university of groningen

Investigating the intricate relationship between Alzheimer's disease and depression:

A search for novel biomarkers and promising insights

Jason Getty
S4117603
j.s.d.getty@student.rug.nl

Neuroscience (Research track) – Biomedical Sciences
Faculty of Science and Engineering (FSE), University of Groningen, the Netherlands
Master Essay

Supervisor and first examiner:
Prof. Dr. U.L.M. Eisel [1]
[1] Groningen Institute for Evolutionary Life Sciences (GELIFES), Groningen, the Netherlands.
Second examiner:
MSc. L.M. Jorna [2]
[2] Faculty of Medical Sciences / UMCG

Table of contents

Abstract

Alzheimer's disease (AD) is the predominant form of dementia, accounting for 60 to 70 percent of dementia cases. Concurrently, depression is a prevalent condition affecting approximately 5% of adults globally. Depression is also a common symptom in patients with AD. A recent network meta-analysis by Zhang and colleagues (2023) revealed that around 40% of patients with AD also suffer from major depressive disorder (MDD), highlighting the complex interplay between these frequently comorbid conditions. Late-life depression (LLD) is associated with 20 to 30 percent of cases with AD and is particularly noteworthy to investigate when establishing a connection between AD and depression. Despite this overlap, there remains a lack of early-stage biomarkers for the diagnosis of comorbid AD and depression.

The pathophysiological mechanisms of both conditions are complex but neuroinflammation emerges as a potential shared mechanism. Amyloid-beta (Aβ) pathology, a hallmark of AD, causes neuroinflammation and has also been implicated in LLD diagnosis. The glucocorticoid receptor, which under normal conditions, decreases inflammation could be the connection between these diseases. Dysregulation of the HPA axis, characterized by glucocorticoid hypersecretion is linked to the development of AD and a strong biological correlate of MDD. Chronic stress and abnormal HPA axis signalling can lead to increased oxidative stress, a common feature observed in both LLD and early-stage AD. A constant elevated level of stress overstimulates the HPA axis causing an excess release of cortisol. As a result, glucocorticoid receptor (GR) resistance happens. This dysregulation, coupled with neuroinflammation, and excessive cortisol release, holds promise for future diagnostic utility in comorbid AD and depression.

Introduction

The relation between Alzheimer's disease and depression

In 2023, roughly 55 million people around the globe suffer from dementia (WHO, 2023). Alzheimer's disease (AD) is the most common form of dementia which represents 60 to 70 percent of cases of dementia (WHO, 2023). AD is a generally considered neurodegenerative disease that mainly affects older people. The prevalence rates, as of 2021, stand at 7.1% and 3.3% in elderly women and men respectively (DeTure & Dickson, 2019; Rosende-Roca, 2021; WHO, 2023). The pathology of the AD brain is characterized by two abnormal structures: amyloid-β (Aβ) plaques and tau neurofibrillary tangles. Aβ peptides, derived from the amyloid precursor protein, form plaques, while tau, a microtubule-associated protein, contributes to tangles (Bloom et al., 2014; van der Kant et al., 2020). The accumulation of these structures in AD causes synaptic damage, correlating with behavioural symptoms and cognitive decline (Bloom et al., 2014).

The incidence of AD is growing, due to ageing of the population (Li et. al., 2022). The causes of AD are not yet fully understood but most studies reveal that it is most likely a combination of age-related changes in the brain, along with genetic, environmental, and lifestyle factors (*What Causes Alzheimer's Disease?*, 2019). While the cause(s) of AD remain unclear, there are certain risk factors associated with its development. These include: age, hypertension, diabetes, obese, smoking, alcohol, inactivity, social isolation and depression (WHO, 2023). The latter is also a common symptom in patients with AD. Depression is a common mental disorder and affects an estimated 5% of adults worldwide (WHO, 2023). Women are more likely to suffer from the condition, but it is often overlooked in men (Salk et al., 2017; Zhao et al., 2020). Depression or its symptoms may be precursors of the dementing process (Guo et al., 2022) and affects as much as 50% of patients with AD (Zhan et al., 2023). Clinical evidence suggests a connection between depression and AD, but it remains unclear whether depression is a risk factor, an early symptom, or a reaction to cognitive decline (Sáiz-Vazquez et al., 2021). AD and depression are prevalent diseases among the elderly, frequently occurring together as comorbidities. For instance, a recent network meta-analysis by Zhang et al. (2023) showed that around 40% of patients with AD have major depressive disorder (MDD). This is supported by another study that revealed that depression is associated with an increased risk of dementia and AD in older men and women after 17 years of follow-up (Saczynski et al., 2010). Moreover, a 50 year cohort study concluded that a diagnosis with depression is linked with a greater likelihood of receiving a dementia diagnosis, even if the depression diagnosis precedes the dementia diagnosis more than 20 years before (Holmquist et al., 2020).

Depression onset and its impact on dementia

Depression can already occur during childhood, adolescence, or early adulthood this is called early-life depression (ELD), which refers to the onset of depression before age of 60 (Salwierz et al., 2023.). Various studies link a history of depression or ELD to an increased risk of later developing dementia (Byers & Yaffe, 2011; Ownby et al., 2006). This is supported by a recent systematic review and meta-analyses that disclosed a twofold increase in dementia risk by ELD (Salwierz et al., 2023). However, Salwierz and colleagues (2023) did not find an association between ELD and AD themselves.

Late-life depression (LLD), on the other hand, occurs in individuals who are typically aged 65 or older (Sekhon, 2023). This age bracket presents a compelling focus for investigating the association between depression and AD. LLD has also been linked to a twofold increased risk of dementia, including AD (Sáiz-Vazquez et al., 2021). LLD is thought to reflect prodromal symptoms of AD instead of being a risk factor like ELD (Sinclair et al., 2023). LLD is associated with 20 to 30 percent of AD cases (Zhao et al., 2023) and is a frequently underdiagnosed and inadequately treated condition. This disease affects one in five individuals over a lifetime (Sekhon, 2023).

Distinguishing LLD from dementia becomes challenging as they exhibit overlapping symptoms, especially when depression impacts cognition, presenting as ''pseudodementia'' (Sekhon, 2023; Sinclair et al., 2023; Zhao et al., 2023). An observational study showcased that 70% of elderly patients initially diagnosed with pseudodementia converted to actual dementia over the course of at least 5 years. This research indicates that cognitive impairment in elderly individuals with moderate-to-severe depression is a strong predictor of dementia (Perini et al., 2019).

According to abovementioned studies there seems to be a strong relation between depression, its time of onset and the development of Alzheimer's disease. Yet, regarding from a molecular perspective, the pathophysiological mechanisms of depression remain unclear, and the pathogenesis of AD is notably complex, influenced by both genetic and environmental factors (Song et al., 2023).

Neuroinflammation as shared pathogenesis between Alzheimer's disease and depression

Neuroinflammation may be of the shared pathophysiological mechanism between AD and depression. A review conducted by Zhan and colleagues (2023) suggests that the development of AD is associated with diverse pathophysiological changes that can trigger depressive emotions. These changes involve abnormalities in monoamine neurotransmitters, disturbances in glutamatergic synaptic signalling, dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis, diminished levels of brain-derived neurotrophic factor (BDNF), hippocampal atrophy and neuroinflammation (Zhan et al., 2023).

Neuroinflammation is the brain's response to injury, infection, trauma or disease. The main purpose of inflammation is to remove or neutralize potentially harmful agents or damaged tissue. This response is primarily coordinated by two cell systems: glia in the central nervous system (CNS) and lymphocytes, monocytes, and macrophages in the hematopoietic system (Hurley et al., 2012). The innate immune cells, mainly microglia and astrocytes release pro-inflammatory cytokines, chemokines, small-molecule messengers, and reactive oxygen species (ROS). Besides, microglia and astrocytes, capillary endothelial cells and infiltrating blood cells also contribute to neuroinflammation. The release of these pro-inflammatory molecules induce synaptic loss and neuronal death, while anti-inflammatory cytokines act as a mechanism to counter excessive neuroinflammation. However, neuroinflammation in AD typically persists as a chronic process without self-resolution, thereby playing a crucial role in the disease (Leng et al., 2021).

