The Role of Elevated Glucocorticoid Levels in Alzheimer's Disease Pathologies

Stacey Woo

Abstract

Alzheimer's disease (AD), the most common type of dementia, is a neurodegenerative disease related to the loss of memory and cognitive functions. Due to the fact that there has been no cure discovered for Alzheimer's disease, researchers have been trying to investigate AD pathologies to reduce the risks and symptoms. Emerging evidence suggests that chronic stress, which leads to elevated levels of glucocorticoids (GC), is thought to be one of the critical factors to the development and progression of Alzheimer's disease. Chronic exposure of glucocorticoids to the brain creates neurotoxic effects, which is thought to impair the brain and contribute to the development of AD. Furthermore, glucocorticoids exacerbate the brain damage caused by AD, such as cerebral atrophy, amyloid-β production, and tau hyperphosphorylation. This review focuses on recent studies over the relationships between elevated levels of glucocorticoids and Alzheimer's disease pathology, such as amyloid-β peptide plaques and tau tangles, neuroinflammation, the cortisol awakening response, and cerebral structures. Elevated levels of glucocorticoids have been shown to have a significant role in the progression of AD. Exploring this relationship can help answer the complexities of this disease. With further research over this correlation, intervention methods to prevent or delay the development of AD may be discovered, potentially through decreasing high glucocorticoid levels.

Keywords: Alzheimer's disease, glucocorticoids, cortisol, hypothalamus-pituitary-adrenal axis, memory impairment

Introduction

There are approximately 50 million Americans that are affected by Alzheimer's disease (AD), and most of them are individuals ranging around 65 years or older [1]. The number of patients with Alzheimer's continues to rise, and there is still no cure that has been discovered. AD, the most common type of dementia, is an irreversible neurodegenerative disease that impairs an individual's cognitive and memory function. The disease is progressive, slowly leading to neuronal death in the brain which can further affect the ability to do every-day tasks, like eating and getting dressed. Pathological changes in the brain that are caused by AD can begin several years before noticeable symptoms appear, and, by the time of symptom presentation, the damages inflicted are irreversible [2]. Although researchers are discovering different methods to prevent the worsening of the disease, there has not been a defined method found to reduce the number of patients being affected by AD. Since there is presently no cure for Alzhiemer's disease, it is crucial for researchers to investigate factors that may contribute to the development of AD.

Glucocorticoids (GC) are the body's steroid hormones that are produced and secreted from the adrenal gland. The hypothalamus–pituitary-adrenal (HPA) axis, which is part of the neuroendocrine system, maintains homeostasis and helps with the body's adaptation during stress [3]. Its functions in the body include mediating stress responses, regulating metabolism, immune functions, and the inflammatory response [4]. Increased levels of GCs have been concluded to be one of the contributing factors to the development of AD, but the mechanisms underlying this relationship are not fully understood [5,6]

This review paper will explore the role of elevated glucocorticoid levels in different pathologies of Alzheimer's disease. It will specifically dive into the effects that increased glucocorticoid levels have on amyloid-β (Aβ) peptide plaques and tau tangles, neuroinflammation, the cortisol awakening response, and cerebral structures. Although previous literature reviews have explored the relationship between GC levels and AD, many of these studies were published nearly over a decade ago. In the years since, a substantial body of new research, including clinical trials and both in vivo and in vitro studies, has been presented, posing implications for understanding the effect of GC levels on AD pathology. This paper thus examines evidence that has been uncovered more recently to create a summary of the current knowledge over the relationship between elevated levels of GCs and Alzheimer's disease.

Neuropathology of Alzheimer's Disease

The progression of Alzheimer's disease is a slow and long process that takes decades for visible symptoms to arise. The first symptoms of AD can vary between individuals, but, for the majority, it begins with problems regarding their cognition. First noticeable symptoms of Alzheimer's include impaired reasoning or judgment [2]. One of the earliest stages of AD is mild cognitive impairment (MCI), and those with MCI are at a greater risk of developing AD [2]. As the disease worsens, they slowly lose basic skills and cognition.

Additionally, changes in AD progression are exceptionally noticeable in the brain's functionality and volume. The limbic system includes major areas in the brain that are affected by this disease, such as the hippocampus and entorhinal cortex (EC). The disease first attacks the area of the brain responsible for memory, but later spreads to other parts of the brain. This causes the AD patient to slowly lose their ability to function independently, with impairments to emotions, cognitive skills, and making decisions [8]. Furthermore, visible shrinkage to cerebral structures are pronounced with different types of brain imaging allowing researchers to further understand the progression of the disease [9,10].

The most significant pathological characteristics of AD are the formation of tau tangles and Aβ plaques. The tau protein is a microtubule-associated protein that stabilizes microtubules allowing them to maintain cytoskeletal organization and trafficking [11,12,13,14]. In AD patients, tau proteins abnormally aggregate into neurofibrillary tangles that disrupt the microtubules and its functions [15]. Meanwhile, the amyloid precursor protein is split by β- and γ-secretase to produce Aβ fragments. When there are excess amounts of Aβ fragments, they clump together in deposits to form Aβ plaques. In AD patients, researchers find excess amounts of tau tangles and Aβ plaques that have been concluded to contribute to memory impairment and cognitive decline.

Mechanism and Functions of Glucocorticoids

Glucocorticoids are the class of steroid hormones that is regulated by the HPA axis. Cortisol is the most abundant and active type of GC in humans [16]. During HPA axis processes, cortisone, an inactive form of cortisol, is activated in the liver to turn into cortisol [17]. Cortisol has the ability to bind to glucocorticoid receptors (GRs) and exhibits wide-ranging effects when bound [16,17]. During an organism's response to stress, GCs are released to provide energy for a "fight or flight" response [18]. After an organism experiences a stressful situation, the HPA axis is activated to terminate the stress response and stabilize GC levels [19,20]. The two types of receptors that have affinity for GCs are mineralocorticoid receptors

and GRs [21]. The activation of these receptors are correlated with systems that are associated with memory, behavior, fear, excitability, and anxiety in an individual [22,23,24]

Effect of Glucocorticoids on Memory

Decline in memory performance is a major sign of AD that patients tend to notice first. The processes of memory consolidation and retrieval should be examined to study if GCs can worsen memory performance. Memory consolidation is the process where newly acquired information is initially held in an unstable state in the short-term memory system before being transferred to a more stable state in the long-term memory system [19]. Memory retrieval is the process of retrieving the memory stored in the long-term memory system [19]. Elevated levels of GCs have been shown to enhance memory consolidation, and low levels of GCs have shown to impair consolidation for neutral and emotional information [25,26]. Interestingly, results with memory retrieval show the opposite. Elevation of GC levels impairs the process to retrieve consolidated memory [27]. Roozendaal, 2003 found that memory retrieval processes are typically impaired by high levels of GCs or the infusion of GR agonists into the hippocampus, but, after activation of GC pathways involving GRs, it enhances memory consolidation [28]. Furthermore, these results demonstrate an inverted U-shape relationship between cortisol levels and memory performance relating to the basolateral complex of the amygdala [27,29,30]. Roozendaal hypothesized that the basolateral complex of the amygdala is a key structure that regulates memory-modulatory systems in regards to stress and GC effects in memory retrieval and consolidation [29]. These findings demonstrate that memory performance and GCs are interlinked together with many different processes in the body. Further research on the levels of GCs with its correlation to AD may be a step forward to discovering the reason for the worsening of memory performance in AD patients.

Another memory process that is affected due to stress hormones is long-term potentiation (LTP), which is a process of long-term strengthening of synaptic connections that contributes to memory formation and consolidation. Research conducted by Dong et al., 2015 tested the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) endocytosis process to see if there was a decay of the activity-dependent LTP [31]. The accumulation of AMPAR is an important procedure in the process of LTP [32]. In their results, they found that high levels of shock (stress) in a mouse model restricted the function of AMPAR and prevented long term memory formation in the mice. These results support that GC-correlated impairment to LTP does have a correlation with memory loss. Furthermore, two different rodent clinical trials presented data that when a group of rats were placed in stressful events, they were found to have an impairment to LTP in hippocampal explants [33,34]. From these findings, elevated levels of stress demonstrated alterations to the LTP process. Although direct evidence to show decline in LTP in AD patients' brains have been limited, researchers have discovered that LTP synapses in a cryopreserved AD brain were shown to be impaired. Due to the relationship shown between stress and the LTP process, it can be suggested that elevated levels of stress may be a contributing factor to the development of AD due to its ability to decline the LTP process.

