Review Article

The Effects of Stress on Alzheimer's Disease Development and Progression

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ABSTRACT

Alzheimer's disease is a progressive neurodegenerative disorder that profoundly impacts patients' memory, cognition, and overall quality of life. Chronic stress is a substantial contributor to Alzheimer's patients' cognitive deterioration. The effects of stress on hippocampus function and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis can lead to higher cortisol levels and is the link between stress and memory dysregulations. Moreover, acute and chronic stress have been linked to increased production of Amyloid Beta plaques and Tau Tangles, the primary pathological hallmarks of Alzheimer's disease. As a result, the cellular mechanisms of memory consolidation and storage are disrupted. This paper reviews ongoing research of how cellular, network and endocrine pathways in the brain are impeded by stress and links these findings to Alzheimer's disease development and progression. Understanding the interplay between stress and the progression of Alzheimer's disease can play a significant role in further development of research, disease-modifying treatments, and potential cures.

Keywords: Alzheimer's; Stress; Progression; Neurodegeneration; Pathology

INTRODUCTION

Alzheimer's disease (AD) represents a looming crisis in public health, predominantly affecting the older adult population (1). Characterized by progressive memory loss, cognitive decline, and behavioral changes, AD currently impacts over 55 million people worldwide, with numbers expected to rise as the global population ages (1). However, beyond the well-known genetic and lifestyle risk factors, such as obesity and a sedentary lifestyle (1) familial inheritance, exposure to aluminium, traumatic brain injury (TBI, there is a crucial yet often overlooked factor in the progression of this disease: stress. Chronic stress has been increasingly recognized as a significant contributor to the onset and exacerbation of AD, prompting a closer examination of its impacts on the brain (2-4).

Stress, both acute and chronic, triggers a cascade of physiological responses that can profoundly affect brain health and aggravate the progression of AD. The body's stress response results in the release of glucocorticoids such as cortisol (2). While these hormones are essential for survival, their prolonged elevation can be detrimental, particularly to the hippocampus—a region of the brain

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critically involved in memory formation and one of the first to be impacted by AD (5).

Emerging research indicates that chronic stress can accelerate brain atrophy in the medial temporal lobes and fusiform gyrus and promote the pathological processes associated with AD (6). Elevated cortisol levels have been shown to exacerbate amyloid-beta accumulation and tau hyperphosphorylation, the two hallmark features of AD pathology (7)which controls circulating levels of glucocorticoid hormones, occurs early in AD, resulting in increased cortisol levels. Disturbances of the HPA axis have been associated with memory impairments and may contribute to the cognitive decline that occurs in AD, although it is unknown whether such effects involve modulation of the amyloid β-peptide (Aβ. Amyloid plaques and Tau Tangles disrupt neuronal function and connectivity, leading to the loss of synapses and neurons, and ultimately resulting in cognitive decline (8).

Moreover, chronic stress (symptom of elevated cortisol) influences other risk factors associated with AD. For instance, stress-induced inflammation in areas such as the hippocampus, amygdala, pre-frontal cortex, and hypothalamus along with oxidative stress can further contribute to neuronal damage (3).

By shedding light on the critical role of stress in the pathogenesis of AD, this review aims to understand the importance of stress and its catalyst-like effects on the progression of AD. Understanding the intricate connections between chronic stress and AD can pave the way for more effective interventions in the future, ultimately improving the quality of life for individuals at risk or suffering from this devastating disease. In addition to examining the neuropathological effects of stress and its association with AD risk and development, the literature on current AD prevalence rates, as well as its underlying etiological mechanisms and pathology, will also be discussed. Below is a brief outline of the topics within this review.

1. **Prevalence**: An in-depth look at how AD affects different demographics and current statistics.
2. **Etiology**: Understanding the multifactorial causes of AD, including genetic predispositions and environmental influences.
3. **Pathology**: Investigating the biological structure of AD and the key players in the development of this devastating disease, focusing on amyloid plaques and Tau Tangles.
4. **Stress in the Brain**: Exploring the significant impact of chronic stress on brain health, focusing on the mechanisms through which stress accelerates AD pathology.
5. **The Link Between Stress and AD Development and Progression:** Investigating the deeper connection between stress and AD progression by diving into cause and effects of hormones released during stressful events.