In the context of depression, neuroinflammation has received increased attention, as evidence suggests its interaction with neurobiological correlates of MDD (Troubat et al., 2021). According to previous research, patients with depression, especially those with LLD, have increased oxidative and nitrosative stress (Berk et al., 2013; Prak et al., 2022). This triggers autoimmune responses which contributes to neuroprogression in depression (Berk et al., 2013). Neuroprogression refers to the alterations in brain structures (i.e., atrophy and volume loss, alongside cognitive decline and increased susceptibility to psychological stress), all of which are linked to a more severe progression of the illness (Serafini et al., 2021). Supporting this, studies have demonstrated that immune challenges, like inflammatory cytokines, can induce depressive-like behaviours (Berk et al., 2013; Troubat et al., 2021) and have been shown to be increased in the blood of older individuals with depression (Su et al., 2016). In addition, previous meta-analyses have shown an increase in proinflammatory cytokines and demonstrated that chemokine levels are significantly affected in depression (Lee & Giuliani, 2019). Furthermore, the link between depression and inflammation has been strengthened by the discovery that treatment with antidepressants resulted in changes in both pro- and anti-inflammatory cytokines (Santiago & Potashkin, 2021; Zhang et al., 2023). Neuroinflammation can therefore be a common pathogenic factor in these two diseases as several recent studies suggests this (Barber, 2011; Guo et al., 2022; Martín-Sánchez et al., 2021; Ly et al.,

2023; Song et al., 2023; Zhan et al., 2023; Zhang et al., 2023).

Considering the social and economic burden each disease has individually, the challenge becomes even greater when they coexist. Comorbid depression and AD impose an even larger burden, leading to increased mortality among patients (Zhang et al., 2023). Therefore, investigating potential biomarkers that can aid not only in early detection and accurate diagnosis but also serve as indicators of the shared pathophysiological mechanisms in comorbid depression and AD is crucial. Neuroinflammation, a key factor in both diseases, could provide a greater understanding and promising insights into the relationship in comorbid depression and AD. This review aims to demonstrate the potential of neuroinflammation as a biomarker in comorbid depression, especially LLD, and AD.

Presentation of research findings

In recent years, a growing body of literature has investigated the relationship between neuroinflammation, depression, and AD. The main focus of studies has been on the symptomatic level to distinguish dementia from depression. However, recent studies showcased that these conditions may share pathophysiological mechanisms which could be a promising approach to understand these prevalent and often comorbid diseases.

As previously mentioned, neuroinflammation has been shown to be a key factor in both conditions, in this section, studies that demonstrated this will be showcased and substantiated by others in more detail. To really understand the relationship in neuroinflammation between these comorbid conditions we will have to evaluate its role in both diseases and see whether neuroinflammation has overlapping pathophysiological mechanisms.

Amyloid beta deposition and neuroinflammation

One of these proposed shared mechanisms is amyloid beta (Aβ) deposition. Aβ deposition refers to the accumulation of Aβ in the brain, which leads to the formation of plaques. This process commonly occurs in AD, where these protein fragments contribute to the development of the disease. Aβ is a peptide composed of amino acids and generated from the amyloid precursor protein (APP) by β- and γ-secretases (Sehar et al., 2022). Generally, these protein fragments are broken down and removed, but in an AD brain, they accumulate and form plaques. The accumulation of Aβ in AD occurs decades before detectable elevations in cerebrospinal fluid (CSF) tau protein levels and clinical cognitive decline (Minter et al., 2015). Figure 1 shows the primary triggers for the initiation of Aβ and tau cascades. Aβ40 is the most abundant form of Aβ in the brain, while Aβ42 is the predominant form in plaques (Butterfield et al., 2013; Sehar et al., 2022). AD pathology can be assessed in vivo through CSF biomarkers such as the Aβ42/40 ratio and phosphorylated tau (Zapater-Fajarí et al., 2023). Additionally, a low concentration of Aβ42 along with a high concentration of Aβ40 in plasma increases the risk of developing AD (Sun et al., 2008). In correspondence with Aβ pathology, a 5-year follow-up study showed that lower Aβ42 and higher tau was associated with increased probability of depression and apathy over time (Banning et al., 2020).

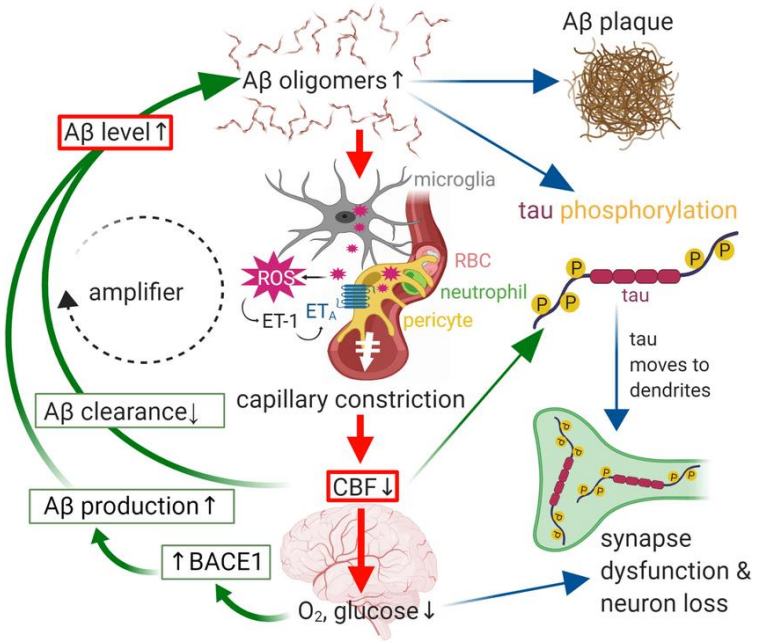

Figure 1: Primary triggers for the initiation of amyloid-beta (Aβ) and tau cascades
Decreased cerebral blood flow (CBF), leading to increased Aβ production, and elevated Aβ levels due to increased production or decreased clearance. Aβ oligomers can form plaques and ROS production from microglia, this eventually leads to a further reduction of CBF. Both increased Aβ oligomers and decreased blood flow result in tau hyperphosphorylation, synaptic dysfunction, and cognitive decline.
From: Korte, N., Nortley, R., & Attwell, D. (2020). Cerebral blood flow decrease as an early pathological mechanism in Alzheimer's disease. *Acta Neuropathologica*, *140*(**6**): 793- 810. https://doi.org/10.1007/s00401-020-02215-w

Moreover, a recent study performed by Pomara and colleagues (2022) showed that a reduced plasma Aβ42/40 ratio is also consistently associated with LLD diagnosis (Pomara et al., 2022). Along with several other studies, these results suggest the relevance of Aβ in both AD and LLD.

The combined neuroinflammatory-amyloid hypothesis suggests that neuroinflammation plays a role in the aggravation of AD and may contribute to the various clinical manifestations of the disease. The hypothesis argues that an initial inflammatory stimulus, such as Aβ, an infection or cellular debris may initiate the activation of microglia in the central nervous system (CNS) (Minter et al., 2015).

Microglia constantly monitor their designated brain areas to detect the presence of pathogens and cellular debris. Simultaneously, microglia release factors that support tissue maintenance. They also play a role in safeguarding and reshaping synapses to ensure the proper maintenance and plasticity of neuronal circuits. This activity is partially supported by the release of trophic factors, including BDNF, known for its role in memory formation. When microglia are activated by pathological triggers, such as neuronal death or protein aggregates, they extend their processes toward the injury site, migrate to the lesion, and initiate an innate immune response (Figure 2). These activated microglia secrete pro-inflammatory cytokines (i.e. interleukin-1β, IL-6, and tumor necrosis factor α) and chemokines (including chemokine ligands CCL2/4/11), recruiting additional microglia and astrocytes to the site of inflammation (Ismail et al., 2020; Minter et al., 2015). The role of astrocytes is to regulate brain functions associated with synaptogenesis and neurogenesis, extracellular homeostasis, and blood-brain barrier permeability. In addition, they interact with neurons, controlling energy metabolism, synaptic remodelling, oxidative stress, and various other functions (Sehar et al., 2022).

