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### Effects of Sleep Deprivation and the Link to Alzheimer's Disease in Night Shift Workers

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**Effects of Sleep Deprivation and the Link to Alzheimer's Disease  
in Night Shift Workers**

A Thesis Presented

by

Aracelia S. Aldrete

To the Keck Science Department  
of Claremont McKenna, Pitzer, and Scripps Colleges

In partial fulfillment of  
The Degree of Bachelor of Arts

Senior Thesis in Neuroscience

December 9<sup>th</sup>, 2019

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## Abstract

Alzheimer's Disease (AD) is a degenerative neurologic disorder that is often defined by beta-amyloid (A $\beta$ ) plaques. These A $\beta$  plaques are formed from protein pieces that are incorrectly cleaved from an amyloid precursor protein (APP). These protein segments, cleaved from APP, are toxic due to increased "stickiness". They cling together to create protofibrils that eventually mature into neuronal plaques. A $\beta$  plaques lead to neuronal cell death causing classic AD symptoms: memory loss, a decline in speech and motor control, and personality changes. One connection between high A $\beta$  plaques levels and AD is chronic sleep loss or disruption. Night shift workers, even if they make up the same hours of sleep after a shift, disrupt their circadian rhythms and alter their sleep-wake cycle. Disruption of sleep leads to A $\beta$  plaque build-up. One suggested function of REM sleep is to "flush" toxins, including these A $\beta$  plaques. Without quality REM sleep, A $\beta$  plaques build in the brain. By using a radiotracer, neuronal plaque level can be measured and the results compared to the varying types of night shift work. Thus, the crucial role that sleep plays in brain health may explain the underlying causes of AD.

## Introduction

### Alzheimer's Disease Background:

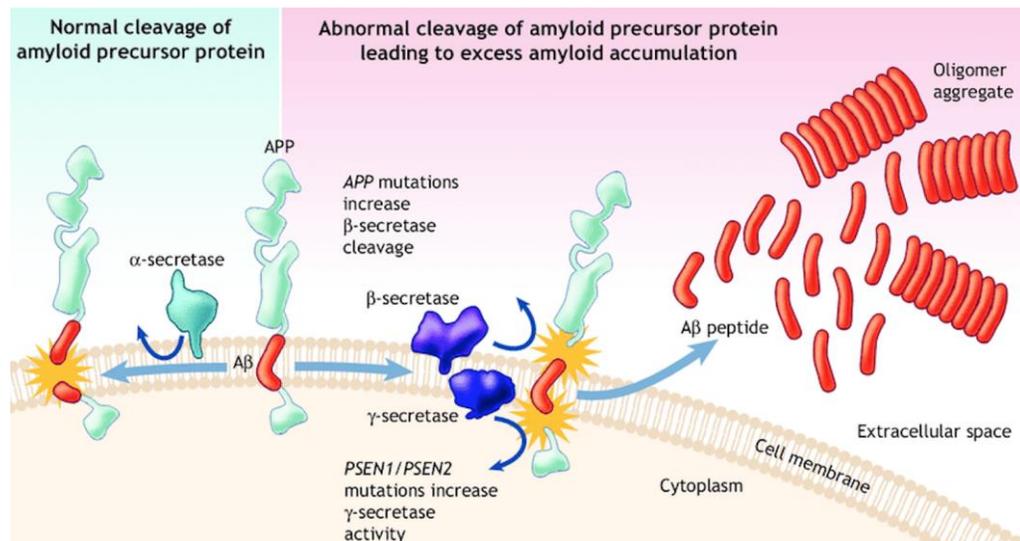
Alzheimer's Disease (AD) is a devastating disease often associated with and described as a progressive neurodegenerative disorder resulting in memory loss, reduction in cognitive function, and confusion (Kumar and Tsao, 2019). It is shockingly common and is the sixth leading cause of death in the United States and is often evaluated based on the Global Deterioration Scale - "GDS" (Kumar and Tsao, 2019). The GDS is a way to classify patients based on observed clinical characteristics related to AD. Stages 1-3 indicate pre-dementia stages while stages 4-7 are associated with dementia. The most notable symptom of AD is memory loss. Often the first few signs of AD are the inability to do small tasks successfully that are usually performed every day. These tasks include: remembering directions to work, being unable to make a meal that has been made several times before, or misplacing personal items, such as car keys in the refrigerator (Kumar and Tsao, 2019). Additional symptoms include issues with speech, mood or personality changes, as well as decreased motor control.

AD is a disease of synaptic failure, which is defined as the diminishing of crucial connections between different parts of the brain, in which the ability for neurons to synapse correctly becomes reduced, decreasing the overall function of the brain. The synapse reduction starts in the hippocampus which is the portion of the brain that primarily deals with memory (Kumar and Tsao, 2019). This would explain why memory loss is one of the first signs of AD. This decreased function is directly correlated with decreased brain mass because as the connections in the hippocampus fail, and neuronal death occurs, these parts of the brain atrophy (Pini et al., 2016). The causes of this synaptic failure in the brain are not fully understood, but some potential causes are: alterations in the blood-brain barrier, decrease in function of metabolic processes, oxidative stress, and brain atrophy caused by A $\beta$  plaques and tau tangles. This last reason has the most support from researchers relating brain changes and AD symptoms (O'Brien and Wong, 2011).

#### Plaques Background:

The main focus of this paper is the beta-amyloid (A $\beta$ ) plaques that are the signature marker of AD (O'Brien and Wong, 2011). The A $\beta$  plaques are formed from sticky A $\beta$  proteins that are cleaved from the amyloid precursor protein (APP). APP is a single-pass transmembrane protein found most densely concentrated in the synapses of neurons (O'Brien and Wong, 2011). The exact function of APP is still unknown. APP in non-AD individuals is cleaved by a non-amyloidogenic process. First, alpha secretase cleaves APP, then, gamma secretase cuts APP, forming a nontoxic beta-amyloid protein. These non-amyloidogenic cleaved portions of APP are thought to help neurons function (Jann, 2010). In contrast, in AD patients, APP is cleaved through an amyloidogenic process. This happens when beta secretase first cuts the APP, followed by cleavage by gamma secretase to form the A $\beta$  protein

