

# Relationship between stress and alzheimer's disease



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## Stress

Stress defined as any change in the homeostasis of an organism. In humans this can be as simple as a change in homeostasis due to a physical factor or something as intricate as a psychological stimulus that generates a reaction from the sympathetic nervous system called the stress response (Sierra-Fonseca & Gosselink, 2018). There are two temporal groupings of stress, acute and chronic, as well as two type categories, physical and psychological. Acute stress is the most common form and is generated from events/stimuli from the recent past or from anticipated events/stimuli that will occur in the near future. Additionally, acute stress because of its short duration does not cause a large amount of lasting disruption or damage to the body or brain (Different Kinds of Stress, APA). Chronic stress is constant prolonged stress lasting weeks to years that occurs in response to daily stressors that are not tended to or traumatic events. Chronic stress unlike acute stress can cause lasting disruption and damage to the body and brain such as anxiety, depression, heart disease, and is believed to have a link to the development and progression of Alzheimer's Disease (Understanding Chronic Stress, APA). Physical stress is a change in homeostasis due to a change in environment such as temperature or physical trauma such as injury or surgery. Psychological stress relates to a person's personal concerns about their ability to fulfil certain demands presented to them as well as perceived experiences/situations both in the future and in the past (Salleh, 2008). Stress has various effects depending on its level and where it falls in relation to the threshold, stress up to the threshold is known to result in stimulation that leads to an increase in memory formation, however over

threshold is actually inhibitory to memory formation and learning (Futch Croft, Truong, Krause, & Golde, 2017).

### HPA Axis

The Hypothalamic-Pituitary-Adrenal Axis is responsible for what is termed and as the stress response. This response involves the periventricular nucleus (PVN) of the hypothalamus releasing cortisol releasing factor (CRF) which binds to the CRF1 receptor located in the anterior pituitary. This then causes the secretion of adrenal corticotrophin hormone (ACTH) by the pituitary gland causing the activation of the adrenal cortex by binding to the MC<sub>2</sub> receptors leading to release of glucocorticoids (GCs) (Yan, Dominguez, Fisher, & Dong, 2018; Futch et al., 2017). The HPA axis is regulated by CRF receptors and glucocorticoid (GC) receptors which are densely pack in the hippocampus. The HPA axis also works as a negative feedback loop keeping the central nervous system from having an extreme response leading to damage because excessive HPA axis activation has been shown to lead to damage which increases GC release producing a vicious cycle (Dong & Csernansky 2009; Yan et al., 2018).

### Epidemiology

Epidemiological studies have shown that age of onset is associated with environmental and adult lifestyle factors that influence AD (Hoeijmakers, Lesuis, Krugers, Lucassen, & Korosi, 2018). Epidemiological research on AD has found that person who are likely to experience chronic psychological stress or who experience with Major Depression or PTSD are at higher risk for

the development of AD. However, like most epidemiological research these findings may be fraught with confounds (Futch et al., 2017).

### *Prevalance*

There are 5.8 million Americans with living AD in 2019, of which 81% or 4.7 million people are 75 or older. Women make up 62.5% of the cases of AD in the 5.6 million Americans 65 and over with AD (predominantly sporadic AD cases). Elderly African Americans are roughly two times as likely to develop AD than elderly white Americans however more white people make up the AD population as there are more white people in the US generally (Alzheimer's Association, 2019).

### *Incidence*

Approximately 487,000 people over the age of 65 will develop AD in the US in 2019. The number of new cases is thought to double by 2050 because there in the US there are more people 65 and older giving rise to a greater number of potential patients. In the US every state is expected to see at least a 12% increase in the number of people living with AD between 2019 and 2025 with the largest increases being in the West and Southeast with Arizona having the highest increase at 42.9%. States with the lowest increases are Iowa (12.3%), Illinois (13.0%), and Ohio (13.6%). Additionally, between 2000 and 2017, the number of deaths linked to AD have risen 145% (Alzheimer's Association, 2019)

TAU

Tau is a cytoskeletal protein that is important for cellular structure maintenance and integrity. Tau is classified as a microtubule associated protein (MAP) which bind and stabilize axon microtubules allowing for axonal transport and synaptogenesis. When tau is hyperphosphorylated (misfolded) it can group together into insoluble structures which leads to neurofibrillary tangles found because it can no longer bind to microtubules and the tau proteins then clump together to form the neurofibrillary tangles (NTFs) (Sierra-Fonseca, & Gosselink, 2018). Neurofibrillary tangles made up of tau proteins are believed to be the catalyst of neuronal death in AD patients which is thought to be made worse by stress as hyperphosphorylated tau levels are increased by stress (Bekris et al., 2010).