Effect of Glucocorticoids on Alzheimer's Pathological Biomarkers

There is substantial evidence that demonstrates that GCs aggravate the formation of Aβ plaques and tau tangles, which are the most well-known and researched pathologies of AD.

Therefore, if evidence is found that GC levels play a role in the development or aggregation of Aβ plaques and tau tangles, then glucocorticoids can be a potential point of intervention for reducing the spread of AD pathology.

Glucocorticoids and Amyloid-β Peptide Plaques

In 1992, Hardy and Higgen hypothesized that the deposition of Aβ protein is the causative agent of AD pathology which they called the amyloid cascade hypothesis [35]. Today, the most common medication for AD is Lecanemab, which plays a role in the clearing of Aβ plaques. Therefore, if GCs are shown to contribute to Aβ pathology, it will be a huge step towards finding intervention methods to treat AD.

The insulin-degrading enzyme (IDE) is specialized in the clearance of Aβ peptides in the brain [36]. This enzyme also improves cognitive impairment associated with AD [36]. Harada et al., 1996 supported that IDE was regulated by GC levels and concluded that increased GC levels worsens the progression of AD [37]. The GC's direct ability to control this enzyme, which promotes degradation of Aβ, can demonstrate that they may have a crucial role in the worsening of the disease. Green et al., 2006 tested for the effects that GCs may have on Aβ pathology in AD using both in vitro and in vivo experiments [38]. In the in vitro experiment, administration of corticosterone and dexamethasone, a potent glucocorticoid, to mouse neuronal N2A cells increased levels of Aβ [38]. Similarly, in the in vivo approach, they found that, after administering dexamethasone to 3×Tg-AD mice, Aβ levels were elevated [38]. To further investigate the underlying mechanism to why GCs may elevate levels of Aβ, they looked into levels of C99 and β-APP cleaving enzymes, which both contribute to the presence of Aβ in AD [38]. Researchers found that due to the administration of GCs there was an upregulation of C99 and β-APP cleaving enzymes, which reveals the cause for an increase in Aβ levels [38]. In another study, Dong et al., 2004 found that after exerting isolation-induced stress for 6 months on Tg2576 mice, a well-known mouse model of AD, there were more Aβ plaques in the cortex and the hippocampus compared to the unstressed Tg2576 mice [39]. In another mouse model of AD, $APPP_{V717I}$-CT100 transgenic mice, Jeong et al., 2006 found that chronic immobilization stress increased the number and densities of vascular and extracellular deposits that contained Aβ peptides and amyloid precursor protein fragments, especially in the hippocampus and the cortex [40]. To further clarify that the aggregation of Aβ plaques were most likely due to the presence of GC rather than from another factor of chronic immobilization stress, another study found that administering GCs to normal, middle-aged mice enhances the production of Aβ [41]. These studies link stress factors to Aβ pathology of AD. Although the work from Jeong et al., 2006 and Dong et al., 2004 used different mouse models, their results were consistent in that high levels of GCs caused the aggregation of Aβ plaques, which further supports that GCs may be a significant contributor to the onset or worsening of AD. The elevation in stress levels from cortisol causes the exacerbation of Aβ plaques in ongoing AD pathogenesis [38,42].

Although there has been much emphasis that elevated levels of stress can increase amounts of Aβ peptides, one study demonstrates the opposite. Justice et al., 2015 found that cortisol can lower Aβ levels, which should be a notable consideration when further studying the effects that GCs have on the formation of Aβ plaques [43]. They hypothesized that elevated and depressed levels of cortisol can worsen the progression of AD [43]. As of now, this is the only research found to show a decrease in Aβ levels. More research should be done on this relationship to understand the effects that stress may have on Aβ plaques.

Glucocorticoids and Neurofibrillary Tangles

Numerous studies show that Aβ plaques and tau tangles affect one another [44,45]. Similar to the formation of Aβ plaques, tau tangles are also exacerbated by the presence of GCs, which have been demonstrated in many research studies. Sotiropoulos et al*.,* 2008 used PC12-htau cells, which are differentiated rodent pheochromocytoma-derived neuronal cells transfected with human tau, to explore the impact of Aβ [42]. They found that the neurotoxic effects of Aβ in PC12-htau cells seemed to be potentiated after the administration of GCs [42]. These results align with the theory that Aβ accumulation is shown to come before significant tau accumulation during AD pathology. Furthermore, it can suggest that tau may be vulnerable to GCs, considering that GCs affect Aβ formation [46].

High concentration of phosphorylated tau is a key pathological feature in AD. Therefore, the effect that stress has on tau phosphorylation should be reviewed. Despite the following studies presenting different stress methodologies, they show a consistent result where increased stress exposure elevates levels of phosphorylated tau. Rissman et al., 2007 showed that 14 consecutive daily exposures to restraint stress shows an elevation and reduced solubility of phosphorylated tau [47]. Lee et al., 2008 reported that after exerting restraint stress for 2 hrs/day for 16 days, there were higher levels of phosphorylated tau in phosphorylated sites, specifically ser199, thr231, and ser296 [48]. Jeong et al., 2006 discovered that, after administering chronic immobilization stress for 8 months to APPV717I-CT100 transgenic mice, tau phosphorylation levels were higher in the hippocampal CA3 region, entorhinal cortex, and piriform cortex of stressed mice compared to non-stressed mice [49]. So, these studies further support that even with different methodologies they consistently demonstrate that exerting stress on AD mouse model causes an increase in phosphorylated tau.

Glucocorticoids are part of an underlying mechanism of oxidative stress, and there is evidence that oxidative stress can be another component to the pathophysiology of tauopathies that contribute to AD. Measures of reactive oxygen species (ROS) are used in many studies as markers for oxidative stress [50]. Kang et al., 2017 treated C58BL/6 mice with 1,2-diacetylbenzene (DAB), which is known to increase oxidative stress, to test the effect that oxidative stress has on tau hyperphosphorylation in the hippocampus [51]. They found that DAB-treated mice had tau hyperphosphorylation because of the ROS produced from DAB [51]. Finding hyperphosphorylation of tau is crucial as it is responsible for the formation of neurofibrillary tangles [52]. Furthermore, tau pathogenesis can be a consequence of elevated levels of oxidative stress. It has been shown that post-translational modifications in tau proteins contribute to tau pathogenesis [53]. An increase in ROS has been shown to have a direct correlation with post-translational modifications, which suggests that elevation of oxidative stress could lead to tau post-translational modifications, and thus cause tau pathology [54,55]. Since the spreading of pathogenic tau contributes to the progression of AD, it can be suggested that GCs aid in the process of oxidative stress and contribute to the progression of the disease.

Furthermore, there are many studies that continue to show the effect that stress has on both the formation of Aβ plaques and tau tangles [40,56,57]. A clear link between glucocorticoids and the two central hallmarks of AD can present another possible neuropathology that should be further investigated to stop the worsening of the disease.

Role of Glucocorticoids in Neuroinflammation

Neuroinflammation is another notable contributor to the development and progression of AD. It is an inflammatory response in the brain that is activated by glial cells, specifically

microglia and astrocytes, which then produce cytokines, chemokines, ROS, and secondary messengers [58]. In early stages of AD, glial cells, primarily microglia, are activated by Aβ and, in turn, helps remove Aβ plaques [59]. So, microglia can provide a neuroprotective function in AD [59]. However, as AD progresses, it creates a chronic inflammatory stimulus for glial cells which causes these cells to become neurotoxic and possibly induce the formation of Aβ [59]. Glial cells, the main mediators for neuroinflammation, are one of the main targets for stress hormones [60]. Due to their relationship, stress and GCs should be further researched to discover if they can help prevent the worsening of neuroinflammation in AD patients.

Astrocyte Loss

There have been multiple studies showing that chronic stress can lead to a loss in astrocytes or a decrease in gliogenesis for astrocytes, which can contribute to the development of AD. In stress related disorders, such as major depressive and bipolar disorder, a decrease in density and number of glial cells have been observed [61]. Furthermore, Sabolek et al., 2006 found that exposure of dexamethasone to mesencephalic neural precursor cells blocked astroglial differentiation, which is what allows for regeneration and homeostasis, to occur [62,63]. Moreover, using in vivo experiments, researchers found that chronic stress in rats depleted gliogenesis in limbic structures, specifically the medial prefrontal cortex and hippocampus [64]. A decrease in gliogenesis may result in a lower brain volume in those affected brain regions. Interestingly, there is evidence that GCs are one of the factors leading to a decrease in volume in AD targeted cerebral structures, like the hippocampus and entorhinal cortex [65,66,67]. However, it is not not clear if the decrease in cerebral volume is solely due to neurons or if depleted gliogenesis is a contributing factor. Future studies should investigate the role of decreased gliogenesis in lower cerebral volume due to stress.

