instead distinguishes three different groups: mild, moderate and severe depressive episodes (Rodriguez et al., 2012). The distinction between these sub-forms is based on the number of symptoms that the patient experiences. According to Maj, these thresholds are rather arbitrary, and result in a lack of clinical relevance of the sub-types (Maj, 2012). It is therefore suggested that depression should no longer be seen as a collection of distinct disorders diagnosed using all-or-none criteria, but that it would be better to look at the disorder as a continuous spectrum of depressed states (Maj, 2012; Rodriguez et al., 2012).

The current situation, however, is that the vast majority of the research only studies patients with major depression (Rodriguez et al., 2012). Based on the criticisms towards the division of depression into different subtypes, this would not be ideal. Nevertheless, since most literature available on the topics discussed in this thesis is about major depression in particular, the emphasis of this thesis will be on major depression or depression in general, rather than on minor depression or the other subtypes distinguished.

2.1.2 Symptoms & treatment

The most commonly noted symptoms of depression are described in the DSM-IV as criteria for the diagnosis of depression. However, besides these criteria, some other (related) symptoms can be distinguished. The symptoms observed in depressive patients can be divided into two categories. First, psychological and cognitive symptoms can be distinguished, which include decreased social interaction, decreased libido, feelings of social isolation, psychomotor slowing, depressed mood, cognitive dysfunction, deficits in short-term memory and anxiety (Christmas et al., 2011; Leonard & Myint, 2009; Walker et al., 2013). The second category comprises neuro-vegetative symptoms, which include anorexia, loss of appetite, fatigue and pain (Walker et al., 2013). The onset of neuro-vegetative symptoms usually precedes the psychological and cognitive symptoms (Walker et al., 2013).

The treatment possibilities for (major) depression can be divided into pharmacological and non-pharmacological interventions. Current pharmacological treatments aim at enhancing the serotonergic or noradrenergic neurotransmission (or a combination of both) (Baghai, Moller, & Rupprecht, 2006). The selective serotonin reuptake inhibitors (SSRI's) are an example of commonly prescribed pharmaceuticals in depressed patients. SSRI's are often combined with non-pharmaceutical treatment in the form of cognitive behavioural therapy (Lovrin, 2009). Established non-pharmaceutical treatment options include electroconvulsive therapy and bright light therapy (effective in subgroups), but little is known about the mechanisms underlying the antidepressant function (Baghai et al., 2006).

However, at this moment the effectiveness of the available treatment is not optimal. The non-response rate to pharmacotherapy is approximately 30% (Baghai et al., 2006), whereas around 35% of the patients shows remission after the initial treatment (Christmas et al., 2011). Together with the significant side effects and the latency of several weeks until the clinical situation improves, this implicates that further research aiming to find a more optimal treatment is desired (Baghai et al., 2006; Christmas et al., 2011).

Indeed, new treatment possibilities are currently under investigation. Potential pharmacological principles include agonists for the serotonin receptor (in particular the 5-HT1A subtype) and several interventions targeting the hypothalamus-pituitary-adrenal (HPA) axis (Baghai et al., 2006). New non-

pharmacological treatment possibilities consist of magnetic seizure therapy, vagus nerve stimulation and transcranial magnetic stimulation (Baghai et al., 2006; Christmas et al., 2011).

2.2 Neuropathology of depression

In the past decades, researchers gathered a huge amount of data about the neuropathology of depression. Multiple studies looked into the possible involvement of biological mechanisms on different levels, varying from neurotransmitters to neuroendocrine and neuropeptide systems, and from neurotropic signalling cascades to signal transduction pathways (Maj, 2012).

In 1973, Akiskal and McKinney claimed to have found a common pathway for all depressive disorders, which would consist of a 'functional impairment of the diencephalic centres of reinforcement' (Maj, 2012). The current opinion, however, is that science does not yet dispose of any conclusive evidence for a biological index that plays a causal role in all subgroups of depressive disorder (Maj, 2012). Below, a short summary of these alternations, as well as the pathways and systems they influence, will be given in order to provide some background on the mechanisms of disease in depression.

2.2.1 HPA-axis

One of the systems that is often associated with the pathophysiology of depression is the HPA axis (Leonard & Myint, 2009), also known as the stress-axis. The involvement of this stress-axis in depression might be explained by the observation that major depression is often precipitated by stress (Leonard & Myint, 2009). Stress is an important factor in the neurogenesis hypothesis of depression, which assumes that neurogenesis plays a key role in pathology of depression, and that it is negatively influenced by stressful experiences (Bewernick & Schlaepfer, 2013). Several lines of research indeed show that the involvement of (chronic) stress and the subsequent hyperactivity of the HPA-axis in depression pathology seems plausible (Bewernick & Schlaepfer, 2013; Leonard & Myint, 2009). Below, the HPA-axis and its changes relevant for depression will be shortly described.

In response to a stressful event, the activation of the HPA-axis is initiated by the hypothalamic secretion of stress neurotransmitters of the corticotrophin releasing hormone (CRH) family, in particular corticotrophin releasing factor (CRF) (221 Silverthorn, 2010. CRH stimulates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH), which in turn induces the production of glucocorticoids (GC) in the adrenal cortex. The function of GCs differs between acute and chronic stress. In acute stress, they have an immunosuppressive function, but chronic stress is associated with reduced glucocorticoid receptor (GR) responsiveness, leading to impaired immunosuppression. Besides inducing GC secretion, ACTH also has effects downstream of the HPA-axis, by inducing the adrenal medulla to produce adrenalin and noradrenalin (Silverthorn, 2010). These adrenal hormones, in cooperation with stress hormones from the pituitary, can activate leukocytes, thereby promoting the secretion of pro-inflammatory cytokines (Leonard & Myint, 2009). These pro-inflammatory cytokines can in turn further increase CHR levels by inducing the hypothalamus.
In the normal situation, this process is regulated by the feedback mechanism of the HPA-axis. Each hormone produced in the HPA-axis feeds back to suppress the secretion of the hormone one step earlier in the pathway. In this way, GCs thus suppress ACTH, which in turn suppresses CRH (Silverthorn, 2010). This feedback mechanism makes sure that the duration and degree of elevated cytokine levels remain within limits (Leonard & Myint, 2009). However, patients with major

depression show aberrations in this feedback mechanism. Consequently, the HPA-axis will become (chronically) hyperactive and produce high levels of cortisol. As a consequence, the levels of glucocorticoids get elevated and different types of immune cells will secrete high levels of pro-inflammatory cytokines (Leonard & Myint, 2009).

2.2.2 Neurotransmitters

Several neurotransmitters show aberrant expression levels in patients with depression. The aim of this section is to briefly discuss the two most studied neurotransmitters involved in the etiology of depression.

The most studied neurotransmitter in depression research is serotonin. Serotonin is involved in the development and plasticity of neural networks and has a wide spectrum of essential neuronal functions including social cognition, sensory processing, cognitive control and emotional responses (Lesch & Waider, 2012). Aberrant serotonin functioning is implicated in multiple neuro-developmental and neuropsychological disorders, amongst which depression. In depression, decreased levels of extracellular serotonin, caused by increased serotonin turnover, have been reported in both human patients and mouse models (Christmas et al., 2011; Corona et al., 2012; Oxenkrug, 2010). Serotonin is known to have major influence on emotions and mood, which accounts for the association between low serotonin levels and low mood. This is illustrated by the fact that the most important group of anti-depressant pharmaceuticals, the selective serotonin reuptake inhibitors (SSRIs), function in normalizing the availability of serotonin in the synaptic cleft (Christmas et al., 2011).

In addition to aberrant levels of serotonin, noradrenalin distortions are implicated in depressive disorders. Noradrenalin (NA) is mainly known for its involvement in the regulation of arousal and stress, but it also plays a role in learning and memory and regulation of inflammation (Brunello et al., 2002; Goddard et al., 2010). In chronic stress, which is suggested to play an important role in depression, elevations as well as decreases in NA levels have been reported (Goddard et al., 2010). The hyperactivity of the HPA-axis suggests that levels of NA would increase in depression. However, based on the literature studied for this thesis, it seems that a majority of studies reports decreases in noradrenalin signalling. For example, in rodent studies, researchers reported decreased NA release and atrophy of NA axons, leading to a reduction in NA neurotransmission. Post mortem studies in humans also reported axonal loss (Goddard et al., 2010) and showed a decrease in noradrenergic neurons in the locus coeruleus (LC) (Leonard, 2001). In addition, decreased NA levels were measured in the urine and CSF of depressed patients (Goddard et al., 2010). Furthermore, Brunello and colleagues (2002) suggest that chronic stress results in decreased sensitivity as well as downregulation of the adrenoreceptors. Corresponding with these findings, depressive symptoms can be reduced by administering selective noradrenalin reuptake inhibitors (NRI) in aim to elevate brain levels of NA (Brunello et al., 2002; Goddard et al., 2010). In conclusion, although the knowledge about the underlying mechanism remains limited, noradrenalin is suggested to be an important factor in the pathology of depression.

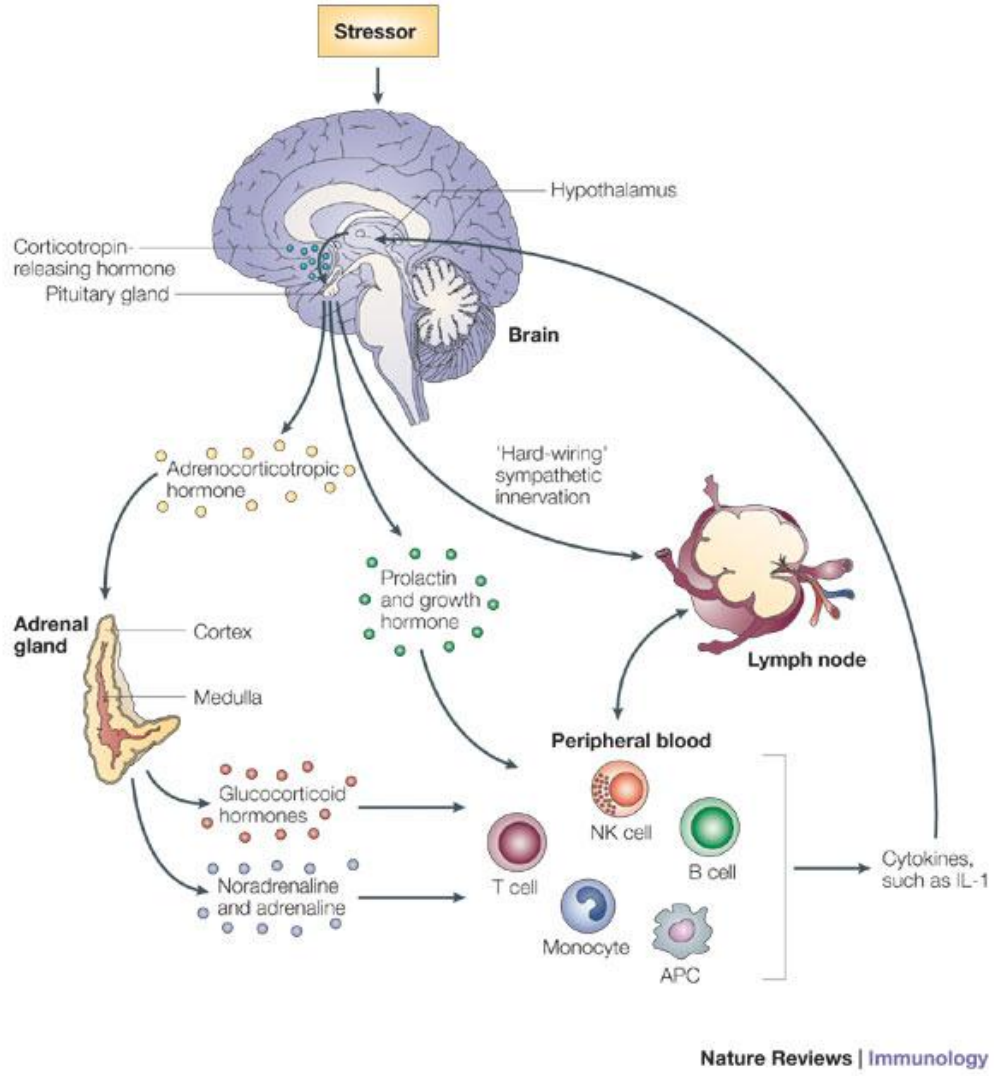

Figure 1 |Activation of the hypothalamus-pituitary- adrenal (HPA) axis. When a stressful situation is experienced, the hypothalamus- pituitary-adrenal (HPA) axis is activated. The hypothalamus produces corticotrophin releasing factor (CRH), which induces secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary. ACTH in turn activated the adrenal cortex to produce glucocorticoid hormones (including cortisol). During acute stress, these glucocorticoids (GCs) have an immunosuppressive function. However, when stress becomes chronic, the responsiveness of glucocorticoid receptors is reduced and the immunosuppressive function is impaired. In addition to stimulating GC production, ACTH induces the adrenal medulla to produce adrenalin and noradrenalin, which in chronic stress will eventually lead to desensitization of the adrenoreceptors (Brunello et al., 2002). These adrenal hormones, together with stress hormones produced by the pituitary, can activate several types of leukocytes. The pro-inflammatory cytokines produced by the activated leukocytes can in turn further influence the activity of the HPA-axis by further stimulating the secretion of CRH from the hypothalamus. APC, antigen-presenting cell; IL-1, interleukin-1; NK, natural killer. Adapted from (Glaser & Kiecolt-Glaser, 2005)

2.2.3 Alternations in brain anatomy and neural activity

Alternations in structure and activity of the depressed brain can provide information about which neuronal pathways might be impaired in depression. Some of the frequently observed changes are therefore summarized here.

Structural changes have been observed in several areas of the brain of depressed patients. These changes include hippocampal atrophy following glucocorticoid induced apoptosis (Leonard & Myint, 2009), a decreased number of astrocytes (Leonard & Myint, 2006a; Leonard, 2007), neural loss from the (pre)frontal cortex and striatum (Leonard & Myint, 2006a) and enlargement of the ventricles (Leonard & Myint, 2009). In addition, changes in the amygdala, basal ganglia and pituitary gland were also observed, but were more ambiguous than the changes in the previously named structures. Furthermore, dendritic branching and neurogenesis showed slight reductions in the frontal cortex and more prominent in the hippocampus, thereby enhancing the degeneration caused by glucocorticoids (Leonard & Myint, 2006a).

Multiple research groups studied the neural activity in patients with major depression, but different studies seem to show little agreement about which changes or even which structures are distinctive for depression. For example, some positron emission tomography (PET) studies found decreased activity in the general, temporal and dorsolateral prefrontal cortical activity, whereas the amygdala showed increased activity (Maj, 2012). However, both findings have been contradicted by studies that found the opposite change in activity or that reported no change at all (Maj, 2012). It might be plausible that (subtypes of) depression show characteristic alterations in activity levels. However, until now, little conclusive evidence seem to be reported about the brain structures that show differential activity patterns and the direction of the alterations.