### Amyloidogenesis

There are two possible pathways from which amyloid precursor protein (APP) can be cleaved, amyloidogenic and non-amyloidogenic. The starting protein APP is formed in the endoplasmic reticulum and is then transported to the Golgi body where it matures before being delivered to the plasma membrane where it then interacts with various secretases and is cleaved forming multiple different products and peptides (Ross, McGonigle, & Van Bockstaele, 2015).

#### *Amyloidogenic*

In the amyloidogenic pathway APP is initially cleaved by  $\beta$ -secretase or BACE 1, a beta-site APP cleavage enzyme. When cleaved it generates an ectodomain APP $\beta$  which is secreted and a C99 terminal fragment is generated. This fragment is then cleaved by  $\gamma$ -secretase and leads to the <https://assignbuster.com/relationship-between-stress-and-alzheimers-disease/>

production of the A $\beta$  peptide and is released where it is likely to either undergo phagocytosis or become a A $\beta$  plaque deposit (Devi, Alldred, Ginsberg, & Ohno, 2010; Bekris, Yu, Bird, & Tsuang, 2010).

### *Non-amyloidogenic*

In the non-amyloidogenic pathway the A $\beta$  domain of APP is cleaved by  $\alpha$ -secretase which makes it impossible for beta amyloid plaque formation to occur (Yan et al. 2018; Gandy, Caporaso, Buxbaum, Frangione, & Greengard, 1994). Additionally, the non-amyloidogenic pathway is stimulated by protein kinase C or the inactivation of okadaic acid-sensitive protein phosphatases (Gandy et al., 1994).

### Alzheimer's Disease

There are two types of Alzheimer's disease, familial Alzheimer's disease (FAD) which is also sometimes referred to as early onset AD and sporadic AD which is the most common form and is the one normally thought of when talking about AD.

### *FAD*

Familial Alzheimer's only makes up about 3-5% of the cases of Alzheimer's in the US and are caused by distinct genetic mutations in A $\beta$ PP, Presenilin 1 (PSEN1), Presenilin 2 (PSEN2) (Yan et al., 2018; Dong & Csernansky, 2009).

The APP gene is located on chromosome 21, its main function is still somewhat unknown, but it is believed to play a role in neural plasticity. FAD APP mutation at the beta-amyloid (A $\beta$ ) domain amino acid terminus has been

linked to an increase in the formation of soluble A $\beta$  meaning that FAD  
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mutations could lead to the increased formation of A $\beta$  (Gandy et al., 1994). Presenilin 1 (PSEN 1) is the most common genetic cause of early onset FAD accounting for around 18% of the 50% of autosomal dominant early onset FAD cases. PSEN1 is on the 14th chromosome specifically the AD3 locus and leads to  $\gamma$ -secretase cleavage of APP. These mutations lead to the most aggressive forms of AD with onset occurring as early as 30 years old (Berkis et al., 2010). If a person inherited either the mutated APP or Presenilin 1 genes they will develop AD (Alzheimer's Association, 2019). Presenilin 2 (PSEN 2) is actually a rare cause of FAD, specifically in white populations. PSEN2 is located on the first chromosome, at locus AD4. PSEN2 cases tend to have an onset age of 45-88 with a wider variability of onset age within a family compared to that of PSEN1 mutation cases. PSEN 2 is also responsible for  $\gamma$ -secretase cleavage of APP resulting in A $\beta$  peptide generation (Berkis et al., 2010). If the Presenilin 2 gene was inherited the person would only have a 95% chance of AD. FAD typically results in symptomology before the typically 65 years old range, some people have been as young as 30 (Yan et al., 2018).

### *Sporadic*

Sporadic AD is thought to be caused by interactions between genetics and environmental factors. Sporadic AD is linked to an imbalance between the production and clearance of A $\beta$  which results in an excess accumulation leading to neurodegeneration, however the cause for this imbalance is still unanswered (Wildsmith, Holley, Savage, Skerrett, & Landreth, 2013). The cause of sporadic AD is still a mystery however, stress is thought to be an

important risk factor for the development and progression of AD (Devi et al., 2010; Sierra-Fonseca, & Gosselink, 2018).