Chronic Microglial Activation

It is believed that the presence of Aβ plaques and tau tangles activate microglia cells to help with the clearance of these toxic proteins. However, with increased formation of plaques and tangles, microglia can not keep up with clearance, which results in the microglia becoming dysfunctional, exerting toxic behavior, and encouraging the development of AD [68,69]. Researchers have found that elevated levels of GCs can result in the activation of microglia, suggesting that stress may induce a pro-inflammatory response in the central nervous system [70]. Sugama et al*.,* 2007 exposed Wistar rats, a rodent model of AD, to restraint and water immersion stress to discover that microglial activation appeared after 1 hour of exposure and intensified after 2 hours [71]. Furthermore, after inflicting immobilization, social isolation, and brief tail-shock stress to rodents, there was an increase in expression of interleukin-1β (IL-1β), which is a key pro-inflammatory cytokine in the rodent brain [71,72,73,74,75]. Chronic activation of microglia cells can cause damage to neurons and be a contributing factor of neurodegenerative disease, in this case AD [76]. One receptor that has been found to be important in the regulation of microglia is the Triggering Receptor Expressed on Myeloid Cells 2 (TREM2). TREM2 regulates microglia responses to exert its neuroprotective effect [77]. Therefore, TREM2 may have an important role in slowing the progression of AD. Several studies have come out supporting that, in AD rodent models, TREM2 promotes Aβ phagocytosis and clearance [78,79]. Another study by Frank et al., 2008 supports that TREM2 expression increased in microglia in plaque-filled regions of AD transgenic mice's brains [80]. As of now, there are yet to be studies that show the direct relationship between TREM2 and stress/GCs.

However, there are some studies that indirectly connect oxidative and inflammatory stress with TREM2 using neurovascular unit mechanisms [78,81,82,83,84]. They state that TREM2 may have an important role in the neurovascular unit components that are controlled by oxidative and inflammatory stress. Nevertheless, there needs to be more research conducted to determine if there is a relationship between GCs and TREM2. Understanding the complex relationship between stress or GCs and neuroinflammation can offer insights on discovering ways to slow the aggravation of AD.

Glucocorticoids and the Cortisol Awakening Response (CAR)

The cortisol awakening response is a key component of the daily circadian cortisol rhythm. Normal CAR increases one's cortisol levels within the first hour of waking up and declines throughout the rest of the day [85,86,87]. Chronic stress has shown to change the CAR in a bi-directional way. For example, in one study, exposure to chronic stress through academic pressure was shown to decrease CAR in young men [88]. They claimed that the CAR was decreased possibly due to the reduction of HPA axis activity after a long period of stress [88]. While, in another study, reduced distress responses were shown to have higher CAR increases [85]. Additionally, Schulz et al., 1998 discovered that chronically stressed individuals showed a larger increase in cortisol levels in their first hour of awakening, which indicates a higher CAR, supporting the bi-directional effects that stress induces on the CAR [89]. Similarly to how GCs can be a biomarker for HPA dysfunction, the CAR also can show if the HPA-axis is dysregulated [16]. Irregularities in the CAR can be one of the biggest biomarkers for a dysfunctional HPA-axis [90,91]. Disruption in neuroendocrine systems, like the HPA-axis, are shown to increase the risk of developing neurodegenerative disorders, including AD [20,92]. Therefore, the relationship that stress hormones have with the CAR can potentially cause disruption in the HPA-axis, creating a higher risk for AD.

Impact of Glucocorticoids on Cerebral Structures

In a healthy brain, cerebral structures work with one another to create homeostasis. However, if a stressor is added to the system, like an elevation of GCs levels, the stressor can cause a disruption in the system of the brain and decrease its function. Patients with Alzheimer’s disease not only show a notable decrease in cognitive function, but also consistently exhibit differences in size of their cerebral structures. An extensive period of exposure to GCs have been found to impair limbic structures, like the hippocampus and the prefrontal cortex, which are crucial in cognitive functioning. The limbic system is a general region of the brain that has been linked to emotional, memory and motivational processes that connect other cerebral structures together [93]. Impairment done to cerebral structures by elevated levels of GCs have been shown to be similar in damage and shrinkage in AD patients.

Entorhinal Cortex: Early Vulnerabilities and Damage

Researchers have found that the entorhinal cortex exhibits early signs of alterations during AD that includes formation of neurofibrillary tangles and cell death [67]. During the MCI state, tau tangles have already begun to form in the EC [67]. Layer II of the entorhinal cortex has been identified as one of the first areas to show neurodegenerative effects in AD patients [94]. The EC contains high amounts of GRs which makes it more vulnerable for the effects of high levels of GCs [95]. In research conducted by Igarashi, 2022, mouse models of preclinical AD revealed early dysfunction of spike activity in the EC during preclinical stages, which is when

there is usually lack of clear memory impairments [67]. This was followed by spike activity impairments in the hippocampus during the dementia stage, where memory impairments emerge [67]. Other findings have found that the accumulation of Aβ plaques and tau tangles from the EC may spread to the hippocampus, where more damage and memory impairment can proceed [96,97]. Due to their relatively close distance to each other, the hippocampus and the EC exchange information and allow for a network to exist between these two structures. The entorhinal-hippocampal circuit is critically involved in memory formation and retrieval, and damages done to this circuit result in memory impairments [98,99]. The correlation between these two cerebral structures allows for the progression of AD in the EC to further continue in the hippocampus.

Hippocampal Atrophy and Memory Impairment

The hippocampus allows for an individual to consolidate information, including short-term, long-term, and spatial memory [100]. It also contains a high concentration of GCs and is the main cerebral structure that is involved in the negative feedback inhibition of stress responses [101,102]. Damages to the hippocampal neurons in guinea pigs after elevated GC exposure were first reported by der Mülen and Ockenfels, 1968 [103]. Later, Dronse et al., 2023 demonstrated the effects in the hippocampus between healthy individuals and individuals with AD using serum cortisol levels [104]. They also discovered that high cortisol levels can result in smaller global and regional gray matter volume, impaired cognitive functioning, cognitive decline, and acceleration of hippocampal atrophy [65,66,105,106]. Frisoni et al., 2011 found visible signs of hippocampus atrophy and reported that patients, at a mild stage of AD, have an increased rate of hippocampal atrophy by 15-30% in comparison to healthy adults [107]. The relationship between the hippocampus and GC levels created the glucocorticoid cascade hypothesis. This hypothesis states that the hippocampus is damaged by elevated levels of GCs which leads to lack of inhibitory control over the HPA axis. There are results from 30 years ago that support this hypothesis which shows that higher cortisol levels in the AD group were found to elevate hippocampal atrophy and dementia severity, and reduce cerebral metabolism [108]. In turn, this causes significantly higher levels of GCs, which further damages the hippocampus [109]. High levels of GCs have been shown to cause hippocampal atrophy and decline in its function. Since hippocampal dysfunction is a significant hallmark of AD, levels of GCs with its relations to AD should be investigated further.

Amygdala Atrophy and Emotional Regulation

The amygdala's role is to process emotional responses, such as fear, anxiety, and aggression, as well as processing memories and making decisions [110,111]. Fowler et al., 2021 found with magnetic resonance imaging of children that the right amygdala was reduced in volume with greater cortisol stress response, while there were no changes made to the left amygdala or either hippocampi [112]. Although this research contradicts what was said previously about hippocampus volume being affected by elevated levels of cortisol, there were differences in the methodology between the two studies, as one study was conducted with adolescents and the other was conducted with elderly. However, there are other studies with similar methodology as Fowler et al., 2021 that shows a relationship with elevated cortisol and reduced hippocampal volume in children [113,114,115]. The hippocampus and the amygdala interact with each other to translate feelings of emotion into certain outcomes and work synergistically to form long-term memories [116]. The LTP process was examined at the

hippocampus after stress was induced on the amygdala through exposure to electrical stimulation and swim stress [117]. Electrical stress stimulation on the amygdala for 30 seconds facilitated the hippocampal LTP, but stimulation one hour before testing impaired it [117]. This can suggest that stress on the amygdala can promote further aggression of memory impairment in AD patients. However, there are many published studies that show inconsistent magnitudes of atrophy on the amygdala in AD patients and the magnitude of its atrophy compared to the hippocampus [118]. Further, it is difficult to discover if GC levels do have a significant effect in the amygdala of AD patients as there aren't enough studies conducted to conclude a relationship. So, even though there are aspects to amygdala atrophy that may be correlated in mild stages of AD, they are currently inconsistent and do not have direct correlations with GCs.