3 Dementia

3.1 General facts

Dementia is a common denominator for several disorders characterized by impaired cognitive abilities. In 2000, the overall prevalence of dementia in Europe was estimated at 6,4% (Misiak, Cialkowska-Kuzminska, Frydecka, Chladzinska-Kiejna, & Kiejna, 2013). The neurodegenerative disorder Alzheimer's disease (AD) is the most prominent form of age-related dementia (Krstic et al., 2012; Yamada, Akimoto, Kagawa, Guillemin, & Takikawa, 2009). AD prevalence is age-dependent and doubles every 5 years for people aged between 65 and 85 (Salloway & Correia, 2009). In the general population, the incidence rate is estimated at 0.3% to 3.9% per year. For people at age 85, the prevalence increased to 30% to 50% (Salloway & Correia, 2009). Since the leading risk factor for AD is high age (Gong et al., 2011), finding preventive strategies is extremely important to prevent a pandemic, now that the population is ageing (Wood, 2012). In the past years, the incidence of AD showed large increases and was associated with premature unemployment and increased mortality (Gong et al., 2011).

3.1.1 Diagnosis

The definite diagnosis of Alzheimer's disease can only be made post-mortem, since autopsy is needed to reveal if beta-amyloid plaques and neurofibrillary tangles are present. Nevertheless, the DSM-IV does describe criteria for the diagnosis of AD in living patients (American Psychiatric Association & American Psychiatric Association. Task Force on DSM-IV., 2000).

The first criterion is the development of multiple cognitive deficits, manifested by 1) memory impairment and 2) one or more cognitive disturbances (i.e., aphasia, apraxia, agnosia or disturbances

in executive functioning). The cognitive deficits should each cause significant impairment in functioning and the course of the deficits should be characterized by gradual onset and continuing decline. (American Psychiatric Association & American Psychiatric Association. Task Force on DSM-IV., 2000).
In addition to the criteria of the DSM-IV, there are several tests that can be used to assess the cognitive capacity of a patient. Several screening tests (including the Mini-Mental State Exam and the more sensitive Montreal Cognitive Assessment Battery) can be used to test cognitive decline (Salloway & Correia, 2009). In addition, brain imaging, genetic factors and the measurement of cerebrospinal fluid markers can help indicating if a patient might suffer from AD (Salloway & Correia, 2009).

Besides the cognitive symptoms, patients with AD often exhibit behavioural and psychological symptoms of dementia (BPSD). Four clusters of symptoms with high prevalence can be distinguished: psychosis (38% of the patients), hyperactivity (64%, including aggression and disinhibition), affective symptoms (59% including anxiety and depression), and apathy (65%) (Popp & Arlt, 2011).

3.1.2 Alzheimer's disease and mild cognitive impairment

The high prevalence of AD explains why most studies relevant for this thesis focus on this form of dementia. This fact, together with the implication of immune alterations in AD is the reason why this thesis will mainly focus on this form of dementia. In addition, some data about mild cognitive impairment (MCI), often seen as a prelude of dementia, will be presented. On yearly basis, 6% to 25% of patients with MCI develop dementia, compared to 0.3% to 3.9% (depending on age) of the general population (Salloway & Correia, 2009). It is therefore important to study how this progression from MCI to AD can be prevented.

The main factor that differentiates between MCI and AD is that MCI does not significantly disrupt the ability to perform daily activities (Salloway & Correia, 2009). In practice, it might however be difficult to discriminate between the symptoms of beginning Alzheimer's disease or MCI, and the cognitive decline that is associated with normal aging. The Alzheimer's Association therefore developed a list with ten key warning signs of AD. This list can be summarized as difficulty with performing familiar tasks, altered behaviour and personality, loss of initiative, disorientation, misplacing things and problems with memory, language, judgment and abstract thought (Salloway & Correia, 2009). Early recognition of Alzheimer's disease is important, because the results of treatment are best when started as early as possible (Salloway & Correia, 2009).

3.1.3 Treatment of Alzheimer's disease

In order to provide some background information about the current prospective for AD patients, a short overview of the different treatment options will be given.
First of all, different pharmacological compounds can be administered to alleviate specific symptoms. Cholinesterase inhibitors (ChEIs) can stabilize the memory of patients during the first year of use and attenuate the decline over time (Popp & Arlt, 2011; Salloway & Correia, 2009). The glutamate *N*-methyl *D*-aspartate (NMDA) antagonist memantine decreases decline in cognition and functioning and is used in more severe forms of AD (Salloway & Correia, 2009). The existing pharmacological treatments for AD thus mainly reach attenuation of cognitive decline over time, rather than improvement of cognitive and behavioural symptoms (Salloway & Correia, 2009).

A non-pharmaceutical way in which cognitive symptoms are attempted to be reduced, is by different kinds of cognitive training. A meta-analysis of cognitive training programs suggests that the effect size is small in patients with mild AD, in contrast to a previous study that did show beneficial effects (Schwarz, Froelich, & Burns, 2012). The effectiveness of cognitive training is thus not clearly evident.

Besides the cognitive symptoms, BPSD can be a major problem in AD patients, especially since it seriously complicates the work of caregivers. Several strategies are used to reduce BPSD, including pharmacological interventions (e.g. antidepressants, antipsychotics and analgesics), behavioural treatment and electroconvulsive therapy (Popp & Arlt, 2011).

Since the currently available treatments are not satisfactory, extensive studies are performed in aim to find better medications for this growing group of patients. In the past decade, many promising compounds were discovered (Popp & Arlt, 2011). In 2009, some promising compounds were amyloid-lowering drugs, gamma secretase inhibitors, active and passive immunotherapy and compounds that prevented tau hyperphosphorylation (Salloway & Correia, 2009). Meanwhile, many of these compounds failed in clinical trials (Popp & Arlt, 2011).

3.2 Neuropathology of Alzheimer's disease

Alzheimer's disease is a neurodegenerative disorder that mainly affects cholinergic neurons (Duleu et al., 2010; Popp & Arlt, 2011). There are two molecules that have an important role in the development of the pathological hallmarks of AD. First, malfunctioning of the amyloid protein precursor (APP) results in extracellular amyloid plaques. Besides, dysfunctional tau protein underlies the formation of intracellular neurofibrillary tangles and dystrophic neurites (Duleu et al., 2010; Yamada et al., 2009). Despite this knowledge about these pathological features, much remains unknown about the etiology of AD (Duleu et al., 2010). The current knowledge about amyloid β and tau, as well as their link with the kynurenine pathway and general inflammatory processes in dementia will be discussed here.

3.2.1 Aβ peptides

Different variants of amyloid β (Aβ) peptides exists, of which the peptides consisting of 40 (Aβ 1-40) and 42 (Aβ1-42) amino acid residues are known to be the most neurotoxic compounds in amyloid plaques (Yamada et al., 2009). Although the exact role of Aβ remains a subject of discussion, increasing amounts of evidence suggest that its role in the pathogenesis of AD is secondary (Bonda et al., 2010). One of the hypotheses is that Aβ accumulates in response to oxidative stress following the activation of the kynurenine pathway (which will be discussed in more detail later in this thesis). The accumulation of Aβ initially serves to protect neurons (Bonda et al., 2010), but at the same time, oxidative stress induces cross-linkages between Aβ molecules, which results in the formation of extracellular senile plaques. These plaques stimulate inflammatory processes (e.g. activation of microglia and astrocytes) (Bonda et al., 2010; Duleu et al., 2010), which in turn leads to a further increase in oxidative stress (Bonda et al., 2010).

The importance of Aβ in the pathology of AD was further confirmed by mutation studies. These studies report that in AD patients, pathological mutations were found in the APP gene, specifically in the region encoding the Aβ peptide (Duleu et al., 2010). Furthermore, mutations were present in the presenilin genes (PS1 and PS2), which are involved in the regulation of APP catabolism (Duleu et al., 2010). Together, the findings of these studies suggest that mutations in genes regulating Aβ levels

might be one possible mechanism that underlies the formation of Aβ plaques in AD patients.

3.2.2 Tauopathies

The other pathological hallmark of Alzheimer's disease are tauopathies, resulting from ghe aggregation of the microtubule-associated protein tau. Tau aggregation is known to be caused by hyperphosphorylation of the tau protein, but the mechanism that mediates this aggregation still has to be unravelled. An indication for a possible mechanism comes from co-localization studies, which hint towards the involvement of tryptophan metabolism in the process of tau aggregation. The enzyme indoleamine 2,3-dioxygenase (IDO) was found to co-localize with tauopathies in a post mortem study observing brain tissue of AD patients. This implicates that the kynurenine pathway, in which IDO is a key enzyme, might be involved in the formation of neurofibrillary tangles (Bonda et al., 2010).

3.2.3 Other pathological processes

Apart from amyloid plaques and neurofibrillary tangles, some other pathological features have been reported in AD. These features will be briefly summarized in this section.
Neuro-inflammation, as well as oxidative and radical processes have been shown to play pivotal roles in AD (Bonda et al., 2010; Duleu et al., 2010). In addition, excitotoxicity, the excessive release of glutamate which leads to overstimulation of neurons, can contribute to AD pathology. The processes described above exhibit their pathological effects amongst others by inducing neuronal death (Duleu et al., 2010). Autopsy studies indicated that indeed, the pathology in the AD brain is characterized by a dramatic loss of neurons in the medial temporal lobe, specifically in the hippocampus and entorhinal cortex (Tweedie et al., 2012).

These pathological changes seem to be most pronounced in specific brain areas (Krstic et al., 2012). For example, in a mouse study, the presence of amyloid plaques was most prominent in the piriform and entorhinal cortices and their axonal projection areas, as well as in the entire hippocampus (Krstic et al., 2012). Besides, tauopaties were observed in all subfields of the hippocampus, a key structure involved in memory-related processes (Krstic et al., 2012).

4 Tryptophan metabolism

As briefly mentioned earlier in this thesis, the kynurenine pathway for tryptophan metabolism is involved in immune processes. Aberrant functioning of this pathway is suggested to be characteristic for both depression and Alzheimer's disease. Therefore, this section will provide some background information on tryptophan metabolism.

Tryptophan is one of the essential amino acids, which means that it cannot be produced by the body and should therefore be supplied in the diet. The amino acid is essential for cell growth and metabolism, but also plays a role in immune related processes. In humans, tryptophan can be degraded via two competing pathways: the tryptophan hydroxylase (THO) pathway and the kynurenine pathway (KP) (Duleu et al., 2010).
The THO pathway is predominant under normal conditions, in the absence of inflammation (Figure 2). Important products of this pathway are serotonin and melatonin. Melatonin is probably best known for its important function in the circadian rhythm, but in fact has a broader range of functions. Melatonin also is an important antioxidant and has anti-inflammatory functions, it is

known to interact with aggregating Aβ and hyperphosphorylated tau and has neuroprotective functions (Duleu et al., 2010). The neurotransmitter serotonin is amongst others associated with regulation of mood, sleep and appetite (Duleu et al., 2010).
The second pathway, the KP, is upregulated during infection and is activated by pro-inflammatory cytokines and Aβ1-42 (Duleu et al., 2010). This pathway produces several neuro-active metabolites, which are summarized in Figure 2 and will be discussed below.

4.1 The role of the kynurenine pathway in inflammation

The two pathways for tryptophan degradation compete for the available extracellular tryptophan. Therefore, when the KP is activated by inflammatory factors, less tryptophan will be catabolised via the THO pathway, resulting a lower availability of serotonin and melatonin (Duleu et al., 2010). However, the depletion of tryptophan is not just an aversive side effect of inflammatory processes. Since tryptophan is necessary for pathogen invasion and bacterial multiplication, the scarcity of tryptophan will impede these processes (Duleu et al., 2010). This makes tryptophan depletion an effective mechanism to prevent pathogenic colonization on the short term. If the elevation of KP activity however becomes chronically, as occurs amongst others in AD, the shortage of serotonin and melatonin in combination with the neurotoxic end products of the KP become problematic and will eventually result in neurodegeneration. This theoretical knowledge is supported by the clinical evidence that decreased blood tryptophan levels and increased serum kynurenine levels (denoting increased KP activity) are associated with increased cognitive deficits in AD patients (Guillemin, Brew, Noonan, Takikawa, & Cullen, 2005). Similarly, the severity of depressive symptoms in patients with major depression was correlated with activity of IDO, the rate-limiting enzyme of the KP (Sublette & Postolache, 2012).

Important interactions between the KP and immune responses are thus observed (Duleu et al., 2010), and are shown to be involved in neuro-immunological disorders including Alzheimer's disease (Bonda et al., 2010) and major depression (Leonard & Myint, 2006a).The key enzymes of the pathway are tryptophan 2,3-dioxygenase (TDO) in the liver and IDO in the lungs, placenta, blood and brain (Leonard & Myint, 2006a). In response to elevated levels of cortisol and pro-inflammatory cytokines, both enzymes show increased activity in patients with depression or dementia (Leonard & Myint, 2006a). The hyperactivity of the enzymes subsequently increases the catabolism of tryptophan via the KP. The detrimental effects of tryptophan catabolism via the KP, which results in the production of neuro-active metabolites, of which quinolinic acid (QUIN) had the most detrimental effects (Guillemin et al., 2005). Increased levels of QUIN are reported to lead to dysfunctioning of neurons and eventually even to neuronal death (Guillemin et al., 2005), thereby inducing permanent damage. In the next sections, the immunological alterations observed in depression and AD will be discussed, as well as the involvement of the KP and IDO in these processes.