In standard conditions, this immune response is well-regulated and immune cells clear the pathogen, leading to the resolution of the inflammatory response. However, in AD,

excessive Aβ production and hyper-phosphorylated tau disrupt this immune clearance mechanism. The recruited microglia and astrocytes struggle to clear Aβ, leading to increased production of pro-inflammatory cytokines and chemokines. Additionally, the inflammatory environment is aggravated due to cellular contents released by degenerating neurons (Ismail et al., 2020; Minter et al., 2015). An imbalance in the equilibrium of anti-inflammatory and proinflammatory signalling causes neuroinflammation (Sehar et al., 2022).

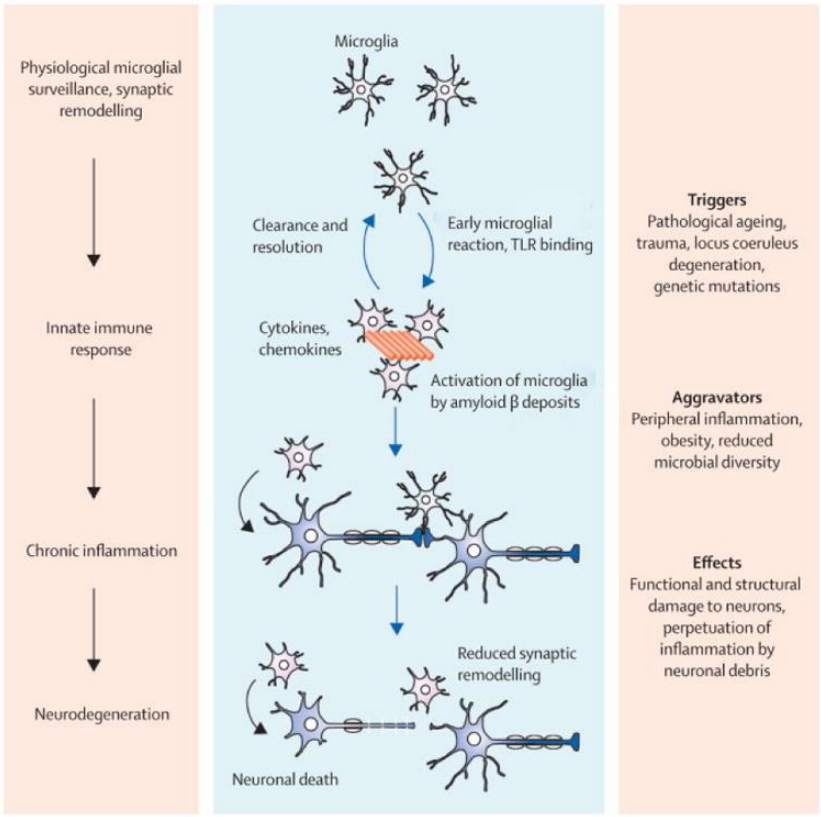

Figure 2: Neurodegeneration due to the innate immune response of microglia
Microglial functions, like tissue surveillance and synaptic remodelling, are impaired by the presence of pathological Aβ accumulations. While acute inflammation initially attempts to clear Aβ and restore tissue balance, prolonged exposure and immune activation lead to chronic inflammation. Prolonged microglial activation and exposure to proinflammatory cytokines result in functional and structural changes, eventually causing neurodegeneration.
From: Heneka, M. T., Carson, M. J., Khoury, J. E., Landreth, G. E., Brosseron, F., Feinstein, D. L., Jacobs, A. H., Wyss-Coray, T., Vitórica, J., Ransohoff, R. M., Herrup, K., Frautschy, S. A., Finsen, B., Brown, G. C., Verkhratsky, A., Yamanaka, K., Koistinaho, J., Latz, E., Halle, A., . . . Kummer, M. P. (2015). Neuroinflammation in Alzheimer's disease. *The Lancet Neurology*, *14*(**4**): 388–405. https://doi.org/10.1016/s1474-4422(15)70016-5

Depression and neuroinflammation

Neuroinflammation impacts one in four patients experiencing depression, leading to poor prognosis, treatment resistance, and a reduced quality of life (Hassamal, 2023). Some depressed patients exhibit a low grade-inflammatory state, as indicated by C-reactive protein (CRP) levels exceeding 3.0mg/L. Approximately one-third of

depressed individuals show CRP levels surpassing 3.0mg/L, which is substantiated by a recent meta-analysis revealing that 27 percent of depressed patients exhibited low-grade inflammation, while over half displayed mildly elevated CRP levels (Orsolini et al., 2022; Pitharouli et al., 2021). CRP levels above 3mg/L are linked to a depressive phenotype resembling ''sickness behavior'' (Hassamal, 2023; Troubat et al., 2020).

Peripheral CRP levels show a strong correlation with CSF CRP levels, making them a reliable indicator for neuroinflammation. Measuring CSF CRP levels in a depressed individual may therefore be a good indicator of establishing neuroinflammation in this very heterogeneous disorder (Orsolini et al., 2022).

Different types of stress exposure have the potential to lead to a melancholic phenotype of depression. These stressors are associated with increased insulin insensitivity and elevated levels of pro-inflammatory cytokines. This is supported by animal models that find consistent upregulation of peripheral levels of interleukin-1β (IL-1β), interleukin-6 (IL-6), and Tumor Necrosis Factor α (TNF-α), all involved in pro-inflammatory processes (Hassamal, 2023). Additionally, research by Lu and colleagues (2022) suggests that disrupted glucocorticoid signalling plays a role in connecting the stress response, inflammation, and depression. These findings indicate that neuroinflammation, especially involving pro-inflammatory cytokines, is implicated in the condition, and measuring neuroinflammation, without specificity for a particular type yet, is possible.

The glucocorticoid receptor

As previously mentioned, the development of AD is linked to several pathophysiological changes that might trigger depressive emotions (Zhan et al., 2023). Dysfunction in the HPA axis is identified as one of these mechanisms. Dysregulation of the HPA axis, characterized by glucocorticoid hypersecretion and altered negative feedback, is a strong biological correlate of MDD (Troubat et al., 2020). Glucocorticoids exhibit a wide range of effects, among them are immunological and cognitive functions, and play a role in providing negative feedback on the HPA axis. This feedback directly impacts the elements of the axis and indirectly influences brain structures such as the hippocampus, prefrontal cortex, and amygdala (Troubat et al., 2020).

Under normal conditions, cortisol decreases inflammation. However, a constant elevated level of stress overstimulates the HPA axis causing an excess release of cortisol. As a result, glucocorticoid receptor (GR) resistance happens due to dysfunction of the glucocorticoid negative feedback loop (Figure 3). Clinical evidence suggest that elevated glucocorticoid levels and inflammation co-occur in depressed patients, with observed GR resistance (Troubat et al., 2020).