(See Figure 1). After the A $\beta$  protein are cleaved from the APP, they form monomers which come together to form oligomers. The oligomers are soluble and, therefore, can spread throughout the brain. The oligomers then convert into protofibrils through a structural change. This change takes the leftover loose A $\beta$  peptide strands and rapidly converts them into  $\alpha$ -helical and parallel  $\beta$ -sheet structures. These newly made protofibrils are now insoluble (Chen et al., 2017). These protofibrils are the precursors to the mature fibrils that are the basis of the plaque formation in neurons. In comparison to the non-amyloidogenic cleaved peptides of APP, which are soluble and non-sticky, these fibrils that undergo the amyloidogenic process are insoluble and sticky. Due to this abnormality, these amyloidogenic A $\beta$  fibrils cling together to form toxic plaques that disable neuron function (Chen et al., 2017). These plaques appear to underlie many of the classic symptoms seen in AD, such as; memory loss, disorientation, mood changes, and motor skill degradation (Kumar and Tsao, 2019).



**Figure 1:** Amyloid precursor protein (APP) cleaving processes in Alzheimer’s Disease (AD) cells and in non-AD cells. The left side, in blue, represents the non-amyloidogenic process creating non-toxic and non-sticky A $\beta$  protein pieces. The right side, in pink, represents the mutated amyloidogenic process that typically occurs in AD patients. Reproduced figure from Patterson et al., 2008.

Although there is extensive research about APP and the different cleaving processes, there is some controversy in how these plaques directly relate to AD symptoms. Although these A $\beta$  plaques initially form in the hippocampus, the progression of their production and dispersion throughout the brain does not necessarily correspond to the symptom advancement that is classically seen in AD. One explanation for this could be the simultaneous creation of tau tangles in the brain. Tau tangles are created from the tau protein, which helps to stabilize microtubules in the axons of neurons. Normally, neuronal axons are entirely lined with this tau protein that holds together and stabilizes the microtubules that make up the neuron. In Alzheimer's, tau is mutated so that it destabilizes, prompting the axon, and, eventually, the entire neuron to degenerate. The axonal tau pieces fall off the neuronal microtubules and combine to form tangles inside the neuron (Jann, 2010). This, in turn, disables the neuron transport system. The neuron transport system is the pathway that neurons use to synapse and communicate with each other. When these portions of the brain die, it causes brain regions to disconnect from each other. These tangles usually originate in the hippocampus, causing tissue shrinkage. This causes the most common and devastating symptom: memory loss (Jann, 2010). The exact mechanism of the relationship between pathology and symptoms is not known, but the current theory is that they work in tandem to cause the classic symptoms we see in AD.

#### Connection with Sleep:

Recently, increased Alzheimer's Disease (AD) risk has been connected to a variety of lifestyle factors. People with poor quality of sleep are more likely to have Alzheimer's compared to those that have quality sleep throughout a lifetime (Brown et al., 2016). As defined by the National Sleep Foundation, shift work is "work that takes place on a schedule

outside the traditional 9 am - 5 pm day. It can involve evening or night shifts, early morning shifts, and rotating shifts” (National Sleep Foundation, 2019). Being a night shift worker means that you get fewer hours of sleep than the rest of the population, therefore not as many REM cycles and not as deep or good quality of sleep (Nabe-Nielsen et al., 2019). One of the most researched theories has been the connection between AD risk with a lack of sleep throughout a lifetime. This bidirectional relationship indicates that the connection between sleep and AD moves both ways because with AD patients, we see a decline in number of sleep hours and an increase in wakefulness during the night time hours (Minakawa et al., 2019). Similarly, people who have had lifetime sleep issues, such as insomnia or sleep apnea, have an increased risk of having AD later in life (Ju et al., 2016).

The main question now is: why? Sleep, specifically rapid eye movement or REM sleep, is believed to help remove the beta-amyloid plaques in the brain (Brown et al., 2016). Studies have shown that 24 hours without sleep significantly raises levels of A $\beta$  plaques in the hippocampus of the human brain (Shokri-Kojori et al., 2018). Based on this research, theoretically, one demographic that would be particularly at risk for AD would be people who work night shifts. A common misconception with people who work night shifts is that they just ‘become nocturnal.’ Night shifts require people to completely alter their sleep-wake cycle by sleep depriving themselves for the shifts. Nocturnal animals, their sleep-wake cycles, and their circadian rhythms are created for the “night shift.” In contrast, the human body cycles are not meant for these hours. For the select few who do work night shifts, it is common to sleep during the day, thereby further altering the natural circadian rhythm of the body. It is inevitable that when working night shifts, the body will lose sleep and be altered in some way for at least 24 hours after the shift.

## Overall Hypothesis:

For the proposed experiment, it is hypothesized that people who participate in a significant amount of night shift work will have higher levels of A $\beta$  plaque buildup in the hippocampus and therefore have an increased risk of developing AD.

## Predictions:

For the Control group getting a regular 6-8 hours of sleep out of 24 hours during a natural daytime sleep-wake cycle, we would expect a significantly lower level of A $\beta$  plaque at both six and twelve months. For the first group, night shift type 1 (NST1), working 4-6 night shifts a month and **not** getting a regular 6-8 hours of sleep out of 24 hours during a natural daytime sleep-wake cycle, we would expect to see a slightly higher than average amount of A $\beta$  plaque level than the Control group at both six and twelve months. For the second group, night shift type 2 (NST2), they will be working 12-18 night shifts a month and **not** getting a regular 6-8 hours of sleep out of 24 hours during a natural daytime sleep-wake cycle. We would expect a significantly higher level of A $\beta$  plaque at both six and twelve months. For the last group, night shift type 3 (NST3), they will be working 18+ night shifts per month and **not** getting a regular 6-8 hours of sleep out of 24 hours during a natural daytime sleep-wake cycle; they will do this for six months. After working night shifts for six months, the group will switch and discontinue all night shift work. For the last six months of the experiment, the NST3 group will stop working all night shifts and will be getting a regular 6-8 hours of sleep out of 24 hours during a natural daytime sleep-wake cycle. Here, for NST3 at six months, we would expect similar results to the NST2 group, therefore, we would see a significantly higher level of A $\beta$ . For months seven-twelve, we would expect the NST3 group to start to mimic the Control group, having a lowered level of A $\beta$  plaque at the

twelve-month measurement. For NST3, it is hypothesized that the results will not be significantly different from the Control group for the third measurement at month twelve.

