

# Sleep and Alzheimer's Disease: Lacking Sleep, Having Enough Sleep, Sleeping Too Much, and Mental Activities during Daytime

Tingting Pan

The Second Foreign Language School Affiliated to Shanghai Normal University  
Shanghai, 201399, China

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Abstract: This work discusses how does sleep influences the incidence rate of Alzheimer's Disease, from 3 scenarios: lacking sleep, having enough sleep, and sleeping too much. Lack of sleep can be further divided into having a snap during the daytime or not. Some studies proved that sleep disturbances are associated with Alzheimer's Disease from experiments by comparing mice with not enough sleep and with enough sleep. However, they didn't concern about the symptoms of oversleeping, and the mental activities during a human being's life compared to a mouse. Therefore, this work will try to demonstrate that sleep disturbances are associated with the risk of developing AD inherently. Alzheimer's Disease is incurable, but there are ways to reduce the potential of getting it.

## 1 INTRODUCTION

Alzheimer's Disease is a progressive disease, with symptoms like confusion, disorientation, poor concentration, and change in personality, which would become worsen over years. "There are over 55 million people worldwide living with dementia in 2020"(Alzheimer's Disease International. (2020), which means there are about 55 million families suffered from it. Moreover, Alzheimer's disease has heredity, which means it is possible to continue this suffering. More understanding of sleep and Alzheimer's Disease could promote the development of new therapeutic approaches, and benefit all human

beings. Therefore, sleep as one of the factors of Alzheimer's Disease is essential to study.

Some studies proved that sleep disturbances are associated with Alzheimer's Disease from experiments by comparing mice with not enough sleep and with enough sleep. However, these experiments are biased because they didn't mention the symptoms of oversleeping. Also, these experiments are not clear about the situations of mice in the daytime, because normal human beings would have much more mental activities in the daytime than mice, and these experimenters might only afford them water and food during experiment days.

In order to determine different kinds of sleep symptoms' relationship to Alzheimer's

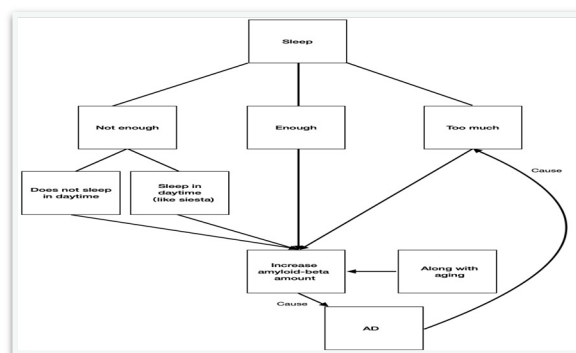


Figure 1: Shows relationships between sleep and AD.

Disease, the experiment would compare the AD pathogenesis in 4 experimental groups and 1 control group. The results might demonstrate that sleep disturbances are associated with the risk of developing AD inherently and explain why people with less sleep and less mental activities are more vulnerable to AD progression.

Sleep can be divide into three kinds: not enough (not enough time or poor quality), enough (about 7 hours), and oversleeping. Lack of sleep can be divide into sleep (like siesta) or doesn't sleep in the daytime. However, all of them will cause the increase of amyloid- $\beta$  ( $A\beta$ ) amount and result in Alzheimer's Disease at a later age.

Studies showed that, "People who slept six hours or less per night in their 50s and 60s were more likely to develop dementia later in life." (Bryant, Erin. 2021). During the sleep, cerebrospinal fluid (CSF) can wash away "harmful waste proteins that build up between brain cells during waking hours."(Hamilton, Jon. 2013)

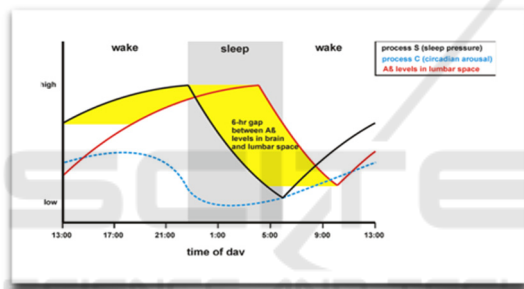


Figure 2: Shows change of  $A\beta$  levels in human between wake and sleep periods. (Cedernaes, Jonathan., et al. 2017).

Therefore, if a person didn't sleep for the whole night, the  $A\beta$  level will increase extremely in his bloodstream and cerebrospinal fluid (CSF). Researchers also found people who are oversleeping (over 9 hours a day) "were twice as likely to develop Alzheimer's" (British Neuroscience Association. 2017). The reason is that most people who are oversleeping have metabolic dysfunction because of obesity and inactivity, which can affect their sleep quality, like diabetes which "can cause sleep loss" (Mann, Denise. 2010). For example, people who are overweight are more likely to have sleep apnea.

Moreover, people with Alzheimer's Disease are often tired during the day but with poor sleeping quality, so it would also cause them to oversleep. Besides, the two kinds (lack of sleep and oversleeping) of sleep disturbances and the normal kind of sleep (enough sleeping during the day) will all be growing the risk of developing Alzheimer's Disease because of aging.

