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The influence of sleep deprivation on the onset and development of Alzheimer's disease

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Abstract
Alzheimer's disease (AD) is a neurodegenerative age-related disease that is mainly known for causing memory, thinking and behavioural impairments. Because of growing life-expectancy AD's occurrence is growing among elderly people. The main characteristics for AD are the Amyloid β plaques and the Neurofibrillary tangles. Amyloid β plaques arise mainly out of the peptide Amyloid β (Aβ), which is cleaved out of the protein Amyloid Precursor Protein (APP). In AD there is a disbalance between the production and the clearance of Aβ from the brain, resulting in an extracellular overload of Aβ. This overload causes the Aβ to stack and form aggregates; plaques. Neurofibrillary tangles arise mainly out of the protein Tau.
Tau provide stability to microtubules in axons and regulates the assembly and stability of microtubules by phosphorylation. In AD, however, the Tau protein is hyperphosphorylated, causing it to lose its binding to the microtubules and aggregate intracellular into tangles. Both plaques and tangles cause a neuron to lose its ability to communicate with other neurons. This will cause the neuron to die. The first region that is affected by AD is the entorhinal cortex, which is important in memory and other cognitive abilities. This often causes the first symptom of a patient to be memory related. After affecting the entorhinal cortex, AD will spread through the brain causing more impairments along the way. Eventually AD is fatal.
AD is affected by a lot of risk factors. One of these risk factors is sleep deprivation (SD). Sleep deprivation is a condition in which a person sleeps less than the recommended hours of sleep for a longer period of time. Sleep is important for the brain, because toxic waste from neurons, like the amyloid β peptide, is cleared from the brain while sleeping. Research shows that SD could lead to reduced clearance of Aβ from the brain, causing it to be more at risk of stacking. This could promote the onset/progression of AD. AD, in turn, affects the sleep regions in the brain (hypothalamus, SCN) in an early stage of the disease. This causes the two to worsen each other, creating a downward spiral. Finding this relation between SD and AD could help in creating a treatment for AD. However, more research has to be done to the discover the gratitude and exact impact of SD on AD.

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Introduction

Alzheimer's disease was first described by Alois Alzheimer in 1907. He described a patient that suffered from memory loss, came across as confused and wasn't capable of understanding simple questions. After autopsy they discovered that the patient's brain was full of unusual accumulations of proteins. At that time, no one had really seen this disease before. Nowadays, more than a 100 years later, Alzheimer's disease (or simply put AD) is the most common cause of dementia in the world (Castellani et al., 2010; Blennow et al., 2006; Bear et al., 2007). The Alzheimer's Associations states that dementia is a conditions were memory, thinking and behavioural impairments decrease a person's ability to function in daily life (Frantz, 2011). These impairments are caused by damage to the nerve cells (neurons) in the brain. The first neurons to be affected by AD are located in the entorhinal cortex. This cortex is a small region located near the hippocampus in the medial temporal lobe and is involved in memory formation (Gómez-Isla et al., 1996). Damage to these neurons will thus lead to memory impairment. After affecting the entorhinal cortex, AD will start to affect other neuronal area's in the brain. In time more processes in the brain will start to fail; easy tasks as putting on clothes or talking will become harder and harder to perform. Eventually AD is fatal (Blennow et al., 2006; Fargo & Bleiler, 2014)

The occurrence and thus interest in AD has grown in the last 30 years. Life expectancy of men has been increased over time because of better healthcare and living conditions. The chance of getting AD increases with inclining age. Although the understanding of the disease is much better than it was a 100 years ago, there is still much not known about the pathogenesis and biological background of AD. The key to finding a cure for AD lies in the understanding of the onset and development of the disease (Ballard et al., 2011; Fargo & Bleiler, 2014).
Furthermore, it is very important to know which risk factors are involved in the pathogenesis of AD. This can help in preventing the disease, but can also be of influence in developing a treatment. Recent research shows that chronic stress is one of those risk factors that play a part in the onset of AD. Chronic stress can often lead to sleep deprivation and sleep deprivation is known to have a wide range of effects on the human body (Di Meco et al., 2014). In this literature thesis I want to examine the influence of sleep deprivation on the onset and development of AD. To do so we first need to answer a few basic questions as: What is the pathogenesis of AD as we know of right now? Which possible proteins and genes play a role in AD? What do we know of sleep deprivation? Eventually we hopefully will be able to answer the main question 'In what way does sleep deprivation influence the onset and development in AD.