PREVALENCE

AD is a progressive neurodegenerative condition that claims the lives of over a million older adult individuals every year (1). It originates in the brain, primarily targeting memory and eventually affecting various bodily functions such as the ability to swallow, manage stool and bladder movements, etc. AD is found in 1 out of 9 people between the ages of 65 and up with a significantly higher incidence of 50% among those older than 85 (1). While all individuals naturally accumulate some level of amyloid and tau proteins in the brain, it is typically not until older adulthood that these proteins reach a threshold significant enough to interfere with normal brain function and contribute to the development of Alzheimer's disease (9). This age-related increase in accumulation helps explain why older adults are at greater risk—most younger individuals have not yet experienced the degree of buildup or biological vulnerability necessary to cross that threshold. While symptoms of Alzheimer's can be detected before the age of 60, there is currently no cure for the disease, and there remains significant gaps in our knowledge about the cause and progression of the disease (1).

ETIOLOGY

Although the precise etiology of AD remains unknown, researchers believe it arises from a complex interplay of genetic, lifestyle, and environmental factors, all of which ultimately lead to the onset and progression of the disease (10).

Genetic and family history are key factors that increase an individual's susceptibility to developing Alzheimer's disease (AD). People with first degree relatives (parents or siblings) with the disease are at a higher risk of developing the disease themselves. This increased risk is partly due to the potential inheritance of specific genes associated with AD, most notably the APOE ε4 allele, which has been shown to raise the likelihood of late-onset Alzheimer's (11). While having the APOE ε4 gene does not guarantee that a person will develop AD, it does significantly elevate their vulnerability compared to those without it. In families with early-onset Alzheimer's, rare mutations

in genes like APP, PSEN1, and PSEN2 can directly cause the disease, often before age 65 (12)presenilin-1 (PSEN1.

Lifestyle factors also play a pivotal role in AD with a sedentary lifestyle emerging as a significant contributor among them (13)affecting many people due to excessive saturated fat consumption, lack of exercise, or a sedentary lifestyle. Leptin is an adipokine secreted by adipose tissue that increases in obesity and has central actions not only at the hypothalamic level but also in other regions and nuclei of the central nervous system (CNS. A sedentary lifestyle is one that involves little to no physical activity and is closely intertwined with obesity, a prominent risk factor for the development of AD (14). The link between obesity and Alzheimer's is notably mediated by leptin, a hormone pivotal in both adipose tissue regulation and central nervous system functioning (13)affecting many people due to excessive saturated fat consumption, lack of exercise, or a sedentary lifestyle. Leptin is an adipokine secreted by adipose tissue that increases in obesity and has central actions not only at the hypothalamic level but also in other regions and nuclei of the central nervous system (CNS. Leptin acts as a mediator by influencing brain function, including memory and learning, through its interactions with hippocampal neurons (15). Dysregulation of leptin signaling, often associated with obesity, can impair these neural processes, thereby increasing the risk of cognitive decline and AD (15).

In addition, a major influence on development of AD in patients are environmental factors such as air pollution. In a study conducted on environmental factors associated with the risk of cognitive decline and AD, abnormal aggregation of Phosphorylated Tau (Tau Tangles) and Amyloid Beta Plaques (Aβ), both of which are hallmarks physical changes in the brain of AD patients, were found in brainstems of children and young adults exposed to air pollution (16). This study shows that air pollution may contribute to the development of symptoms and neurological signs of AD in young individuals. These uncontrollable environmental factors have been shown to increase signs and cause neurological deficits regardless of age, leading to a heightened risk of AD.

PATHOLOGY

Alzheimer's carries a very distinctive characteristic seen in the brain. AD is marked by observable changes in parts of the brain such as Amyloid plaques and Tau Tangles, which result in the loss of neurons and their connections eventually leading to cell death (17) (18).

Amyloid Beta Plaques result from the accumulation of amyloid beta, a peptide fragment, outside neurons (See Figure 1). Amyloid beta exerts a toxic effect, often leading to the death of neurons (19). These plaques are made by Beta-Secretase and Alpha-Secretase which work together to cut the peptide as opposed to Alpha-Secretase and Gamma-Secretase being used to cut the peptide (20). When Beta-Secretase cuts the peptide, instead of Gamma-Secretase, it renders the peptide insoluble, resulting in the formation of Amyloid Beta (20). Amyloid Beta monomers possess strong adhesive properties, binding together outside neurons through hydrogen bonds to form clusters known as plaques (20) (Figure 2). If these plaques accumulate between neurons, they can disrupt and prevent neuron-to-neuron signaling. Such signaling is essential for cognitive functions, and its disruption can severely impair memory (8). Moreover, Amyloid Beta Plaques trigger an immune response, leading to inflammation that may damage surrounding neurons, compounding the impairment of brain function (21).