### *Genetics Risk Factors*

There are few genetic risk factors involved in sporadic AD, one of which is trisomy 21 (Down's Syndrome). Trisomy 21 leads to an increase in the likelihood of developing AD because there is an extra copy of the twenty-first chromosome. This is important because the gene that encodes APP is on the twenty-first chromosome, thus having a third copy could lead to an increase in the chance of an APP mutation. Building on that, this could lead to an increase in A $\beta$  peptide production if the amylogenic pathway is taken during cleavage.

The APOE is also thought to play a role in increasing the risk of AD. The APOE gene is located on the 19th chromosome and allows for the transport of cholesterol in the bloodstream. There are three forms of the APOE gene, e2, e3, and e4. The e2 form has the least risk for developing AD followed by e3 and finally e4. Inheriting one copy of e4 leads to three times the risk of developing AD, if two copies are inherited, there is an eight to twelve-fold increase in the risk. APOE e4 individuals have higher plaque and tangle pathology as well as increased mitochondrial damage compared to the other polymorphisms (Alzheimer's Association).

### *Non-genetic Risk Factors*

It is believed that hypertension in mid-life leads to an increased risk of AD later in life. This is most likely due to how it can damage the blood-brain



barrier resulting in protein extravasation which can reduce neuronal and synaptic function and increase A $\beta$  accumulation. This risk actually goes away and becomes a potential protective effect after mid-life because of changes in vessel function and the autonomic systems moderation of blood flow.

Type 2 diabetes has been shown to increase the risk of AD development by nearly double. Insulin is able to cross the blood-brain-barrier and peripheral insulin infusion increase A $\beta$ 42 levels in older populations. Additionally, there are insulin receptors in the hippocampus and the insulin degrade enzyme (IDE) has been shown to also be responsible for the clearing of A $\beta$  thus if there is more insulin in the brain IDE will clear insulin leaving more A $\beta$  and tau proteins to deposit in the brain (Reitz, & Mayeux, 2014).

### Sex Difference

Women make up more than half of the people in the US living with AD (Alzheimer's Association, 2019) leading scientists to question if there is an underlying reason for this disparity. Women tend to outlive men, which leads to the formation of a gender gap within the population and women tend to reach the age of development and onset of AD (Yan et al., 2018). However, a specific biological mechanism for increase AD risk such as sex-specific genetic interactions may be the catalyst for a difference between males and females (Yan et al., 2018). Age related hormonal changes, sex dimorphism in the brain and female specific alterations in the inflammation and microglial function could be to blame for the difference. Along those lines, it is believed that women respond differently to chronic stress on a cellular and molecular level (Yan et al., 2018). It has been shown that a sex difference that is likely

to explain the difference in the prevalence of AD between men and women is the biased CRF<sub>1</sub> coupling and elevated CRF levels in females that leads to tau phosphorylation and generation of A $\beta$ . Additionally, increased CRF expression was shown to lead to tau phosphorylation on Ser396/Ser404 in female mice which generated insoluble tau. This supported the idea that in females, CRF overexpression can lead to the generation of AD pathology. Additionally, CRF was shown to mimic the effects of stress regarding its ability to increase A $\beta$  levels and plaque formations. When CRF is overexpressed, it is believed that the female bias to CRF<sub>1</sub>-PKA signaling encourages BACE1 phosphorylation which promotes  $\beta$ -amyloidogenesis and the formation of AB (Bangasser, Dong, Carroll, Plona, Ding, Rodriguez, McKennan, Csernansky, Seeholzer, & Valentino, 2017).

### Stress and Alzheimer's Disease

Major life stress events have been shown to lead an earlier/faster onset of Alzheimer's disease (Sierra-Fonseca, & Gosselink, 2018). Stress is linked to an acceleration in the progression of AD in general, this effect is most likely regulated by stress hormones and neuropeptides glucocorticoids and CRF. Stress can regulate A $\beta$  progression simply by driving amyloidogenesis from the non-amyloidogenic pathway towards the amyloidogenic pathway resulting in APP being cleaved by  $\beta$ -secretase rather than  $\alpha$ -secretase. This shift in secretase leads to the formation of A $\beta$  peptides/proteins that will result in damage (Hoeijmakers, 2018).