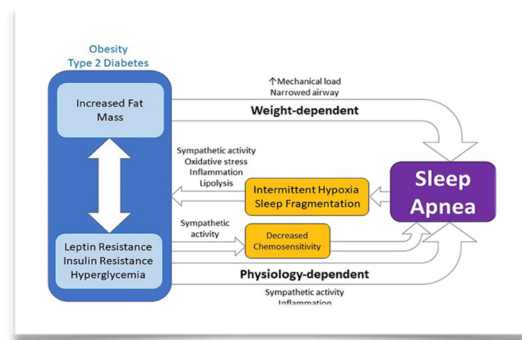


Figure 3: Shows circular relationship between Obesity (Type 2 Diabetes) and Sleep Apnea. (Framnes, Sarah., et al. 2018).

## 2 METHODS AND RESULTS

### 2.1 Animals

In this study, transgenic C57BL/6J mice are used as a model of Alzheimer's disease. The mice are most commonly used as the human disease model because of their availability of homogeneous strains and they are easy to breed. Moreover, the C57BL/6J mice have always been used to study sleep disturbances, because after acute hypoxia, they showed different symptoms of sleep disturbances, like "greater amount of irregular breathing during rest" (Chai, Sam., et al. 2011), which would influence sleep quality.

Because of the average life span for C57BL/6J mice is about 550 days, the experiment starts at the ages of 10 months with 6 mice per cage (3 female and 3 male animals) as a group. Before the experiment started, mice are ad libitum to access water and food at 23 degrees Celsius with 12h-day/12h-night cycles. When the experiment started, four groups of C57BL/6J mice are used for these studies: normal sleep with normal activity (eating, etc.) in the daytime (n=6, 3 female and 3 male animals), abnormal sleep with normal activities, and allowed to take a rest (like siestas in human) during the daytime (n=6), abnormal sleep with normal activities and not allowed to take a rest in the daytime (n=6), and abnormal sleep with mind training in the daytime (n=6). Non-transgenic littermates with normal sleep and mind training in the daytime (n=6) act as the control group because it's closer to normal human beings' daily routine. The animal experiments mentioned above conform to the requirements given by the institutional animal care and animal use committee.

## 2.2 Brain Training

To simulate normal human beings' daily routine, brain training is necessary for the experiment. Clicker training is introduced to certain experiment groups for the enrichment of the cognition of the mice. The training session is last for three weeks, and studies showed “trained mice displayed less of this depression-related behavior” (Leidinger, Charlotte., et al. 2017).

One benefit of this training is that it could be achieved successfully in almost all the mice (“100% of female mice and 83% of male mice”) (Leidinger, Charlotte., et al. 2017).

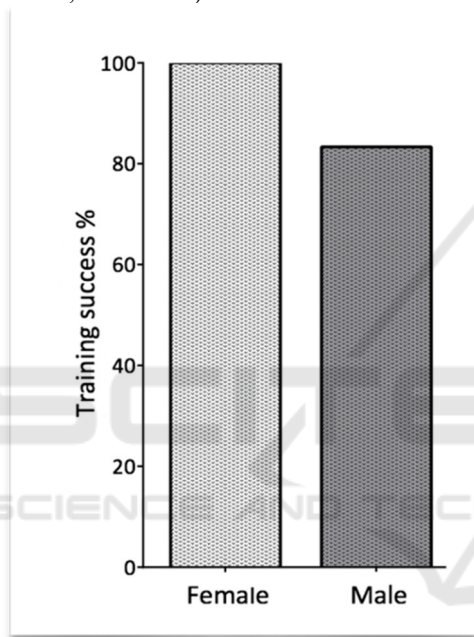


Figure 4: Shows training success rate (Leidinger, Charlotte., et al. 2017)

## 2.3 Histology Aβ Plaque Detection

Positron emission tomography (PET) imaging can “measure physiological function by looking at blood flow, metabolism, neurotransmitters, and radiolabelled drugs” (Berger, Abi. 2003), which include Aβ plaques of a certain region. To detect the Aβ plaques level in five groups of mice, 18F-FC119S, which is a radiopharmaceutical is injected into the mouse. Later, the Aβ plaque level in the brain and also in the cerebrospinal fluid (CSF) can be seen by using PET scanning.

### Tau protein detection:

Positron emission tomography (PET) imaging can also be used for tau protein detection in five groups of mice. To detect the tau protein, 18F-AV-1451 is

injected into the mice's brain as a radio-diagnostic agent. “F-FC119S is a positron emission tomography (PET) tracer for imaging β-amyloid (Aβ) plaques in Alzheimer’s disease (AD)” (Oh, Se Jong., et al., 2018). After that, the tau protein aggregation can be seen by using PET scanning.