Prefrontal Cortex and Cognitive Decline

The prefrontal cortex is another region of the brain that interacts with the limbic system that specializes in decision-making and controlling stress [119]. Like the hippocampus and the EC, the medial prefrontal cortex is also targeted by GCs due to the presence of GRs [120]. Cook and Wellman, 2004 found that there were reductions of apical dendrites in stressed male rats in number and length by 18 and 32%, respectively [121]. Apical dendrites are one of the two types of dendrites that emerge from the apex of the pyramidal cells, and layer III pyramidal cells are found in the prefrontal cortex [122,123]. They also concluded that reduction in apical dendrites may have reflected the atrophy observed of terminal branches, which reduced in number and length by 19 and 35% [121]. So, higher levels of stress lead to atrophy in the prefrontal cortex which can contribute to functional changes, such as in cognitive skills [121]. Also, the prefrontal cortex is responsible for a huge part in regulating the HPA-axis, which introduces the question if there is a relationship between glucocorticoids, the prefrontal cortex, and the dysfunctioning of the HPA-axis [124].

Due to the overwhelming trials that show the effects that high levels of GCs have on cerebral structures correlating to AD, impairment occurring in these limbic structures and potentially other cerebral structures should be further investigated by researchers in order to determine their pathological contribution to the development of the disease.

Conclusion

This review consistently observed that elevated levels of GCs are correlated with an increased risk and progression of AD. More specifically, there exist significant impacts that GCs have on AD pathology like Aβ peptide plaques and tau tangles, neuroinflammation, the CAR, and cerebral structures. It was found that elevation in GCs caused further exacerbation of plaques and tangles, reduction in cerebral volume, chronic activation of glial cells, neuroinflammation, and disruption of the HPA-axis. These findings demonstrate the importance of regulating GC levels and avoiding chronic stress as a potential way to prevent an increased risk of developing the disease. It also can suggest potential interventions to block the adverse effects that AD inflicts on the brain. Although there is overwhelming evidence that shows an indirect relationship with GCs and AD, there needs to be more research conducted on the direct relationship between elevation of GCs and the progression of AD. In conclusion, elevated levels of GCs demonstrate a significant role in the development and progression of AD. Also, as there is currently no cure or prevention, it is important for researchers to investigate potential factors that may provide a solution to this incurable neurodegenerative disease. By advancing the

current knowledge of the complexities of this disease, effective interventions can be developed to improve the outcomes for individuals affected by AD.

References

[1] Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S. G., Dias, A., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Kivimäki, M., Larson, E. B., Ogunniyi, A., Orgeta, V., Ritchie, K., Rockwood, K., Sampson, E.L., Samus, Q., Schneider, L. S., Selbæk, G., Teri, L., Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet,* 396(10248), 413–446. https://doi.org/10.1016/S0140-6736(20)30367-6

[2] Alzheimer's Disease Fact Sheet. (2023). *National Institute on Aging.* https://www.nia.nih.gov/health/alzheimers-and-dementia/alzheimers-disease-fact-sheet

[3] Dunlavey, C. J. (2018). Introduction to the Hypothalamic-Pituitary-Adrenal Axis: Healthy and Dysregulated Stress Responses, Developmental Stress and Neurodegeneration. *Journal of Undergraduate Neuroscience Education*, 16(2), R59–R60. https://www.funjournal.org/wp-content/uploads/2018/06/june-16-r59.pdf?x36670

[4] Thau, L., Gandhi, J., Sharma, S. (2023). Physiology, Cortisol. *StatPearls [Internet]*. https://www.ncbi.nlm.nih.gov/books/NBK538239/

[5] Lesuis, S. L., Weggen, S., Baches, S., Lucassen, P. J., Kruger, 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

[6] Ouanes, S., Popp, J. (2019). High Cortisol and the Risk of Dementia and Alzheimer's Disease: A Review of the Literature. *Frontiers in Aging Neuroscience*, 11, 43. https://doi.org/10.3389/fnagi.2019.00043

[7] Justice, N. J. (2018). The relationship between stress and Alzheimer's disease. *Neurobiology of Stress*, 8, 127–133. https://doi.org/10.1016/j.ynstr.2018.04.002

[8] What Happens to the Brain in Alzheimer's Disease? (2024). *National Institute on Aging.* https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/what-happens-brain-alzheimers-disease

[9] Reynolds, S. (2022). Imaging technique shows Alzheimer’s impact on brain connections. *National Institute of Aging*. https://www.nia.nih.gov/news/imaging-technique-shows-alzheimers-impact-brain-connections

[10] How Biomarkers Help Diagnose Dementia. (2022). *National Institute on Aging.* https://www.nia.nih.gov/health/alzheimers-symptoms-and-diagnosis/how-biomarkers-help-diagnose-dementia#brain_imaging

[11] Bertrand, A., Khan, U., Hoang, D. M., Novikov, D. S., Krishnamurthy, P., Sait, H. B. R., Little, B. W., Sigurdsson, E. M., Wadghiri, Y. Z. (2013). Non-invasive, in vivo monitoring of neuronal transport impairment in a mouse model of tauopathy using MEMRI. *NeuroImage*, 64, 693-702. https://doi.org/10.1016/j.neuroimage.2012.08.065

[12] Aamodt, E. J., Williams, R. C., Jr. (1984). Microtubule-associated proteins connect microtubules and neurofilaments in vitro. *Biochemistry,* 23(25). https://doi.org/10.1021/bi00320a019

[13] González-Billault, C., Engelke, M., Jiménez-Mateos, E. M., Wandosell, F., Cáceres, A., Avila, J. (2002). Participation of structural microtubule-associated proteins (MAPs) in the development of neuronal polarity. *Journal of Neuroscience Research*, 67(6), 713–719. https://doi.org/10.1002/jnr.10161

[14] Zhang, B., Higuchi, M., Yoshiyama, Y., Ishihara, T., Forman, M. S., Martinez, D., Joyce, S., Trojanowski, J. Q., Lee, V. M. (2004). Retarded axonal transport of R406W mutant tau in transgenic mice with a neurodegenerative tauopathy. *The Journal of Neuroscience*, 24(19), 4657–4667. https://doi.org/10.1523/JNEUROSCI.0797-04.2004

[15] d'Errico, P., Meyer-Luehmann, M. (2020). Mechanisms of Pathogenic Tau and Aβ Protein Spreading in Alzheimer's Disease. *Frontiers in Aging Neuroscience*, 12, 265. https://doi.org/10.3389/fnagi.2020.00265

[16] Stephens, M. A., Wand, G. (2012). Stress and the HPA axis: role of glucocorticoids in alcohol dependence. *Alcohol Research: Current Reviews*, 34(4), 468–483. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3860380/

[17] Chourpiliadis, C., Aeddula, N. R. (2023). Physiology, Glucocorticoids. *StatPearls [Internet]*. https://www.ncbi.nlm.nih.gov/books/NBK560897/

[18] Whirledge, S., Cidlowski, J. A. (2010). Glucocorticoids, stress, and fertility. *Minerva Endocrinologica*, 35(2), 109–125. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3547681/

[19] de Souza-Talarico, J. N., Marin, M. F., Sindi, S., Lupien, S. J. (2011). Effects of stress hormones on the brain and cognition: Evidence from normal to pathological aging. *Dementia & Neuropsychologia,* 5(1), 8–16. https://doi.org/10.1590/S1980-57642011DN05010003

[20] Sheng, J. A., Bales, N. J., Myers, S. A., Bautista, A. I., Roueinfar, M., Hale, T. M., Handa, R. J. (2021). The Hypothalamic-Pituitary-Adrenal Axis: Development, Programming Actions of Hormones, and Maternal-Fetal Interactions. *Frontiers in Behavioral Neuroscience*, 14, 601939. https://doi.org/10.3389/fnbeh.2020.601939