The pathogenesis of Alzheimer's disease

The most important cells in the human brain are neurons. These cells typically have many protruding parts which can reach far into the brain or body. In the brain neurons ends (called synapses) are connected to each other in a complex web. They communicate by sending electrical signals (electrical currents) or by sending chemical signals (neurotransmitters) to each other. One neuron can send signals to many neurons at the same time and can even signal itself. By this 'communication' the brain is able to control the whole human body; it can regulate things as movement, homeostasis, emotions and, important in this case, memory (Bear et al., 2007).
In Alzheimer's disease neurons get damaged. This causes them to fail in sending signals to other neurons. Once a neuron can't signal anymore, it will die. The death of a couple of neurons will not cause any serious damage to a patient. This is simply because the human brain consist of so many neurons that if some neurons die, there are always other neurons that can replace them. (Fargo & Bleiler, 2014; Villemagne et al., 2013). According to the guidelines made by the National Institute for Aging and the Alzheimer's Association in 2011 there are three stages of AD (Frantz, 2011; Fargo & Bleiler, 2014):

- Preclinical AD; in this stage there are no visible symptoms, but the first neurons will start to die due to the onset of AD. It can take up to 20 years before the first symptoms will start to arise.
- Mild Cognitive Impairment due to AD; in this stage the patient will start to show a mild decline in memory and other cognitive abilities, but these impairments do not stand in the way of day to day activities.
- Dementia due to AD; at this stage the progressing symptoms will affect the ability to perform daily activities.

The first symptoms will be small. The patient will, for example, have a slight form of memory loss or is unable to store new information; nothing a 'normal elderly' wouldn't have. This causes only close relatives or friends to see that something is wrong. At this stage the patient will be designated as having mild cognitive impairment (MCI). This mostly precedes Alzheimer's disease, but can also just be part of the normal ageing process (Blennow et al., 2006). After affecting the neurons in the entorhinal cortex, AD will spread to other regions in the brain. As the illness progresses, new symptoms will occur; people will lose their complete memory, lose their personalities or become disoriented. The progressing symptoms are, however, different in every patient. This is explained by the fact that every brain is different and that the path of neurodegeneration is not a set course. Which neuron is to falter and die next is never clear. Patient will also progress differently through every stage of AD (mild to severe). Some patient will deteriorate very slowly or have a positive reaction to available medicine. Others will deteriorate fast. It is, however, inevitable that every patient will at some point reach the final stages of AD. Individuals will not be able to do simple tasks as eating or using the restroom. They will also lose the ability to recognize loved ones. Eventually patient will become bed bound and will need care day and night. The disease itself mostly doesn't kill the patient directly; a pneumonia or other infections are often the cause of death. This is because patients at the end stage are barely moving, eating and hygiene is often poor, which causes them to be very susceptible to infections (Fargo & Bleiler, 2014).

Proteins involved in AD

What causes the neurons to die? As said earlier, Alois Alzheimer found unusual accumulations of proteins in the patient's brain. The two main pathological hallmarks of AD are amyloid plaques and neurofibrillary tangles (Ballard et al., 2011).

Amyloid plaques

Amyloid plaques are found outside the neuron and consist mainly of the Amyloid β (Aβ) peptide. Aβ is an peptide cut from the protein Amyloid Precursor Protein (APP), which is a highly expressed protein in the human brain and is cleaved by two different pathways. The first pathway is non-amyloidogenic and cleaving occurs by two proteolytic (breaking down of proteins) enzymes; α- and γ-secretase. The second amyloidogenic pathway uses β- and γ- secretase as cleaving-enzymes and this pathway leads to cleavage of the Amyloid β peptide (it has two subtypes in humans; Aβ1-40 and Aβ1-42) (see figure 1) (Blennow et al., 2006; Sadigh-Eteghad et al., 2014).