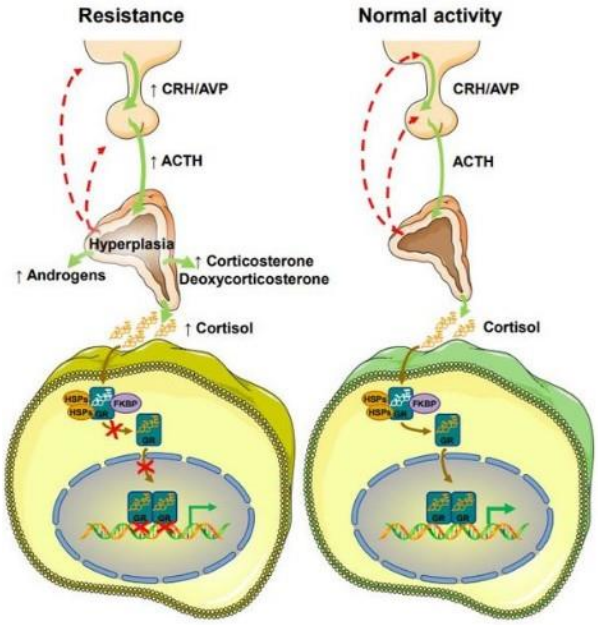

Figure 3: Pathophysiologic mechanisms of the glucocorticoid receptor in normal activity and in receptor resistance

Glucocorticoid receptor resistance happens due to dysregulation in the HPA axis. Stress overstimulates the HPA axis causing an excess release of cortisol. ACTH: adrenocorticotropic hormone; AVP: arginine-vasopressin; CRH: corticotropin-releasing hormone; GR: glucocorticoid receptor.

Adapted from: Nicolaides, N. C., & Charmandari, E. (2021). Primary Generalized Glucocorticoid Resistance and Hypersensitivity Syndromes: A 2021 update. *International Journal of Molecular Sciences*, *22*(**19**): 10839. https://doi.org/10.3390/ijms221910839

Chronic stress and abnormal HPA axis signalling can lead to an increase in oxidative stress via many mechanisms (Patani et al., 2023). Oxidative stress manifests when there is an imbalance between the production of ROS and the body's ability to eliminate them (Pizzino et al., 2017). Cortisol, released during the stress response, can contribute to the generation of ROS, resulting in oxidative damage in cells. In addition, there is a close interconnection between oxidative and inflammatory pathways. In fact, oxidative stress triggers inflammation through Nuclear Factor-kB (NF-kB), potentially leading to an elevated production of free radicals (Orsolini et al., 2022).

Patients with MDD, particularly those with LLD, have increased oxidative and nitrosative stress (Berk et al., 2013; Prak et al., 2022). In addition, oxidative stress increases the production of APP and Aβ (Guglielmotto et al., 2010), which makes it an early-stage hallmark of AD that precedes Aβ aggregation and tau deposition (Ly et al., 2023). Furthermore, both in vivo and in vitro experiments have showcased that stress-level glucocorticoid administration elevates Aβ formation and accelerates formation of neurofibrillary tangles, leading to memory impairments. Therefore, cortisol may amplify the damaging effects on the brain of Aβ (Juszczyk et al., 2021). Furthermore, depressed individuals exhibit the presence of pathological tau and Aβ proteins in their brains. Studies in mice have demonstrated that stress or chronic glucocorticoid administration accelerates the formation of these pathological proteins in the mice's brains. When mice are treated with mifepristone, a GR antagonist, the production of these proteins is inhibited, suggesting a potential link between increased cortisol levels and the onset of AD (Juszczyk et al., 2021).

Moreover, a study by Czéh et al. (2001) already showed that induction of glucocorticoid levels lead to hippocampal atrophy and excessive release of the corticoid-releasing hormone thus leading to the development of AD (Czéh et al., 2001).

Considering all the findings, it is suggested that neuroinflammation is one of many examples of a

complicated relationship between depression, especially LLD, and AD. The influence of the glucocorticoid receptor on oxidative stress and inflammation could be one of the shared mechanisms to better understand and indicate comorbid depression and AD. Figure 4 shows the suggested interplay of the aforementioned findings; however, this is a simplified representation. There are additional connections between these mechanisms and other pathways and mechanisms that are not included in this figure.

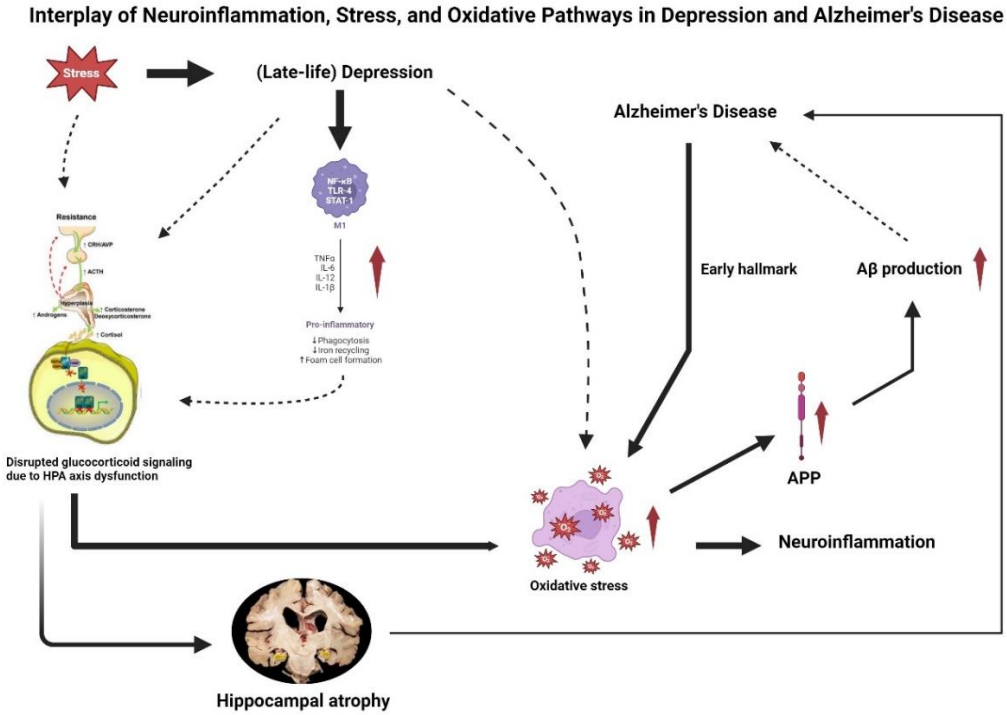

Figure 4: Interplay of Neuroinflammation, Stress, and Oxidative Pathways in Depression and Alzheimer's Disease

Different stressors can lead to depression, which causes increased pro-inflammatory cytokines. Chronic stress can also lead to disrupted glucocorticoid signaling. Firstly, disrupted glucocorticoid signaling connects stress, inflammation and depression. Secondly, disrupted glucocorticoid signaling (hypersecretion) results in elevated oxidative stress, and hippocampal atrophy which contributes to AD development. Increased oxidative stress leads to neuroinflammation but also to increases in the production of APP and therefore increases the production of Aβ. Oxidative stress is associated with MDD and considered an early hallmark of AD.

Created with BioRender.com

Discussion

The dramatic increase in both AD and depression underscores the need for advanced therapeutic intervention, involving the investigation of new pathways and mechanisms to identify potential biomarkers that may lead to greater understanding and insights regarding the relation between these conditions. The significance of this study cannot be overstated, as the discovery of reliable biomarkers would initiate a crucial breakthrough in potentially predicting the comorbidity of AD

and depression. This could lead to improved treatment outcomes and would ultimately reduce the burden of these conditions within our population.

Several studies have indicated a correlation between depression and AD. This is supported by multiple studies, including clinical evidence and meta-analyses, which suggest a link between AD and depression (Guo et al., 2022; Holmquist et al., 2020; Saczynski et al., 2010; Sáiz-Vazquez et al., 2021; Zhan et al., 2023; Zhang et al., 2023). However, whether depression is considered a risk factor, or a prodromal symptom could depend on the time of onset of depression. This study primarily focused on LLD and AD because LLD is associated with older individuals, which translates better to AD, as the risk of developing AD doubles about every 5 years beyond the age of 65 (*What Causes Alzheimer's Disease?*, 2019). LLD may therefore indicate a clearer link between these comorbid conditions. LLD is thought to reflect prodromal symptoms of AD instead of being a risk factor like ELD (Sinclair et al., 2023). Nevertheless, both conditions solely consist of complex causes and mechanisms, so establishing a connection between them is very difficult.