To control for stress levels during night shifts, cortisol measurements were taken as a control variable. It has been shown that cortisol levels tend to be elevated after a night of sleep loss (Leproult et al., 1997). Therefore, it is hypothesized that cortisol levels would be elevated per amount of sleep lost. Therefore, for NST1, cortisol levels would be slightly elevated throughout the experiment, whereas for NST2, cortisol levels would be elevated in comparison to the control group. For NST3, it is hypothesized that cortisol levels would be elevated for the six months when working night shifts. But, after not working night shifts for six months, we would see a near normal cortisol level measurement at month 12.

Additionally, it is hypothesized that the control group will have normal cortisol levels throughout the entirety of the experiment as they are having no sleep pattern changes.

## Proposed Materials and Methods

### Subjects:

Each subject was given a questionnaire prior to joining the study. This questionnaire inquired about previous sleep habits and jobs, as well as household life. See Supplemental Information #1 for more details. Control group ( $n_{control}=50$ ), NST1 ( $n_{NST1}=50$ ), NST2 ( $n_{NST2}=50$ ), and NST3 ( $n_{NST3}=50$ ) were nurses ( $n_{total}=200$ ) working across three teaching hospitals in one county. Each participant will take a Mini-Mental State Exam (MMSE) at the start of the experiment to ensure a non-abnormal score (between 25-30). See Supplemental Information #2 for more details. See Table 1 for more information per group.

	Mean Age (years)	MMSE Score (average score)	Mean Total Night Shifts Worked at Baseline	Mean Total Night Shifts Worked After 6 Months per Participant	Mean Total Night Shifts Worked After 12 Months per Participant
Control	29	29	0	0	0
NST1	30	30	0	24	48
NST2	28	30	0	90	180
NST3	29	29	0	100	100

**Table 1.** Evaluation of specific characteristics of each group (Control, NST1, NST2, NST3). These include mean age (years), mean MMSE score (average MMSE score), and mean number of total night shifts worked at baseline, six, and twelve months for each participant.

**Setup:**

There were four groups in this experiment (Control, NST1, NST2, NST3). All participants were under the age of 35 and were in their first year of working night shift rotations. The Control group was a group of nurses that had never worked night shifts and therefore slept, at minimum, seven to nine hours a night for one year. NST1 involved nurses who work four-night shifts a month for one year (one night shift a week), therefore getting fewer than five hours of sleep at least four times in every 30 days. NST2 consisted of nurses that work 12 - 18 night shifts a month for one year (3-5 night shifts a week), therefore getting fewer than 5 hours of sleep at least ten times in every 30 days. NST3 comprised of nurses who work 18+ night shifts for 3-6 months and then return to a regular sleep schedule (7+ hours a night) for the remainder of the experimental year.

**Measuring AB Plaques:**

To measure the A $\beta$  plaques in the brain, a radiotracer called Pittsburgh Compound B (PiB) was used. PiB is one of the most widely used ligands for tracing A $\beta$  plaques in living human subjects as it is one of the more accurate tracers (Rowe et al., 2008). In mice testing

trials, PiB was found to have a rapid response in the brain, as well as, to clear out quickly after. In addition, it has been found that PiB has no toxic side effects (Klunk et al., 2004). These results are the reasons why PiB was used for this experiment (Klunk et al., 2004). PiB binds to both A $\beta$ 40 and A $\beta$ 42 plaques, but for the purpose of this experiment, only A $\beta$ 42 was measured. A $\beta$ 42 has been found to be the most insoluble and sticky form of A $\beta$ , therefore the most harmful plaque and the one that would cause the most neuronal damage. For this reason, it will be the only form that will be measured throughout the proposed experiment. The amount of PiB retention in a brain region is equivalent to the amount of A $\beta$  plaques in that portion of the brain (Klunk et al., 2004). PiB was intravenously injected with a similar concentration to what has been used in previous other studies (Klunk et al., 2004). Positron Emission Tomography, or a PET Scan, was used to visualize the PiB retention throughout the brain. The resolution was similar to what has been used in previous other studies (Klunk et al., 2004). Although the entire brain was imaged, the main focus was in the hippocampus.

Each of the four groups would have PiB levels would be measured one month, six months, and 12 months after the start of the experiment can compared to baseline levels at the start of the study: the first, six, and twelfth month of the proposed experiment.

#### Measuring Cortisol Levels:

In addition to measuring plaque accumulation, cortisol levels in the blood were tested to compare the amount of sleep with stress levels. If cortisol levels change during the course of the experiment, then other parts of the brain may also be affected. Cortisol levels were measured directly before, and then after, a night shift. The first measurement took place during the initial portion of the study during one of the first night shifts during the first month of the study. The second measurement was at the six-month marker and was within 24 hours

after a night shift. The last measurement was in the twelfth and last month of the measured year. This was also after a night shift. The measurement consisted of a saliva test that was then analyzed in order to look at cortisol levels.

### Phone Application:

In order to help participants keep track of their sleep-wake cycle, each participant used a smart phone application. This helped eliminate participant memory bias because each person had the ability to record real-time information. This gave the study the best and most up to date information possible therefore eliminating as much variation or bias. This eliminated participants' having to recall or estimate how many hours they worked weeks or months later.

Participants recorded information about each work shift, for both regular day or night shifts. For work times, they recorded the hours worked per shift, the perceived stress level per shift, and their perceived general well-being before and after each shift. Perceived stress level per shift will be measured on a twenty-point scale, from 1 being relaxed and not stressed to 20 being most stress ever felt. The app works so that the participants input their monthly shift schedule into their phone application. From that, the app reminded them before their shift to fill out the "pre-shift" survey. Then, about 8-10 hours later, the "post-shift" survey was made available. Participants were also asked to record their nightly sleep hours and perceived sleep quality.