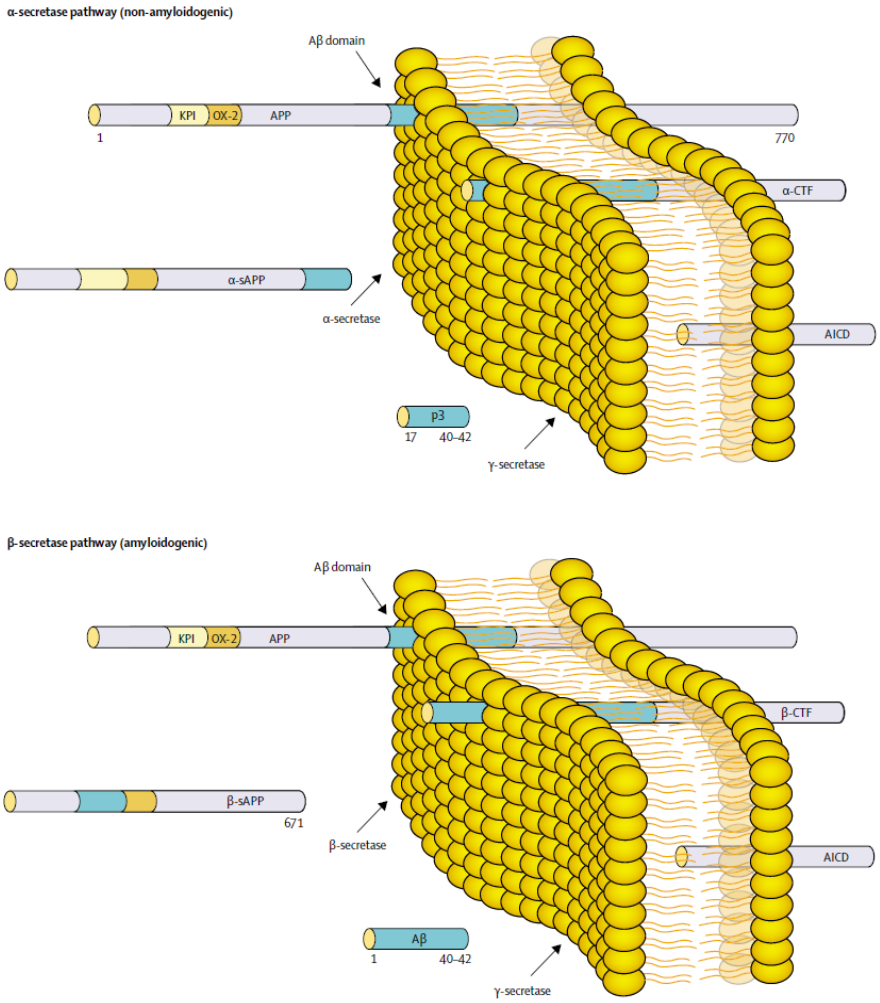

Figure 1 This figure shows the cleaving of APP in its two separate ways. The non-amyloidogenic pathway produces p3 and alfa-sAPP. The amyloidogenic pathway produces beta-sAPP and A-beta (1-40 or 1-42) out of APP. (Blennow et al., 2006)

Thus far the normal physiological function of Amyloid β peptide in the human brain is poorly understood (Hiltunena et al., 2009; Nussbaum et al, 2013). In a healthy brain the production and removal of Aβ is in balance, keeping the level of Aβ constant. One hypothesis that is often used in explaining the onset of AD is the amyloid cascade hypothesis. This hypothesis states that there is a disbalance in either the production or clearance of Aβ in the human brain, which causes Aβ to accumulate. This disbalance can occur through familiar mutations in the protein or enzyme coding genes such as APP or γ-secretase or because of sporadic age and/ or environmental related causes (Blennow et al., 2006; Sadigh- Eteghad et al., 2014).

In AD the disbalance of Aβ always means that there is relatively more production/cleavage of Aβ then there is clearance. This means that Aβ starts to stack. Of the two subtypes mentioned earlier Aβ1-42 is more prone to aggregate than Aβ1-40. Once it starts to stack it will be transported to the outside of the cell, where it normally would be broken down and/ or cleared from the brain. In this

case, however, the load of Aβ will be higher or the degradation rate of Aβ will be lower than normal. This causes the stacking to continue outside the cell. It is believed that Aβ somehow undergoes conformational change that makes it susceptible to aggregation (Blennow et al., 2006). First small, soluble aggregates of Aβ oligomers will start to form. While more Aβ will start to stack the oligomers will grow into larger, insoluble fibrils. These fibrils packed together form plaques. Both the small, soluble oligomers and the large, insoluble plaques are believed to be neurotoxic and cause synaptic dysfunction which ultimately lead to cell death of the neuron because the neuron becomes incapable of communication (Blennow et al, 2006; Ballard et al, 2011; Sadigh- Eteghad et al., 2014).

Neurofibrillary tangles (NFT)

Neurofibrillary tangles are composed out of paired helical filaments (PHF) and straight filaments (SF) (Alonso et al., 2001; Iqbal et al., 2005). The major component of NFTs is the protein tau. Tau is a microtubule- associated protein (MAP) and is primarily found in neurons (Iqbal et al., 2005). It provides stability to microtubules in the neurons extensions (axons) by binding to the microtubules with its microtubule-binding domains. By doing this it also promotes the assembly of microtubules (Blennow et al., 2006). Tau regulates the assembly and stability of microtubules by its amount of phosphorylation (Iqbal et al., 2005)

In AD tau is hyperphosphorylated. If the amyloid cascade hypothesis is to stand, tau hyper-phosphorylation would occur because of the toxic elevated Aβ levels (Ballard et al., 2011). Another hypothesis (the dual hypothesis) mentions that both Aβ levels and tau hyperphosphorylation happen independently, but are caused by a common molecular defect originating in an earlier process (Small & Duff, 2008). Still, both hypotheses have the same outcome; the phosphorylation of tau will increase dramatically. This will cause it to lose its binding to microtubules, which in turn causes the microtubules to lose stability. This will lead to decrease in axonal transport and thus to decline in neural and synaptic function (Blennow et al., 2006; Castellani et al., 2010). Tau itself redistributes away from the axon, towards the somatodendritic parts of the neuron. Here the soluble tau will aggregate together into insoluble fibrils in tangles .The presence of NFTs in the neuron is believed to be neurotoxic, just like the amyloid plaques outside the neuron (Sadigh- Eteghad et al., 2014; Blennow et al., 2006). The tangles would block transport of essential nutrients/molecules in the neuron, which will lead to the neurons death (Fargo & Bleiler, 2014).