Neuroinflammation as common denominator

Depression is a very heterogeneous condition, and its pathophysiological mechanisms may involve genetics, neurotransmitter systems, HPA axis, neurotrophins and neurogenesis, metabolic disorders, microbiome-gut-brain axis, neuroinflammation and other systems (Tian et al., 2022). On the other hand, neuroinflammation plays a crucial role in the disease progression of AD. As previously explained, microglia, the brain's immune cells, initially attempt to clear Aβ plaques but can become persistently activated. Consequently, excessive Aβ production and hyper-phosphorylated tau disrupt this immune clearance mechanism and the microglia and astrocytes struggle to clear Aβ, leading to an increased production of pro-inflammatory cytokines and chemokines (Ismail et al., 2020; Minter et al., 2015).

Aβ pathology is one of the hallmark features of AD. However, emerging research also suggests that Aβ pathology may be implicated in depression and neuroinflammation (Ly et al., 2023; Song et al., 2023; Zhan et al., 2023; Zhang et al., 2023). The ratio between Aβ42/40 can predict AD pathology, whereas a low concentration of Aβ42 along with high concentration of Aβ 40 in plasma increases the risk of developing AD (Sun et al., 2008). These concentrations are also showed to be correlated in a 5-year follow up study that revealed that lower Aβ42 and higher tau was associated with increased probability of depression and apathy over time (Banning et al., 2020). As mentioned before, Aβ pathology is closely associated with neuroinflammatory processes in the brain. The presence of Aβ plaques can trigger immune response and lead to microglial cell-activation which are involved in inflammation. Additionally, microglia cell-activation is also a key feature of depression (Ly et al., 2023) and inflammation has been linked to depression by various studies (Lee et al., 2019; Song et al., 2023; Zhang et al., 2023). Therefore, one of the key components that could link neuroinflammation in depression and AD can be Aβ pathology. Previously mentioned, Aβ42/40 ratio is consistently associated with LLD diagnosis and early pet studies found that people with LLD had higher amyloid binding in multiple brain regions (Sinclair et al., 2023).Previous studies showed the relevance of Aβ pathology in both conditions and its usefulness for future research to further examine its connection and find possible biomarkers in the pathophysiological mechanisms involved. However, this study did not solely focus on Aβ pathology but rather signified its relevance due to the inflammation processes it is involved in.

Inflammation, oxidative stress, and the glucocorticoid receptor

Inflammatory cells release reactive species causing oxidative stress, which in turn promotes intracellular signalling and pro-inflammatory gene expression. Oxidative stress and neuroinflammation can reinforce each another, especially in diseased conditions (Teleanu et al.,

2022). In fact, a recent review indicates that neuroinflammation can cause oxidative stress and contribute to neurodegeneration (Fabisiak & Patel, 2022), while others suggest that the oxidative stress state induces neuroinflammation and neurodegeneration (Solleiro-Villavicencio & Rivas-Arancibia, 2018). These studies indicate the intricate interrelationship between neuroinflammation, oxidative stress, and neurodegeneration.

Moreover, oxidative stress increases the production of APP and Aβ (Guglielmotto et al., 2010). This makes oxidative stress an early-stage hallmark of AD that precedes Aβ aggregation and tau deposition (Ly et al., 2023). In addition, patients with depression, especially LLD, have been linked to oxidative stress (Berk et al., 2013; Prak et al., 2022).

In depression, dysregulation of the HPA axis, which is characterized by glucocorticoid hypersecretion is a strong biological correlate of MDD (Troubat et al., 2020). This causes an excess release of cortisol, leading to GR resistance. Elevated glucocorticoid levels and inflammation co-occur in depressed patients, with observed GR resistance (Troubat et al., 2020). In addition, HPA axis dysregulation in AD is also associated with elevated levels of glucocorticoids and cortisol in plasma and CSF (Canet et al., 2018). While glucocorticoids are typically thought to supress the immune system, acute episodes of glucocorticoid exposure enhance innate inflammatory responses, especially within the CNS (Herman et al., 2019). Moreover, stress-level glucocorticoid administration accelerates Aβ and tau protein formation, impairing memory. Therefore, cortisol may amplify the damaging effects on the brain of Aβ. Studies in mice have shown that blocking the GR with a GR antagonist inhibits the production of tau and Aβ proteins, suggesting a potential link between increased cortisol levels and the onset of AD (Juszczyk et al., 2021).

In addition, another study performed by Lesuis et al. (2018) demonstrated that short treatment with a GR antagonist reduced Aβ levels and rescued cognitive deficits in AD after early-life stress, which highlights the therapeutic potential of targeting the GR. It is worth mentioning that one of the GR antagonists used in the previous studies was mifepristone. This antagonist has also demonstrated potential side-effects, limiting its therapeutic usefulness. Nonetheless, other ''selective GR modulators'' have been shown to induce a receptor shape that activates only specific downstream pathways, clarifying how they can function as both agonists and antagonists (Canet et al., 2018). However, this study was not initially focussed on therapeutic usefulness but more on predicting comorbid AD and depression.

The potential of excess release of cortisol as biomarker for both conditions has been implicated, but it also comes with certain limitations. Firstly, the GR is a key player in this process, but it has a very complex gene structure, making it difficult to identify specific patterns of GR that are associated with AD. Moreover, glucocorticoid response elements are present, which makes linking altered cortisol and assumed downstream events very difficult (Herbert & Lucassen, 2016). Secondly, inflammation may impair the function of GR, and the elevation of inflammatory markers is associated with depression severity. This makes the interpretation of cortisol levels as a biomarker for comorbid AD and depression very difficult (Linnemann & Lang, 2020). Lastly, the relationship between cortisol, AD and depression may be way more complicated than a simple correlation between cortisol levels and inflammation. Inflammation may be a common link, but this has not been systematically proven.

Conclusion

In conclusion, the development of comorbid AD and depression involves several contributing mechanisms. Considering the social and economic burden each disease has individually, the need for biomarkers is necessary as they impose an even greater burden when they coexist. Among the potential biomarkers, neuroinflammation, the GR, and excessive cortisol release show promise for future diagnostic utility in comorbid AD and depression. Nevertheless, these potential biomarkers face notable limitations, necessitating

further investigation to elucidate their role fully. Exploring alternative processes and mechanisms may also uncover additional biomarkers, such as genetic factors (Appendix: Table 1A & Table 1B), hippocampal atrophy, vascular disease, glucose metabolism, anosmia, and circadian dysfunction (Guo et al., 2022; Martín-Sánchez et al., 2021; Moulinet et al., 2022; Salwierz et al., 2023; Song et al., 2023; Zhang et al., 2023). Therefore, continuous research is of great importance to fully understand these conditions and uncover impactful biomarkers.

References

Alemi, M., Gaiteiro, C., Ribeiro, C. A., Santos, L. M., Gomes, J. R., Oliveira, S. M., Couraud, P., Weksler, B. B., Romero, I. A., Saraiva, M. J., & Cardoso, I. (2016). Transthyretin participates in beta-amyloid transport from the brain to the liver- involvement of the low-density lipoprotein receptor-related protein 1? *Scientific Reports*, *6*: 20164. https://doi.org/10.1038/srep20164

Banning, L. C., Ramakers, I. H., Rosenberg, P. B., Lyketsos, C. G., Leoutsakos, J. M. S., & Initiative, A. D. N. (2020). Alzheimer's disease biomarkers as predictors of trajectories of depression and apathy in cognitively normal individuals, mild cognitive impairment, and Alzheimer's disease dementia. *International Journal of Geriatric Psychiatry*, *36*(**1**): 224–234. https://doi.org/10.1002/gps.5418

Barber, R. C. (2011). Inflammatory signaling in Alzheimer disease and depression. *Cleveland Clinic Journal of Medicine*, *78*(**8**): S47–S49. https://doi.org/10.3949/ccjm.78.s1.08