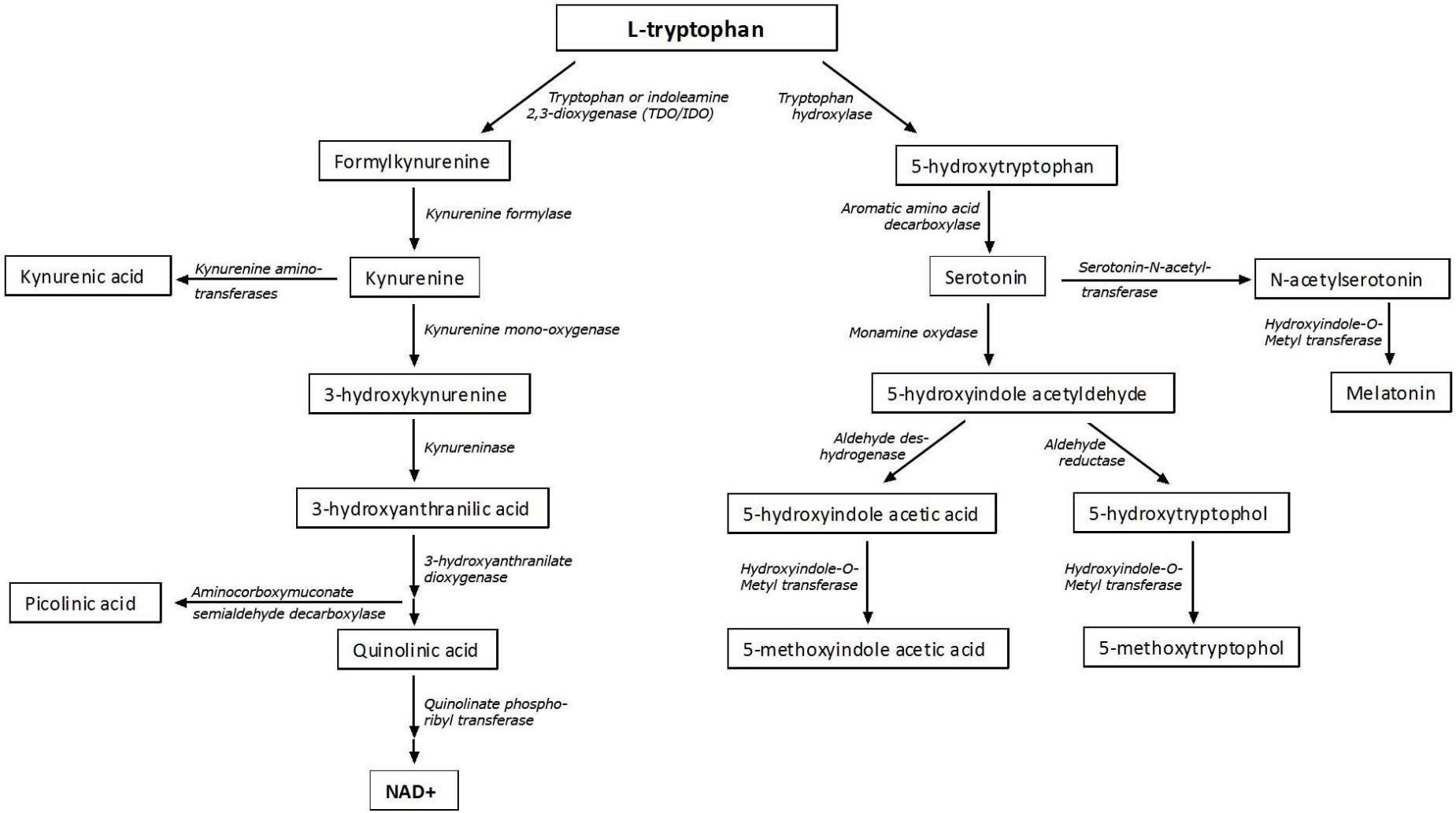

Figure 2. Schematic representation of the pathways of tryptophan catabolism. *On the left, the kynurenine pathway (KP) for tryptophan degradation is depicted. The KP becomes active upon inflammation. The end product of this pathway is NAD+. However, the enzyme Quinolinate phosphoribyl transferase is easely satureated, resulting in the accumulation of the toxic metabolite quinolinic acid. On the right, the THO pathway for tryptophan is depicted. This pathway is dominant under normal conditions. NAD+, nicotinamide adenine dinucleotide. Figure inspired by (Chen & Guillemin, 2009; Duleu et al., 2010).*

4.2 The role of indoleamine 2,3-dioxygenase (IDO)

Upon activation by pro-inflammatory factors, IDO induces upregulation of tryptophan catabolism via the KP. This upregulation influences both immunological factors and neurotransmitter availability. Therefore, IDO can be seen as a link between the regulation of immune processes and monoaminergic systems (Sublette & Postolache, 2012). The reduced availability of tryptophan influences the monoaminergic systems by reducing the formation of serotonin and melatonin. Since serotonin is reported to be involved in the activation of T-lymphocytes, the KP induced decrease in serotonin availability will result in reduced T-lymphocytes activation (Elovainio et al., 2012). However, the mechanism of action and the *in vivo* significance of these effects remains to be determined.

It was recently discovered that the enzyme IDO is transcribed in two distinct isoforms: IDO-1 and IDO-2 (Chen & Guillemin, 2009). IDO-1 is the predominant enzyme in extra-hepatic tissue and is found in multiple cell types, of which neurons, microglia, astrocytes and macrophages are the most important with respect to depression and AD. In response to pro-inflammatory factors, both enzymatic activity and gene expression of IDO-1 can be induced (Chen & Guillemin, 2009). The recently identified enzyme IDO-2 is related to IDO-1 and their structural characteristics and enzymatic activity seem to be similar. Although the expression and function of IDO-2 are well explored in a mouse model, little is known about the expression patterns and functional significance in humans (Murakami et al., 2013). Since IDO-2 was only recently discovered and its biological function remains unclear, many studies only focus on IDO-1 or do not make any distinction between both subtypes.

5 The immune system and depression

In 1969, the immune system was first described to play an important role in the pathophysiology of depression (Lapin & Oxenkrug, 1969). The inflammatory changes in the brain are thought by some to play an important role in the pathology of depression (Christmas et al., 2011; Hermida et al., 2012; Leonard & Myint, 2006a). It took some time until the role of inflammatory processes was generally accepted by scientists, but during the past two decades, this topic of research gained much attention (Dantzer, O'Connor, Lawson, & Kelley, 2011). There are however some inconsistencies between studies. Some studies do not prove an association between depression and inflammation, which might suggest that inflammation contributes to the pathogenesis of depression only in certain subgroups of patients (Hermida et al., 2012; Leonard, 2007). For example, data from a population-based study suggest that the association between IDO activity and depression is much stronger in women than in men (Elovainio et al., 2012). Further research should verify in which subgroups of depression patients inflammation is a major neuropathological factor.

Several of the symptoms observed in depressed patients could be explained by the occurrence of inflammatory processes. The atrophic changes in hippocampus and frontal cortex might result from the increased levels of apoptosis following inflammatory responses (Hermida et al., 2012; Leonard & Myint, 2006a). In addition, anatomical changes such as neurotransmitter effects and vascular alterations in the brain might also be linked to chronic inflammation (Hermida et al., 2012). A strong clinical indication for the occurrence of immune reactions is the increased body temperature of depressed patients. In the normal situation, the body temperature increases upon pathogenic

invasion and returns to normal when the pathogen is cleared. In depression, however, the body temperature remains elevated during the course of disease (Christmas et al., 2011). It is therefore hypothesized that depression might be a maladaptive version of cytokine-induced sickness, which might occur in people when the intensity and/or duration of the innate immune response is exacerbated and in people with increased vulnerability to develop depression (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008).

5.1 Causes of immune alterations

What factors might account for the depressogenic effect of alterations in the immune system? Several mechanisms of action have been proposed, but no conclusive answer has been given yet (Dantzer et al., 2011). The hypothesized mechanisms include the development of glucocorticoid resistance, the involvement of serotonin and its transporter and the induction of tryptophan metabolism and its key enzyme IDO.

5.1.1 Glucocorticoid resistance

As previously mentioned, depression is characterized by HPA-axis hyperactivity. At first sight, it might appear contradictive that HPA-axis hyperactivity results in inflammation. Activation of the HPA-axis results in the secretion of large amounts of glucocorticoids (GC), which are known for their immuno-suppressive function. Since the HPA-axis hyperactivity in depression is of a chronic nature, the GCs are consistently present, which eventually can lead to decreased GC responsiveness or even resistance of the glucocorticoid receptor (Hermida et al., 2012). In the normal situation, GCs make sure that inflammatory processes remain within limits, by providing a negative feedback on the hypothalamus. The development of GC resistance however results in impaired negative feedback. As a consequence, the inflammatory processes which are normally under control of the HPA-axis will get out of control. In this way, the impaired feedback regulated by GCs contributes to the development of the excessive inflammation seen in depression (Hermida et al., 2012; Leonard, 2007). The glucocorticoid resistance hypothesis thus suggests that stress plays an important role in the eventual dysregulation of the immune system.

5.1.2 Serotonin and serotonin transporters

The role of the neurotransmitter serotonin in inflammatory processes is extensively researched and discussed, but until now little consensus seems to be reached. In addition to its role as neurotransmitter, serotonin can function as an inflammatory mediator which is released in high concentrations at inflammatory sites (Elovainio et al., 2012). In depression, however, serotonin turnover was increased leading to decreased levels of serotonin in plasma and brain (Dantzer et al., 2011). It was therefore first hypothesized that decreased serotonergic neurotransmission was responsible for inflammation in depression. Dantzer and colleagues indeed showed that low levels of tryptophan, the precursor of serotonin, did not inevitably lead to decreased serotonin levels. This suggests that increased activity of other processes can compensate for the increased serotonin degradation and low tryptophan availability (Dantzer et al., 2011). Degradation of serotonin is indeed only one of the mechanisms that regulates serotonin levels. Additionally, serotonin levels are regulated by the reuptake of serotonin from the synaptic cleft into the presyntaptic neurons, via the serotonin transporter (SERT). It can be concluded that, even though it has been an important subject of research since 1969 (Oxenkrug, 2010), there is still much unknown about the precise nature of

serotonins involvement in depression (Oxenkrug, 2013). However, the fact that selective serotonin reuptake inhibitors (SSRIs) have proven to be effective in treating depression underpins that the decreased levels of serotonin in the synaptic cleft in some way influence the pathology of depression.

5.1.3 Tryptophan metabolism via the kynurenine pathway

Induction of tryptophan metabolism via the KP is known to occur during immune activation. In depressed patients, increased levels of IDO, the rate-limiting enzyme of the KP, were found. Increased IDO expression was thought to be responsible for the major decrease in tryptophan levels observed during immune activation (Dantzer et al., 2011; Elovainio et al., 2012). Since a tryptophan depletion study in humans indeed observed a linear relationship between decreased tryptophan levels and the severity of depressive symptoms, IDO activation was hypothesized to be involved in the transition from cytokine-induced sickness to major depression (Dantzer et al., 2008). Besides, increased IDO activity was found to result in increased stimulation and decreased inhibition of the NMDA-receptor, thereby affecting glutamate neurotransmission. The data reviewed by Dantzer and colleagues thus indicates that inflammation-associated depression indeed seems to be dependent on the activation of IDO (Dantzer et al., 2011).

5.2 Cytokines

Cytokines are small signaling proteins that can be released from leukocytes and various other cell types in reaction to a certain trigger. They can regulate various biological processes, including both pro- and anti-inflammatory responses (Hurley & Tizabi, 2013). Cytokines function in the transmission of information between the immune system, the endocrine system and the nervous system in a multidirectional way. Thereby, they can influence brain function both in a direct and an indirect way. In scope of this thesis, cytokines are very relevant since they are important modulators of IDO activity, and thus regulate the amount of tryptophan degradation via the kynurenine pathway.

5.2.1 The role of cytokines

In contrast to the different hypotheses about the causes of inflammation, researchers do agree about the fact that cytokines play an important role in mediating inflammatory processes and are (thereby) able to induce neurodegeneration in depression (Bewernick & Schlaepfer, 2013). Numerous clinical studies have shown that the levels of several pro-inflammatory cytokines, including interleukin (IL) 6 , tumor necrosis factor (TNF)-α and interferon (INF) γ, are elevated in the blood of patients with depression (Hermida et al., 2012; Hurley & Tizabi, 2013; Leonard & Myint, 2006b). It is proposed that the symptoms of major depression might result from the changes induced by the increased levels of cytokines (Dantzer et al., 2008; Hurley & Tizabi, 2013; Leonard & Myint, 2006a). However, inflammation seems to contribute to the pathogenesis of depression in some, but not all, patients (Hermida et al., 2012). Whereas some researchers hypothesize that the inflammation in depression occurs in reaction to an external stimulus, others rather think that internal or age-related factors are a more likely cause of the activation of the immune system (Hurley & Tizabi, 2013). Even though researchers thus do not agree about the precise cause of the immune activation, the consensus seems to be that cytokines might play an important role.

5.2.2 Disbalance between pro- and anti-inflammatory cytokines

Leonard and colleagues hypothesized that in depressed patients, an imbalance between the

inflammatory and anti-inflammatory arms of the immune system might exist (Leonard & Myint, 2009). This hypothesis was based on the observation that the plasma levels of pro-inflammatory cytokines such as IL-6, IFN-γ and TNF-α are increased in depressed patients. In the healthy situation, anti-inflammatory cytokines are generally released in response, in aim to regulate the pro-inflammatory cytokines (Hurley & Tizabi, 2013). Some studies indicate that the cytokines of the Th2 pathway (including IL-4 and IL-10) can (in certain situations) have anti-inflammatory properties, by inhibiting the aggressive Th1 response (Leonard & Myint, 2006a; Leonard & Myint, 2006b; Leonard, 2007). Since a concomitant increase in these cytokines lacks in depressed patients, this would suggest an imbalance between the pro- and anti-inflammatory arms of the immune system. However, while the data showing increased levels of pro-inflammatory cytokines are abundant, the data on the identity and levels of pro-inflammatory cytokines, as well as the role of regulatory T-cells are, to my knowledge, only very limitedly discussed in literature. Based on this information, it seems interesting to more thoroughly study the identity and involvement of anti-inflammatory cytokines and regulatory T-cells in depression, in aim to test if a disturbed balance between pro-and anti-inflammatory cytokines indeed plays a role in the pathology of depression.

5.3 Indoleamine 2,3-dioxygenase (IDO)

In response to this increased pro-inflammatory profile observed in depressed patients, the levels of IDO increase and the enzyme becomes activate. Since IDO is the rate-limiting enzyme of the KP, catabolism via this route will subsequently increase. Below, the data indicating aberrant IDO expression in depressed patients will be discussed.

Several clinical studies indicate that IDO might be involved in the pathophysiology of depression. A study in patients suffering from major depression showed an upregulation of IDO in the brain, as well as throughout organs and in immune cells (i.e. macrophages and microglia) (Christmas et al., 2011). This finding is underpinned by the increased levels of the KP metabolite QUIN and the lack of concomitant increase in kynurenic acid observed in the brain of depressed patients (Leonard & Myint, 2009). In addition, the plasma levels of tryptophan, the substrate of the KP, were found to be reduced in depression. The decreased tryptophan levels are suggested to be a consequence of increased KP activity, leading to decreased availability of tryptophan for serotonin production (Sublette & Postolache, 2012). As previously described, decreased levels of serotonin are commonly treated by pharmaceutically increasing serotonin levels using SSRIs (Christmas et al., 2011).

Experimental studies confirm the clinical observation that IDO is involved in depression pathogenesis. Christmas and colleagues demonstrate the depressogenic role of IDO in an animal study, showing that the depressive symptoms following an immune reaction seen in wild-type mice are absent in IDO knockout animals (Christmas et al., 2011). In addition, inhibition of IDO by the IDO antagonist MT-1 was shown to abrogate depressive behaviour in a mouse model for depression (Corona et al., 2012). Since IDO-induced activation of the KP results in increased amounts of NMDA-receptor agonizing metabolites, it was suggested that depressive behaviour would diminish upon administration of a NMDA-receptor antagonist. Walker and colleagues showed that the development of depressive behaviour in mice could indeed be prevented by administering a NMDA antagonist (Walker et al., 2013).
Interestingly, a human model for the role of IDO in inflammation-based depression is also available. Patients with hepatitis C are commonly treated by administrating the pro-inflammatory cytokine

interferon-α (IFN-α) (Oxenkrug, 2007). This pro-inflammatory medication is however associated with high rates of depression, ranging from 25-33% (Christmas et al., 2011). The administration of IFN-α results in increased levels op pro-inflammatory cytokines, including IL-6 and TNF-α, which are also elevated in patients with major depression (Christmas et al., 2011). More importantly, IFN- α treatment increases the kynurenin:tryptophan ratio, which reflects increased activity of IDO. This suggests that the cytokine mediated activation of IDO might play an important role in both IFN- α treated patients and patients with major depression (Christmas et al., 2011). The fact that the patients are such a high-risk population for development of depression, in combination with the similarities in mechanism of action, makes cohorts of hepatitis C patients very appropriate for prospective studies (Christmas et al., 2011).