Mutations found in the genes encoding for tau can lead to hyperphosphorylation of tau, but thus far there has been no evidence of these mutations causing AD. It has been found, however, that these mutations do lead to other types of dementia (Small & Duff, 2008)

Sporadic vs. Familial AD

Sporadic AD

Over 95% of AD patients have so called sporadic AD (Chen et al., 2009). Sporadic AD does not arise because of one (genetic) flaw in the human body. It arises because of changes in multiple environmental and genetic factors. These factors are called risk factors (Fargo & Bleiler, 2014; Chen et al., 2009). The biggest risk factor in AD is age; most patients that are diagnoses are over 65 years old. Early onset AD exists, but this often has other reasons (see 'Familial AD'). Age alone is, however, not enough to obtain AD and AD is not a normal 'side effect' of aging. Other risk factors leading to Alzheimer's Disease are (Blennow et al., 2006; Chen et al., 2009; Fargo & Bleiler, 2014; Ballard et al., 2011; Ruitenberg et al., 2001):

- Brain activity (education): being socially and mentally active should reduce the risk of AD. Levels of education, social skills and brain activity could all play a part in the development of AD. Some researchers believe that by having education you build a so called 'cognitive reserve'; more education/brain activity leads to increased connections between neurons. This would compensate for the connections lost in AD. However, this would only postpone the progress of AD, considering the fact that the other neuronal connections will eventually be affected as well.

- Lifestyle: differences in lifestyle can mean great differences in health. Brain and body are believed to be strongly connected which means that unhealthy habits as drinking or smoking heavily, having diabetes and/or being obese will have a great impact on the human body and thus also on the brain. Cardiovascular diseases like coronary heart disease or atherosclerosis often form a risk factor for developing AD.
- Family: it is more likely for someone to develop AD if a first-degree relative (parents or siblings) has AD.
- Genetics: there are certain genes that can cause a higher risk of developing AD. One of the most discussed/researched genes that is a risk factor to AD is apolipoprotein E(ApoE) ε4. This gene is originally encoding a protein involved in cholesterol transport (also in neurons) and is believed to influence amyloid β. All humans can inherit 3 isoforms of ApoE genes: ApoE ε2, ApoE ε3 and ApoE ε4. The most common gene is the ApoE ε3 variant. This variant is found not to increase or decrease the risk of AD. The least common gen is the ApoE ε2 variant. This variant is believed to decrease the risk of AD. If an individual only inherited one copy of the ApoE ε4 the risk of disease would be increased by 3 times. Inheriting two copies would mean an increase of risk by 7-15 times.
- Other (environmental) factors such as traumatic brain injuries or even dietary intake of certain vitamins.

Familial AD

Several genes have a direct effect on the onset and development of Alzheimer's disease. This monogenetic form of AD inherits by autosomal dominant transmission. This means that if you inherit one mutated gene you will get AD. Familial AD is also an early onset disease, which means that AD occurs at a much earlier age than in sporadic AD (Sadigh- Eteghad et al, 2014; Blennow et al., 2006; Fargo & Bleiler, 2014). There are 3 known genes that can cause AD (Castellani et al., 2010; Ballard et al., 2014; Goate et al., 1991; Hartley et al., 2015):

- PSEN 1 and PSEN 2: these genes encode the protein presenilin. Presenilin is a protein that's part of γ- secretase. As we discussed earlier, γ- secretase plays a role in cleaving AB from APP. Mutations in PSEN1/2 lead to an increased cleavage of the Aβ1-42. This makes it possible for disbalance to occur in Aβ production and degradation. A higher production of the Aβ1-42 variant also means that aggregations and plaques from more readily, as mentioned earlier. PSEN 1 mutations are the most common cause of familial AD. PSEN 2 mutations are rare.
- APP: the APP gene encodes the protein Amyloid Precursor Protein. APP mutations are the second most common cause of familial AD. In which way this mutation leads to AD is not well understood, but it is believed to stimulate/prefer the cleaving via amyloidogenic pathway and thus Aβ production. This theory is strengthened by the fact that The APP gene is located on chromosome 21. Research shows that people with down's syndrome are often more prone to get AD. This is because of the fact that they have 3 chromosomes 21, which means there a more APP genes. More APP genes encode for more Aβ- protein and so the production of Aβ would be higher than normal.