### Proposed Results

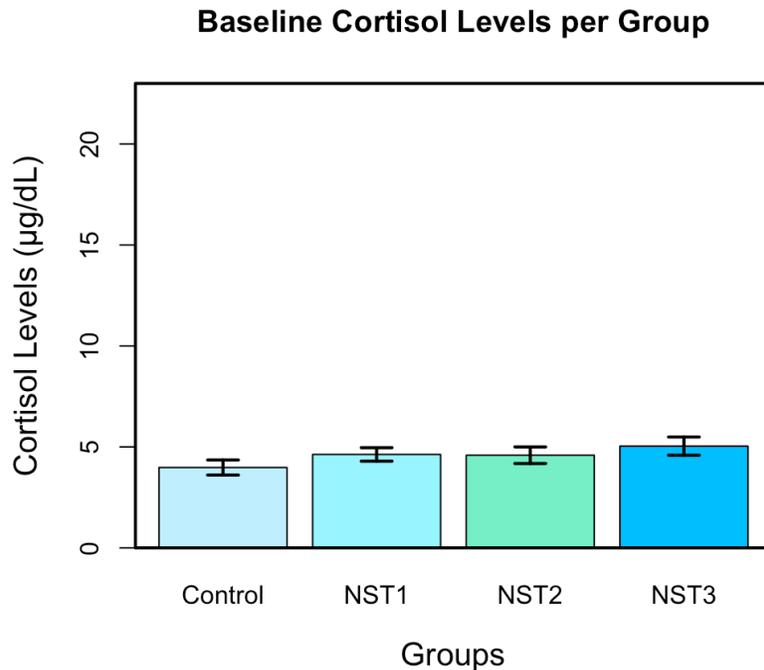
Cortisol levels were measured before the experiment began, at month six, and month twelve. The measurements were taken within the 24 hours after a recent work shift. The cortisol level averages for the control, NST1, NST2, and NST3 groups were 3.98, 4.62, 4.58,

and 5.03, respectively. For the baseline measurements there was no difference among the four groups as no participants had worked a night shift and therefore the body's stress and cortisol levels were relatively low. The six-month measurements of the average cortisol levels for the control, NST1, NST2, and NST3 groups, were 4.88, 11.62, 17.39, and 20.27, respectively. At the six-month measurement, it was seen that the more average total night shifts worked per person directly correlated with a higher cortisol level (Table 1, Figure 2). This was found to be true again, during the twelve-month measurement, where the mean cortisol levels for the control, NST1, NST2, and NST3, groups were 5.82, 16.88, 20.61, and 11.62 respectively (Figure 2).

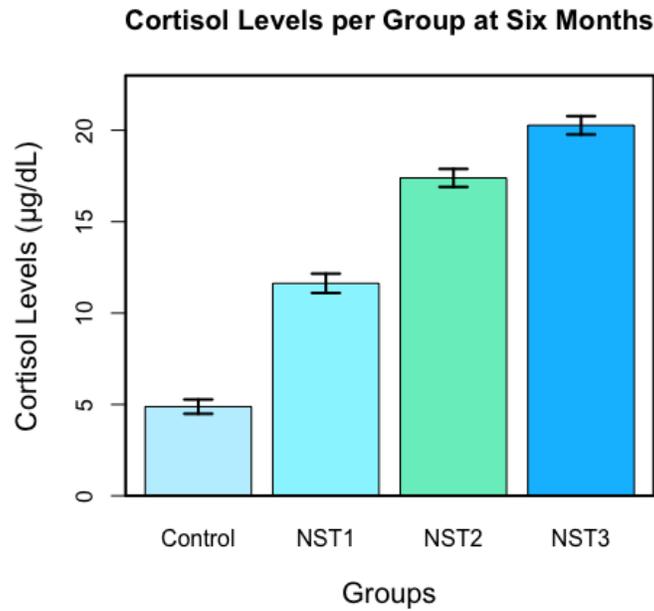
For the A $\beta$ 42 plaque measurement, each of the four groups were measured three times: at baseline, six months, and twelve months. During each measurement period, there were three time measurements taken at 10, 20, and 30 minutes' post radiotracer injection. Because PiB actively binds to A $\beta$ 42 plaques, it can be assumed that the more PiB in the brain over time is indicating a higher A $\beta$ 42 plaques level. The higher the amount of PiB retention, the larger the amount of A $\beta$ 42 plaques in the brain. The baseline measurements were nearly all identical, as none of the participants had worked any night shifts yet. Throughout the experiment, the control group stayed relatively the same, with little to no sleep loss almost no A $\beta$ 42 plaque accumulation throughout the brain. Once the NST1, NST2, and NST3 groups began working night shifts, there was a steady spike in PiB retention. For NST1 at six months, there was some A $\beta$ 42 plaque accumulation in the brain, but it returned to a relatively normal level (Figure 4b). For NST2 at six months, the participants on average worked 90 night shifts (Table 1). PiB retention levels and the A $\beta$ 42 plaque accumulations were significantly higher than the control group. For NST3, there was the highest level of A $\beta$ 42

plaque build up, as well as the longest and largest PiB retention, because at six months this group had worked the highest number of night shifts compared to all other groups (Table 1, Figure 4b). This showed that the participants were working a significant amount of night shifts during the first half (six months) of the experiment, and therefore had some A $\beta$ 42 plaque accumulation. However, as the experiment went on, and they stopped working night shifts for the second half of the experiment, the PiB retention time recovered back to baseline levels at the twelve-month measurement for the NST3 group (Figure 4c). In contrast, in the NST1 and NST2 groups there was an increasingly higher level of PiB retention as they continued to work the most night shifts in comparison to the control and NST3 groups (Figure 4c).