Berk, M., Williams, L. J., Jacka, F. N., O'Neil, A., Pasco, J. A., Moylan, S., Allen, N. B., Stuart, A. L., Hayley, A. C., Byrne, M., & Maes, M. (2013). So depression is an inflammatory disease, but where does the inflammation come from? *BMC Medicine*, *11*(**1**):200. https://doi.org/10.1186/1741-7015-11-200

Bloom, G. S. (2014). Amyloid-B and Tau. *JAMA Neurology*, *71*(**4**): 505-8. https://doi.org/10.1001/jamaneurol.2013.5847

Butterfield, D. A., Swomley, A. M., & Sultana, R. (2013). Amyloidβ-Peptide (1–42)-Induced Oxidative Stress in Alzheimer Disease: Importance in Disease Pathogenesis and Progression. *Antioxid Redox Signal*, *19*(**8**): 823–835. https://doi.org/10.1089/ars.2012.5027

Byers, A. L., & Yaffe, K. (2011). Depression and risk of developing dementia. *Nature Reviews Neurology*, *7*(**6**): 323–331. https://doi.org/10.1038/nrneurol.2011.60

Canet, G., Chevallier, N., Zussy, C., Desrumaux, C., & Givalois, L. (2018). Central role of glucocorticoid receptors in Alzheimer's disease and depression. *Frontiers in Neuroscience*, *12*:739. https://doi.org/10.3389/fnins.2018.00739

Czéh, B., Michaelis, T., Watanabe, T., Frahm, J., De Biurrun, G., Van Kampen, M., Bartolomucci, A., & Fuchs, E. (2001). Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(**22**): 12796–12801. https://doi.org/10.1073/pnas.211427898

DeTure, M., & Dickson, D. W. (2019). The neuropathological diagnosis of Alzheimer's disease. *Molecular Neurodegeneration*, *14*(**1**):32. https://doi.org/10.1186/s13024-019-0333-5

Dinarello, C. A. (2017). Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunological Reviews*, *281*(**1**): 8–27. https://doi.org/10.1111/imr.12621

Fabisiak, T., & Patel, M. (2022). Crosstalk between neuroinflammation and oxidative stress in epilepsy. *Frontiers in Cell and Developmental Biology*, *10*: 976953. https://doi.org/10.3389/fcell.2022.976953

Guglielmotto, M., Giliberto, L., Tamagno, E. & Tabaton, M. (2010). Oxidative stress mediates the pathogenic effect of different Alzheimer's disease risk factors. *Front Aging Neurosci, 2*: 3. https://doi.org/10.3389/neuro.24.003.2010

Guo, P., Chen, S., Wang, H., Wang, Y., & Ju, W. (2022). A systematic analysis on the genes and their interaction underlying the comorbidity of Alzheimer's disease and major depressive disorder. *Frontiers in Aging Neuroscience*, *13*:789698. https://doi.org/10.3389/fnagi.2021.789698

Hassamal, S. (2023). Chronic stress, neuroinflammation, and depression: an overview of pathophysiological mechanisms and emerging anti-inflammatories. *Frontiers in Psychiatry*, *14*. https://doi.org/10.3389/fpsyt.2023.1130989

Heneka, M. T., Carson, M. J., Khoury, J. E., Landreth, G. E., Brosseron, F., Feinstein, D. L., Jacobs, A. H., Wyss-Coray, T., Vitórica, J., Ransohoff, R. M., Herrup, K., Frautschy, S. A., Finsen, B., Brown, G. C., Verkhratsky, A., Yamanaka, K., Koistinaho, J., Latz, E., Halle, A., . . . Kummer, M. P. (2015). Neuroinflammation in Alzheimer's disease. *The Lancet Neurology*, *14*(**4**): 388–405. https://doi.org/10.1016/s1474-4422(15)70016-5

Herbert, J., & Lucassen, P. J. (2016). Depression as a risk factor for Alzheimer's disease: Genes, steroids, cytokines and neurogenesis – What do we need to know? *Frontiers in Neuroendocrinology*, *41*: 153–171. https://doi.org/10.1016/j.yfrne.2015.12.001

Herman, F., Simkovic, S., & Pasinetti, G. M. (2019). Neuroimmune nexus of depression and dementia: Shared mechanisms and therapeutic targets. *British Journal of Pharmacology*, *176*(**18**): 3558–3584. https://doi.org/10.1111/bph.14569

Holmquist, S., Nordström, A., & Nordström, P. (2020). The association of depression with subsequent dementia diagnosis: A Swedish nationwide cohort study from 1964 to 2016. *PLOS Medicine*, *17*(**1**): e1003016. https://doi.org/10.1371/journal.pmed.1003016

Hurley, L. L., & Tizabi, Y. (2012). Neuroinflammation, Neurodegeneration, and Depression. *Neurotoxicity Research*, *23*(**2**): 131–144. https://doi.org/10.1007/s12640-012-9348-1

Ismail, R., Parbo, P., Madsen, L. S., Hansen, A. K., Hansen, K. V., Schaldemose, J. L., Kjeldsen, P. L., Stokholm, M. G., Gottrup, H., Eskildsen, S. F., & Brooks, D. J. (2020). The relationships between neuroinflammation, beta-amyloid and tau deposition in Alzheimer's disease: a longitudinal PET study. *Journal of Neuroinflammation*, *17*(**1**): 151. https://doi.org/10.1186/s12974-020-01820-6

Juszczyk, G., Mikulska, J., Kasperek, K., Pietrzak, D., Mrozek, W., & Herbet, M. (2021). Chronic stress and oxidative stress as common factors of the pathogenesis of depression and Alzheimer's disease: The role of antioxidants in prevention and treatment. *Antioxidants*, *10*(**9**): 1439. https://doi.org/10.3390/antiox10091439

Korte, N., Nortley, R., & Attwell, D. (2020). Cerebral blood flow decrease as an early pathological mechanism in Alzheimer's disease. *Acta Neuropathologica*, *140*(**6**): 793-810. https://doi.org/10.1007/s00401-020-02215-w

Lee, C., & Giuliani, F. (2019). The role of inflammation in depression and fatigue. *Frontiers in Immunology*, *10*:1696. https://doi.org/10.3389/fimmu.2019.01696

Leng, F., & Edison, P. (2020). Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? *Nature Reviews Neurology*, *17*(**3**):157–172. https://doi.org/10.1038/s41582-020-00435-y

Lesuis, S. L., Weggen, S., Baches, S., Lucassen, P. J., & Krugers, H. J. (2018). Targeting glucocorticoid receptors prevents the effects of early life stress on amyloid pathology and cognitive performance in APP/PS1 mice. *Translational Psychiatry*, *8*: 53. https://doi.org/10.1038/s41398-018-0101-2

Li, X., Feng, X., Sun, X., Hou, N., Han, F., & Liu, Y. (2022). Global, Regional, and National Burden of Alzheimer's Disease and other Dementias, 1990–2019. *Frontiers in Aging Neuroscience*, *14*: 937486. https://doi.org/10.3389/fnagi.2022.937486

Linnemann, C., & Lang, U. E. (2020). Pathways Connecting Late-Life Depression and Dementia. *Frontiers in Pharmacology*, *11*:279. https://doi.org/10.3389/fphar.2020.00279

Lu, C., Ren, J., Mo, J., Fan, J., Guo, F., Chen, L., Wen, Y., Li, S., Fang, Y., Z, W., Li, Y., Gao, T., & Cao, X. (2022). Glucocorticoid Receptor–Dependent astrocytes mediate stress vulnerability. *Biological Psychiatry*, *92*(**3**): 204–215. https://doi.org/10.1016/j.biopsych.2021.11.022

Ly, M., Yu, G. Z., Mian, A., Cramer, A., Meysami, S., Merrill, D. A., Samara, A., Eisenstein, S. A., Hershey, T., Babulal, G. M., Lenze, E. J., Morris, J. C., Benzinger, T. L., & Raji, C. A. (2023). Neuroinflammation: A Modifiable Pathway Linking Obesity, Alzheimer's disease, and Depression. *The American Journal of Geriatric Psychiatry*, *31*(**10**): 853–866. https://doi.org/10.1016/j.jagp.2023.06.001