Another major hallmark associated with AD pathology is the presence of Tau Tangles (Figure 1). Tau Tangles consist of a fibular protein that develops inside neurons microtubules (22). Microtubules form part of the neuronal exoskeleton which hold together the neurons. Microtubules, which are track-like structures essential for transporting nutrients within cells, rely on Tau proteins for stability (23). Tau Tangles are made up of helical filaments made up of hyperphosphorylated tau (24). Tau pathology usually begins in the allocortex of the medial temporal lobe, but then spreads to the associative isocortex, affecting multiple brain regions (25).

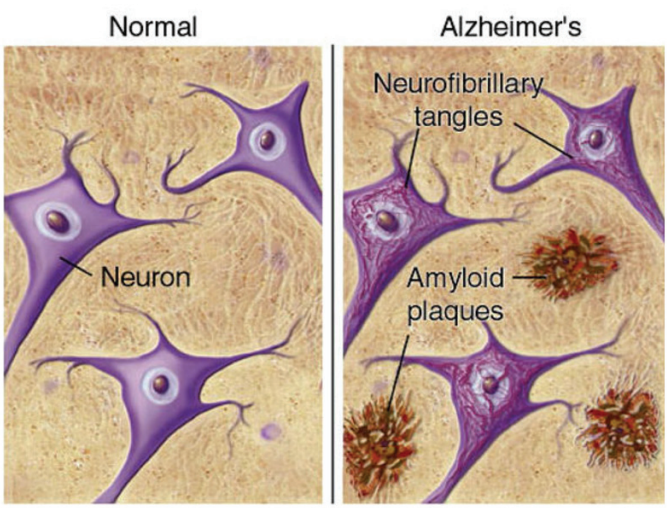

Figure 1. Amyloid Beta aggregates into plaques and interferes with neuron signaling (68)