Many more factors are believed to play a part in the onset and development of AD. There are a lot more proteins, enzymes, genes and environmental influences that can be related to AD. The brain has so many complex pathways, which all seem intertwined that the real, full pathology of AD is not nearly explained. However, because this is a small thesis, I will not further elaborate on the different proteinpathways.

AD and sleep deprivation

Normally people live in a circadian rhythm. This rhythm is based on a 24 hour, sleep and wake cycle (Fuller et al., 2006). The average amount of sleep a person should get is about 7 to 8,5 hours a day. The function of sleep has always been a bit of a mystery for researchers, but what we do know is that sleep is important for our body to recover. Sleep keeps our energy reserves levelled, regulates our body temperature and lets the brain (neurons) rest after a full day of activity . Sleep is also important for our cognitive skills; when people lack sleep they usually have a declined cognitive performance. Sleep is even more important for our memory retention; if we do not sleep enough, our capability to store information will be impaired (Alhola & Polo-Kantola, 2007). If we do not sleep, which could be due to fatal insomnia, we would could die in months (Xie et al., 2013) There are a lot of factors that influence our sleeping behaviour. For example (Lim et al., 2013; Peter- Derex et al., 2014):

- Sex: in general men sleep lighter than women.
- Lifestyle: lifestyle choices can affect our sleep efficiency (eq. smoking, obesity but also working night shifts).
- Sleeping disease: these illnesses, such as insomnia or sleep apnea, cause lack of sleep.
- environmental influences: climate, light, noises and (bed)comfort are all factors from the outside that can influence our sleep.
- age: our sleep cycle changes with age. With increasing age, sleep efficiency decreases (Redline et al., 2004). Elderly people have shorter sleep cycles, night-time awakenings and are more prone to sleep at daytime. Their circadian rhythm chances into a fragmented rhythm. Sleep that is constantly 'interrupted' by awakening is believed to lead to cognitive decline.

All these factors mentioned above can lead to sleep deprivation (SD). SD is a condition in where a person doesn't get enough sleep. This results in sleepiness, concentration problems and mood swings, but also in serious symptoms as impaired immune response and cognitive impairment. There are two main types of sleep deprivation:

- total SD: in this case a person is kept awake for a long period of time, generally for 24-72 hours.
- partial SD: in this case a person sleeps shorter periods of time than the recommended 7 to 8.5 hours for a longer period of time.

Both types impair attention and working memory, but total SD is as known to affect other functions, such as long-term memory and decision-making. Partial SD is more common in the current society, but total SD is far more studies. This has probably to do with the fact that depriving humans from sleep for longer periods of time is not (ethically) allowed .

Sleep deprivation* is often seen in patients with AD and it appears quite early in the disease. The hypothalamus is believed to be responsible for the on an off switch of sleep (Saper et al., 2011). Part of the hypothalamus is the suprachiasmatic nucleus (SCN). This nucleus regulates our circadian rhythm; it's our internal clock. Research of Baloyannis in 2014 showed that the hypothalamus, SCN in particular, is affected early in the pathogenesis of AD by plaques and tangles. Characterised phenotypes of mild/moderate AD, such as being awake at night, sleeping in the day and being agitated, comply with this theory. The presence of both plaques and tangles in the brain have been found to lead to SD, even in the preclinical state of AD (Ju et al., 2014; Roh et al., 2012). As AD worsens, SD worsens as well (Peter- Derex et al., 2014).

Recent studies, however, suggest that not only does AD cause SD, but SD might also cause (or at least help cause) AD.

Influences of sleep deprivation on factors of AD

Amyloid B

Research show that sleep plays a vital role in the clearance of Aβ in the brain. The brain consists of two types of extracellular fluid; interstitial fluid (ISF), which is found between the neurons, and cerebrospinal fluid (CSF), which is found in the ventricular system and it surrounds the brain and spine. These two fluids are responsible for the disposal of toxic waste from the neurons (Weller et al., 1998). During sleep the interstitial space is said to increase. This increase would cause an osmotic flow between ISF and CSF, which would make it possible to exchange contents. CSF then removes the waste form the brain. Aβ, which is present in soluble form in the interstitial fluid, is removed from the brain via this pathway at night. There is a diurnal (daily) fluctuation of Aβ levels in the brain: when awake the body produces soluble Aβ peptide and when asleep soluble Aβ peptide is removed from the brain. Researchers believe that sleep could play an important role in removing potentially dangerous neurotoxins from the brain (Xie et al., 2013; Ju et al., 2014). Knowing this, studies were launched to see what sleep deprivation means for the presence of (soluble) Aβ in the brain. These studies have thus far only been done on mice, which is understandable considering causing (chronic) sleep deprivation in humans is not ethically approved. These studies showed that causing acute sleep deprivation in mice led to higher levels of Aβ in interstitial fluid than under normal sleeping conditions (Kang et al., 2009). Causing chronic sleep deprivation in mice even led to an increased and accelerated chance of formations of insoluble amyloid plaques. Although these studies were performed on mice, it is known that the same pathways are active in mice and humans regarding sleep and Aβ deposition (Ju et al., 2014). These studies contribute to the thought that not only AD causes sleep deprivation, but sleep deprivation could also play a part in causing AD. Not only do these two influence each other, they also enhance each other. More Aβ plaques (in the sleep regions of the brain) leads to more sleep deprivation, which in turn leads to more Aβ deposition and plaques. It's a positive feedback loop, shown in figure 2.