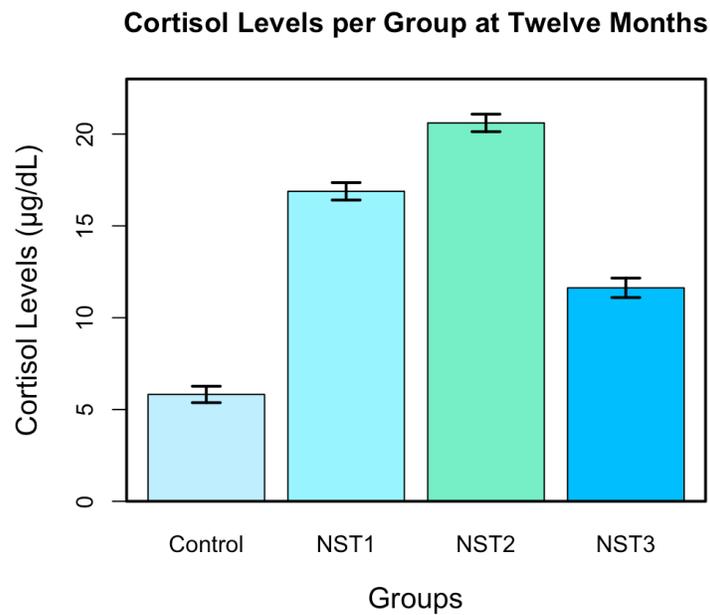
**a)**



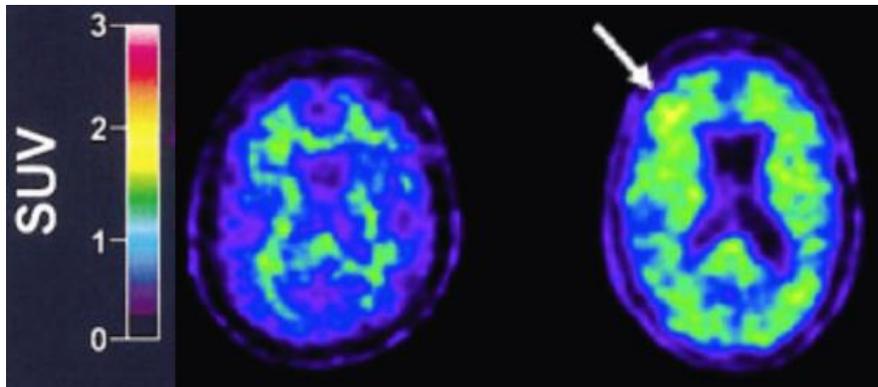
b)



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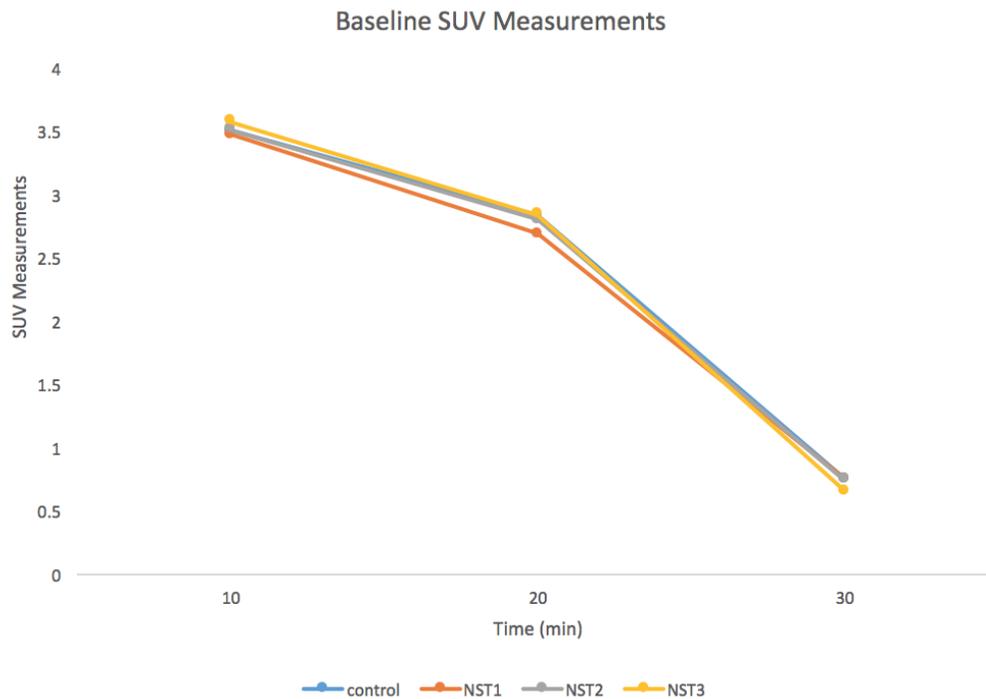


**Figure 2:** Mean cortisol levels measured at each interval of the proposed experiment for Control, NST1, NST2, and NST3 groups. Plasma cortisol levels were recorded from a blood draw from each participant, and then a mean from each group was taken (units:  $\mu\text{g/dL}$ ). Error bars represent 95%  $\pm$  confidence interval. **a)** Baseline cortisol measurement during the first month of the proposed experiment. **b)** Halfway cortisol measurement during the sixth month of the proposed experiment. **c)** End cortisol measurement during the last (twelfth) month of the proposed experiment.

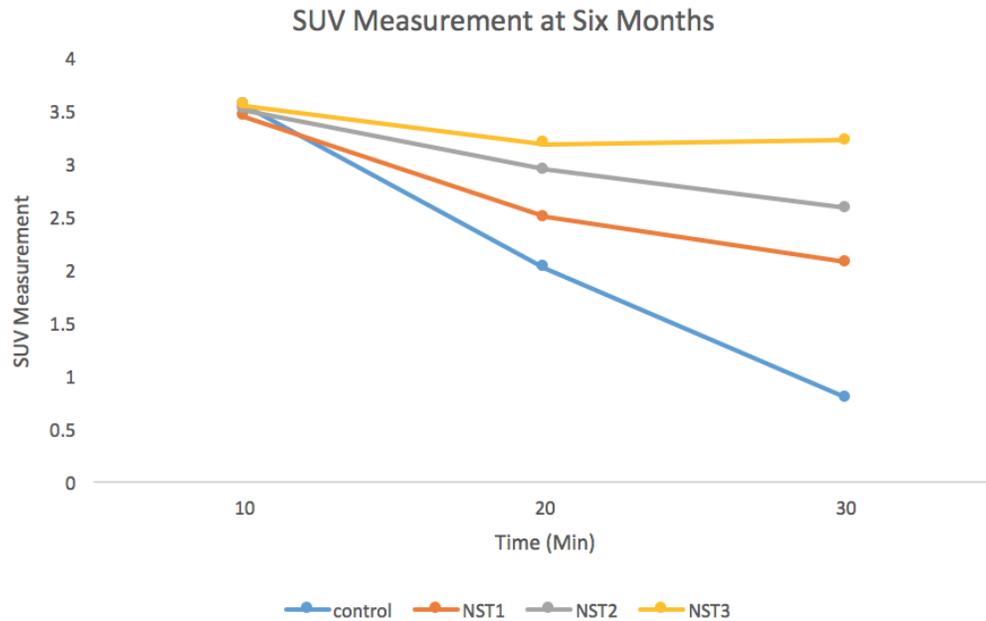


**Figure 3:** PET scan of the brain with PiB standardized uptake value<sup>3</sup> (in green) in a healthy control subject's brain (Left) in comparison to a subject after six months of prolonged sleep-wake cycle disruption (Right). Reproduced figure from (Leyton et al., 2011).