[21] Tertil, M., Skupio, U., Barut, J., Dubovyk, V., Wawrzczak-Bargiela, A., Soltys, Z., Golda, S., Kudla, L., Wiktorowska, L., Szklarczyk, K., Korostynski, M., Przewlocki, R., Slezak, M. (2018). Glucocorticoid receptor signaling in astrocytes is required for aversive

memory formation. *Translational Psychiatry*, 8(1), 255. https://doi.org/10.1038/s41398-018-0300-x

[22] de Kloet, E. R., Oitzl, M. S. Joëls, M. (1993). Functional implications of brain corticosteroid receptor diversity. *Cellular and Molecular Neurobiology*, 13, 433–455. https://doi.org/10.1007/BF00711582

[23] Joëls, M. (2006). Corticosteroid effects in the brain: U-shape it. *Trends in Pharmacological Sciences*, 27(5), 244–250. https://doi.org/10.1016/j.tips.2006.03.007

[24] de Kloet, E. R., Joëls, M., Holsboer, F. (2005). Stress and the brain: From Adaptation to Disease. *Nature Reviews Neuroscience*, 6(6), 463–475. https://doi.org/10.1038/nrn1683

[25] Andreano, J. M., Cahill, L. (2006). Glucocorticoid Release and Memory Consolidation in Men and Women. *Psychological Science*, 17(6), 466-470. https://doi.org/10.1111/j.1467-9280.2006.01729.x

[26] Roozendaal, B., Williams, C. L., McGaugh, J. L. (1999). Glucocorticoid receptor activation in the rat nucleus of the solitary tract facilitates memory consolidation: involvement of the basolateral amygdala. *The European Journal of Neuroscience*, 11(4), 1317–1323. https://doi.org/10.1046/j.1460-9568.1999.00537.x

[27] Het, S., Ramlow, G., Wolf, O. T. (2005). A meta-analytic review of the effects of acute cortisol administration on human memory. *Psychoneuroendocrinology*, 30(8), 771–784. https://doi.org/10.1016/j.psyneuen.2005.03.005

[28] Roozendaal, B., Griffith, Q. K., Buranday, J., De Quervain, D. J., McGaugh, J. L. (2003). The hippocampus mediates glucocorticoid-induced impairment of spatial memory retrieval: Dependence on the basolateral amygdala. P*roceedings of the National Academy of Sciences of the United States of America*, 100(3), 1328–1333. https://doi.org/10.1073/pnas.0337480100

[29] Roozendaal, B. (2002). Stress and memory: opposing effects of glucocorticoids on memory consolidation and memory retrieval. Neurobiology of Learning and Memory, 78(3), 578–595. https://doi.org/10.1006/nlme.2002.4080

[30] Roozendaal, B. (2003). Systems mediating acute glucocorticoid effects on memory consolidation and retrieval. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 27(8), 1213–1223. https://doi.org/10.1016/j.pnpbp.2003.09.015

[31] Dong, Z., Han, H., Li, H., Bai, Y., Wang, W., Tu, M., Peng, Y., Zhou, L., He, W., Wu, X., Tan, T., Liu, M., Wu, X., Zhou, W., Jin, W., Zhang, S., Sacktor, T. C., Li, T., Song, W., Wang, Y. T. (2015). Long-term potentiation decay and memory loss are mediated by AMPAR endocytosis. *The Journal of Clinical Investigation*, 125(1), 234–247. https://doi.org/10.1172/JCI77888

[32] Makino, H., Malinow, R. (2009). AMPA receptor incorporation into synapses during LTP: the role of lateral movement and exocytosis. *Neuron*, 64(3), 381–390. https://doi.org/10.1016/j.neuron.2009.08.035

[33] Foy, M. R., Stanton, M. E., Levine, S., Thompson, R. F. (1987). Behavioral stress impairs long-term potentiation in rodent hippocampus. *Behavioral and Neural Biology*, 48(1), 138–149. https://doi.org/10.1016/s0163-1047(87)90664-9

[34] Shors, T. J., Seib, T. B., Levine, S., Thompson, R. F. (1989). Inescapable versus escapable shock modulates long-term potentiation in the rat hippocampus. *Science*, 244(4901), 224–226. https://doi.org/10.1126/science.2704997

[35] Hardy, J. A., Higgins, G. A. (1992). Alzheimer's disease: The Amyloid Cascade Hypothesis. *Science*, 256(5054), 184–185. https://doi.org/10.1126/science.1566067

[36] Tian, Y., Jing, G., Zhang, M. (2023). Insulin-degrading enzyme: Roles and pathways in ameliorating cognitive impairment associated with Alzheimer's disease and diabetes. *Ageing Research Reviews*, 90, 101999. https://doi.org/10.1016/j.arr.2023.101999

[37] Harada, S., Smith, R. M., Hu, D. Q., Jarett, L. (1996). Dexamethasone inhibits insulin binding to insulin-degrading enzyme and cytosolic insulin-binding protein p82. *Biochemical and Biophysical Research Communications*, 218(1), 154–158. https://doi.org/10.1006/bbrc.1996.0027

[38] Green, K. N., Billings, L. M., Roozendaal, B., McGaugh, J. L., LaFerla, F. M. (2006). Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. *The Journal of Neuroscience*, 26(35), 9047–9056. https://doi.org/10.1523/JNEUROSCI.2797-06.2006

[39] Dong, H., Goico, B., Martin, M., Csernansky, C. A., Bertchume, A., Csernansky, J. G. (2004). Modulation of hippocampal cell proliferation, memory, and amyloid plaque deposition in APPsw (Tg2576) mutant mice by isolation stress. *Neuroscience*, 127(3), 601–609. https://doi.org/10.1016/j.neuroscience.2004.05.040

[40] Jeong, Y. H., Park, C. H., Yoo, J., Shin, K. Y., Ahn, S. M., Kim, H. S., Lee, S. H., Emson, P. C. Suh, Y. H. (2006). Chronic stress accelerates learning and memory impairments and increases amyloid deposition in APPV717I-CT100 transgenic mice, an Alzheimer's disease model. *The FASEB Journal*, 20, 729-731. https://doi.org/10.1096/fj.05-4265fje

[41] Wang, Y., Li, M., Tang, J., Song, M., Xu, X., Xiong, J., Li, J., Bai, Y. (2011). Glucocorticoids facilitate astrocytic amyloid-β peptide deposition by increasing the expression of APP and BACE1 and decreasing the expression of amyloid-β-degrading proteases. *Endocrinology*, 152(7), 2704–2715. https://doi.org/10.1210/en.2011-0145

[42] Sotiropoulos, I., Catania, C., Riedemann, T., Fry, J. P., Breen, K. C., Michaelidis, T. M., Almeida, O. F. (2008). Glucocorticoids trigger Alzheimer disease-like pathobiochemistry

in rat neuronal cells expressing human tau. *Journal of Neurochemistry*, 107(2), 385–397. https://doi.org/10.1111/j.1471-4159.2008.05613.x

[43] Justice, N. J., Huang, L., Tian, J., Cole, A., Pruski, M., Hunt, A. J., Jr., Flores, R., Zhu, M. X., Arenkiel, B. R., Zheng, H. (2015). Posttraumatic Stress Disorder-Like Induction Elevates β-Amyloid Levels, Which Directly Activates Corticotropin-Releasing Factor Neurons to Exacerbate Stress Responses. *Journal of Neuroscience*, 35(6) 2612-2623. https://doi.org/10.1523/JNEUROSCI.3333-14.2015

[44] Pickett, E. K., Herrmann, A. G., McQueen, J., Abt, K., Dando, O., Tulloch, J., Jain, P., Dunnett, S., Sohrabi, S., Fjeldstad, M. P., Calkin, W., Murison, L., Jackson, R. J., Tzioras, M., Stevenson, A., d'Orange, M., Hooley, M., Davies, C., Colom-Cadena, M., Anton-Fernandez, A., King, D., Oren, I., Rose, J., McKenzie, C., Allison, E., Smith, C., Hardt, O., Henstridge, C. M., Hardingham, G. E., Spires-Jones, T. L. (2019). Amyloid Beta and Tau Cooperate to Cause Reversible Behavioral and Transcriptional Deficits in a Model of Alzheimer's Disease. *Cell Reports*, 29(11), 3592–3604. https://doi.org/10.1016/j.celrep.2019.11.044

[45] Zhang, H., Wei, W., Zhao, M., Ma, L., Jiang, X., Pei, H., Cao, Y., Li, H. (2021). Interaction between Aβ and Tau in the Pathogenesis of Alzheimer's Disease. *International Journal of Biological Sciences*, 17(9), 2181–2192. https://doi.org/10.7150/ijbs.57078