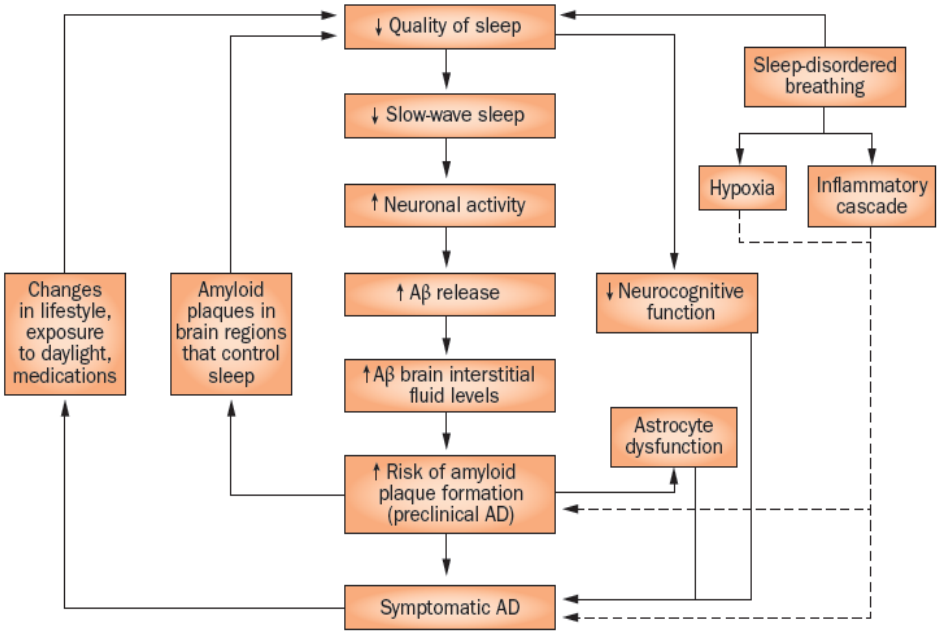

Figure 2 This figure shows the positive feedback loop between AD and sleep deprivation. In this case we leave Astrocyte dysfunction, hypoxia and inflammatory cascade aside (Ju et al., 2014)

Neurofibrillary tangles (NFT)

As is discussed earlier NFT arise either because of the toxic elevated Aβ levels or because of a common molecular defect that originates out of an earlier process. So it might be logical to assume that if sleep deprivation causes a higher level of Aβ leading to plaques, it will also lead to an higher level of NFT in the brain. The research of Di Meco et al. found that there was no change in the levels

of soluble tau, but they did discover there were increased levels of insoluble tau in mice undergoing sleep deprivation, suggesting a possible change in its conformation. These data would imply that sleep deprivation in mice would lead to accelerated tau pathology. This could contribute to an earlier onset of the disease and/or a quicker progression of the disease (Di Meco et al., 2014)

ApoE 4

Studies claim there is a complex relationship between the ApoE ε4 and sleep deprivation. Some of these studies suggest that having the ApoE ε4 gene makes you more prone to sleep deprivation and thus, via that way more susceptible for AD. Other studies show that both ApoE ε4 and sleep deprivation amplify each other in a negative way, causes a cognitive decline (Lim et al., 2013). The study of Lim et al. itself found that if sleep consolidation is improved, the negative effect that the ApoE ε4 could have as a risk of AD attenuates.