In conclusion, several authors hypothesized that IDO might be the linking factor between inflammation and the mood disturbances observed in depression (Christmas et al., 2011; Elovainio et al., 2012; Leonard & Myint, 2006a). This hypothesis is underpinned by experimental and clinical data, but not all studies succeeded to prove a causative link between mood, inflammation and IDO (Christmas et al., 2011). Additionally, the exact mechanisms substantiating the hypothesized link between IDO and depression remains to be elucidated. It is however clear that IDO is a modifier of inflammation status, and might therefore be a potentially interesting therapeutic target (Sublette & Postolache, 2012).

5.4 Other alterations in the immune system

5.4.1 Alterations in other inflammatory factors

Inflammation is a complicated process in which many factors are involved and which is characterized by multiple feedback mechanisms. Therefore, this section will not give a complete overview of immune functioning but it will rather describe some of the important changes observed in depression and how these might be related to each other.

Levels of cytokines

Cytokines are important mediators of the inflammation observed in depression. One of the cytokines involved in depression pathology is transforming growth factor β1 (TGFβ1). TGFβ1 can be secreted by multiple types of leukocytes, amongst which regulatory T-cells seem to be an important source of TGFβ1 (Cerwenka & Swain, 1999).The function of TGFβ1 is immuno-modulatory, which implicates that it plays a role in maintaining the balance between the pro- and anti-inflammatory pathways (Leonard, 2007). Maintaining this balance is thought to be the responsibility of a population of T-cells called the Th3 population. Is seems that this Th3 population encompasses a group of regulatory T-cells that secrete TGFβ1, which is therefore also known under the name 'Th3 cytokine'. TGFβ1 is thought to function trough inhibiting other cytokines (including IFNγ and TNF-α), thereby preventing the production of the apoptosis promoting factor nitric oxide (NO) (Letterio & Roberts, 1998). In contrast, TGFβ1 can also increase the production of monocytic cytokines such as Il-1 and TFN-α (Letterio & Roberts, 1998). It seems contradictory that TGFβ1 can both promote and inhibit cytokines, but this observation might be explained by the role of TGFβ1 balancing pro- and anti-inflammatory events. It is therefore not surprising that in depression, which is thought to be characterized by a disturbed balance between these events, levels of TGFβ1 are found to be decreased (Leonard & Myint, 2006a; Leonard & Myint, 2006b; Leonard, 2007).

Although in general, the levels of pro-inflammatory cytokines are increased, this elevation is most sustained for IL-6 (Hermida et al., 2012) and its receptor (Elovainio et al., 2012). Elevated levels of IL-1β and IFN-γ were observed in multiple studies (Hermida et al., 2012; Leonard & Myint, 2006a; Leonard, 2007; Leonard & Myint, 2009; Sublette & Postolache, 2012), whereas increases in IL-2 were associated with depression by Sublette and colleagues only (Sublette & Postolache, 2012). The last pro-inflammatory cytokine that was commonly observed to be increased in depression is TNF-α (Hermida et al., 2012; Leonard & Myint, 2006a; Leonard & Myint, 2009; Sublette & Postolache, 2012). Increased levels of TNF-α are in turn a potent inducer of other pro-inflammatory cytokines, thereby further increasing the levels of inflammatory factors (Leonard, 2007).
In addition to the increased levels of pro-inflammatory factors, levels of anti-inflammatory cytokines are shown to be lower in depression. Leonard and colleagues concluded that levels of IL-4 and IL-10, two cytokines that may exert an anti-inflammatory function by inhibiting the Th1 response, seemed to be decreased in depressed patients (Leonard & Myint, 2006b; Leonard & Myint, 2009). This would even further disturb the balance between both arms of the immune system. However, the amount of data about altered anti-inflammatory processes in depression seem to be significantly smaller than for pro-inflammatory events, suggesting that further research into anti-inflammatory processes in depression would be desirable.

Downstream targets of cytokines
The increased levels of pro-inflammatory cytokines provoke their detrimental effects by increasing the expression of several downstream targets. These downstream targets, and the relevance of their elevated expression for the pathology of depression will be discussed below.

One of the important targets of pro-inflammatory cytokines is cyclooxygenase-2 (COX-2). COX-2 is an inducible enzyme that is unexpressed under normal conditions, but becomes expressed upon inflammation. Elevated neuronal levels of COX-2 were indeed found in the brain of depressed patients (Leonard & Myint, 2006a). The major function of COX-2 is the production of prostaglandins, amongst which prostaglandin E2 (PGE2) (Leonard & Myint, 2009). The elevated levels of COX-2 in depression would suggest PGE2 levels to be elevated as well. Indeed, multiple studies reported elevated levels of PGE2 in the cerebrospinal fluid (CSF), serum and saliva of patients with major depression as well as rat models (Leonard & Myint, 2006a; Leonard & Myint, 2006b; Leonard, 2007; Leonard & Myint, 2009). PGE2 is an important immune modulator, which is involved in the regulation of the balance between the Th1 and Th2 (Kalinski, 2012). In chronic inflammation, PGE2 suppresses the aggressive cytotoxic (type 1) immunity, and promotes the less aggressive Th2 immunity, amongst others by inducing regulatory T-cells (Kalinski, 2012). With respect to depression, this would suggest that the increased levels of PGE2 would have beneficial effects. On the other hand, another resource indicates that PGE2 elevates levels of IL-6, which would suggest that the Th1 immunity would be elevated, which would further increase the harmful effects of neuro-inflammation (Kasper, Boer, & Sitsen, 2003). This contradiction might be due to the fact that Kasper et al. describe the function of PGE2 early in the inflammatory process, where it promotes active inflammation, whereas Kalinski et al. studied chronic inflammation. However, it can be concluded that exact consequences of elevated PGE2 levels for depression are not too clear and that further research to clarify these effects would be desirable.

Another consequence of elevated levels of pro-inflammatory factors is an increased production of

nitric oxide (NO) (Leonard & Myint, 2006a). Nitric oxide is a free radical, which can induce apoptosis. In case of neuroinflammation, increased levels of apoptosis following NO secretion constitute a serious risk for neurodegeneration. The main activators of NO are TNF- -α and TGF-β, which are present in higher levels in depressed patients (Leonard & Myint, 2006a). At the same time, depression is associated with decreases in IL-4 and IL-10, the factors that inhibit NO production (Leonard & Myint, 2006a). Based on this information, it would be expected that depression is associated with increased levels of NO. Indeed, elevated levels of NO were observed in the plasma of patients with major depression (Leonard & Myint, 2006a).

5.4.2 Alterations in immune cell activity

The alternated levels of pro- and anti-inflammatory factors described above also have effects on immune cells. Overall, it seems that the majority of immune cells are found to be upregulated in the blood of depressed patients. Increased activity was For macrophages and monocytes, both the number of cells and their activity show increases (Leonard & Myint, 2006b; Leonard, 2007; Leonard & Myint, 2009). Besides, several studies indicate that the number of T-helper and T-memory cells, as well as the number of activated B- and T-cells, are elevated in depression (Leonard & Myint, 2006b; Leonard, 2007; Leonard & Myint, 2009). In addition, Leonard and colleagues showed an increase in microglia activity (Leonard, 2007).

Decreases in activity were also observed, although in a smaller range of cell types. Natural killer (NK) cells showed a decrease in activity and T-cell proliferation and neutrophil phagocytosis were lower in patients than in healthy controls (Leonard & Myint, 2009). According to Leonard et al., these changes are mainly explained by the imbalance between pro-and anti-inflammatory cytokines (Leonard & Myint, 2009). In addition, many of the quantitative changes described above correspond with the effects of the increased PGE2 levels observed in depressed patients (Kalinski, 2012).

5.5 Conclusion

The observations described above supports the hypothesis that inflammation is involved in at least a subset of depressed patients. Abnormalities in the neuro-immune system, including astroglia loss, activation of microglia and increased levels of several inflammation markers, are commonly observed in depressed patients (Sublette & Postolache, 2012). Stress-related responses have an important influence on these inflammatory alterations, as is illustrated by the complex interplay between the HPA-axis and the immune system (Leonard & Myint, 2006a). The knowledge about the role of inflammation in depression is currently not sufficient to describe a conclusive mechanism of action. However, the current information indicates that pro-inflammatory cytokines are key factor that can induce the development of depression via several mechanisms, of which the activation of IDO represents one interesting option (Dantzer et al., 2008).

6 The immune system and Alzheimer's disease

In 1907, Alois Alzheimer described neuroinflammation as one of the prominent pathological hallmarks in his first case report about Alzheimer's disease (Krstic et al., 2012). Further research showed that the involvement of the immune system was limited to the innate response, and was only observed in the areas lesioned in the AD brain (McGeer & McGeer, 2002). The link between inflammation and AD is demonstrated by multiple studies in both animals (Tweedie et al., 2012; Yamada et al., 2009) and humans. Krstic and colleagues provide experimental evidence for the

involvement of the immune system by showing that a prenatal immune challenge resulted in AD-like pathology when mice aged, and that this phenotype was strongly exacerbated by a second immune challenge in adulthood (Krstic et al., 2012). Human studies showing a role for inflammation in AD includes measurements of inflammatory factors in blood and CSF (Duleu et al., 2010; Gong et al., 2011), as well as epidemiological and genome-wide association studies (Krstic et al., 2012). It is thus clear that neuroinflammation is an important hallmark of AD, however, little consensus seems to be reached about its precise role. There are hypotheses that point inflammation out as a causative factor, while others see it as a by-product of the disease, or even as a beneficial process (Krstic et al., 2012). An overview of the data on the role of inflammation in depression and the different factors involved will be provided below.

6.1 Role of astrocytes and microglia

Astrocytes are the most abundant cell type in the human brain. They are mainly known for their function as supportive cells, which provide nutritients to nervous tissue and are involved in repair processes following injuries in both brain and spinal cord. Microglia are glial cells that are the resident macrophages of the nervous system. They act as the first and most important form of immune defence in the brain (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2012). Both astrocytes and microglia are known to be important mediators of neuroinflammation in AD (Bonda et al., 2010; Leonard & Myint, 2006a). Activated microglia (Guillemin et al., 2005; Tweedie et al., 2012; Yamada et al., 2009) and astrocytes (Guillemin et al., 2005) were found to surround amyloid plaques, and are thought to play an important role in AD pathology by activate the KP in response to pro-inflammatory cytokines (Yamada et al., 2009). Both cell types activate the KP in other cells, but can also be involved in KP catabolism themselves. Microglia contain all enzyms needed for the KP, whereas astrocytes lack kynurenin hydroxylase (Guillemin et al., 2001; Leonard & Myint, 2009). This makes that astrocytes produce large amounts of kynurenine and kynurenic acid (a QUIN antagonist) (Leonard & Myint, 2009), but that these cells cannot produce the neurotoxic QUIN (Guillemin et al., 2001; Leonard & Myint, 2006a). In addition, astrocytes are known to further reduce the neurotoxic impact by metabolizing QUIN (Leonard & Myint, 2006a). This neuroprotective function of the astrocytic kynurenic acid production is however (partly) abolished by infiltrated macrophages, which produce QUIN from the kynurenine produced by astrocytes (Guillemin et al., 2001). As a result, the AD brain is characterized by increased QUIN levels and decreased kynurenic acid concentrations when compared to the healthy brain (Guillemin et al., 2005), resulting in decreased neuroprotection. This makes the AD brain more vulnerable for (further) neurodegeneration and worsening of the symptoms.

6.2 Indoleamine 2,3-dioxygenase (IDO)

As can be seen in figure 2, one of the key enzymes in the KP is indoleamine 2,3-dioxygenase (IDO) (Yamada et al., 2009). The levels of this enzyme, which is the rate-limiting step in the KP, were found to be elevated in patients with AD. Upregulation of IDO was observed in astrocytes, microglia and infiltrated macrophages in the brains of patients that died of AD (Guillemin et al., 2005). This upregulation was most prominent in the proximity of amyloid plaques (Bonda et al., 2010; Guillemin et al., 2005; Yamada et al., 2009), and is recently also observed at the site of neurofibrillary tangles (Bonda et al., 2010). It is known that IDO expression can be increased in response to inflammatory factors and Aβ1-42 in amyloid plaques (Guillemin et al., 2005; Yamada et al., 2009), which are both present in high amounts in the AD brain. Since a mouse study showed that Aβ1-42 was not able to

induce IDO in the absence of the pro-inflammatory cytokines IFN-γ and TNF-α, it is suggested that cytokines induce IDO over-expression in microglia primed by Aβ1-42 presence (Yamada et al., 2009).

6.3 Metabolites of the kynurenine pathway

The over-expression of IDO results in activation of the KP, of which the metabolites are involved in many processes in the course of disease. Below, most metabolites and their effects will shortly be discussed. More emphasis is placed on the final metabolite QUIN, which is thought to be of major importance in AD development and progression.

The elevated levels of IDO induce an upregulation of the catabolic steps that degrade kynurenine into quinolinic acid. As a consequence, the levels of the metabolites 3-hydroxykynurenine (3-HK) and 3-hydroxanthranilic acid (3-HAA), as well as those of the end product quinolinic acid (QUIN), are higher in the brain of AD patients compared to healthy persons (Bonda et al., 2010). In contrast, the neuroprotective branch of the pathway, which converts kynurenine into kynurenic acid, is reduced in AD patients (Guillemin et al., 2005).
With kynurenic acid as the only exception, all KP metabolites have potential neurotoxic effects. QUIN is the most prominent neurotoxic compound and will therefore be discussed in more detail. Both 3-HK and 3-HAA are known to generate potent oxidative species (i.e. O2-, H- and H2O2), which significantly damage neuronal tissue (Bonda et al., 2010). Kynurenic acid, in contrast, exerts its neuroprotective function by antagonizing QUIN (Guillemin et al., 2001).

6.3.1 Quinolinic acid (QUIN)

High levels of QUIN have several detrimental effects. First of all, QUIN functions as a NMDA receptor agonist. High amounts of QUIN will therefore over-stimulate NMDA receptors in the hippocampus, leading to excitotoxicity and eventually to hippocampal atrophy (Gong et al., 2011). Regarding the function of the hippocampus in memory consolidation, this atrophy might be one of the causative factors of the cognitive decline in AD. Secondly, QUIN is shown to cause oxidative stress via its role in lipid peroxidation (Bonda et al., 2010). Besides, it stimulate tau hyperphosphorylation (Bonda et al., 2010), thereby promoting the formation of neurofibrillary tangles. Finally, QUIN can possess further neurotoxic effects by influencing astrocytes to produce the monocytic chemoattractant MCP-1 (Guillemin et al., 2005). MCP-1 will attract additional macrophages, which in turn will lead to a further elevation in QUIN levels. QUIN is known to activate astrocytes, but also to be involved in the induction of astrocytic apoptosis (Bonda et al., 2010). In conclusion, it thus seems that QUIN can in various ways contribute to the neurodegenerative changes characteristic for AD.

6.4 Other alterations in the immune system

IDO can thus be seen as a central factor in the neuro-immunological changes observed in AD, but additional inflammatory factors are also known to contribute to AD pathology. A brief summary of some of these factors will be provided below.