[46] Näslund, J., Haroutunian, V., Mohs, R., Davis, K. L., Davies, P., Greengard, P., Buxbaum, J. D. (2000). Correlation between elevated levels of amyloid beta-peptide in the brain and cognitive decline. *Journal of the American Medical Association*, 283(12), 1571–1577. https://doi.org/10.1001/jama.283.12.1571

[47] Rissman, R. A., Lee, K. F., Vale, W., Sawchenko, P. E. (2007). Corticotropin-releasing factor receptors differentially regulate stress-induced tau phosphorylation. *The Journal of Neuroscience*, 27(24), 6552–6562. https://doi.org/10.1523/JNEUROSCI.5173-06.2007

[48] Lee, K. W., Kim, J. B., Seo, J. S., Kim, T. K., Im, J. Y., Baek, I. S., Kim, K. S., Lee, J. K., Han, P. L. (2009). Behavioral stress accelerates plaque pathogenesis in the brain of Tg2576 mice via generation of metabolic oxidative stress. *Journal of Neurochemistry*, 108(1), 165–175. https://doi.org/10.1111/j.1471-4159.2008.05769.x

[49] Jeong, Y. H., Park, C. H., Yoo, J., Shin, K. Y., Ahn, S. M., Kim, H. S., Lee, S. H., Emson, P. C. Suh, Y. H. (2006). Chronic stress accelerates learning and memory impairments and increases amyloid deposition in APPV717I-CT100 transgenic mice, an Alzheimer's disease model. *The FASEB Journal*, 20, 729-731. https://doi.org/10.1096/fj.05-4265fje

[50] 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*. https://doi.org/10.1155/2017/8416763

[51] Kang, S. W., Kim, S. J., Kim, M. S. (2017). Oxidative stress with tau hyperphosphorylation in memory impaired 1,2-diacetylbenzene-treated mice. *Toxicology Letters*, 279, 53–59. https://doi.org/10.1016/j.toxlet.2017.07.892

[52] Miao, J., Shi, R., Li, L., Chen, F., Zhou, Y., Tung, Y. C., Hu, W., Gong, C. X., Iqbal, K., Liu, F. (2019). Pathological Tau From Alzheimer's Brain Induces Site-Specific Hyperphosphorylation and SDS- and Reducing Agent-Resistant Aggregation of Tau in vivo. *Frontiers in Aging Neuroscience*, 11, 34. https://doi.org/10.3389/fnagi.2019.00034

[53] Alquezar, C., Arya, S., Kao, A. W. (2021). Tau Post-translational Modifications: Dynamic Transformers of Tau Function, Degradation, and Aggregation. *Frontiers in Neurology*, 11. https://doi.org/10.3389/fneur.2020.595532

[54] Finelli, M. J. (2020). Redox Post-translational Modifications of Protein Thiols in Brain Aging and Neurodegenerative Conditions-Focus on S-Nitrosation. *Frontiers in Aging Neuroscience*, 12. https://doi.org/10.3389/fnagi.2020.00254

[55] Xiang, W., Weisbach, V., Sticht, H., Seebahn, A., Bussmann, J., Zimmermann, R., Becker, C. M. (2013). Oxidative stress-induced posttranslational modifications of human hemoglobin in erythrocytes. *Archives of Biochemistry and Biophysics*, 529(1), 34–44. https://doi.org/10.1016/j.abb.2012.11.002

[56] Carroll, J. C., Iba, M., Bangasser, D. A., Valentino, R. J., James, M. J., Brunden, K. R., Lee, V. M., Trojanowski, J. Q. (2011). Chronic stress exacerbates tau pathology, neurodegeneration, and cognitive performance through a corticotropin-releasing factor receptor-dependent mechanism in a transgenic mouse model of tauopathy. *The Journal of Neuroscience*, 31(40), 14436–14449. https://doi.org/10.1523/JNEUROSCI.3836-11.2011

[57] Saeedi, M., Rashidy-Pour, A. (2021). Association between chronic stress and Alzheimer's disease: Therapeutic effects of Saffron. *Biomedicine & pharmacotherapy*, 133. https://doi.org/10.1016/j.biopha.2020.110995

[58] DiSabato, D. J., Quan, N., Godbout, J. P. (2016). Neuroinflammation: the devil is in the details. *Journal of Neurochemistry*, 139, 136–153. https://doi.org/10.1111/jnc.13607

[59] Kim, Y. S., Jung, H. M., Yoon, B. E. (2018). Exploring glia to better understand Alzheimer's disease. *Animal Cells and Systems*, 22(4), 213–218. https://doi.org/10.1080/19768354.2018.1508498

[60] Jauregui-Huerta, F., Ruvalcaba-Delgadillo, Y., Gonzalez-Castañeda, R., Garcia-Estrada, J., Gonzalez-Perez, O., Luquin, S. (2010). Responses of glial cells to stress and glucocorticoids. *Current Immunology Reviews*, 6(3), 195–204. https://doi.org/10.2174/157339510791823790

[61] Rajkowska, G., Miguel-Hidalgo, J. J. (2007). Gliogenesis and glial pathology in depression. *CNS & Neurological Disorders Drug Targets*, 6(3), 219–233. https://doi.org/10.2174/187152707780619326

[62] Sabolek, M., Herborg, A., Schwarz, J., Storch, A. (2006). Dexamethasone blocks astroglial differentiation from neural precursor cells. *Neuroreport*, 17(16), 1719–1723. https://doi.org/10.1097/01.wnr.0000236862.08834.50

[63] Lattke, M., Guillemot, F. (2022). Understanding astrocyte differentiation: Clinical relevance, technical challenges, and new opportunities in the omics era. *WIREs Mechanisms of Disease*, 14(5), e1557. https://doi.org/10.1002/wsbm.1557

[64] Czéh, B., Müller-Keuker, J. I., Rygula, R., Abumaria, N., Hiemke, C., Domenici, E., Fuchs, E. (2007). Chronic social stress inhibits cell proliferation in the adult medial prefrontal cortex: hemispheric asymmetry and reversal by fluoxetine treatment. *Neuropsychopharmacology*, 32(7), 1490–1503. https://doi.org/10.1038/sj.npp.1301275

[65] Geerlings, M. I., Sigurdsson, S., Eiriksdottir, G., Garcia, M. E., Harris, T. B., Gudnason, V., Launer, L. J. (2015). Salivary cortisol, brain volumes, and cognition in community-dwelling elderly without dementia. *Neurology*, 85(11), 976–983. https://doi.org/10.1212/WNL.0000000000001931

[66] Echouffo-Tcheugui, J., Conner, S. C., Himali, J. J., Beiser, A. S., Seshadri, S. (2019). Circulating cortisol and cognitive and structural brain measures: The Framingham Heart Study. *Neurology*, 93(15), 685–686. https://doi.org/10.1212/WNL.0000000000008256

[67] Igarashi, K. M. (2023). Entorhinal cortex dysfunction in Alzheimer's disease. *Trends in Neurosciences*, 46(2), 124–136. https://doi.org/10.1016/j.tins.2022.11.006

[68] Streit, W. J., Mrak, R. E., Griffin, W. S. (2004). Microglia and neuroinflammation: a pathological perspective. *Journal of Neuroinflammation*, 1(1), 14. https://doi.org/10.1186/1742-2094-1-14

[69] Kettenmann, H., Hanisch, U. K., Noda, M., Verkhratsky, A. (2011). Physiology of microglia. *Physiological Reviews*, 91(2), 461–553. https://doi.org/10.1152/physrev.00011.2010

[70] Nair, A., Bonneau, R. H. (2006). Stress-induced elevation of glucocorticoids increases microglia proliferation through NMDA receptor activation. *Journal of Neuroimmunology*, 171(1-2), 72–85. https://doi.org/10.1016/j.jneuroim.2005.09.012

[71] Sugama, S., Fujita, M., Hashimoto, M., Conti, B. (2007). Stress induced morphological microglial activation in the rodent brain: involvement of interleukin-18. *Neuroscience*, 146(3), 1388–1399. https://doi.org/10.1016/j.neuroscience.2007.02.043

[72] Minami, M., Kuraishi, Y., Yamaguchi, T., Nakai, S., Hirai, Y., Satoh, M. (1991). Immobilization stress induces interleukin-1 beta mRNA in the rat hypothalamus. *Neuroscience Letters*, 123(2), 254–256. https://doi.org/10.1016/0304-3940(91)90944-o