Martín-Sánchez, A., Piñero, J., Nonell, L., Arnal, M., Ribé, E. M., Nevado-Holgado, A. J., Lovestone, S., Sanz, F., Furlong, L. I., & Valverde, O. (2021). Comorbidity between Alzheimer's disease and major depression: a behavioural and transcriptomic characterization study in mice. *Alzheimer's Research & Therapy*, *13*(**1**):73. https://doi.org/10.1186/s13195-021-00810-x

Minter, M. R., Jm, T., & Crack, P. J. (2015). The contribution of neuroinflammation to amyloid toxicity in Alzheimer's disease. *Journal of Neurochemistry*, *136*(**3**): 457–474. https://doi.org/10.1111/jnc.13411

Moulinet, I., Touron, E., Mézenge, F., Dautricourt, S., De La Sayette, V., Vivien, D., Marchant, N. L., Poisnel, G., & Chételat, G. (2022). Depressive symptoms have distinct relationships with neuroimaging biomarkers across the Alzheimer's clinical continuum. *Frontiers in Aging Neuroscience*, *14*:899158 https://doi.org/10.3389/fnagi.2022.899158

Nicolaides, N. C., & Charmandari, E. (2021). Primary Generalized Glucocorticoid Resistance and Hypersensitivity Syndromes: A 2021 update. *International Journal of Molecular Sciences*, *22*(**19**): 10839. https://doi.org/10.3390/ijms221910839

Orsolini, L., Pompili, S., Valenta, S. T., Salvi, V., & Volpe, U. (2022). C-Reactive protein as a biomarker for major depressive disorder? *International Journal of Molecular Sciences*, *23*(**3**): 1616. https://doi.org/10.3390/ijms23031616

Ownby, R. L., Crocco, E., Acevedo, A., John, V., & Loewenstein, D. (2006). Depression and risk for Alzheimer disease. *Archives of General Psychiatry*, *63*(**5**): 530-538. https://doi.org/10.1001/archpsyc.63.5.530

Patani, A., Balram, D., Yadav, V. K., Lian, K., Patel, A., & Sahoo, D. K. (2023). Harnessing the power of nutritional antioxidants against adrenal hormone imbalance-associated oxidative stress. *Frontiers in Endocrinology*, *14*. https://doi.org/10.3389/fendo.2023.1271521

Perini, G., Ramusino, M. C., Sinforiani, E., Bernini, S., Petrachi, R., & Costa, A. (2019). Cognitive impairment in depression: recent advances and novel treatments. *Neuropsychiatric Disease and Treatment*, *15*: 1249–1258. https://doi.org/10.2147/ndt.s199746

Pitharouli, M. C., Hagenaars, S. P., Glanville, K., Coleman, J. R. I., Hotopf, M., Lewis, C. M., & Pariante, C. (2021). Elevated C-Reactive protein in patients with depression, independent of genetic, health, and psychosocial factors: results from the UK Biobank. *American Journal of Psychiatry*, *178*(**6**): 522–529. https://doi.org/10.1176/appi.ajp.2020.20060947

Pizzino, G., Irrera, N., Cucinotta, M., Pallio, G., Mannino, F., Arcoraci, V., Squadrito, F., Altavilla, D., & Bitto, A. (2017). Oxidative stress: Harms and benefits for human health. *Oxidative Medicine and Cellular Longevity*, *2017*, 1–13. https://doi.org/10.1155/2017/8416763

Pomara, N., Bruno, D., Plaska, C. R., Ramos-Cejudo, J., Osorio, R. S., Pillai, A., Imbimbo, B. P., Zetterberg, H., & Blennow, K. (2022). Plasma Amyloid-β dynamics in late-life major depression: a longitudinal study. Translational Psychiatry, 12(**1**). https://doi.org/10.1038/s41398-022-02077-8

Prak, E. T. L., Brooks, T. G., Makhoul, W., Beer, J., Zhao, L., Girelli, T., Skarke, C., & Sheline, Y. I. (2022). No increase in inflammation in late-life major depression screened to exclude physical illness. *Translational Psychiatry*, *12*(**1**):118 https://doi.org/10.1038/s41398-022-01883-4

Rosende-Roca, M., Abdelnour, C., Esteban, E., Tartari, J. P., Alarcon, E. I., Martínez-Atienza, J., González-Pérez, A., Sáez, M. E., Lafuente, A., Buendía, M., Pancho, A., Aguilera, N., Ibarria, M., Diego, S., Jofresa, S., Hernández, I., López, R. L., Gurruchaga, M. J., Tárraga, L., . . . Boada, M. (2021). The role of sex and gender in the selection of Alzheimer patients for clinical trial pre-screening. *Alzheimer's Research & Therapy*, *13*(**1**):95. https://doi.org/10.1186/s13195-021-00833-4

Saczynski, J. S., Beiser, A., Seshadri, S., Auerbach, S., Wolf, P. A., & Au, R. (2010). Depressive symptoms and risk of dementia. *Neurology*, *75*(**1**): 35–41. https://doi.org/10.1212/wnl.0b013e3181e62138

Sáiz-Vazquez, O., Gracia-García, P., Landa, S. U., Puente-Martínez, A., Casado-Yusta, S., Olaya, B., & Santabárbara, J. (2021). Depression as a risk factor for Alzheimer's disease: A Systematic Review of Longitudinal Meta-Analyses. *Journal of Clinical Medicine*, *10*(**9**): 1809. https://doi.org/10.3390/jcm10091809

Salk, R. H., Hyde, J. S., & Abramson, L. Y. (2017). Gender Differences in Depression in Representative National samples: Meta-analyses of diagnoses and symptoms. *Psychological Bulletin*, *143*(**8**):783–822. https://doi.org/10.1037/bul0000102

Salwierz, P., Thapa, S., Taghdiri, F., Vasilevskaya, A., Anastassiadis, C., Tang-Wai, D. F., Golas, A. C., & Tartaglia, M. C. (2023). Investigating the association between a history of depression and biomarkers of Alzheimer's disease, cerebrovascular disease, and neurodegeneration in patients with dementia. *GeroScience*. https://doi.org/10.1007/s11357-023-01030-x

Santiago, J. A., & Potashkin, J. A. (2021). The impact of disease comorbidities in Alzheimer's disease. *Frontiers in Aging Neuroscience*, *13*: 631770. https://doi.org/10.3389/fnagi.2021.631770

Sehar, U., Rawat, P., Reddy, A. P., Kopel, J., & Reddy, P. H. (2022). Amyloid beta in aging and Alzheimer's disease. *International Journal of Molecular Sciences*, *23*(**21**): 12924. https://doi.org/10.3390/ijms232112924

Sekhon, S. ,Patel, J. & Sapra, A. (2023). *Late-Life Depression*. StatPearls - NCBI Bookshelf. Retrieved from: https://www.ncbi.nlm.nih.gov/books/NBK551507/

Serafini, G., Pardini, M., Monacelli, F., Orso, B., Girtler, N., Brugnolo, A., Amore, M., & Nobili, F. (2021). Neuroprogression as an Illness Trajectory in Bipolar Disorder: A Selective Review of the Current literature. *Brain Sciences*, *11*(**2**): 276. https://doi.org/10.3390/brainsci11020276

Sinclair, L. I., Lawton, M., Palmer, J. C., & Ballard, C. (2023). Characterization of depressive symptoms in dementia and examination of possible risk factors. *Journal of Alzheimer's Disease Reports*, *7*(**1**): 213–225. https://doi.org/10.3233/adr-239000

Solleiro-Villavicencio, H., & Rivas-Arancibia, S. (2018). Effect of chronic oxidative stress on neuroinflammatory response mediated by CD4+T cells in neurodegenerative diseases. *Frontiers in Cellular Neuroscience*, *12*: 114. https://doi.org/10.3389/fncel.2018.00114