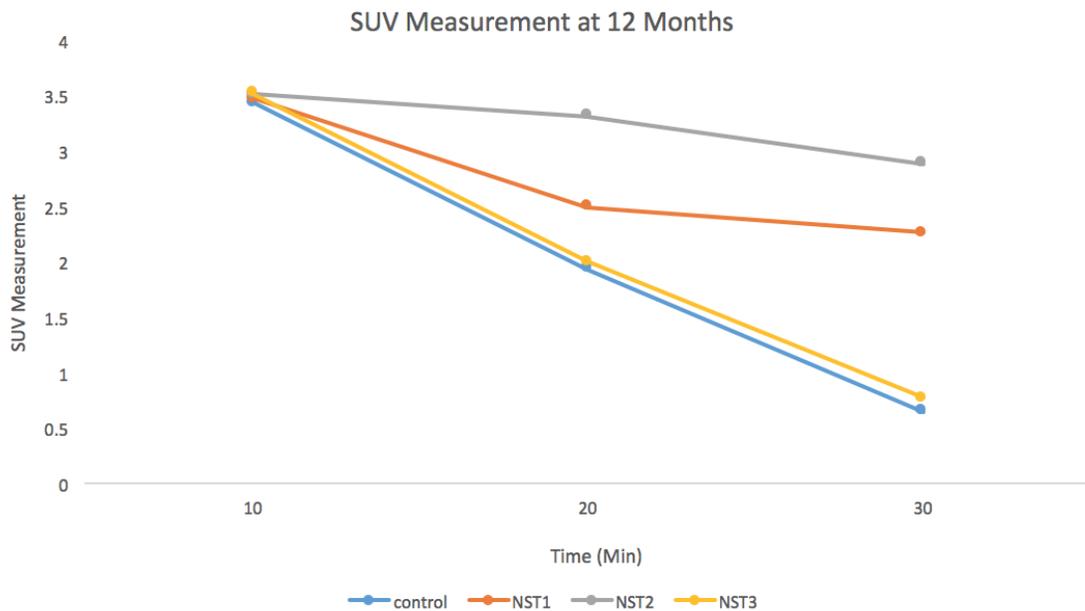
a)



b)



c)



**Figure 4:** Mean of reported standardized uptake value ( $SUV_R$ ) of PiB in the right hippocampus. The  $SUV_R$  correlates to the amount of  $A\beta_{42}$  plaques being bound in the brain. The more  $SUV_R$  measurements after 30 minutes post-PiB injection, the more  $A\beta_{42}$  plaques in the brain. **a)** Baseline  $SUV_R$  measurement before any worked night shifts. **b)** Halfway  $SUV_R$  measurement during the sixth month of the proposed experiment. **c)** End  $SUV_R$  measurement during the twelfth month of the proposed experiment.

## Discussion

The data has shown that there is a strong correlation between chronic sleep deprivation and an increase in A $\beta$ 42 plaques in the brain, in particular, in the hippocampus. Because we know that the sticky A $\beta$ 42 plaques are a large factor in causing AD, it can be seen that sleep disturbance due to night shift work, over a prolonged period of time, can lead to an increased risk of AD (Shokri-Kojori et al., 2018). In order to observe the effects of sleep alteration on the brain, a radiotracer, PiB, as well as a PET scan, were used. PiB binds to the sticky plaque material of A $\beta$ 42, therefore, the higher the levels of A $\beta$ 42 in the brain, the longer PiB will be retained in the brain because it has more material to bind. This peak in A $\beta$ 42 plaque levels was seen to be most prevalent in NST2 at both six and twelve months, as well, as NST3 at six months. Because the PiB retention time recovered back to baseline levels, it can be seen that the brain is able to clear out the A $\beta$ 42 plaque accumulations after a prolonged period of quality sleep recovery (Figure 4c).

For cortisol measurements, there was a significant increase seen in the data for groups working the most amount of night shifts. The NST1 and NST2 groups had the highest cortisol measurements at 12 months. The control groups cortisol measurements were relatively stable and normal throughout the experiment. In contrast, the NST3 group was had the highest measure of cortisol at six months because they had worked the highest number of night shifts. But, after a six-month recovery period, the NST3 cortisol levels decreased significantly, although not entirely back to baseline. These results show that even with a prolonged amount of sleep recovery after working a large total number of night shifts, cortisol levels are not able to entirely return to normal. These results prove that prolonged night shift work, even with a significant recovery period, does act detrimentally on the body.

## Limitations and Follow Up Studies:

One potential limitation for this study could be the fact that PiB has a short half-life. A short half-life has been suggested to make the imaging of the PET scan more difficult because it clears out of the brain faster (Rowe et al., 2008). This is one reason that several studies looking into the connection between sleep deprivation and AD have chosen other radiotracers, such as  $^{18}\text{F}$ -florbetaben (Shokri-Kojori et al., 2018). Another, more novel, radiotracer is  $^{18}\text{F}$ -BAY94-9172, which is a combination of  $^{18}\text{F}$ -florbetaben and PiB, which has also been used in some studies (Rowe et al., 2008). Although having a short half-life has downsides, it has some positives because it is less invasive and clears out of the brain faster, making the analyzing process much quicker for both researchers and participants.

Additionally, another potential limitation for this study could be the fact that a lot of the information is self-reported. The questionnaire, as well as all the information reported in the phone application, is self-reported. Although participants would be asked to be truthful, it would be understandable to see some bias in terms of reporting an incorrect number of sleeping hours, which could potentially skew the researchers' understanding of each participant's sleep-wake cycle. One way to correct this would be to do a minimized version of the study in the lab. For example, having participants be sleep deprived while being observed in the lab and then having their A $\beta$ 42 plaque accumulation levels measured could be a way to significantly control for that sort of bias.