Immunoglobulins

A major finding published by Duleu and colleagues is that all circulating factors in AD patients are of the IgA isotype. This might implicate that the immune system was stimulated by exogenous factors like bacterial components (Duleu et al., 2010). This hypothesis is substantiated by the fact that IDO can be induced by lipopolysacharides of gram-positive bacteria, as well as by the interleukins that

leukocytes produce in response to exogenous compounds. Krstic and colleagues show that in mice, AD can indeed be induced by a systemic inflammation (Krstic et al., 2012). In contrast, the review of McGeer and McGeer states that the lesions in the AD brain were sterile, suggesting that the inflammatory response in AD is the result of autotoxicity (McGeer & McGeer, 2002). It would therefore be interesting to further examine the involvement of bacterial infections or other exogenous compounds in AD pathology in both human and mice.

Complement activation

Complement, an important component of the innate immune system, was shown to be activated in the brain of AD patients (McGeer & McGeer, 2002). In AD, complement was found to be strongly activated by Aβ, and to a lesser extent by C-reactive protein (CRP) and amyloid P. These three factors are all found to be upregulated in amyloid plaques (McGeer & McGeer, 2002). As early as in 1984, it was shown that certain complement fragments were upregulated in the affected regions of the AD brain. However, no alterations were seen in the factors that protect the host tissue against the consequences of (excessive) complement activation (McGeer & McGeer, 2002). Patients with AD thus exhibit excessive complement activation in the brain, whereas upregulation of the concomitant protective mechanism, aimed to prevent tissue damage, seems to lack.

Pro-inflammatory cytokines

As previously described, levels of the pro-inflammatory cytokine TNF-α were found to be elevated in both clinical studies as well as in animal models of AD (Tweedie et al., 2012). TNF-α is a major mediator of inflammation that is produced by glial cells in response to infection, or abnormal aggregation of endogenous protein (e.g. amyloid plaques in AD). Besides, TNF-α is one of the major activators of IDO.

In addition, levels of the activity-regulated cytoskeleton-associated protein (Arc), a regulator of synaptic plasticity, show abnormal elevations in the dentate gyrus during neuroinflammation. High levels of TNF-α are associated with increased levels of Arc protein, thereby suggesting that TNF-α over-expression can lead to impairments in synaptic plasticity and thereby affect long-term memory. As would be expected based on this information, a reduction in TNF-α was shown to result in normalization of Arc levels and restored memory functioning (Tweedie et al., 2012). Other experiments with a TNF-α lowering agent showed multiple beneficial effects in an animal model for AD. Here, levels of amyloid precursor protein (APP), oxidative damage and neuroinflammation were reduced, neuronal plasticity was restored and synaptic functioning was preserved (Tweedie et al., 2012). These findings confirm that TNF-α indeed seems to be involved in the neuro-inflammatory processes underlying AD, potentially by influencing Arc levels.

In addition, the levels of multiple other inflammatory mediators are found to be altered in AD patients. The pro-inflammatory cytokine IFN-γ is suggested to strongly enhance IDO expression in the microglia surrounding amyloid plaques in a mouse model for AD (Yamada et al., 2009). Increased levels of multiple cytokines, including IL-1α and β and IL-6 were observed in another animal study (Krstic et al., 2012). Studies in human AD patients agreed on the observation of elevated levels of IL-1 (Krstic et al., 2012; Tweedie et al., 2012) and IL-6 (Tweedie et al., 2012) in AD. In addition, human patients showed rises in IL-12 levels (Tweedie et al., 2012). Aβ in amyloid plaques was shown to promote the expression of several chemokines (cytokines that specifically induced chemotaxis of inflammatory cells), including IL-8, monocyte chemotactic protein-1 (MCP-1) and macrophage

inflammatory protein-1β (MIP-1β) (McGeer & McGeer, 2002).

Downstream targets of cytokines

Cyclooxygenase (COX) is the rate-controlling enzyme in production of prostaglandins. There are two variants of COX; COX-1 is the stable form that accounts for the baseline production of prostaglandins and COX-2 is the inducible form that increases prostaglandin availability during inflammation. Both variants of COX can be targeted by non-steroidal anti-inflammatory drugs (NSAIDs). Both COX-1 and COX-2 are known to be upregulated in affected brain areas of AD patients. Since COX-2 is highly expressed in pyramidal neurons of both the healthy and the AD brain (Choi et al., 2013; McGeer & McGeer, 2002), it is suggested by some researchers to be the most important COX enzyme in AD. Reducing the availability of COX-2 to physiological levels would therefore seem beneficial (McGeer & McGeer, 2002). Epidemiological and preclinical studies indeed showed that NSAIDs lowered Aβ production and neuroinflammation in AD patients (Choi et al., 2013). However, follow-up studies failed to show any beneficial effects of COX-2 inhibitors. Choi and colleagues therefore suggest that not COX-2, but COX-1 is implicated in AD. COX-1 is predominantly expressed in microglia (surrounding amyloid plaques) and its expression increases with aging. They indeed show that selective inhibition of COX-1 in a mouse model for AD reduces neuropathology and neuroinflammation, while it improves cognitive functioning (Choi et al., 2013).

Based on the upregulation of both COX variants, it would be expected that levels of prostaglandins would in response also be elevated. A recent study indeed suggests prostaglandin E2 (PGE2) to be a key player in the inflammatory processes that contribute to the development of AD (Wood, 2012). PGE2 can interact with four different E-prostanoid receptors: EP 1, 2, 3 and 4. EP2 was found to be involved in neuro-inflammatory diseases in previous studies (Choi et al., 2013), and an association between EP3 and AD was observed in post-mortem analysis (Wood, 2012). A mouse study confirmed this finding and showed that EP3 expression was indeed increased in the hippocampus at the onset of inflammation (Wood, 2012). A recent study showed that deletion of one EP3 allele is sufficient to prevent inflammation and the formation of amyloid plaques in the mouse brain (Wood, 2012). This would make PGE2 in combination with the EP3 receptor an important target for further research.

6.5 Polymorphisms in inflammation-related genes

In several genes coding for inflammatory factors, polymorphisms in the non-coding regions have been associated with an increased risk to develop AD. Most of these polymorphisms are relatively common in the general population, but occur more frequently in AD patients than in the restof the population (McGeer & McGeer, 2002). The association between a single polymorphism and the risk to develop AD is relatively weak. However, for some genes, polymorphisms do lead to a significantly increased risk for AD. One of these genes is apolipoprotein E (apoE), for which the apoE4 variant was shown to substantially increase the risk to develop AD (McGeer & McGeer, 2002; Salloway & Correia, 2009). It was shown that this risk was especially increased in individuals carrying two high risk alleles (McGeer & McGeer, 2002).

6.6 Conclusion

It can be concluded that the innate immune system seems to be an important factor in the development and progression of AD. Multiple factors involved in inflammatory processes are involved in AD pathology. In particular, tryptophan metabolism and its key enzyme IDO seem to play

a central role. Epidemiological studies indicated that inflammatory drugs have a protective effect on the development of AD, but until now, clinical trials failed to show large effect sizes for these drugs. Possible explanations might be that anti-inflammatory medicines only have a preventive function (Krstic et al., 2012), or that drugs targeting other (isoforms of) enzymes in the inflammatory pathways might be more effective (Choi et al., 2013). Nevertheless, the growing prevalence of AD and the detrimental effects of neuroinflammation make it very relevant to further study the potentials of inhibitors of the innate immune response.

7 The link between depression and dementia

Based on the evidence provided above, it can be concluded that inflammation is an important factor in both depression and dementia. This raised the question if the inflammatory changes in both diseases might be related, or might even represent a shared mechanism of disease. Epidemiological evidence suggests that in patients with Alzheimer's disease, a lifetime history of depression is more commonly present than in the general population (Leonard & Myint, 2006b). In this section, the likelihood of a link between both diseases is examined. Studies evaluating the potential role for inflammatory processes as a linking factor will be discussed. This section will also focus on the main question of this thesis, and will therefore discuss the hypothesized role for the enzyme indoleamine 2,3-dioxygenase as a linking factor between depression and AD.

7.1 Epidemiological indications for a link between depression and AD

Case-control and longitudinal studies show that patients with a history of depression have an increased risk to develop dementia (particulary AD) later in life (Leonard & Myint, 2006a; Leonard & Myint, 2006b; Leonard & Myint, 2009), although there were also a few studies that did not report a significant increased dementia risk in depressed patients (Richard et al., 2013). One of the studies that did find the association between both diseases reported that each episode of depression is associated with an 13-14% increased risk to develop dementia (Hermida et al., 2012). However, not all studies were able to replicate this increased risk. One possible reasone for this discrepancy, as suggested by Hermida and colleagues, is the imprecise diagnosis of both diseases (Hermida et al., 2012).

Conversely, increased levels of depressive symptoms were found in a population of Alzheimer's disease patients. The degree of association between depressive symptoms and AD differed between studies. In a study in residents of nursing homes in the USA, the prevalence of major depression was reported to be 35-50% in AD patients (Leonard & Myint, 2006b), compared to 6-32% in residents with normal cognition. Other studies agree that the incidence of comorbid depression in AD patients is approximately 50% (Bewernick & Schlaepfer, 2013; Leonard, 2007). Richard and colleagues however state that the prevalence rate of 40-50% encompasses the occurrence of depressive symptoms rather than depression, and that the prevalence of major depression in AD is limited to 10-20% of the patients (Richard et al., 2013).

A different subfield of research focuses on mild cognitive impairment (MCI). MCI is often seen as a stage in between normal cognition and dementia (Hermida et al., 2012), with the main difference between MCI and dementia being that MCI patients are still able to perform relatively well on daily life activities. It was hypothesized that depression might increase the risk of conversion from normal cognition to MCI, and from MCI to dementia. Although data from different studies are contradictive,

it seems that the majority of studies reports a role for depression in both the conversion of normal cognition to MCI, and from MCI to dementia (Geerlings et al., 2000; Hermida et al., 2012). Leonard and colleagues agree that in patients with both MCI and depression, the risk to progress to dementia is twice or even three times higher than in MCI patients without depression (Leonard & Myint, 2006a; Leonard, 2007). In agreement with this, a study performed by Richard and colleagues showed that in two large cohorts, depression was associated with an increased progression from MCI to dementia. In addition, they found that the rate of depression was higher in patients with MCI than in cognitively intact people, suggesting that an association might exist between depression and development of MCI (Richard et al., 2013).

It is however important to realize that not all studies show an influence of depression on the progression of normal cognition, via MCI or directly, to dementia. Additionally, there are studies that do show effects of depression, but only in subgroups of MCI patients (Sierksma, van den Hove, Steinbusch, & Prickaerts, 2010). For example, Geerlings studied two cohorts of depressed patients and found that depression was associated with cognitive decline in healthy subjects with higher levels of education (>8 years), but not in patients with lower education levels (Geerlings et al., 2000). Richard and colleagues describe that the association between depression and dementia was shown in a cohort of patients in a memory clinic, but that the results were not reproduced in a population-based study (Richard et al., 2013). The contradictive results in Richard et al. may be explained by a difference in severity of the symptoms between both cohorts. In conclusion, epidemiological studies suggest that depression might indeed be a risk factor for the development of dementia, but possibly only in a subset of the dementia patients.

7.2 Similarities in mechanisms of disease

When studying the pathological alteration that occur in depression and in Alzheimer's disease, several similarities occur. These will shortly be discussed here, with emphasis on the alterations in tryptophan metabolism.

7.2.1 HPA-axis

As discussed previously, it is generally accepted that disturbances in de HPA-axis are an important pathological factor in major depression (Bewernick & Schlaepfer, 2013; Leonard & Myint, 2009). The hyperactivity of the HPA-axis might result from chronic stress, a common comorbidity in depression. The increased HPA-axis activity results in elevated levels of glucocorticoids, and indirectly promotes the secretion of pro-inflammatory cytokines. Since aberrations in these factors are not only observed in depressed patients, but also in patients suffering from AD, it would be interesting to see if similar alterations in the HPA-axis occur in AD.

In patients with major depression, hyperactivity of the HPA-axis is demonstrated by the concomitant occurrence of increased levels of CRH, the first hormone of the HPA-axis (Hermida et al., 2012). Rat models for AD implicated that levels of CRH might be elevated in this disease as well (Brureau et al., 2013). Similarly, elevated levels of CRH were observed in human AD patients (Raadsheer et al., 1995). Increased HPA-axis activity was stated to be a common (and possibly linking) factor in both diseases (Leonard & Myint, 2006a). The hypothesis that the HPA-axis might play a role in the suggested association between depression and AD is further substantiated by the finding that chronic stress may lead to the development of depression, and that psychological stress in elderly increases the risk

to develop dementia (Caraci, Copani, Nicoletti, & Drago, 2010).

Based on the knowledge that HPA-axis hyperactivity results in increased levels of GC, elevated levels of cortisol would be expected in depression and AD. Indeed, depression (Leonard & Myint, 2006a) as well as AD (Brureau et al., 2013) are associated with increased levels of cortisol in blood samples of patients. In AD, larger increases in glucocorticoid levels were associated with more rapid cognitive decline (Sierksma et al., 2010). The prolonged increase in glucocorticoid availability can eventually damage the hippocampus, resulting in a reduce number of GRs, which worsens the already developed glucocorticoid resistance (Sierksma et al., 2010). Histological analysis in a rat model for AD confirmed that a reduced number of GRs might indeed be present in this disease (Brureau et al., 2013). As expected, the elevated levels of glucocorticoids were found to be associated with the cognitive impairments in both depression and AD. In several studies, healthy volunteers were injected to induce an acute rise in cortisol levels. These injections lead to similar impairments in cognitive functioning as observed in depression and AD, including impairments in the domains of explicit and declarative memory, spatial thinking and selective attention (Sierksma et al., 2010).

The chronic increased activity of the HPA-axis has a broad range of downstream effects; it decreases the signalling of the neurotransmitters adrenalin and noradrenalin, stimulates the secretion of cytokines leading to immune activation and it induces anatomical changes, including hippocampal atrophy. For some of these factors, different researchers disagree about if these are cause or consequence of the HPA-axis activity. The alterations that may link both diseases, as well as their known causes or consequences are discussed below. This description will however not be exhaustive and is not able to provide a conclusive mechanism of disease.

7.2.2 Neurotransmitter levels

Decreases in some of the monoamines are found in both depression and dementia. The monoamine which is most intensively studied in depression research is serotonin, a neurotransmitter synthesized from the essential amino acid tryptophan. An increase in serotonin turnover, resulting in decreased levels of serotonin is found in human depressed patients and in mice models (Corona et al., 2012; Oxenkrug, 2010). Pharmaceutical treatment with SSRIs, which functions through normalizing serotonin levels, is a common treatment method for depression (Christmas et al., 2011). But is serotonin also involved in Alzheimer's disease? Although less intensively studied than in depression, some publication do suggest a role for serotonin in AD pathology. Decreased serotonin levels, accompanied by a loss of serotonergic neurons and nerve terminals, were found in post-mortem brain studies (Lanctot, Herrmann, & Mazzotta, 2001). At first, serotonin was implicated in the non-cognitive features of AD, known as behavioural and psychological symptoms of dementia (BPSD) (Cross, 1990). Of these BPSD, serotonin showed the strongest association with aggressive and psychotic behaviour (Lanctot et al., 2001). More recently, Geldenhuys *et al* reviewed the role of serotonin in the cognitive symptoms of AD as well. Three of the serotonin receptors have been associated with cognitive functioning, and might therefore be promising candidates for the development of curative medication (Geldenhuys & Van der Schyf, 2011).
The fact that serotonin aberrations are a common pathological feature between depression and AD was recently put forward in a review (Hochstrasser, Hohsfield, Sperner-Unterweger, & Humpel, 2013). Some clinical trials observing the effect of SSRIs on BPSD in AD patients have already been performed. In open-label studies, significant improvements in BPSD were reported following the

normalization of serotonin levels by SSRI administration. However, double-blind placebo-controlled studies found less promising results. Only for the SSRI citalopram, significant improvement in all BPSD were reported, other SSRIs were only found to significantly improve depressive symptoms (Lanctot et al., 2001). These data suggest that it might be interesting to more thoroughly investigate the potential of SSRIs in AD patients, but that based on this study, the administration of SSRI in AD is less promising than was hoped for. Since these data are relatively old, it would be interesting to more thoroughly search if more recent clinical trials studying the effectiveness of SSRIs in AD do exist.