### *Oxidative Stress*

Oxidative stress plays a very widespread role in the onset and progression of AD. One way is through transient hypoxia which in sporadic AD can lead to a dysregulation of mitochondria, changes to the membrane integrity, and alterations in APP cleavage (Chong, Li, & Maiese, 2005). It is believed that behavioral stressors may increase the generation of free radicals in the mitochondria creating an association between generate free radicals and A $\beta$  proteins. Oxidative damage has been shown to accelerate the progression of neuro loss in AD (Dong & Csernansky, 2009). The damage that occurs in AD pathology is believed to occur not only from the actual oxidative stress events but also from faulty repair mechanisms of the oxidative stress (Chong et al., 2005). Oxidative stress damage such as apoptosis and regeneration are known to occur prior to the hallmark manifestations of AD senile plaques and NTFs. More oxidative damage is also present in patients with more plaques or shorter disease length, resulting it in being implied that A $\beta$  plaque formation is in response to oxidative stress (Nunomura, Castellani, Zhu, Moreira, Perry, & Smith, 2006).

Microglia have also been shown to contribute to AD typical damage both through the generation of reactive oxygen species but also through the production of cytokines and the destruction of nearby cell. Tumor necrosis factor-a (TNF-a) produced by microglia may be connected to neurodegeneration through an increase in neuronal sensitivity to free radicals (Chong et al., 2005). The relationship between microglia and AD is the impaired removal of A $\beta$  plaques by faulty microglial activity. Plaques attract microglia however they complicate phagocytosis; the microglia are able to phagocytose the A $\beta$  fibrils however they become activated by

interaction with the A $\beta$  receptor. This microglial activation leads to an inflammatory response that damages surrounding cells. There are three gene mutations that have been identified as being associated with AD; TREM2, TYROBP, and CD33. TREM2 is associated with TYROBP and they promote the removal of bacteria and neuronal cell apoptosis as well as recruitment of microglia to A $\beta$  plaques deposits. CD33 is linked to a reduction in the removal of A $\beta$  and an increase in proinflammatory microglia (Dong & Csernansky, 2009).

### *Vicious Cycle of Stress*

The Vicious Cycle of Stress is composed of two arcs, the right arc represents the influence of stress on disease and the left arc represents the mechanism of disease progression. The cycle proposes that disease is progressed/intensified by stress along with the addition of neurological complications, and disease progression causes more stress, and it keeps repeating living up to the name vicious cycle. Specifically related to AD - stress intensifies AD and leads to an acceleration of disease progression resulting in neurodegeneration and cognitive deficits (Justice, 2018).

### *Animal Studies*

Behavioral stress has been demonstrated to accelerate the development of  $\beta$ -amyloid plaques and memory decline in mouse models. In 5XFAD mice who overexpress five FAD linked traits, restraint stress was not shown to cause an increase in A $\beta$  levels in the cerebral cortex of male or female mice.

Restraint stress however did lead to an increase in APP full length fragments, BACE1, C99 Fragments, and A $\beta$  protein levels in the hippocampus of only <https://assignbuster.com/relationship-between-stress-and-alzheimers-disease/>

female mice. Additionally, restraint stress was shown to have a significant effect on translation initiation factor eIF2a leading to an increase in concentration in the hippocampus of female mice and not in males. However, there was significant difference in the eIF2a levels in the cerebral cortex of stressed mice regardless of sex (Devi et al, 2010). Transgenic mice exposed to stress have been shown to have truncated and insoluble tau proteins. However, mice who are missing the tau protein do not exhibit damage or cognitive deficits due to chronic stress revealing the importance of the relationship between stress and tau for neuronal pathogenesis (Sierra-Fonseca, & Gosselink, 2018). The clearing of misfolded and accumulated proteins is controlled by two pathways of the proteostasis network which acts as a quality control center in the brain. The two pathways are the ubiquitin-proteasome system (UPS) and the autophagy-lysosomal pathway (ALP). This “ quality control” system like other systems in the body is known to slow down as we age and, in this case, this decrease in productivity has been shown to allow for proteins to group and lead to neuronal cell death (Sierra-Fonseca, & Gosselink, 2018). Corticosteroids are also known to induce A $\beta$  plaque distribution and lead to a hyperphosphorylated tau levels in transgenic mice. This was shown to be reduced by the use of glucocorticoid receptor antagonists (Futch et al., 2017) which supports the claims made within the scientific community that stress and the secretion of glucocorticoids can lead to the development and progression of AD.

### *Hippocampus*

Stress has been shown to lead to a decrease in neuronal density on the hippocampus as well as atrophy of dendrites. Intense repeated stress lead to <https://assignbuster.com/relationship-between-stress-and-alzheimers-disease/>

a constant increase in GC levels that cause structural and functional changes to the brain specifically the hippocampus because of the large number of GC receptors. Previous studies have found that stress and CRF receptors contribute to the formation of hippocampal tau phosphorylation (Dong & Csernansky, 2011; Yan et al., 2018). Additionally, stress has been shown to impact the connection between the hippocampus and the prefrontal cortex as well as altering dendritic and synaptic plasticity in the pre frontal cortex interfering with executive functions. The impact on the prefrontal cortex is also thought to lead to changes in the regulation of the HPA which displays a link between HPA regulation gone wrong and oversecreting of GC in relation to AD pathology (Vyas, Rodrigues, Silva, Tronche, Almida, Sousa, & Sotiropoulos, 2016).