[73] Pugh, C. R., Nguyen, K. T., Gonyea, J. L., Fleshner, M., Wakins, L. R., Maier, S. F., Rudy, J. W. (1999). Role of interleukin-1 beta in impairment of contextual fear conditioning caused by social isolation. *Behavioural Brain Research*, 106(1-2), 109–118. https://doi.org/10.1016/s0166-4328(99)00098-4

[74] Nguyen, K. T., Deak, T., Owens, S. M., Kohno, T., Fleshner, M., Watkins, L. R., Maier, S. F. (1998). Exposure to acute stress induces brain interleukin-1beta protein in the rat. *The Journal of Neuroscience,*18(6), 2239–2246. https://doi.org/10.1523/JNEUROSCI.18-06-02239.1998

[75] Lopez-Castejon, G., Brough, D. (2011). Understanding the mechanism of IL-1β secretion. *Cytokine & Growth Factor Reviews*, 22(4), 189–195. https://doi.org/10.1016/j.cytogfr.2011.10.001

[76] Dheen, S. T., Kaur, C., Ling, E. A. (2007). Microglial activation and its implications in the brain diseases. *Current Medicinal Chemistry*, 14(11), 1189–1197. https://doi.org/10.2174/092986707780597961

[77] Ulland, T. K., Colonna, M. (2018). TREM2 - a key player in microglial biology and Alzheimer disease. *Nature Reviews Neurology*, 14(11), 667–675. https://doi.org/10.1038/s41582-018-0072-1

[78] Wang, Y., Cella, M., Mallinson, K., Ulrich, J. D., Young, K. L., Robinette, M. L., Gilfillan, S., Krishnan, G. M., Sudhakar, S., Zinselmeyer, B. H., Holtzman, D. M., Cirrito, J. R., Colonna, M. (2015). TREM2 lipid sensing sustains the microglial response in an Alzheimer's disease model. *Cell*, 160(6), 1061–1071. https://doi.org/10.1016/j.cell.2015.01.049

[79] Ulland, T. K., Song, W. M., Huang, S. C., Ulrich, J. D., Sergushichev, A., Beatty, W. L., Loboda, A. A., Zhou, Y., Cairns, N. J., Kambal, A., Loginicheva, E., Gilfillan, S., Cella, M., Virgin, H. W., Unanue, E. R., Wang, Y., Artyomov, M. N., Holtzman, D. M., Colonna, M. (2017). TREM2 Maintains Microglial Metabolic Fitness in Alzheimer's Disease. *Cell*, 170(4), 649–663. e13. https://doi.org/10.1016/j.cell.2017.07.023

[80] Frank, S., Burbach, G. J., Bonin, M., Walter, M., Streit, W., Bechmann, I., Deller, T. (2008). TREM2 is upregulated in amyloid plaque-associated microglia in aged APP23 transgenic mice. *Glia*, 56(13), 1438–1447. https://doi.org/10.1002/glia.20710

[81] Ulrich, J. D., Ulland, T. K., Colonna, M., Holtzman, D. M. (2017). Elucidating the Role of TREM2 in Alzheimer's Disease. *Neuron*, 94(2), 237–248. https://doi.org/10.1016/j.neuron.2017.02.042

[82] Bekris, L. M., Khrestian, M., Dyne, E., Shao, Y., Pillai, J. A., Rao, S. M., Bemiller, S. M., Lamb, B., Fernandez, H. H., Leverenz, J. B. (2018). Soluble TREM2 and biomarkers of central and peripheral inflammation in neurodegenerative disease. *Journal of Neuroimmunology*, 319, 19–27. https://doi.org/10.1016/j.jneuroim.2018.03.003

[83] Carbajosa, G., Malki, K., Lawless, N., Wang, H., Ryder, J. W., Wozniak, E., Wood, K., Mein, C. A., Dobson, R. J. B., Collier, D. A., O'Neill, M. J., Hodges, A. K., Newhouse, S. J. (2018). Loss of Trem2 in microglia leads to widespread disruption of cell coexpression networks in mouse brain. *Neurobiology of Aging*, 69, 151–166. https://doi.org/10.1016/j.neurobiolaging.2018.04.019

[84] Poggesi, A., Pasi, M., Pescini, F., Pantoni, L., Inzitari, D. (2016). Circulating biologic markers of endothelial dysfunction in cerebral small vessel disease: A review. *Journal of Cerebral Blood Flow and Metabolism*, 36(1), 72–94. https://doi.org/10.1038/jcbfm.2015.116

[85] Powell, D. J., Schlotz, W. (2012). Daily life stress and the cortisol awakening response: testing the anticipation hypothesis. *PloS One*, 7(12), e52067. https://doi.org/10.1371/journal.pone.0052067

[86] Chong, L. S., Thai, M., Cullen, K. R., Lim, K. O., Klimes-Dougan, B. (2017). Cortisol Awakening Response, Internalizing Symptoms, and Life Satisfaction in Emerging Adults. *International Journal of Molecular Sciences*, 18(12), 2501. https://doi.org/10.3390/ijms18122501

[87] Pruessner, J. C., Wolf, O. T., Hellhammer, D. H., Buske-Kirschbaum, A., von Auer, K., Jobst, S., Kaspers, F., Kirschbaum, C. (1997). Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. *Life Sciences*, 61(26), 2539–2549. https://doi.org/10.1016/s0024-3205(97)01008-4

[88] Duan, H., Yuan, Y., Zhang, L., Qin, S., Zhang, K., Buchanan, T. W., Wu, J. (2013). Chronic stress exposure decreases the cortisol awakening response in healthy young men. *Stress*, 16(6), 630–637. https://doi.org/10.3109/10253890.2013.840579

[89] Schulz, P., Kirschbaum, C., Prüßner, J., Hellhammer, D. (1998). Increased free cortisol secretion after awakening in chronically stressed individuals due to work overload. *Stress & Health*, 14(2), 91-97. https://doi.org/10.1002/(SICI)1099-1700(199804)14:2%3C91::AID-SMI765%3E3.0.CO;2-S

[90] Incollingo Rodriguez, A. C., Epel, E. S., White, M. L., Standen, E. C., Seckl, J. R., Tomiyama, A. J. (2015). Hypothalamic-pituitary-adrenal axis dysregulation and cortisol activity in obesity: A systematic review. *Psychoneuroendocrinology*, 62, 301–318. https://doi.org/10.1016/j.psyneuen.2015.08.014

[91] Junghanns, K., Horbach, R., Ehrenthal, D., Blank, S., Backhaus, J. (2007). Cortisol awakening response in abstinent alcohol-dependent patients as a marker of HPA-axis

dysfunction. *Psychoneuroendocrinology*, 32(8-10), 1133–1137. https://doi.org/10.1016/j.psyneuen.2007.06.012

[92] Newhouse, A., Chemali, Z. (2020). Neuroendocrine Disturbances in Neurodegenerative Disorders: A Scoping Review. *Psychosomatics*, 61(2), 105–115. https://doi.org/10.1016/j.psym.2019.11.002

[93] Torrico, T. J., Abdijadid, S. (2023). Neuroanatomy, Limbic System. *StatPearls [Internet]*.https://www.ncbi.nlm.nih.gov/books/NBK538491/

[94] Alonso, A., Klink, R. (1993). Differential electroresponsiveness of stellate and pyramidal-like cells of medial entorhinal cortex layer II. *Journal of Neurophysiology*, 70(1), 128–143. https://doi.org/10.1152/jn.1993.70.1.128

[95] Akan, O., Bierbrauer, A., Kunz, L., Gajewski, P. D., Getzmann, S., Hengstler, J. G., Wascher, E., Axmacher, N., Wolf, O. T. (2023). Chronic stress is associated with specific path integration deficits. *Behavioural Brain Research*, 442, 114305. https://doi.org/10.1016/j.bbr.2023.114305

[96] Harris, J. A., Devidze, N., Verret, L., Ho, K., Halabisky, B., Thwin, M. T., Kim, D., Hamto, P., Lo, I., Yu, G. Q., Palop, J. J., Masliah, E., Mucke, L. (2010). Transsynaptic progression of amyloid-β-induced neuronal dysfunction within the entorhinal-hippocampal network. *Neuron*, 68(3), 428–441. https://doi.org/10.1016/j.neuron.2010.10.020