## Conclusion

This proposed study attempts to correlate sleep loss and circadian rhythm disruption with an increased risk for Alzheimer's Disease. The link between these two is the presence of beta-amyloid plaques. These mutated protein segments become toxic and sticky, unlike their

non-mutated counterparts, and eventually create plaques. The clinging nature of these plaques causes disruption of neuronal connections, often causing memory loss, the hallmark symptom of Alzheimer's Disease (Kumar and Tsao, 2019). As lots of previous background research has suggested, losing even one night of sleep can cause significant A $\beta$ 42 plaque accumulation in the brain, and, more specifically, in the hippocampus (Shokri-Kojori et al., 2018). After tracking participants on varying work and night shift schedules, it can be seen that there was a significant increase in A $\beta$ 42 plaque accumulation over a prolonged period of disturbing the sleep-wake cycle. These results implicate that shift work is unhealthy and that the way night shifts are assigned needs to be changed. If a different system could be put in place to allow for adequate recovery, the overall risk of AD could potentially decrease.

## Acknowledgments

I would like to thank Professor Melissa Coleman for her endless support and guidance throughout the process of writing this thesis. I would also like to thank Professor Brian Duistermars for helping me by giving me important comments and posing thoughtful questions. Lastly, I would like to thank the W.M. Keck Science Department, as, without them, this project would not have been possible.

## Supplemental Information

### Supplemental Information #1: Sleep Study Questionnaire

Name: \_\_\_\_\_

Date of birth: \_\_\_\_\_

Address: \_\_\_\_\_

Phone: \_\_\_\_\_ E-mail address: \_\_\_\_\_

In case of emergency, whom may we contact?

Name: \_\_\_\_\_

Relationship: \_\_\_\_\_

Phone: \_\_\_\_\_

Personal physician

Name: \_\_\_\_\_

Phone: \_\_\_\_\_ Fax: \_\_\_\_\_

### Present/Past History

Have you had OR do you presently have any of the following conditions? (Check if yes.)

\_\_\_\_ Recent operation

\_\_\_\_ High blood pressure

\_\_\_\_ Seizures

\_\_\_\_ Diabetes

\_\_\_\_ High cholesterol

\_\_\_\_ Chest pains

\_\_\_\_ Palpitations or tachycardia (unusually strong or rapid heartbeat)

\_\_\_\_ Intermittent claudication (calf cramping)

\_\_\_\_ Pain, discomfort in the chest, neck, jaw, arms, or other areas with or

without physical exertion

\_\_\_\_ Insomnia

\_\_\_\_ Sleep Apnea

\_\_\_\_ Other:

### Family History

Have any of your first-degree relatives (parent, sibling, or child) experienced the following conditions? (Check if yes.) In addition, please identify at what age the condition occurred.

\_\_\_\_ Alzheimer's Disease

\_\_\_\_ Dementia

\_\_\_\_ Parkinson's Disease

\_\_\_\_ Heart attack

\_\_\_\_ Heart operation

\_\_\_\_ Congenital heart disease

\_\_\_\_ Premature death before age 50

\_\_\_\_ Significant disability secondary to a heart condition

- Marfan syndrome
- High blood pressure
- High cholesterol
- Diabetes
- Other major illness:

Explain checked items:

## Activity History

How were you referred to this program? (Please be specific.)

Date of your last physical examination performed by a physician:

Do you have, or have you ever had, issues sleeping, either too much or not enough?

Yes  No  If yes, briefly describe:

Do you have injuries (bone or muscle disabilities) that may interfere with exercising?

Yes  No  If yes, briefly describe:

Do you smoke? Yes  No  If yes, how much per day and what was your age when you started? Amount per day \_\_\_\_\_ Age \_\_\_\_\_

List the medications you are presently taking.

From NSCA, 2012, NSCA's essentials of personal training, 2nd ed., J. Coburn and M. Malek (eds.), (Champaign, IL: Human Kinetics).

**MONTREAL COGNITIVE ASSESSMENT (MOCA)**  
Version 7.1 Original Version

NAME : \_\_\_\_\_  
Education : \_\_\_\_\_ Date of birth : \_\_\_\_\_  
Sex : \_\_\_\_\_ DATE : \_\_\_\_\_

VISUOSPATIAL / EXECUTIVE							POINTS
		Copy cube	Draw CLOCK (Ten past eleven) (3 points)				
[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	___/5	
NAMING							
						___/3	
[ ]	[ ]	[ ]					
MEMORY	Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.	FACE	VELVET	CHURCH	DAISY	RED	No points
	1st trial						
	2nd trial						
ATTENTION	Read list of digits (1 digit/ sec.).	Subject has to repeat them in the forward order [ ] 2 1 8 5 4					___/2
		Subject has to repeat them in the backward order [ ] 7 4 2					
	Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors	[ ] FBACMNAAJKLBAFAKDEAAA JAMOF AAB					___/1
	Serial 7 subtraction starting at 100	[ ] 93	[ ] 86	[ ] 79	[ ] 72	[ ] 65	___/3
		4 or 5 correct subtractions: <b>3 pts</b> , 2 or 3 correct: <b>2 pts</b> , 1 correct: <b>1 pt</b> , 0 correct: <b>0 pt</b>					
LANGUAGE	Repeat : I only know that John is the one to help today. [ ] The cat always hid under the couch when dogs were in the room. [ ]					___/2	
	Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)					___/1	
ABSTRACTION	Similarity between e.g. banana - orange = fruit [ ] train - bicycle [ ] watch - ruler					___/2	
DELAYED RECALL	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUEd recall only ___/5
Optional	Category cue						
	Multiple choice cue						
ORIENTATION	[ ] Date	[ ] Month	[ ] Year	[ ] Day	[ ] Place	[ ] City	___/6
© Z.Nasreddine MD		www.mocatest.org		Normal ≥ 26 / 30		TOTAL	___/30
Administered by: _____							Add 1 point if ≤ 12 yr edu