In addition to the altered serotonin levels, aberrant NA signalling was reported in both diseases. Anatomical studies show a loss of noradrenergic neurons in the LC of patients with depression (Leonard, 2001) and in patients with AD (Fitzgerald, 2010; Herrmann, Lanctot, & Khan, 2004). Patients in which both diseases are comorbid show an even further increase in neuronal loss when compared to patients with AD only (Herrmann et al., 2004). Similarly to depression, AD was previously reported to be associated with decreased levels of NA (Herrmann et al., 2004). Since NA can suppress neuroinflammation, its decreased availability is suggested to further contribute to the disbalance between pro-and anti-inflammatory processes which is thought to be common to both diseases. Fitzgerald however postulates that it is not yet irrefutably proven that AD is characterized by decreased NA levels. According to Fitzgerald, there are other studies that report elevations rather than decreases in NA levels, a finding which might be explained by compensatory mechanisms for LC neuron loss. Fitzgerald concludes that both elevated and decreased NE levels might be involved in AD pathology, and that the pathological effect might be due to degradation of noradrenergic LC neurons rather than the elevation or decrease in NA per se. This suggests that alternations in NA levels might be a consequence of AD rather than a cause.

Multiple other neurotransmitter and neuropeptides influence the neuropathology of these two diseases (Lanctot et al., 2001), but less is known about their precise function in these processes.

7.2.3 Immune cells

The literature about the role of inflammatory processes in general in depression and AD reviewed in this thesis, arouses the impression that little overlap seemed to exist between the levels of immune cells altered in both diseases. Therefore, a more specific literature search was conducted to find out if the alterations seen in one of these diseases, were also observed in the other disease. The results will be displayed below.

The only similarities between altered immune cell levels directly found, were that both diseases are characterized by increased activity of microglia (Leonard, 2007; Sublette & Postolache, 2012) and astrocytes (Duleu et al., 2010; Guillemin et al., 2005). These two cell types are the main cause of neuroinflammation in AD (Bonda et al., 2010), which can eventually result in hippocampal atrophy (Gong et al., 2011), a pathological hallmark that is characteristic for both depression (Leonard & Myint, 2009) and AD (Tweedie et al., 2012).

Literature was search to see if the altered immune cell activity described in depression, were also reported in patients with AD. It was indeed found that blood-born macrophages were able to infiltrate in both the depressed and AD brain. Since macrophages produce large amounts of pro-inflammatory cytokines and thereby exacerbate neuro-inflammatory processes, the infiltration of these cells would be undesirable in both diseases. In addition, the number of monocytes, the

precursors of i.e. macrophages, was shown to be not only elevated in depression but also in AD (Feng, Li, & Sun, 2011).
In depression, the number of activated B- and T-cells, as well as T-helper and T-memory sub-populations were reported to be increased (Leonard & Myint, 2006b). Little literature was found on the ratio between helper T-cells (CD4+) and cytotoxic T-cells (CD8+) in depression, but one article suggested the ratio of CD4+/CD8+ to be increased (Maes et al., 1996). In Alzheimer's disease, the alteration in CD4+/CD8+ ratio appears to be in the opposite direction. Here, a decrease in CD4+ cells as observed, whereas levels of CD8+ cells remained constant (Larbi et al., 2009). However, for both diseases, the data on alterations in number and activity of T-cell populations are very limited .

The last category of cells discussed here are natural killer (NK) cells, which were found to exhibit decreased activity in depression (Leonard & Myint, 2009). The findings on NK cell activity in AD are quite controversial. Whereas the results from Solerte et al. suggest an increase in NK cell activity in AD patients to be inversely correlated with cognition (Solerte et al., 1998), others reported decreased NK-cell activity (Higuchi et al., 2010) or no alterations at all in the number and activity of NK cells (Prolo et al., 2007) .

In conclusion, increased activity of microglia, astrocytes, monocytes and macrophages are commonly reported in both diseases. For other immune cells, the possible alterations in both cell number and activity are less clear, and it might be of interest to closer study this in the future.

7.2.4 Pro- and anti-inflammatory factors

In both depression and Alzheimer's disease, several inflammatory factors are upregulated. In general, both diseases are characterized by an increase in inflammatory processes (Caraci et al., 2010) and elevated levels of pro-inflammatory cytokines (Hochstrasser et al., 2013; Leonard, 2007). More precise, a disbalance between the pro- and anti-inflammatory arms of the immune system is suggested to be a shared pathological feature between depression and AD (Leonard & Myint, 2009).

Besides these studies looking at groups of inflammatory factors, research into the alterations in levels of individual pro- and anti-inflammatory compounds was performed. Probably the most important similarity between depression and AD, is that levels of key pro-inflammatory cytokines IL-1β, IL-6 and TNF-α appeared to be abnormally high in both diseases (Hermida et al., 2012; Leonard & Myint, 2006a). Since TNF-α also functions as a potent inducer of other pro-inflammatory cytokines, the elevated levels of this cytokine can even further exacerbate neuroinflammation (Leonard, 2007).

An important target of pro-inflammatory cytokines is COX. COX2, the inducible form of COX, was found to be upregulated in both depression (Leonard & Myint, 2009) and AD (McGeer & McGeer, 2002) when compared to healthy controls. The main function of COX2 is the production of prostaglandins, including PGE2. As would be expected from the increase in COX activity, a concomitant increase in PGE2 is observed in both depression (Leonard & Myint, 2006a) and AD (Wood, 2012). The precise role of PGE2 in depression and AD is still under discussion. According to Leonard and colleagues, PGE2 mainly functions as a potent inducer of neuro-inflammation, which additionally inhibits anti-inflammatory pathways (Leonard & Myint, 2006b). In contrast, Kalinski *et al* state that PGE2 indeed stimulates inflammation via the Th2 pathway, but that it also inhibits the more aggressive Th1 pathway and thereby decreases rather than increase the detrimental effects

(Kalinski, 2012).
Additionally, there are two factors that were not mentioned in the reviews discussed in this thesis, but that did turn up in separate articles about AD and depression. First, elevated levels of IFNγ were described in multiple studies into depression (Hermida et al., 2012; Leonard & Myint, 2009; Sublette & Postolache, 2012), as well as in a mouse model for AD (Yamada et al., 2009). IFNγ strongly enhances IDO activity and thereby stimulates tryptophan catabolism via the KP. Second, C-reactive protein, a positive acute phase protein that induces complement activation, is found to be upregulated in separate studies about depression (Elovainio et al., 2012) and AD (Elovainio et al., 2012; McGeer & McGeer, 2002). It is therefore not surprising that activation of complement is was observed in both diseases as well (Leonard & Myint, 2009; McGeer & McGeer, 2002).

In addition to these increases in pro-inflammatory factors, alterations in the levels of anti-inflammatory factors were observed in depressed patients. These alterations include decreases in negative acute phase proteins (Leonard & Myint, 2006b), TGF-β1 (Leonard, 2007) and in IL-4 and IL-10 (Leonard & Myint, 2009). However, it is not completely correct to describe IL-4 as a anti-inflammatory cytokine, since it indeed does inhibit the Th1 pathway, but at the same time can induce Th2 based inflammatory processes. The finding that levels of anti-inflammatory factors were found to be decreased in depression raises the question if inhibitors of inflammation would also be implicated in AD. Indeed, elevated IL-4 levels were found to attenuate pathological features in a mouse model for AD (Kiyota et al., 2010). However, no data were found on the endogenous levels of IL-4 in AD, nor for the levels of IL-10 or negative acute phase proteins. For TGF-β1 availability in AD, however, the results are quite contradictive. Whereas some studies show a similar decrease as observed in depression, other studies found increased TGF-β1 levels or no difference at all compared to controls.

7.2.5 Anatomical changes

Alzheimer's disease is commonly known for its neurodegenerative effect, but neuronal loss was also found to occur in patients with major depression. Interestingly, similar brain areas were found to be affected in AD and depression. This similarity seems to have encouraged researchers to have a better look at the anatomical changes in these diseases.
The most replicated similarity exists of atrophic changes in the hippocampus, the brain structure with memory consolidation as its most important function (Hermida et al., 2012; Leonard & Myint, 2009). The hippocampal atrophy explains the occurrence of cognitive deficits seen in AD, as well as the (less severe) deficits observed in depression. Other similarities between the brains of both patients groups are loss of astroglia (Sublette & Postolache, 2012) and atrophy of the (pre)frontal cortex (Leonard & Myint, 2006a) and the temporal lobes (Leonard & Myint, 2009). Additionally, for some areas, neurodegeneration was reported only in one of the diseases.

Neurodegeneration is thought to result from excessive inflammatory responses (Leonard & Myint, 2006a). Neuroinflammation can induce neurodegeneration via different pathways. Pro-inflammatory cytokines can lead to increased nitric oxide (NO) levels by induction of nitric oxide synthase (NOS). Both NO and the free radicals produced by Aβ can subsequently lead to oxidative stress and eventually apoptosis (Leonard & Myint, 2006b). Secondly, pro-inflammatory cytokines activate the kynurenine pathway, which produces multiple neurotoxic end products (Leonard, 2007). Inflammation is also known to promote the formation of Aβ plaques, which in turn results in the

formation of free radicals and a further rise in pro-inflammatory cytokine levels (Hochstrasser et al., 2013). For this reason, Hockstrasser and colleagues suggest Aβ plaques to be responsible for inflammation driven neurodegeneration. It was already known that large numbers of Aβ plaques were associated with more severe forms of AD, and that the brain of AD patients with comorbid depression contains even more Aβ plaques than that of patients with AD only (Sierksma et al., 2010). Surprisingly, however, a PET study in patients with major depression indicated an association between high levels of Aβ plaques and the severity of depressive complaints (Sierksma et al.,2010). This study thus indicates that levels of Aβ are not only associated with more severe disease states in AD, but also in major depression.

A change that further contributes to the anatomical changes, is the decrease in brain derived neurotropic factor (BDNF) levels, which is observed in both diseases (Bewernick & Schlaepfer, 2013). This factor exhibits a neuroprotective function, via the regulation of hippocampal plasticity and neuronal repair mechanisms. Decreased levels of BDNF are associated with decreased neurogenesis and dendritic branching (Sierksma et al., 2010), thereby making the brain of depressed people and AD patients more vulnerable for neurodegeneration. Decreased BDNF levels are hypothesized to contribute to the increased risk of depressed patients to develop AD (Sierksma et al., 2010). Taken together, these data thus suggest that the combination of neurodegenerative processes and impairments in neuroprotection and -repair might account for the atrophic changes observed in AD and depression.

7.2.6 Tryptophan metabolism & IDO

Tryptophan was first associated with depression and dementia as early as in 1990, when decreased levels of tryptophan were measured in a subgroup of AD patients suffering from depression. Besides, both depression and dementia were associated with the disease pellagra, which can be caused by tryptophan deficiency (Maurizi, 1990; Oxenkrug, 2011). Recent studies confirmed that depression can originate from changes in the tryptophan availability following KP activation, and that similar alterations in KP activity were observed in AD patients (Plangar, Majlath, & Vecsei, 2012). Both the neurotoxic end products of the KP and the reduced tryptophan availability are thought to play a role in the development of cognitive impairments and neuropathology characteristic for the diseases (Plangar et al., 2012).

IDO, the rate-limiting enzyme of the KP, has been an important subject of study in the field of both major depression and Alzheimer's disease. Multiple data implicate a function for pro-inflammatory cytokines as potent inducers of IDO activity (Oxenkrug, 2011). The chronic activation of IDO has multiple detrimental effects on the brain. The metabolite QUIN is a NMDA agonist which accumulates in neurons and astrocytes, resulting in increased neurodegeneration (Leonard, 2007). Most of the KP metabolites contribute to the production of free radicals (Oxenkrug, 2011), and thereby promote oxidative stress-induces neurodegeneration (Bewernick & Schlaepfer, 2013). In addition, KP activity reduces the availability of the neuroprotective metabolite kynurenic acid, which has a role in limiting the damage of the previously mentioned KP metabolites (Leonard, 2007). Together, these findings suggest IDO to be an important factor in the pathological processes of both Alzheimer's diseases and depression.

8 Discussion

In this thesis, the role of inflammatory processes in the development of depression and Alzheimer's disease is reviewed. The central hypothesis is that indoleamine 2,3-dioxygenase (IDO), the key enzyme of the kynurenine pathway for tryptophan degradation, is (one of) the linking mechanism(s) between depression and Alzheimer's disease. In order to test this final hypothesis, several sub questions were answered first, in aim to get an overview of the background of both diseases.

The central hypothesis is based on the assumption that similarities between depression and Alzheimer's diseases exist. The assessment of reviews and research articles on the neuropathology in depression and AD revealed several similarities between the diseases. Inflammation was shown to be a key factor in depression as well as AD, and multiple of the involved inflammatory factors show comparable changes in both diseases. Importantly, the alterations in the kynurenine pathway (KP) for tryptophan metabolism and activity of the key enzyme IDO were comparable in both diseases and were consistent between studies. Additional systems for which similar impairments were observed in both diseases are the chronic hyperactivity of the HPA-axis, as well as increased neurodegeneration and decreased neuroprotection and –repair and probably. Of these processes, it is suggested that they might underlie the similarities in the neuro-anatomical changes observed in both diseases (of which hippocampal atrophy is most prominent). Although the potential link between depression and AD is not commonly acknowledged yet, and the data supporting the link are relatively recent and small in number, it seems worthwhile to further explore the possible shared mechanisms between both diseases.
Levels of the neurotransmitters serotonin and noradrenalin are studied in both diseases, but the data resulting from these studies are more ambiguous. Especially for noradrenalin, the role in depression and dementia separately seems to be not completely clear yet. These two neurotransmitters do seem to be involved in both depression and AD separately. However, too little is known about the exact nature and direction of the alternation in serotonin and noradrenalin levels to conclude if these neurotransmitters might represent a shared mechanisms of action between AD an depression. It might eventually be interesting to study if the alternations in these neurotransmitters might represent a link between depression and AD. However, it might be more relevant to first clarify the precise role of especially noradrenalin in both diseases separately.