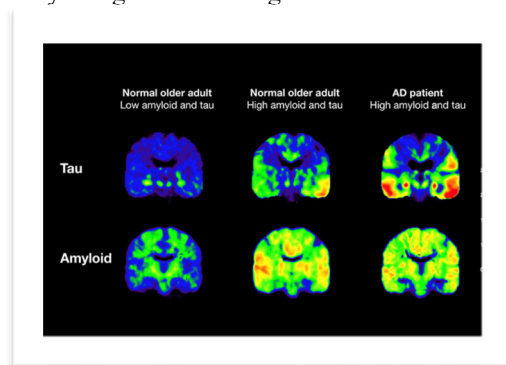


Figure 5: Shows PET scans for Aβ plaque and Tau protein from normal older adult (with low Aβ plaque and Tau protein level), normal older adult (with high Aβ plaque and Tau protein level), and AD patient. (Yang, Sarah. (2016)

## 2.4 Results

Experiment groups with abnormal sleep are assumed to have higher tau protein and Aβ levels, whereas groups with normal sleep have less tau protein because the tau protein and Aβ protein are normally cleared by the glymphatic system, “a cleaning mechanism that functions in the removal of potentially harmful metabolites and proteins from the brain” (Cai, XueZhu., et al. 2020), during sleep.

Take the average and standard deviation of the data (Aβ level, tau protein level) in each group. Then, do the following tests:

### T-test:

H0: There is no difference between 5 groups

H1: group 1 < group 2, 3, 4 < group 5

If  $P \leq 0.05$ , then the results reject the null hypothesis; if  $P > 0.05$ , then the results failed to reject the null hypothesis.

### One-way ANOVA test:

H0: There is no difference among the means of the three test groups.

H1: There is a difference among means of five test groups, and the data of the group 2, 3, 4 lies between group 1 and group 5.

If  $p \leq 0.05$ , then the results reject the null hypothesis; if  $p > 0.05$ , then the results fail to reject the null hypothesis.

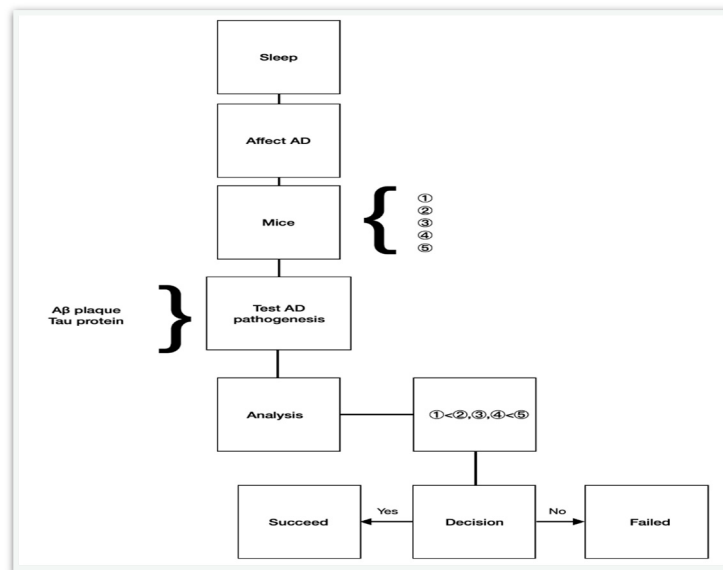


Figure 6: Shows experiment process of the work.

### 3 CONCLUSIONS

#### 3.1 Experiments Review

It is no doubt that sleep can affect the risk of Alzheimer's Disease. Therefore, in the experiment, four groups of transgenic C57BL/6J mice are used as experiment groups, and the non-transgenic mice are the control group.

- ① Non-transgenic littermates with normal sleep and mind training in the daytime (n=6, 3 female and 3 male animals) act as the control group.
- ② normal sleep with normal activity (eating etc.) in the daytime (n=6)
- ③ abnormal sleep with normal activities and allowed to take a rest (like siestas in humans) during the daytime (n=6)
- ④ abnormal sleep with normal activities and not allowed to take a rest in the daytime (n=6)
- ⑤ abnormal sleep with mind training in the daytime (n=6)

After the experiments, A $\beta$  plaques level and Tau protein are detected as AD pathogenesis. After analyzing the data, if it matches the hypothesis that the tau protein and A $\beta$  plaques level in group 1 is less than group 2, 3, 4, and less than group 5, the experiments succeed, and if not, the experiments failed.

#### 3.2 Future Directions

As mentioned in the results, the glymphatic system in the mice brain can clear amyloid- $\beta$  and tau protein during sleep, but it is only in the mice brain. The glymphatic system in the human brain still needs to explore.

Notably, sleep is related to inflammation in the brain, and Alzheimer's Disease can also lead to inflammation. Therefore, the connection between sleep, inflammation, and Alzheimer's Disease is also an essential area to be understood.

Along with aging, the sleeping time will normally decrease in older people, how to improve their sleep quality is a problem that remains unsolved. Moreover, how to lengthen older people's sleep, and if that is helpful to reduce the risk of developing Alzheimer's Disease remains unknown.

The proposed model still needs further research to improve, and here are some suggestions for decrease the risk of developing Alzheimer's Disease.

1. Sleep about 8 hours a day, not less than 6 hours and no more than 9 hours.
2. Siesta should be less than 1 hour a day
3. Focus on sleep quality as well, can use eye patch and sleep aromatherapy, etc. to improve sleep quality.

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