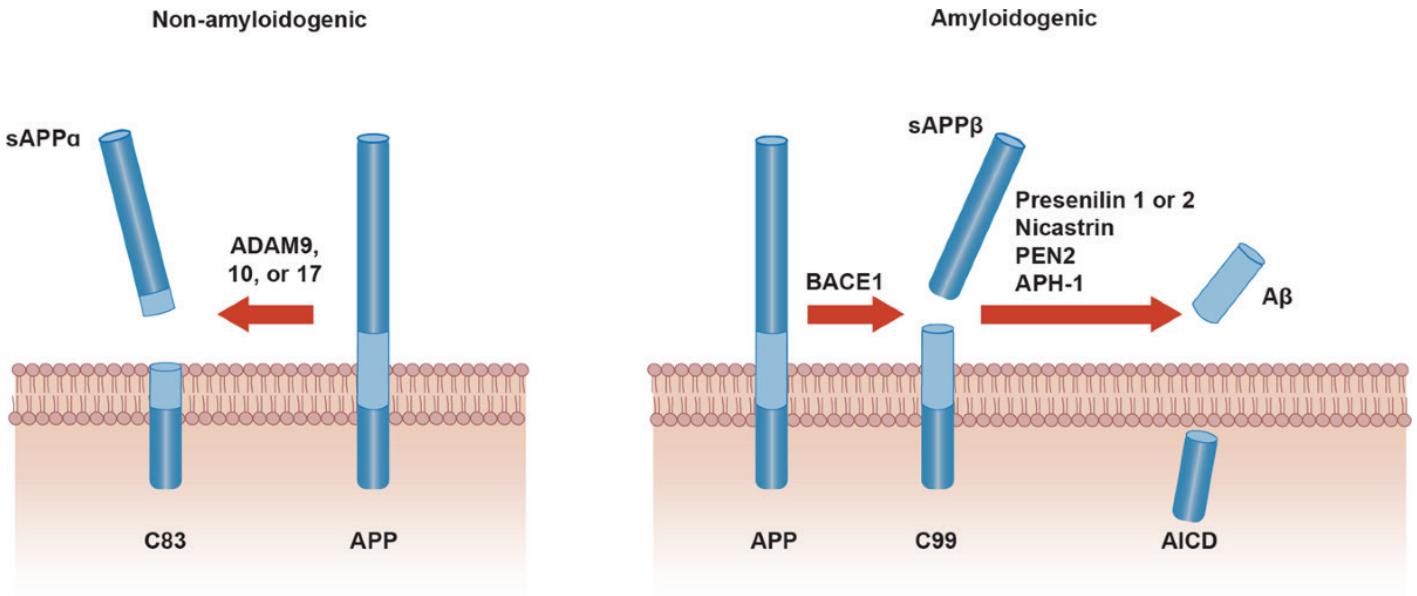

Figure 2. The improper cuts in Amyloidogenic, above the Amyloid Beta Monomers, lead to an aggregation of Amyloid Beta and creates plaques (69). A typical cut, shown on the left (Non-amyloidogenic), is made by α-secretases which allows for a soluble APP-alpha to be released leaving behind a membrane-bound C83 fragment. However, in an Amyloidogenic pathway (shown on the right), the APP is cut by β-secretases and leaves behind a soluble APP-alpha and a C99 fragment. The C99 undergoes a y-secretase mediated cut, resulting in the production of Amyloid Beta and the APP intracellular domain (AICD). This pathway is associated with Amyloid Beta accumulation in AD.

It is theorized that the Amyloid Beta Plaque buildup outside the cell initiates intracellular pathways, activating the enzyme Kinase (26). Kinase transfers phosphate groups to the Tau protein, which causes the proteins to change shape and start to clump up with other Tau proteins (27). As these proteins clump together, they separate from the Microtubule. The clumps that these proteins form end up getting tangled, thus the name Tau Tangles (28).

In response to toxic substances, the immune system releases microglia to clear toxic protein substances and dead neurons such as Tau Tangles and Amyloid-beta plaques (29). While this process is initially protective, the chronic activation of microglia leads to sustained inflammation and the release of neurotoxic factors, exacerbating neuronal injury and accelerating cell death (30). With continued rapid cell death, affected brain regions progressively shrink, and behavioral and cognitive symptoms begin to show. Eventually, Alzheimer's may impact areas responsible for essential functioning such as swallowing and breathing (1). At this stage, Alzheimer's patients eventually develop pneumonia, and other diseases that tragically lead to death.

STRESS IN THE BRAIN

The Hypothalamic-Pituitary-Adrenal (HPA) axis orchestrates the body's response to stress through a cascade of hormonal signals. Activation first happens in the hypothalamus, which releases corticotropin-releasing hormone (CRH) to stimulate the pituitary gland (31). The pituitary then secretes adrenocorticotropic hormone (ACTH), which prompts the adrenal glands to release cortisol and adrenaline (31). Cortisol regulates metabolism, immune response, and stress adaptation but, if it's produced in excess, it can suppress immunity and disrupt brain regions like the prefrontal cortex (PFC; 32). Chronic HPA axis activation, often linked to early-life stressors, leads to neuronal remodeling in the PFC, which can result in impaired cognitive tasks such as short-term memory (33). This structural remodeling, driven by glucocorticoids and CRH receptor interactions, increases the risk for AD (34).

Another critical stress-affected region is the basolateral amygdala, which regulates emotional processing and memory in coordination with the hippocampus. Chronic

stress disrupts PFC regulation of the amygdala, enhancing excitatory signaling and anxiety (35). Dysregulation of N-methyl-D-aspartate receptors (NMDARs) - ion channels that play a key role in memory, learning, and synaptic plasticity - further exacerbates stress effects (36). This, in turn, contributes to excitotoxicity and insulin resistance which impairs hippocampal function and memory (37). Excessive NMDAR activation elevates reactive oxygen species (ROS), disrupting synaptic plasticity and accelerating cognitive decline associated with AD (38).

THE LINK BETWEEN STRESS AND AD DEVELOPMENT AND PROGRESSION

Stress and AD share many significant overlaps through the formation of Tau Tangles (39), Amyloid Beta Plaques (40), and Ion Channel Dysregulation (41). In both stress and AD, clinical data show atrophic alterations in the same parts of the brain: the hippocampus and PFC (15, 42).