In conclusion, multiple similar pathological features are found in depression and AD, of which many involve inflammatory or inflammation-related processes. Together with the epidemiological finding that the prevalence of AD is increased in patients with a history of depression, this raises questions about the nature of the association between the diseases. An unequivocal answer to this question however is lacking, since there are data to support different hypotheses. Some researchers assume that depression might be a risk factor for the development of AD, whereas others rather see it as a prodromal clinical phase (Hermida et al., 2012). It could however also be possible that the changes in brain anatomy arose during prenatal development. This leads to a new hypothesis, suggesting that depression and AD might be linked by (prenatal) developmental abnormalities, whereby the changes observed in both diseases would precede the onset of major depression (Leonard & Myint, 2006a). It might be interesting to evaluate if a combination of these hypothesis might be true, whereby moderate short-term depression could represent a risk factor for AD by worsening the neurodegeneration, while the early neurodegenerative changes proceeding clinical AD might be able to induce prodromal depressed feelings.

Second, for answering the central research question, it was of interest to validate if aberrant IDO expression does indeed have pathological effects in depression and AD. For both diseases, the involvement of IDO was first shown more than two decades ago and is confirmed by numerous studies afterwards. In AD increased expression of IDO can be induced by pro-inflammatory cytokines and the Aβ-42 peptide in Aβ plaques. In response, IDO possesses its pathological effect by inducing the kynurenine pathway, leading to the production of nitric oxide and the neurotoxic NMDA agonist QUIN, while decreasing the production of serotonin by decreasing the extracellular levels of tryptophan. Quantitative evidence for the involvement of IDO in depression was provided by the finding that activity of IDO was correlates with the severity of depressive symptoms (Sublette & Postolache, 2012). Furthermore, the increased kynurenine:tryptophan ratio that results from IDO was associated with reduced cognitive performance in patients with AD (Widner et al., 2000). In both diseases, higher levels of IDO were thus correlated with an increased severity of the symptoms.

Does this implicate that IDO might indeed be a key linking factor between depression and dementia? The data reviewed in the previous part of this thesis do support this hypothesis. The strongest evidence seems to be that activation of IDO both qualitatively and quantitatively contributes to depressive symptoms as well as the cognitive symptoms of AD. There is however also considerable evidence that points to other mechanisms as linking factor, including pro-inflammatory cytokines, neurotransmitter systems and the HPA-axis. In addition, only a sub group of patients with AD has a history of depression, and not all depressed individuals will develop AD later in life. Besides, whereas inflammatory changes are commonly seen in AD, they are detectable in part of the depressed patients only. The most probable conclusion might therefore be that IDO does not form a stand-alone link, but that several systems together are responsible for the link between depression and AD in a subgroup of patients. Despite of this, IDO was suggested to be a linking factor between AD and depression by several researchers, which suggests that there seems to be substantial support for this link. This implicates that further research into IDO and the link between AD and depression might be of interest. Therefore, it would first be relevant to confirm the link in an experimental or prospective study. In view of the increasing prevalence of AD, it might thereafter be an interesting possibility to study if certain subgroups of depressed patients do have a particularly elevated risk to develop AD (compared to other groups of people with depression). Besides, it might be very relevant to explore if IDO would be a potential target for pharmaceutical interventions. If this is indeed the case, a major application on the long-term could be to preventively prescribe this IDO-based medication to depressed patients with a high risk to develop AD.

If the HPA-axis is activated, levels of pro-inflammatory cytokines, glucocorticoids and the neurotransmitters serotonin and noradrenalin are (initially) increased. The pro-inflammatory cytokines further activate the HPA-axis and induce IDO to produce neurotoxic end products and at the same time decreases serotonin availability. Serotonin in turn is also involved in regulation of HPA-axis activity. When HPA-axis activation becomes chronic, this leads to glucocorticoid resistance, which impairs the negative feedback on the HPA-axis. It is difficult to determine the starting point of this vicious circle, but it appears any of these factors might result in the changes observed in these two diseases.

Every field of research has its strong points and limitations. One of the strong points in this field is that reliable animal models are available for both AD and depression. In addition, inflammation-based depression can be studied prospectively in populations of hepatitis C patients treated with the pro-inflammatory cytokine IFN-α.
The major limitation of the research into IDO involvement in depression and AD might be the inadequate diagnostic criteria for both diseases. Depression, similar to most other psychiatric disorders, is diagnosed based on symptoms rather than a physiological measure. It is therefore likely that there is much heterogeneity in the patient population, which might negatively impact the ability to find significant results. The definite diagnosis of AD can only be made post-mortem, since the presence of Aβ plaques and neurofibrillary tangles has to be determined by autopsy. Therefore, the identification of biomarkers that would enable more accurate diagnoses would be desirable for both diseases, in order to make both research and treatment more efficient.

At some points, the different studies discussed in this thesis did not completely agree with each other. The most important point of discussion is the nature of the link between both diseases, and the exact role of IDO in this link. Depression is hypothesized to be 1) a risk factor for AD or 2) a predromal or early stage of dementia, but it is also suggested that 3) both diseases have a common neurodevelopmental origin. At least the first two hypotheses are substantiated by data, but a disagreement between different research groups exists about which hypothesis best describes the connection. About the role of IDO in this process, more agreement seems to exist. It appears to be generally accepted that IDO exhibits detrimental effects by activating the KP, and that these effects exacerbate neurodegeneration in both depression and dementia.

But what would be the applicability of the knowledge that IDO levels are elevated in depressed patients as well as people with Alzheimer's disease? If levels of IDO could serve as a biomarker for specific forms of depression or dementia, this would be advantageous in the clinic as well as for research. The benefit for research would be that biomarkers could be used to better define study populations. Besides, IDO could be a new, promising target for new pharmaceuticals. Clinically, it would finally be possible to base the diagnoses of both diseases on objective measures. Hopefully, this will contribute to the developments of specific medicines which alleviate the elevations in IDO. It might thus be concluded that IDO might be a promising target for both diseases and that further research is desired.

Some preliminary studies have already been performed on pharmaceuticals which engage on this inflammatory link between depression and dementia. First, SSRIs were tested for efficiency in treating AD, and seemed to have some effect on the non-cognitive symptoms of this disease (Lanctot et al., 2001). Another trial aimed to pharmaceutically reduce IDO activity in depression patients, by targeting both IDO itself and other enzymes involved in the KP (Christmas et al., 2011). Direct inhibition of IDO was effective in animal models, but it is not sure yet if it will be functional in humans as well. A clinical trial with 1-methyltryptophan, which has been show to inhibit IDO *in vitro,* has commenced as an anti-cancer therapy. However, it is reported that there is some discussion about whether the agent can also inhibit human IDO activity *in vivo* (Christmas et al., 2011). A second possibility might be inhibiting the pro-inflammatory cytokines that induce IDO. However, it should be considered that these cytokines do have a much broader function than solely inducing IDO. Nevertheless, a clinical trial with the TNF-α antagonist infliximab indeed resulted in reduced

depressive symptoms in patients with treatment-resistant depression, who had increased levels of inflammation at baseline (Mehta et al., 2013) .
The third approach would be to inhibit the downstream effectors of IDO. Since the most detrimental end products of the kynurenine pathway are NMDA agonists, this makes NMDA-antagonists an interesting group of candidates. Administration of a NMDA-receptor antagonist indeed prevented the development of depressive behaviour in mice (Walker et al., 2013), and are according to some sources already prescribed as treatment for AD. However, many NMDA antagonists are associated with serious side effects in humans (Christmas et al., 2011).

Since this field of research is very new, it is of great interest to further explore the implications of the link between both diseases, as well as IDO's role, for both clinical and diagnostic purposes. Future research might be aimed at improving diagnostics based on neurobiology, by making use of neuroimaging and CSF markers for inflammatory factors. More fundamental research would be desirable, in aim to better understand the role of inflammation and to determine the exact mechanisms of disease. Based on the knowledge obtained from these kind of studies, eventually new therapeutic targets could be developed. Until then, it would be of interest to further test the effect of approved anti-inflammatory drugs in depression and Alzheimer's disease. Hopefully, this knowledge will eventually lead to improved and more effective treatment for patients with both these devastating diseases.

9 Glossary

3-HK	3-hydroxykynurenine
3-HAA	3-hydroxanthranilic acid
5-HT	serotonin
Aβ	amyloid beta
ACTH	adrenocorticotropic hormone
AD	Alzheimer's disease
AIDS	acquired immune deficiency syndrome
apoE	apolipoprotein E
APP	amyloid protein precursor
Arc	activity-regulated cytoskeleton-associated protein
BDNF	brain derived neurotropic factor
BPSD	behavioural and psychological symptoms of dementia
COX	cyclooxygenase
CRF	corticotrophin releasing factor
CRH	corticotrophin releasing hormone
CRP	C-reactive protein
CSF	cerebrospinal fluid
GC	glucocorticoids
GR	glucocorticoid receptor
HIV-1	human immunodeficiency virus-type 1
HPA-axis	hypothalamus-pituitary-adrenal axis
IDO	indoleamine 2,3-dioxygenose
IFN	interferon
IL	interleukin
LC	locus coeruleus
MCI	mild cognitive impairment
NA	noradrenaline
NAD^+	nicotinamide adenine dinucleotide
NMDA	N-methyl *D*-aspartate
NO	nitric oxide
NOS	nitric oxide synthase
NRI	noradrenalin reuptake inhibitors
NSAID	non-steroidal anti-inflammatory drug
PNI	psychoneuroimmunology
KP	kynurenine pathway
QUIN	quinolinic acid
PET	positron emission tomography
PGE2	prostaglandin E2
SSRI	selective serotonin reuptake inhibitors
TDO	tryptophan 2,3-dioxygenase
TGF	transforming growth factor
Th	T-helper cell
THO	tryptophan hydroxylase
TNF	tumor necrosis factor

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11 References

American Psychiatric Association, & American Psychiatric Association. Task Force on DSM-IV. (2000). *Diagnostic and statistical manual of mental disorders: DSM-IV-TR.* American Psychiatric Publishing, Inc.

Baghai, T. C., Moller, H. J., & Rupprecht, R. (2006). Recent progress in pharmacological and non-pharmacological treatment options of major depression. *Current Pharmaceutical Design, 12*(4), 503-515.

Bewernick, B. H., & Schlaepfer, T. E. (2013). Chronic depression as a model disease for cerebral aging. *Dialogues in Clinical Neuroscience, 15*(1), 77-85.

Bonda, D. J., Mailankot, M., Stone, J. G., Garrett, M. R., Staniszewska, M., Castellani, R. J., et al. (2010). Indoleamine 2,3-dioxygenase and 3-hydroxykynurenine modifications are found in the neuropathology of alzheimer's disease. *Redox Report : Communications in Free Radical Research, 15*(4), 161-168. doi:10.1179/174329210X12650506623645; 10.1179/174329210X12650506623645

Brunello, N., Mendlewicz, J., Kasper, S., Leonard, B., Montgomery, S., Nelson, J., et al. (2002). The role of noradrenaline and selective noradrenaline reuptake inhibition in depression. *European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology, 12*(5), 461-475.

Brureau, A., Zussy, C., Delair, B., Ogier, C., Ixart, G., Maurice, T., et al. (2013). Deregulation of hypothalamic-pituitary-adrenal axis functions in an alzheimer's disease rat model. *Neurobiology of Aging, 34*(5), 1426-1439. doi:10.1016/j.neurobiolaging.2012.11.015; 10.1016/j.neurobiolaging.2012.11.015

Caraci, F., Copani, A., Nicoletti, F., & Drago, F. (2010). Depression and alzheimer's disease: Neurobiological links and common pharmacological targets. *European Journal of Pharmacology, 626*(1), 64-71. doi:10.1016/j.ejphar.2009.10.022; 10.1016/j.ejphar.2009.10.022

Center for Substance Abuse Treatment. (2008).

Chen, Y., & Guillemin, G. J. (2009). Kynurenine pathway metabolites in humans: Disease and healthy states. *International Journal of Tryptophan Research : IJTR, 2*, 1-19.

Choi, S. H., Aid, S., Caracciolo, L., Minami, S. S., Niikura, T., Matsuoka, Y., et al. (2013). Cyclooxygenase-1 inhibition reduces amyloid pathology and improves memory deficits in a mouse model of alzheimer's disease. *Journal of Neurochemistry, 124*(1), 59-68. doi:10.1111/jnc.12059; 10.1111/jnc.12059

Christmas, D. M., Potokar, J., & Davies, S. J. (2011). A biological pathway linking inflammation and depression: Activation of indoleamine 2,3-dioxygenase. *Neuropsychiatric Disease and Treatment, 7*, 431-439. doi:10.2147/NDT.S17573; 10.2147/NDT.S17573

Corona, A. W., Norden, D. M., Skendelas, J. P., Huang, Y., O'Connor, J. C., Lawson, M., et al. (2012). Indoleamine 2,3-dioxygenase inhibition attenuates lipopolysaccharide induced persistent microglial activation and depressive-like complications in fractalkine receptor (CX(3)CR1)-deficient mice. *Brain, Behavior, and Immunity,* doi:10.1016/j.bbi.2012.08.008

Cross, A. J. (1990). Serotonin in alzheimer-type dementia and other dementing illnesses. *Annals of the New York Academy of Sciences, 600*, 405-15; discussion 415-7.

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews.Neuroscience, 9*(1), 46-56. doi:10.1038/nrn2297

Dantzer, R., O'Connor, J. C., Lawson, M. A., & Kelley, K. W. (2011). Inflammation-associated depression: From serotonin to kynurenine. *Psychoneuroendocrinology, 36*(3), 426-436. doi:10.1016/j.psyneuen.2010.09.012; 10.1016/j.psyneuen.2010.09.012

Duleu, S., Mangas, A., Sevin, F., Veyret, B., Bessede, A., & Geffard, M. (2010). Circulating antibodies to IDO/THO pathway metabolites in alzheimer's disease. *International Journal of Alzheimer's Disease, 2010*, 10.4061/2010/501541. doi:10.4061/2010/501541; 10.4061/2010/501541

Elovainio, M., Hurme, M., Jokela, M., Pulkki-Raback, L., Kivimaki, M., Hintsanen, M., et al. (2012). Indoleamine 2,3-dioxygenase activation and depressive symptoms: Results from the young finns study. *Psychosomatic Medicine, 74*(7), 675-681. doi:10.1097/PSY.0b013e318266d0f5; 10.1097/PSY.0b013e318266d0f5

Feng, Y., Li, L., & Sun, X. H. (2011). Monocytes and alzheimer's disease. *Neuroscience Bulletin, 27*(2), 115-122. doi:10.1007/s12264-011-1205-3; 10.1007/s12264-011-1205-3

Fitzgerald, P. J. (2010). Is elevated norepinephrine an etiological factor in some cases of alzheimer's disease? *Current Alzheimer Research, 7*(6), 506-516.

Fuchs, D., Moller, A. A., Reibnegger, G., Stockle, E., Werner, E. R., & Wachter, H. (1990). Decreased serum tryptophan in patients with HIV-1 infection correlates with increased serum neopterin and with neurologic/psychiatric symptoms. *Journal of Acquired Immune Deficiency Syndromes, 3*(9), 873-876.

Gate, D., Rezai-Zadeh, K., Jodry, D., Rentsendorj, A., & Town, T. (2010). Macrophages in alzheimer's disease: The blood-borne identity. *Journal of Neural Transmission (Vienna, Austria : 1996), 117*(8), 961-970. doi:10.1007/s00702-010-0422-7; 10.1007/s00702-010-0422-7

Geerlings, M. I., Schoevers, R. A., Beekman, A. T., Jonker, C., Deeg, D. J., Schmand, B., et al. (2000). Depression and risk of cognitive decline and alzheimer's disease. results of two prospective community-based studies in the netherlands. *The British Journal of Psychiatry : The Journal of Mental Science, 176*, 568-575.