Discussion & Conclusion

It can be established that Alzheimer's disease is an very complex disease in were a lot is yet to be discovered. However, the importance of Amyloid β plaques and Tau tangles is made clear in this research. In most cases AD arises sporadic, being influenced by a lot off risk factors. One of these factors is sleep deprivation. Sleep deficit can cause Amyloid β to stack in the brain, which can accelerate the progression of AD. AD, in turn, affects the sleep regions in the brain (hypothalamus, SCN) in an early stage of the disease. This causes the two to worsen each other, creating a downward spiral. However, to really know if and how sleep deprivation plays a role in AD further studies, preferably longitudinal studies, need to be done. This is because the fact that formation of plaques and tangles start way before the disease is clinically noticeable. When researching the impact of sleep deprivation on AD, the AD is probably already in an advanced state. The occurring SD could then already be a result of AD, instead of being a separate condition. Although researches have been done in mice, where sleep deprivation could be caused at a very young age (before the onset of AD), we have to keep in mind that mice are not humans. Although results show promising similarities, this does not mean that the process in mice is exactly the same as in humans. The problem is, of course, that we can't do these same studies on humans, because that would be ethically incorrect. (Ju et al., 2014)
In this research we have not made a distinction between partial and total SD, but these two could possibly have a different influence on AD. Total SD would lead to a lack of Aβ clearance for a couple of days, but this might not be the case in partial SD. A lack of clearance gives a higher risk of stacking of Aβ and so total SD would be the more 'dangerous' form. Research has to be done whereby difference is made between the two types of SD to confirm this hypothesis.

To further understand AD and contrive a possible medicine more research needs to be done. I believe that understanding the normal physiological function of Aβ would give us new perspectives on how to treat the disease. It is also important to focus on the risk factors that cause AD, such as sleep deprivation. Knowing more about their contributions to the disease could help in finding a treatment for this disease. Preventing the risk factors will not per se cure AD, but it could delay the onset and/or slow down the progression.

Finally, I wonder in what extend sleep deprivation influences AD. Is it possible that because I lack sleep now (at a relatively young age) I am already more prone to get AD? Or is SD just a small risk factor that could contribute to the onset of AD, but only in small degree? Again, more research needs to be done to reveal a correlation between AD and SD.

Alzheimer's disease is a heterogeneous disease, in which a lot of risk factors are involved. The need to finding treatments grows every day in this world were an ever ageing population is a growing issue.

Acknowledgments

This thesis is dedicated to my grandmother, Gerharda Aleida Maria 'Eddy' Muizer-Wissink who died during the writing of this thesis due to the consequences of Alzheimer's.

References

Alhola, P., & Polo-Kantola, P. (2007). Sleep deprivation: Impact on cognitive performance. *Neuropsychiatric Disease and Treatment* 3(5): 533-567

Alonso, del A.C., Zaidi, T., Novak,M., Grundke-Iqbal, I., & Iqbal, K. (2001) Hyperphosphorylation induces self-assembly of t into tangles of paired helical filaments/straight filaments. *PNAS* 98 (12): 6923-6928

Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., & Jones, E. (2011). Alzheimer's disease. *Lancet*, 377: 1019-1031.

Baloyannis, S.J., Mavroudis, I., Mirilineos, D., Baloyannis, I.S., & Costa, V.G. (2014) The Hypothalamus in Alzheimer's Disease: A Golgi and Electron Microscope Study. *American Journal of Alzheimer's Disease & Other Dementias*: 1-10

Bear, M.F., Connors, B.W., & Paradiso, M.A. (2007). *Neuroscience, Exploring the Brain* (third edition). Box 2.3; Alzheimer's Disease and the Neuronal Cytoskeleton. Baltimore: Lippincott WIlliams & Wilkins. 36-37

Blennow, K., Leon, de M.J., & Zetterberg, H. (2006). Alzheimer's disease. *The lancet*, 368: 387–403.

Castellani, R.J., Rolston R.K. & Smith, M.A. (2010). Alzheimer disease. *Disease-a-month: DM*, 56(9): 484-546.

Chen, J.H., Lin, K.P, & Chen, Y.C. (2009). Risk Factors for Dementia. *Journal of the Formosan Medical Association* 108 (10): 754-764

Di Meco, A., Joshi, Y.B., & Practicò, D. (2014). Sleep deprivation impairs memory, tau metabolism, and synaptic integrity of a mouse model of Alzheimer's disease with plaques and tangles. *Neurobiology of Aging* 35: 1813-1820

Fargo, K., Bleiler, L. (*Alzheimer's Association*) (2014). Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, 10: 47-92.

Frantz, N. (2011). New Criteria and Guidelines for the Diagnosis of Alzheimer's Disease Published for firt time in 27 Years. *Alzheimer's Association:* 1-11

Fuller, P.M., Gooley, J.J., & Saper, C.B. (2006). Neurobiology of the sleep-wake cycle: Sleep Architecture, Circadian Regulation, and Regulatory Feedback. *Journal of biological rhythms* 21 (6): 482-493

Goate, A., Chartier-Harlin, M.C., Mullan, M., Brown, J., Crawford, F., Fidani, L., Giuffra, L., Haynes, A., Irving, N., James, L., Mant, R., Newton, P., Rooke, K., Roques, P., Talbot, C., Pericak-Vance, M., Roses, A., Williamson, R., Rossor, M., Owen, M., & Hardy, J. (1991). Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* 349: 704-706