Song, J., Ma, Z., Zhang, H., Liang, T. & Zhang, J. (2023). Identification of novel biomarkers linking depressive disorder and Alzheimer's disease based on an integrative bioinformatics analysis. *BMC Genom Data 24*(**1**): 22. https://doi.org/10.1186/s12863-023-01120-x

Su, L., Faluyi, Y.O., Hong, Y.T., Fryer, T.D., Mak, E., Gabel, S., Hayes, L., Soteriades, S., Williams, G.B., Arnold, R., Passamonti, L., Rodríguez, P.V., Surendranathan, A., Bevan-Jones, R.W., Coles, J., Aigbirhio, F., Rowe, J.B., O'Brien, J.T. (2016). Neuroinflammatory and morphological changes in late-life depression: the NIMROD study. *Br J Psychiatry, 209*(**6**):525-526. https://doi.org/10.1192/bjp.bp.116.190165

Sun, X., Steffens, D. C., Au, R., Folstein, M. F., Summergrad, P., Yee, J., Rosenberg, I. H., Mwamburi, D. M., & Qiu, W. Q. (2008). Amyloid-Associated Depression. *Archives of General Psychiatry*, *65*(**5**): 542-550. https://doi.org/10.1001/archpsyc.65.5.542

Teleanu, D. M., Niculescu, A., Lungu, I. I., Radu, C., Vladâcenco, O. A., Roza, E., Costăchescu, B., Grumezescu, V., & Teleanu, R. I. (2022). An overview of oxidative stress, neuroinflammation, and neurodegenerative diseases. *International Journal of Molecular Sciences*, *23*(**11**): 5938. https://doi.org/10.3390/ijms23115938

Tian, H., Hu, Z., Xu, J., & Wang, C. (2022). The molecular pathophysiology of depression and the new therapeutics. *MedComm*, *3*(**3**): e156. https://doi.org/10.1002/mco2.156

Troubat, R., Barone, P., Leman, S., Desmidt, T., Cressant, A., Atanasova, B., Brizard, B., El-Hage, W., Surget, A., Belzung, C., & Camus, V. (2020). Neuroinflammation and depression: A review. *European Journal of Neuroscience*, *53*(**1**): 151–171. https://doi.org/10.1111/ejn.14720

Van Der Kant, R., Goldstein, L. S., & Ossenkoppele, R. (2019). Amyloid-B-independent regulators of TAU pathology in Alzheimer disease. *Nature Reviews Neuroscience*, *21*(**1**): 21–35. https://doi.org/10.1038/s41583-019-0240-3

What causes Alzheimer's disease? (2019). National Institute on Aging. Retrieved from: https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/what-causes-alzheimers-disease

World Health Organization. (2023). Dementia. https://www.who.int/news-room/fact-sheets/detail/dementia

Zapater-Fajarí, M., Diaz-Galvan, P., Cedrés, N., Sterner, T. R., Rydén, L., Sacuiu, S., Wærn, M., Zettergren, A., Zetterberg, H., Blennow, K., Kern, S., Hidalgo, V., Salvador, A., Westman, E., Skoog, I., & Ferreira, D. (2023). Biomarkers of Alzheimer's disease and cerebrovascular disease in relation to depressive symptomatology in individuals with subjective cognitive decline. *The Journals of Gerontology: Series A*, *79*(**2**). https://doi.org/10.1093/gerona/glad216

Zhan, Q., Kong, F., Shao, S., Zhang, B., & Huang, S. (2023). Pathogenesis of depression in Alzheimer's disease. *Neurochemical Research*. https://doi.org/10.1007/s11064-023-04061-0

Zhang, Y., Geng, R., Liu, M., Deng, S., Ding, J., Zhong, H., & Tu, Q. (2023). Shared peripheral blood biomarkers for Alzheimer's disease, major depressive disorder, and type 2 diabetes and cognitive risk factor analysis. *Heliyon*, *9*(**3**): e14653. https://doi.org/10.1016/j.heliyon.2023.e14653

Zhao, N., Ren, Y., Yu, Y. W., Qiao, W., Li, F., Felton, L. M., MahmoudianDehkordi, S., Kueider-Paisley, A., Sonoustoun, B., Arnold, M., Shue, F., Zheng, J., Attrebi, O. N., Martens, Y. A., Li, Z., Bastea, L. I., Meneses, A., Chen, K., Thompson, J. W., St John-Williams, L., Tachibana, M., Aikawa, T., Oue, H., Job, L., Yamazaki, A., Liu, C.C., Storz, P., Asmann, Y.W., Ertekin-Taner, N., Kanekiyo, T., Kaddurah-Daouk, R., Bu, G. (2020). Alzheimer's risk factors age, APOE genotype, and sex drive distinct molecular pathways. *Neuron*, *106*(**5**):727-742.e6. https://doi.org/10.1016/j.neuron.2020.02.034

Zhao, Y., Wu, X., Tang, M., Shi, L., Gong, S., Mei, X., Zhao, Z., He, J., Huang, L., & Cui, W. (2023). Late-life depression: Epidemiology, phenotype, pathogenesis and treatment before and during the COVID-19 pandemic. *Frontiers in Psychiatry*, *14*: 1017203. https://doi.org/10.3389/fpsyt.2023.1017203

Appendix

Table 1A: Co-expressed genes that may serve as potential biomarkers (Zhang et al., 2023).

Co-expressed genes	Protein	Function	Expression
MANI-CDC27-APC[1]	CDC-27[1]	Regulation of neurite outgrowth[1]	Alterations of protein expression in both AD and MDD [1]
CUX1[1]	CASP[1]	Gene expression, morphogenesis, and differentiation and it may also play a role in the cell cycle progression [1]	Downregulated in AD / Upregulated in MDD[1]
PDLIM5[1]	PDZ and LIM domain protein 5[1]	Cardiomyocyte expansion and inhibition of postsynaptic growth of excitatory synapses[1]	Downregulated in both AD and MDD[1]
TTR[1]	Transthyretin[1]	Protect against amyloid-beta deposition[2]	Downregulated in both AD and MDD[1]
TMEM106b[1]	106B[1]	TPD-43 clearance[1]	Downregulated in AD / Upregulated in MDD[1]

[1] Zhang, Y., Geng, R., Liu, M., Deng, S., Ding, J., Zhong, H., & Tu, Q. (2023). Shared peripheral blood biomarkers for Alzheimer's disease, major depressive disorder, and type 2 diabetes and cognitive risk factor analysis. *Heliyon*, *9*(**3**): e14653. https://doi.org/10.1016/j.heliyon.2023.e14653

[2] Alemi, M., Gaiteiro, C., Ribeiro, C. A., Santos, L. M., Gomes, J. R., Oliveira, S. M., Couraud, P., Weksler, B. B., Romero, I. A., Saraiva, M. J., & Cardoso, I. (2016). Transthyretin participates in beta-amyloid transport from the brain to the liver- involvement of the low-density lipoprotein receptor-related protein 1? *Scientific Reports*, *6*(**1**):20164. https://doi.org/10.1038/srep20164

Table 1B: Differentially expressed immune-related genes that may serve as potential biomarkers (Song et al., 2023)

Shared DEIRGS	Function	Expression	Finding
IL1R1[3]	Mediator involved in many cytokine-induced immune and inflammatory responses[4]	Upregulated in both AD and MDD[3]	Decreased neuroinflammation in AD[3]
NRG1[3]	Synaptic plasticity and neural development[3]	NRG-1 regulation involved in AD and MDD[3]	Plays vital role in psychiatric diseases like depression and NRG1 improves neuropathology and cognitive deficits in AD mice[3]

[3] Song, J., Ma, Z., Zhang, H., Liang, T. & Zhang, J. (2023). Identification of novel biomarkers linking depressive disorder and Alzheimer's disease based on an integrative bioinformatics analysis. *BMC Genom Data 24*(**1**): 22. https://doi.org/10.1186/s12863-023-01120-x

[4] Dinarello, C. A. (2017). Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunological Reviews*, *281*(**1**): 8–27. https://doi.org/10.1111/imr.12621