## Bibliography

- Brown BM, Rainey-Smith SR, Bucks RS, Weinborn M, Martins RN (2016) Exploring the bi-directional relationship between sleep and beta-amyloid. *Curr Opin Psychiatr* 29:397–401.
- Chen G, Xu T, Yan Y, Zhou Y, Jiang Y, Melcher K, Xu HE (2017) Amyloid beta: structure, biology and structure-based therapeutic development. *Acta Pharmacol Sin* 38:1205–1235.
- Devore EE, Grodstein F, Schernhammer ES (2013) Shift Work and Cognition in the Nurses Health Study. *Am J Epidemiol* 178:1296–1300.
- Jann S (2010) Inside the Brain: Unraveling the Mystery of Alzheimer's Disease [HQ]. Available at: <https://www.youtube.com/watch?v=NjgBnx1jVIU> [Accessed November 17, 2019].
- Jorgensen JT, Karlsen S, Stayner L, Hansen J, Andersen ZJ (2017) Shift work and overall and cause-specific mortality in the Danish nurse cohort. *Scand J Work Environ Health* 43:117–126.
- Ju Y-ES, Finn MB, Sutphen CL, Herries EM, Jerome GM, Ladenson JH, Crimmins DL, Fagan AM, Holtzman DM (2016) Obstructive sleep apnea decreases central nervous system-derived proteins in the cerebrospinal fluid. *Ann Neurol* 80:154–159.
- Klunk WE et al. (2004) Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol* 55:306–319. <http://www.ncbi.nlm.nih.gov/pubmed/1499180>
- Kumar A, Tsao JW (2019) Alzheimer Disease. In: StatPearls. Treasure Island (FL): StatPearls Publishing. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK499922/> [Accessed November 10, 2019].
- Leproult R, Copinschi G, Buxton O, Van Cauter E (1997) Sleep loss results in an elevation of cortisol levels the next evening. *Sleep* 20:865–870.
- Leyton CE, Villemagne VL, Savage S, Pike KE, Ballard KJ, Piguet O, Burrell JR, Rowe CC, Hodges JR (2011) Subtypes of progressive aphasia: application of the International Consensus Criteria and validation using  $\beta$ -amyloid imaging. *Brain* 134:3030–3043.
- Lucey BP, McCullough A, Landsness EC, Toedebusch CD, McLeland JS, Zaza AM, Fagan AM, McCue L, Xiong C, Morris JC, Benzinger TLS, Holtzman DM (2019) Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease. *Sci Transl Med* 11 Available at: <file:///Users/celia/Downloads/Lucey-2019-Reduced-nonrapid-eye-movement-sleep.pdf>.
- Minakawa EN, Wada K, Nagai Y (2019) Sleep Disturbance as a Potential Modifiable Risk Factor for Alzheimer's Disease. *Int J Mol Sci* 20.

- Nabe-Nielsen K, Hansen ÅM, Ishtiak-Ahmed K, Grynderup MB, Gyntelberg F, Islamoska S, Mortensen EL, Phung TKT, Rod NH, Waldemar G, Westendorp RGJ, Garde AH (2019) Night shift work, long working hours and dementia: a longitudinal study of the Danish Work Environment Cohort Study. *BMJ Open* 9:e027027.
- National Sleep Foundation (2019) What is Shift Work? | National Sleep Foundation. Available at: <https://www.sleepfoundation.org/shift-work-disorder/what-shift-work> [Accessed December 4, 2019].
- O'Brien RJ, Wong PC (2011) Amyloid Precursor Protein Processing and Alzheimer's Disease. *Annu Rev Neurosci* 34:185–204.
- Patterson C, Feightner J, Garcia A, Hsiung G-Y, MacKnight C, Sadovnick AD (2008) Diagnosis and treatment of dementia: 1. Risk assessment and primary prevention of Alzheimer disease. *CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne* 178:548–556. [https://www.researchgate.net/profile/Ging-Yuek-Hsiung/publication/5551917\\_Diagnosis\\_and\\_treatment\\_of\\_dementia\\_1\\_Risk\\_assessment\\_and\\_primary\\_prevention\\_of\\_Alzheimer\\_disease/links/00b7d5276b77c114b1000000/Diagnosis-and-treatment-of-dementia-1-Risk-assessment-and-primary-prevention-of-Alzheimer-disease.pdf](https://www.researchgate.net/profile/Ging-Yuek-Hsiung/publication/5551917_Diagnosis_and_treatment_of_dementia_1_Risk_assessment_and_primary_prevention_of_Alzheimer_disease/links/00b7d5276b77c114b1000000/Diagnosis-and-treatment-of-dementia-1-Risk-assessment-and-primary-prevention-of-Alzheimer-disease.pdf)
- Pini L, Pievani M, Bocchetta M, Altomare D, Bosco P, Cavedo E, Galluzzi S, Marizzoni M, Frisoni GB (2016) Brain atrophy in Alzheimer's Disease and aging. *Ageing Res Rev* 30:25–48.
- Rowe CC et al. (2008) Imaging of amyloid beta in Alzheimer's disease with 18F-BAY94-9172, a novel PET tracer: proof of mechanism. *Lancet Neurol* 7:129–135.
- Shokri-Kojori E, Wang G-J, Wiers CE, Demiral SB, Guo M, Kim SW, Lindgren E, Ramirez V, Zehra A, Freeman C, Miller G, Manza P, Srivastava T, De Santi S, Tomasi D, Benveniste H, Volkow ND (2018) beta-Amyloid accumulation in the human brain after one night of sleep deprivation. *Proc Natl Acad Sci U S A* 115:4483–4488.
- Van Egroo M, Narbutas J, Chylinski D, Villar González P, Maquet P, Salmon E, Bastin C, Collette F, Vandewalle G (2019) Sleep–wake regulation and the hallmarks of the pathogenesis of Alzheimer's disease. *Sleep* 42 Available at: <https://academic.oup.com/sleep/article/doi/10.1093/sleep/zsz017/5289316> [Accessed October 22, 2019].

Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O'Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T, Deane R, Nedergaard M (2013) Sleep drives metabolite clearance from the adult brain. *Science* 342:373–377.

Yamin G, Teplow DB (2017) Pittsburgh Compound-B (PiB) binds amyloid  $\beta$ -protein protofibrils. *J Neurochem* 140:210–215.