Gómez-Isla, T., Price, J.L., McKeel Jr., D.W., Morris, J.C., Growdon, J.H., & Hyman, B.T. (1996). Profound Loss of Layer II Entorhinal Cortex Neurons Occurs in Very Mild Alzheimer's Disease. *The Journal of Neuroscience* 16(14): 4491– 4500

Hartley, D., Blumenthal, T., Carrillo, M., DiPaolo, G., Esralew, L., Gardiner, K., Granholm, A., Iqbal, K., Krams, M., Lemere, C., Lott, I., Mobley, W., Ness, S., Nixon, R., Potter, H., Reeves, R., Sabbagh, M., Silverman, W., Tycko, B., Whitten, M., & Wisniewski, T. (2015) Down syndrome and Alzheimer's disease: Common pathways, common goals. *Alzheimer's & Dementia* 11 (6): 700–709

Hiltunena, M., Groenb, van T., Jolkkonena, J. (2009). Functional Roles of Amyloid-β Protein Precursor and Amyloid-β Peptides: Evidence from Experimental Studies. *Journal of Alzheimer's Disease* 18: 401-412

Iqbal, K., Alonso, del A.C., Chen, S., Chohan, M.O., El-Akkad, E., Gong, C., Khatoon, S., Li, B., Liu, F., Rahman, A., Tanimukai, H., & Grundke-Iqbal, I. (2004) Tau pathology in Alzheimer disease and other tauopathies. *Biochimica et Biophysica Acta* 1739 (2-3): 198-210

Ju, Y.E.S., Lucey B.P., & Holtzman D.M. (2014). SLeep and Alzheimer disease pathology- a bidirectional relationship. *Nature Reviews; Neurology* 10: 115-119

Kang, J.E., Lim, M.M., Bateman, R.J., Lee, J.J., Smyth, L.P., Cirrito, J.R., Fujiki, N., Nishino, S., & Holtzman, D.M. (2009). Amyloid-B dynamics are regulated by Orexin and the sleep-wake cyle. *Science* 326 (5955): 1005-1007

Lim, A.S.P., Yu, L., Kowgier, M., Schneider, J.A., Buchman, A.S., & Bennett, D.A. (2013). Modification of the Relationship of the Apolipoprotein E e4 Allele to the Risk of Alzheimer Disease and Neurofibrillary Tangle Density by Sleep. *Journal of the American Medical Association* 70 (12): 1544-1551

Peter-Derex, L., Yammine, P., Bastuji, H., & Croisile, B. (2014). Sleep and Alzheimer's Disease. *Sleep Medicine Reviews* 19: 29-38

Redline, S., Kirchner H.L., Quan, S.F., Gottlieb, D.J., Kapur, V., & Newman, A. (2004). The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. *Journal of the American Medical Association* 164 (4): 406-418

Roh, J.H., Huang, Y., Bero, A.W., Kasten, T., Stewart, F.R., Bateman, R.J., & Holtzman, D.M. (2012). Disruption of the sleep-wake cycle and diurnal fluctuation of Amyloid-B in mice with Alzheimer's disease pathology. *Science Translational Medicine* 4 (150): 1-10

Sadigh-Eteghad, S., Sabermarouf, B., Majdi, A., Talebi, M., Farhoudi, M., Mahmoudi, J. (2014). Amyloid-Beta: A Crucial Factor in Alzheimer's Disease. *Medical Principles and Practice* 24: 1-10

Saper, C.B., Chou, T.C. & Scammell, T.E. (2001). The sleep switch: hypothalamic control of sleep and wakefulness. *Neurosciences* 24 (12): 726-731

Small, A.S., Duff, K. (2008). Linking A and Tau in Late- Onset Alzheimer's Disease: A Dual Pathway Hypothesis. *Neuron* 60 (4): 534-542

Villemagne, V.L., Burnham, S., Bourgeat, P., Brown, B., Ellis, K.A., Salvado, O., Szoeke, C., Macaulay, S.L., Martins, R., Maruff, P., Ames, D., Rowe, C.C., & Masters C.L. (2013) Amyloid B deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *The Lancet, Neurology,* 12 (4): 357-367.

Weller, R.O. (1998). Pathology of Cerebrospinal Fluid and Interstitial Fluid of the CNS: Significance for Alzheimer Disease, Prion Disorders And Multiple Sclerosis. *Journal of Neuropathology and Experimental Neurology* 57 (10); 885-894

Xie, L., Kang, H., Xu, Q., Chen, M.J., Liao, Y., Thiyagarajan, M., O'Donnell, J., Christensen, D.j.,Nicholson, C., Iliff, J.J., Takano, T., Deane, R., & Nedergaard, M. (2013). *Science* 342 (6156): 373-377