One of the main connectors between AD and stress is the change in ion channel regulation. Ion channels are vital components of cellular membranes that allow for the regulation of ions across cell boundaries (43). This regulation influences cell function and maintains the electrochemical balance (43). When the body undergoes large amounts of stress, the excess cortisol release can lead to drastic changes in the ion channels, which then progressively worsens AD (43).

These ion channels are found in various tissues including the heart, limbs, and brain. They facilitate ion passage such as sodium, potassium, and calcium through the lipid bilayer of cells. Further, ion channels are involved in regulating various physiological processes, such as electrical conduction in neuronal cells, muscular contraction, and release of neurotransmitters. A 2002 study on rats by researchers at Birmingham University attempted to find the effect of Cortisol on neuromodulation. By adding micro-dosages of cortisol, they found that potassium ion channels were no longer in use because of the flow of the potassium current being inhibited (44). This result showed resistance and was became insensitive to cortisol's antagonist - mifepristone (44).

The consequences of stress-induced changes in ion channels persist throughout synaptic transmission and neural circuitry. Increased neuronal excitability can disrupt neurotransmitters balance, adversely affecting inter-neuronal communication (45). This disruption in synaptic transmission may contribute to alterations in neural circuits, potentially leading to changes in behavior, cognition, and emotional regulation, all symptoms of AD (46).

Specifically, cortisol acts by binding to specific receptors on the cell membrane, allowing it to initiate a signaling cascade that can lead to alterations in ions, which lead to a change in conductance. This modulation of ion channel activity is a critical component of the body's adaptive response to stress, allowing for adjustments in cellular function to cope with the different conditions. Stress-induced alterations in ion channels can disrupt neuronal function, leading to cascading effects such as cell death, blood clot formation, and Lewy body accumulation, all characteristic of AD (4, 47).

These negative effects are also seen in the context of neurodegenerative conditions like AD. In neurodegenerative diseases, the relationship between stress, ion channels, and neuronal dysfunction becomes particularly relevant. Chronic stress and the associated dysregulation of ion channels may contribute to the progression of neurodegenerative processes. Disrupted calcium homeostasis, often linked to altered ion channel function, is a common feature in neurodegenerative diseases. The sustained imbalance in ion channel activity may lead to increased vulnerability of neurons to degeneration and cell death (48, 49).

An experiment done in 2020 on mice illustrated the connection between oxidative stress and the development of AD. Researchers from Shanghai University of Traditional Medicine observed mice carrying SAMP8, considered an ideal model for AD research. The researchers found that these mice exhibited AD-like effects such as memory decline, Amyloid Beta deposits, tau hyperphosphorylation, endoplasmic reticulum stress, abnormal autophagy activity, and disruption of intestinal flora, linking oxidative stress to these pathologies (70). SAMP8 mice are seen to display many of the symptoms seen in AD patients such as memory decline and age-related learning disorders. Biologically, these mice manifest many pathologies commonly found in AD patients.

Stress also plays a role through the development and alteration of steroids such as glucocorticoids. Stressful stimuli induce a cascade of events in the hypothalamic–pituitary–adrenal (HPA) axis, which leads to the activation of the adrenal cortex and the release of glucocorticoids, such as cortisol in humans and corticosterone (CORT) in rats and mice (50, 51). Although the neural pathways of stress responses in the brain differ depending on the stressor type, activation of the HPA axis is thought to be a final common pathway, which results in a net increase

in circulating glucocorticoids (52). Excessive stress levels of glucocorticoids, acting via Amyloid Beta, Tau Tangles, and neuroinflammation-dependent mechanisms in the brain, exacerbate synaptic plasticity disruption and thereby promote cognitive impairment characteristic of early AD symptoms (53).

This body of work suggests stress exerts profound effects on the body through the intricate interplay of various physiological mechanisms, including the release of glucocorticoids. The activation of the hypothalamic-pituitary-adrenal (HPA) axis in response to stressors leads to the synthesis and secretion of glucocorticoids, such as cortisol in humans. These glucocorticoids play a crucial role in orchestrating the body's adaptive response to stress, mobilizing resources and energy to cope with challenging situations (54).

Additionally, chronic or excessive stress levels can dysregulate glucocorticoid signaling pathways, contributing to the pathophysiology of neurodegenerative diseases such as AD (55). Glucocorticoids and dysregulation of ion channels have been implicated in the dysregulation of Tau protein phosphorylation, promoting the formation of Tau Tangles - a hallmark of AD pathology (7). Furthermore, glucocorticoids exacerbate synaptic dysfunction, neuroinflammation, and oxidative stress, further contributing to neuronal damage and cognitive decline in AD (71).