Geldenhuys, W. J., & Van der Schyf, C. J. (2011). Role of serotonin in alzheimer's disease: A new therapeutic target? *CNS Drugs, 25*(9), 765-781. doi:10.2165/11590190-000000000-00000; 10.2165/11590190-000000000-00000

Glaser, R., & Kiecolt-Glaser, J. K. (2005). Stress-induced immune dysfunction: Implications for health. *Nature Reviews.Immunology, 5*(3), 243-251. doi:10.1038/nri1571

Goddard, A. W., Ball, S. G., Martinez, J., Robinson, M. J., Yang, C. R., Russell, J. M., et al. (2010). Current perspectives of the roles of the central norepinephrine system in anxiety and depression. *Depression and Anxiety, 27*(4), 339-350. doi:10.1002/da.20642; 10.1002/da.20642

Gong, C. Y., Li, Z., Wang, H. M., Liu, J., Chen, L., Zhang, H. W., et al. (2011). Targeting the kynurenine pathway as a potential strategy to prevent and treat alzheimer's disease. *Medical Hypotheses, 77*(3), 383-385. doi:10.1016/j.mehy.2011.05.022; 10.1016/j.mehy.2011.05.022

Guillemin, G. J., Brew, B. J., Noonan, C. E., Takikawa, O., & Cullen, K. M. (2005). Indoleamine 2,3 dioxygenase and quinolinic acid immunoreactivity in alzheimer's disease hippocampus. *Neuropathology and Applied Neurobiology, 31*(4), 395-404. doi:10.1111/j.1365-2990.2005.00655.x

Guillemin, G. J., Kerr, S. J., Smythe, G. A., Smith, D. G., Kapoor, V., Armati, P. J., et al. (2001). Kynurenine pathway metabolism in human astrocytes: A paradox for neuronal protection. *Journal of Neurochemistry, 78*(4), 842-853.

Hermida, A. P., McDonald, W. M., Steenland, K., & Levey, A. (2012). The association between late-life depression, mild cognitive impairment and dementia: Is inflammation the missing link? *Expert Review of Neurotherapeutics, 12*(11), 1339-1350. doi:10.1586/ern.12.127; 10.1586/ern.12.127

Herrmann, N., Lanctot, K. L., & Khan, L. R. (2004). The role of norepinephrine in the behavioral and psychological symptoms of dementia. *The Journal of Neuropsychiatry and Clinical Neurosciences, 16*(3), 261-276. doi:10.1176/appi.neuropsych.16.3.261

Heyes, M. P., Mefford, I. N., Quearry, B. J., Dedhia, M., & Lackner, A. (1990). Increased ratio of quinolinic acid to kynurenic acid in cerebrospinal fluid of D retrovirus-infected rhesus macaques: Relationship to clinical and viral status. *Annals of Neurology, 27*(6), 666-675. doi:10.1002/ana.410270614

Higuchi, M., Hatta, K., Honma, T., Hitomi, Y. H., Kambayashi, Y., Hibino, Y., et al. (2010). Association between altered systemic inflammatory interleukin-1beta and natural killer cell activity and subsequently agitation in patients with alzheimer disease. *International Journal of Geriatric Psychiatry, 25*(6), 604-611. doi:10.1002/gps.2381; 10.1002/gps.2381

Hochstrasser, T., Hohsfield, L. A., Sperner-Unterweger, B., & Humpel, C. (2013). Beta-amyloid induced effects on cholinergic, serotonergic, and dopaminergic neurons is differentially counteracted by anti-inflammatory drugs. *Journal of Neuroscience Research, 91*(1), 83-94. doi:10.1002/jnr.23126; 10.1002/jnr.23126

Kaestner, F., Hettich, M., Peters, M., Sibrowski, W., Hetzel, G., Ponath, G., et al. (2005). Different activation patterns of proinflammatory cytokines in melancholic and non-melancholic major depression are associated with HPA axis activity. *Journal of Affective Disorders, 87*(2-3), 305-311. doi:10.1016/j.jad.2005.03.012

Kalinski, P. (2012). Regulation of immune responses by prostaglandin E2. *Journal of Immunology (Baltimore, Md.: 1950), 188*(1), 21-28. doi:10.4049/jimmunol.1101029; 10.4049/jimmunol.1101029

Kindt, T. J., Osborne, B. A., & Goldsby, R. A. (2006). *Kuby immunology* (6th ed.). Ney York: W. H. Freeman & Company.

Kiyota, T., Okuyama, S., Swan, R. J., Jacobsen, M. T., Gendelman, H. E., & Ikezu, T. (2010). CNS expression of anti-inflammatory cytokine interleukin-4 attenuates alzheimer's disease-like pathogenesis in APP+PS1 bigenic mice. *FASEB Journal : Official Publication of the Federation of American Societies for Experimental Biology, 24*(8), 3093-3102. doi:10.1096/fj.10-155317; 10.1096/fj.10-155317

Krstic, D., Madhusudan, A., Doehner, J., Vogel, P., Notter, T., Imhof, C., et al. (2012). Systemic immune challenges trigger and drive alzheimer-like neuropathology in mice. *Journal of Neuroinflammation, 9*, 151-2094-9-151. doi:10.1186/1742-2094-9-151; 10.1186/1742-2094-9-151

Lanctot, K. L., Herrmann, N., & Mazzotta, P. (2001). Role of serotonin in the behavioral and psychological symptoms of dementia. *The Journal of Neuropsychiatry and Clinical Neurosciences, 13*(1), 5-21.

Lapin, I. P., & Oxenkrug, G. F. (1969). Intensification of the central serotoninergic processes as a possible determinant of the thymoleptic effect. *Lancet, 1*(7586), 132-136.

Larbi, A., Pawelec, G., Witkowski, J. M., Schipper, H. M., Derhovanessian, E., Goldeck, D., et al. (2009). Dramatic shifts in circulating CD4 but not CD8 T cell subsets in mild alzheimer's disease. *Journal of Alzheimer's Disease : JAD, 17*(1), 91-103. doi:10.3233/JAD-2009-1015; 10.3233/JAD-2009-1015

Leonard, B. E. (2001). Stress, norepinephrine and depression. *Journal of Psychiatry & Neuroscience : JPN, 26 Suppl*, S11-6.

Leonard, B. E. (2007). Inflammation, depression and dementia: Are they connected? *Neurochemical Research, 32*(10), 1749-1756. doi:10.1007/s11064-007-9385-y

Leonard, B. E., & Myint, A. (2006a). Changes in the immune system in depression and dementia: Causal or coincidental effects? *Dialogues in Clinical Neuroscience, 8*(2), 163-174.

Leonard, B. E., & Myint, A. (2006b). Inflammation and depression: Is there a causal connection with dementia? *Neurotoxicity Research, 10*(2), 149-160.

Leonard, B. E., & Myint, A. (2009). The psychoneuroimmunology of depression. *Human Psychopharmacology, 24*(3), 165-175. doi:10.1002/hup.1011; 10.1002/hup.1011

Lesch, K. P., & Waider, J. (2012). Serotonin in the modulation of neural plasticity and networks: Implications for neurodevelopmental disorders. *Neuron, 76*(1), 175-191. doi:10.1016/j.neuron.2012.09.013; 10.1016/j.neuron.2012.09.013

Letterio, J. J., & Roberts, A. B. (1998). Regulation of immune responses by TGF-beta. *Annual Review of Immunology, 16*, 137-161. doi:10.1146/annurev.immunol.16.1.137

Lovrin, M. (2009). Treatment of major depression in adolescents: Weighing the evidence of risk and benefit in light of black box warnings. *Journal of Child and Adolescent Psychiatric Nursing : Official Publication of the Association of Child and Adolescent Psychiatric Nurses, Inc, 22*(2), 63-68. doi:10.1111/j.1744-6171.2009.00174.x; 10.1111/j.1744-6171.2009.00174.x

Maes, M., Vandoolaeghe, E., Ranjan, R., Bosmans, E., Van Gastel, A., Bergmans, R., et al. (1996). Increased serum soluble CD8 or suppressor/cytotoxic antigen concentrations in depression: Suppressive effects of glucocorticoids. *Biological Psychiatry, 40*(12), 1273-1281.

Maj, M. (2012). Development and validation of the current concept of major depression. *Psychopathology, 45*(3), 135-146. doi:10.1159/000329100; 10.1159/000329100

Maurizi, C. P. (1990). The therapeutic potential for tryptophan and melatonin: Possible roles in depression, sleep, alzheimer's disease and abnormal aging. *Medical Hypotheses, 31*(3), 233-242.

McGeer, P. L., & McGeer, E. G. (2002). Local neuroinflammation and the progression of alzheimer's disease. *Journal of Neurovirology, 8*(6), 529-538. doi:10.1080/13550280290100969

Mehta, D., Raison, C. L., Woolwine, B. J., Haroon, E., Binder, E. B., Miller, A. H., et al. (2013). Transcriptional signatures related to glucose and lipid metabolism predict treatment response to the tumor necrosis factor antagonist infliximab in patients with treatment-resistant depression. *Brain, Behavior, and Immunity, 31*, 205-215. doi:10.1016/j.bbi.2013.04.004; 10.1016/j.bbi.2013.04.004

Misiak, B., Cialkowska-Kuzminska, M., Frydecka, D., Chladzinska-Kiejna, S., & Kiejna, A. (2013). European studies on the prevalence of dementia in the elderly: Time for a step towards a methodological consensus. *International Journal of Geriatric Psychiatry,* doi:10.1002/gps.3948; 10.1002/gps.3948

Oxenkrug, G. (2011). Interferon-gamma - inducible inflammation: Contribution to aging and aging-associated psychiatric disorders. *Aging and Disease, 2*(6), 474-486.

Oxenkrug, G. (2013). Serotonin - kynurenine hypothesis of depression: Historical overview and recent developments. *Current Drug Targets,*

Oxenkrug, G. F. (2007). Genetic and hormonal regulation of tryptophan kynurenine metabolism: Implications for vascular cognitive impairment, major depressive disorder, and aging. *Annals of the New York Academy of Sciences, 1122*, 35-49. doi:10.1196/annals.1403.003

Oxenkrug, G. F. (2010). Tryptophan kynurenine metabolism as a common mediator of genetic and environmental impacts in major depressive disorder: The serotonin hypothesis revisited 40 years later. *The Israel Journal of Psychiatry and Related Sciences, 47*(1), 56-63.

Plangar, I., Majlath, Z., & Vecsei, L. (2012). Kynurenines in cognitive functions: Their possible role in depression. *Neuropsychopharmacologia Hungarica : A Magyar Pszichofarmakologiai Egyesulet Lapja = Official Journal of the Hungarian Association of Psychopharmacology, 14*(4), 239-244.

Popp, J., & Arlt, S. (2011). Pharmacological treatment of dementia and mild cognitive impairment due to alzheimer's disease. *Current Opinion in Psychiatry, 24*(6), 556-561. doi:10.1097/YCO.0b013e32834b7b96; 10.1097/YCO.0b013e32834b7b96

Prolo, P., Chiappelli, F., Angeli, A., Dovio, A., Perotti, P., Pautasso, M., et al. (2007). Physiologic modulation of natural killer cell activity as an index of alzheimer's disease progression. *Bioinformation, 1*(9), 363-366.

Richard, E., Reitz, C., Honig, L. H., Schupf, N., Tang, M. X., Manly, J. J., et al. (2013). Late-life depression, mild cognitive impairment, and dementia. *JAMA Neurology, 70*(3), 374-382. doi:10.1001/jamaneurol.2013.603

Rodriguez, M. R., Nuevo, R., Chatterji, S., & Ayuso-Mateos, J. L. (2012). Definitions and factors associated with subthreshold depressive conditions: A systematic review. *BMC Psychiatry, 12*, 181-244X-12-181. doi:10.1186/1471-244X-12-181; 10.1186/1471-244X-12-181

Salloway, S., & Correia, S. (2009). Alzheimer disease: Time to improve its diagnosis and treatment. *Cleveland Clinic Journal of Medicine, 76*(1), 49-58. doi:10.3949/ccjm.76a.072178; 10.3949/ccjm.76a.072178

Schwarz, S., Froelich, L., & Burns, A. (2012). Pharmacological treatment of dementia. *Current Opinion in Psychiatry, 25*(6), 542-550. doi:10.1097/YCO.0b013e328358e4f2; 10.1097/YCO.0b013e328358e4f2

Sierksma, A. S., van den Hove, D. L., Steinbusch, H. W., & Prickaerts, J. (2010). Major depression, cognitive dysfunction and alzheimer's disease: Is there a link? *European Journal of Pharmacology, 626*(1), 72-82. doi:10.1016/j.ejphar.2009.10.021; 10.1016/j.ejphar.2009.10.021

Solerte, S. B., Fioravanti, M., Pascale, A., Ferrari, E., Govoni, S., & Battaini, F. (1998). Increased natural killer cell cytotoxicity in alzheimer's disease may involve protein kinase C dysregulation. *Neurobiology of Aging, 19*(3), 191-199.

Sublette, M. E., & Postolache, T. T. (2012). Neuroinflammation and depression: The role of indoleamine 2,3-dioxygenase (IDO) as a molecular pathway. *Psychosomatic Medicine, 74*(7), 668-672. doi:10.1097/PSY.0b013e318268de9f; 10.1097/PSY.0b013e318268de9f

Tweedie, D., Ferguson, R. A., Fishman, K., Frankola, K. A., Van Praag, H., Holloway, H. W., et al. (2012). Tumor necrosis factor-alpha synthesis inhibitor 3,6'-dithiothalidomide attenuates markers of inflammation, alzheimer pathology and behavioral deficits in animal models of neuroinflammation and alzheimer's disease. *Journal of Neuroinflammation, 9*, 106-2094-9-106. doi:10.1186/1742-2094-9-106; 10.1186/1742-2094-9-106

Walker, A. K., Budac, D. P., Bisulco, S., Lee, A. W., Smith, R. A., Beenders, B., et al. (2013). NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology,* doi:10.1038/npp.2013.71; 10.1038/npp.2013.71

Widner, B., Leblhuber, F., Walli, J., Tilz, G. P., Demel, U., & Fuchs, D. (2000). Tryptophan degradation and immune activation in alzheimer's disease. *Journal of Neural Transmission (Vienna, Austria : 1996), 107*(3), 343-353.

Wood, H. (2012). Alzheimer disease: Prostaglandin E(2) signalling is implicated in inflammation early in the alzheimer disease course. *Nature Reviews.Neurology, 8*(8), 411. doi:10.1038/nrneurol.2012.145; 10.1038/nrneurol.2012.145

Yamada, A., Akimoto, H., Kagawa, S., Guillemin, G. J., & Takikawa, O. (2009). Proinflammatory cytokine interferon-gamma increases induction of indoleamine 2,3-dioxygenase in monocytic cells primed with amyloid beta peptide 1-42: Implications for the pathogenesis of alzheimer's disease. *Journal of Neurochemistry, 110*(3), 791-800. doi:10.1111/j.1471-4159.2009.06175.x; 10.1111/j.1471-4159.2009.06175.x