### *Locus Coeruleus*

The locus coeruleus has not been really studied in relation to AD so there is so much more that needs to be investigated so see the full capacity of the role that it plays in pathogenesis. The locus coeruleus (LC) is thought to be one of the first brain regions that is affected by AD. The LC projects to many areas throughout the brain to provide norepinephrine, and one projection area that is important in AD pathology is to the hippocampus. It also projects to the amygdala, and the prefrontal cortex which are both important for the stress response. The LC and its degeneration is hypothesized to play a role in pathogenesis of AD because it plays a role in synaptic function and blood-brain-barrier permeability as well as A $\beta$  plaque distribution and related cell death. Another proposed role LC plays in the pathogenesis of AD is its role in the hypocretin-orexin system which has been shown to be involved in A $\beta$

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formation. Postmortem AD brains have shown a significant decrease in orexinergic signaling. The LC contains a large number of orexinergic receptors and thus if these receptors are linked to AB formation and accumulation this could be an explanation for the degeneration of the LC however more research needs to be done to confirm.

### *CRF/CRF1 Pathway*

Corticotrophin Releasing factor is a neuropeptide that is mediated through the activation of the CRF1 receptor (Futch et al. 2017). CRH and urocortin (UNC) 1, 2, and 3 play a very important role in the stress response because UNCs bind to and activate the CRH1 and CRH2 receptors (Futch et al. 2017). Stress has been shown to lead to an increase in CRF transmission specifically at the CRF<sub>1</sub> site causing an increase in A $\beta$  42 levels. This finding has been thought to imply that behavioral stress and thus CRF signaling could be a contributing factor to an increase in AD pathogenesis. CRF<sub>1</sub> signaling plays a major role in the formation of A $\beta$  because it has been shown to play a role in multiple stages of  $\beta$ -amyloidogenesis such as APP proteolysis and mediated toxicity. CRF overexpression in the forebrain has the potential to lead to an increase in A $\beta$  plaque formation and tau specifically through the CRF1-Gs-PKA pathway which is an important factor in the modulation of  $\beta$ -secretase and  $\gamma$ -secretase. This is important because these secretases are the major cleaving enzymes in the amyloidogenic pathway. Increased CRF<sub>1</sub> activation can lead to a change in PKA pathway activation which is also believed to play a role in the proteolysis of APP by effecting the  $\alpha$ ,  $\beta$ , and  $\gamma$  secretases that regulate how APP is cleaved. PKA signaling has also been shown to affect

the phosphorylation of tau which is another protein that has a major role in AD pathogenesis. Overactivation of PKA is believed to lead to a shift in amylogenesis from the non-amyloidogenic pathway to the amyloidogenic pathway resulting in an increase in A $\beta$  production. CRF  $\alpha$  1 signal increases may lead to a worsening of symptomology in person who already have AD through PKA signaling which causes a decrease in neuronal firing specifically in the hippocampus and an increase in working memory deficits (Yan et al., 2018).

## Conclusions

Alzheimer's disease is a rapidly growing problem within the US with prevalence rates almost doubling in the next thirty years. With no real definitive cause for the development of sporadic AD we have been left without treatment options. However, as discussed in this paper scientists have found reasonable evidence to support the fact that one environmental factor is likely to play a big role in both the development and the progression of Alzheimer's disease. Not only has the research used in this paper found that stress in general could be a risk factor for AD but there is also evidence of potential pathways in which the gender divide in AD can be explained. The studies in the paper also show that not only does psychological and behavioral stress impact the potential for AD but also that the plaque formations of AD may actually be a response to damage caused by oxidative stress. With this information hopefully, scientists can pinpoint what about stress causes the AD pathology and can come up with ways to reduce this stress and discover a tangible treatment method for sporadic AD.

Additionally with the knowledge that beta-amyloid can only be formed  
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through  $\beta$  and  $\gamma$  secretase cleavage of APP through the amyloidogenic pathway, a good area for future study would be how to coax the brain to undergo cleavage of APP through the use of  $\alpha$ -secretase and the non-amyloidogenic pathway.

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