[97] Lee, W. J., Brown, J. A., Kim, H. R., La Joie, R., Cho, H., Lyoo, C. H., Rabinovici, G. D., Seong, J. K., Seeley, W. W., Alzheimer's Disease Neuroimaging Initiative (2022). Regional Aβ-tau interactions promote onset and acceleration of Alzheimer's disease tau spreading. *Neuron*, 110(12), 1932–1943.e5. https://doi.org/10.1016/j.neuron.2022.03.034

[98] Scoville, W. B., Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry*, 20(1), 11–21. https://doi.org/10.1136/jnnp.20.1.11

[99] Squire, L. R., Stark, C. E., Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience*, 27, 279–306. https://doi.org/10.1146/annurev.neuro.27.070203.144130

[100] Squire, L. R. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychological Review*, 99(2), 195–231. https://doi.org/10.1037/0033-295x.99.2.195

[101] McEwen, B. S., Weiss, J. M., Schwartz, L. S. (1968). Selective retention of corticosterone by limbic structures in rat brain. *Nature*, 220(5170), 911–912. https://doi.org/10.1038/220911a0

[102] McEwen, B. S., Weiss, J. M., Schwartz, L. S. (1969). Uptake of corticosterone by rat brain and its concentration by certain limbic structures. *Brain Research*, 16(1), 227–241. https://doi.org/10.1016/0006-8993(69)90096-1

[103] aus der MÜhlen, K., Ockenfels, H. (1968). Morphologische Veränderungen im Diencephalon und Telencephalon nach Störungen des Regelkreises Adenohypophyse-Nebennierenrinde. *Zeitschrift für Zellforschung und Mikroskopische Anatomie*, 93, 126–141. https://doi.org/10.1007/BF00325028

[104] Dronse, J., Ohndorf, A., Richter, N., Bischof, G. N., Fassbender, R., Behfar, Q., Gramespacher, H., Dillen, K., Jacobs, H. I. L., Kukolja, J., Fink, G. R., Onur, O. A. (2023). Serum cortisol is negatively related to hippocampal volume, brain structure, and memory performance in healthy aging and Alzheimer's disease. *Frontiers in Aging Neuroscience,* 15, 1154112. https://doi.org/10.3389/fnagi.2023.1154112

[105] Lupien, S., Lecours, A. R., Lussier, I., Schwartz, G., Nair, N. P., Meaney, M. J. (1994). Basal cortisol levels and cognitive deficits in human aging. *The Journal of Neuroscience*, 14(5 Pt 1), 2893–2903. https://doi.org/10.1523/JNEUROSCI.14-05-02893.1994

[106] Lupien, S., de Leon, M., de Santi, S., Convit, A., Tarshish, C., Nair, N. P. V., Thakur, M., McEwen, B. S., Hauger, R. L., Meaney, M. J. (1998) Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nature Neuroscience* 1, 69–73. https://doi.org/10.1038/271

[107] Frisoni, G. B., Fox, N. C., Jack, C. R., Jr, Scheltens, P., Thompson, P. M. (2010). The clinical use of structural MRI in Alzheimer disease. *Nature Reviews Neurology*, 6(2), 67–77. https://doi.org/10.1038/nrneurol.2009.215

[108] Davis, K. L., Davis, B. M., Greenwald, B. S., Mohs, R. C., Mathé, A. A., Johns, C. A., Horvath, T. B. (1986). Cortisol and Alzheimer's disease, I: Basal studies. *The American Journal of Psychiatry*, 143(3), 300–305. https://doi.org/10.1176/ajp.143.3.300

[109] Sapolsky, R. M., Krey, L. C., McEwen, B. S. (1986). The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. *Endocrine Reviews*, 7(3), 284–301. https://doi.org/10.1210/edrv-7-3-284

[110] Gupta, R., Koscik, T. R., Bechara, A., Tranel, D. (2011). The amygdala and decision-making. *Neuropsychologia*, 49(4), 760–766. https://doi.org/10.1016/j.neuropsychologia.2010.09.029

[111] Hermans, E. J., Battaglia, F. P., Atsak, P., de Voogd, L. D., Fernández, G., Roozendaal, B. (2014). How the amygdala affects emotional memory by altering brain network properties. *Neurobiology of Learning and Memory*, 112, 2–16. https://doi.org/10.1016/j.nlm.2014.02.005

[112] Fowler, C. H., Bogdan, R., Gaffrey, M. S. (2021). Stress-induced cortisol response is associated with right amygdala volume in early childhood. *Neurobiology of Stress*, 14, 100329. https://doi.org/10.1016/j.ynstr.2021.100329

[113] Blankenship, S. L., Chad-Friedman, E., Riggins, T., Dougherty, L. R. (2019). Early parenting predicts hippocampal subregion volume via stress reactivity in childhood. *Developmental Psychobiology*, 61(1), 125–140. https://doi.org/10.1002/dev.21788

[114] VanTieghem, M., Korom, M., Flannery, J., Choy, T., Caldera, C., Humphreys, K. L., Gabard-Durnam, L., Goff, B., Gee, D. G., Telzer, E. H., Shapiro, M., Louie, J. Y., Fareri, D. S., Bolger, N., Tottenham, N. (2021). Longitudinal changes in amygdala, hippocampus and cortisol development following early caregiving adversity. *Developmental Cognitive Neuroscience*, 48, 100916. https://doi.org/10.1016/j.dcn.2021.100916

[115] Merz, E. C., Desai, P. M., Maskus, E. A., Melvin, S. A., Rehman, R., Torres, S. D., Meyer, J., He, X., Noble, K. G. (2019). Socioeconomic Disparities in Chronic Physiologic Stress Are Associated With Brain Structure in Children. *Biological Psychiatry*, 86(12), 921–929. https://doi.org/10.1016/j.biopsych.2019.05.024

[116] Yang, Y., Wang, J. Z. (2017). From Structure to Behavior in Basolateral Amygdala-Hippocampus Circuits. *Frontiers in Neural Circuits*, 11, 86. https://doi.org/10.3389/fncir.2017.00086

[117] Akirav, I., Richter-Levin, G. (1999). Biphasic modulation of hippocampal plasticity by behavioral stress and basolateral amygdala stimulation in the rat. *The Journal of Neuroscience*, 19(23), 10530–10535. https://doi.org/10.1523/JNEUROSCI.19-23-10530.1999

[118] Poulin, S. P., Dautoff, R., Morris, J. C., Barrett, L. F., Dickerson, B. C., Alzheimer's Disease Neuroimaging Initiative (2011). Amygdala atrophy is prominent in early Alzheimer's disease and relates to symptom severity. *Psychiatry Research*, 194(1), 7–13. https://doi.org/10.1016/j.pscychresns.2011.06.014

[119] Hika, B., Khalili, Y. A. (2023). Neuronatomy, Prefrontal Association Cortex. *StatPearls [Internet].* https://www.ncbi.nlm.nih.gov/books/NBK545214/

[120] McKlveen, J. M., Myers, B., Flak, J. N., Bundzikova, J., Solomon, M. B., Seroogy, K. B., Herman, J. P. (2013). Role of prefrontal cortex glucocorticoid receptors in stress and emotion. *Biological Psychiatry*, 74(9), 672–679. https://doi.org/10.1016/j.biopsych.2013.03.024

[121] Cook, S. C., Wellman, C. L. (2004). Chronic stress alters dendritic morphology in rat medial prefrontal cortex. *Journal of Neurobiology*, 60(2), 236–248. https://doi.org/10.1002/neu.20025

[122] Larsen, N. Y., Vihrs, N., Møller, J., Sporring, J., Tan, X., Li, X., Ji, G., Rajkowska, G., Sun, F., Nyengaard, J. R. (2022). Layer III pyramidal cells in the prefrontal cortex reveal morphological changes in subjects with depression, schizophrenia, and suicide. *Translational Psychiatry*, 12(1), 363. https://doi.org/10.1038/s41398-022-02128-0

[123] Wu, Y. K., Fujishima, K., Kengaku, M. (2015). Differentiation of apical and basal dendrites in pyramidal cells and granule cells in dissociated hippocampal cultures. *PloS One*, 10(2), e0118482. https://doi.org/10.1371/journal.pone.0118482

[124] Sullivan, R. M., Gratton, A. (2002). Prefrontal cortical regulation of hypothalamic-pituitary-adrenal function in the rat and implications for psychopathology: side matters. *Psychoneuroendocrinology*, 27(1-2), 99–114. https://doi.org/10.1016/s0306-4530(01)00038-5