Glucocorticoids have been implicated in the dysregulation of Tau phosphorylation as seen in Tau Tangles found in AD. Research has shown that elevated levels of glucocorticoids can stimulate the phosphorylation of Tau proteins through various molecular mechanisms (56). One such mechanism involves the activation of specific kinases, such as glycogen synthase kinase-3β (GSK-3β) and cyclin-dependent kinase-5 (CDK5), which are known to phosphorylate Tau residues (57).

Additionally, glucocorticoids can modulate the activity of phosphatases, enzymes responsible for removing phosphate groups from Tau proteins (7). By either inhibiting phosphatase activity or promoting the expression of phosphatase inhibitors, glucocorticoids can disrupt the balance between Tau phosphorylation and dephosphorylation, leading to the accumulation of hyperphosphorylated Tau species (58).

The aggregation of hyperphosphorylated Tau proteins into Tau Tangles has several negative effects on neuronal function (59). Firstly, Tau Tangles interfere Tau proteins' ability to bind to microtubules leading to impaired axonal transport and disrupted cellular trafficking processes which are essential to neuron survival and proper function (60). This disruption can also lead to synaptic dysfunction and neuronal degeneration which significantly contributes to cognitive decline in AD patients.

Additionally, the accumulation of Tau Tangles is associated with a cell's response to stress and also neuroinflammatory processes (61). In AD, Tau proteins go through a process called hyperphosphorylation. This excessive phosphorylation disrupts the normal structure and function of Tau proteins, leading to their aggregation into insoluble tangles known as neurofibrillary tangles (NFTs) (62). Neurons that have been affected by Tau Tangles exhibit increased susceptibility to oxidative stress and also excitotoxicity, which furthers neuronal damage and cell death (61).

Research shows that glucocorticoids stimulate the opening of the mitochondrial permeability transition pore via transcriptional upregulation of its activating component, cyclophilin D. Inhibition of cyclophilin D has been shown to be protective against glucocorticoid-induced mitochondrial damage as well as Tau phosphorylation and oligomerization in cultured neurons (63). When cyclophilin D is activated, it allows for Tau phosphorylation leading to a numerous amount of effects all part of the symptoms observed in Alzheimer's (64).

CONCLUSION

Chronic stress plays a significant role in the development of AD by disrupting the hypothalamic-pituitary-adrenal (HPA) axis, leading to prolonged elevation of glucocorticoids like cortisol. These hormonal changes impair essential functions in neurons, driving pathological processes such as tau protein hyperphosphorylation and the accumulation of amyloid-beta plaques—two defining features of AD. Stress activates enzymes like GSK-3β and CDK5, which hyperphosphorylate tau proteins (8). This process forms neurofibrillary tangles that destabilize microtubules which disrupts the transport of nutrients and signals within neurons (62). Additionally Amyloid-beta plaques cause inflammation and oxidative stress, leading to impaired neuronal communication and accelerates cell death (8). Together, these mechanisms initiate a cascade of neurodegeneration, ultimately resulting in extensive neuronal loss and cognitive decline.

Stress also profoundly affects the brain regions responsible for memory, cognition, and emotional regulation. In the hippocampus, elevated cortisol interferes with synaptic plasticity and ion channel function, which are essential for memory formation (65). Chronic stress causes structural changes in the prefrontal cortex, impairing

executive functions such as decision-making and working memory (35). Meanwhile, overactivation of the amygdala amplifies emotional reactivity and anxiety, perpetuating a harmful cycle of stress and neurodegeneration (66). Additionally, chronic stress triggers oxidative stress and mitochondrial dysfunction, producing reactive oxygen species that exacerbate neuronal damage (67).

Recognizing stress as a major, modifiable risk factor for AD provides an opportunity for targeted interventions. This review aims to consolidate information about stress and Alzheimer's and propose potential links between the two in order to prompt future research. Future research could focus on strategies to regulate the HPA axis, mitigate oxidative stress, or even address Tau Tangles and Amyloid-Beta pathology to slow the progression of AD and improve quality of life for individuals and families affected by this devastating and tragic disease.

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DECLARATION OF CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest regarding the publication of this article.

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