5-2020

Sleep Deprivation Induced Tauopathies

Peter V. Rovito
Philadelphia College of Osteopathic Medicine

Philadelphia College of Osteopathic Medicine
Graduate Program in Biomedical Sciences
School of Health Sciences

Sleep Deprivation Induced Tauopathies

A Capstone in Neurobehavioral Sciences by Peter V. Rovito

Submitted in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Biomedical Sciences, Neurobehavioral Concentration

May 2020

Abstract

Sleep deprivation is a common occurrence among many adults that can have inherently negative effects. While some of these effects are apparent, such as fatigue, irritability, and depressed mood, some are less apparent. One less apparent effect is the increased neural activity that results from being sleep deprived. Chronic Sleep Deprivation leads to increased neurological activity over a prolonged period of time. Researchers have shown that increased neurological activity results in an increase in extracellular tau protein and increased cerebrospinal fluid levels of amyloid beta. Tau protein in particular has been implicated in neurodegeneration because of its propensity for becoming neurofibrillary tangles upon aggregation. Physicians in training in all medical specialties, also known as residents and fellows, airplane pilots, and truck drivers have been known to suffer from sleep deprivation due to the unforgiving hours and context of their work. Understanding exactly how sleep deprivation causes neurological issues and who is most likely to suffer from them is of utmost importance in attempting to reduce the incidence of neurological disorders caused by “Tauopathies” secondary to sleep deprivation. In order to assess potential risk of sleep deprivation amongst individuals in professions with unforgiving hours this review focused on the effects of sleep deprivation as it relates to neurological functions. This investigation specifically examined medical residents and follows who are highly sleep deprived when compared to the rest of the population. An additional literature review was performed in order to determine if sleeping strategies, primarily changing sleep schedules as an interventional effort, could minimize the effects of reduced sleep. If these strategies prove to be effective, this would suggest that implementation of the sleep strategies would be beneficial for the neurological wellbeing of those in training to become physicians.

Introduction

Sleep Fundamentals

No one disputes that sleep is a basic requirement for life. It is commonly believed that a human can exist for around 11 days without sleeping, although it is difficult to imagine anyone managing to stay awake, much less managing to function, for that long. It is interesting to note that there is a rare genetic disorder called fatal familial insomnia; those who suffer from this rare condition can be so seriously unable to sleep and may ultimately result in death. Symptoms of the fatal familial insomnia disorder, due to that the lack of sleep in these patients, may lead to serious cognitive impairment and significant motor disorders, and eventually the body shuts down completely (Llorens et al. 2017). While the vast majority of the population will certainly never have to deal with a genetic disorder which prevents them from being able to sleep at all, the existence of a condition like fatal familial insomnia is a powerful indication for the importance of sleep in human beings.

Sleep deprivation causes some fairly common symptoms in normal individuals. Yawning, moodiness, fatigue, irritability, depressed mood, and forgetfulness are all symptoms that, if observed by others, are often blamed on lack of sleep. These symptoms are commonly seen among students and, when observed, are sometimes utilized by teachers to assess the physical wellbeing of their students. In general, people need around nine hours of sleep for optimal rest in order to avoid these and other negative symptoms resulting from lack of sleep. Additionally, the quality of an individual's sleep is also an important factor which determines the duration required.

Sleep-wake cycle

Sleep is generally separated into two main categories. Each sleep category is identified with its own unique features. These categories are rapid eye movement sleep (REM) which occurs during around 20% of the time an individual is asleep and non-rapid eye movement sleep (NREM) which occurs during around 80% of the time an individual is asleep. NREM sleep is characterized by considerable muscle tone, minor reductions in heart rate, and little or no dreaming; a person sleeping in the NREM stage is easily aroused. REM sleep is characterized by inhibition to muscle tone (sometimes referred to as sleep paralysis), irregular heart rate, and frequent dreaming; an individual sleeping in REM sleep is generally difficult to wake. These two categories are further broken down by duration and stages of unique brain waves.

Sleep begins with non-rapid eye movement sleep for the first three stages. In the first stage the individual is falling asleep, gradually transitioning from being awake into being asleep. Stage 1 NREM sleep is often considered to be the lightest sleep stage and is associated with alpha and theta brain waves. As sleep continues, stage 2 NREM sleep begins; at this point the individual goes into a deeper state of relaxation. stage 2 NREM sleep is associated with primarily theta brain waves, K-complexes, and few spikes referred to as sleep spindles. Some professionals divide stage 3 of NREM into what is often referred to as stage 3 and stage 4. Stage 3 of NREM sleep is associated with delta brain waves, also referred to as slow wave sleep. According to the American Academy of Sleep Medicine, the slow wave portion of the NREM sleep is the most restorative. It has been observed that having an abnormal stage 3 of NREM sleep can cause a wide variety of problems, including issues with the immune system, increased risk of diabetes, problems with memory consolidation, psychiatric disorders, and hypertension (Golrou et al. 2018).

The final stage of sleep before the cycle repeats itself, as it does several times during an average person's sleep period, is REM sleep. REM sleep shows a marked increase in brain activity and an EEG that is very similar to that of an individual who is awake. REM sleep is thought to have an effect on memory, learning, mood, and development. This is the part of sleep during which dreaming occurs. REM sleep brain waves are very similar to those seen when a person is awake.

Sleep rebound is a phenomenon that occurs when an individual is sleep deprived. This lack of sleep causes significant differences in the sleep-wake cycle. When this occurs, the proportion of NREM and REM sleep is altered, resulting in sleep consisting of greater than 80% NREM sleep and less than 20% REM sleep. It is believed that slow wave sleep, which starts in stage 3, is required to maintain homeostasis following a prolonged period of increased neural activity due to wakefulness. (Reichert et al., 2019).

Insomnia

Insomnia is a disorder associated with difficulty falling asleep or continuing to remain asleep once sleep has been achieved. Insomnia is more prevalent in females than males and is believed to occur more often in people who work at odd hours or have irregular shifts. (Winkelman, 2015) Insomnia is the most common sleep disorder and it has a prevalence of 10%15% of the population. The severity of insomnia fluctuates over time. Since people who suffer from insomnia get significantly less sleep than the normal population and it is usually a chronic issue, many of them suffer a variety of symptoms similar to those associated with sleep deprivation. Other sleep disorders can cause insomnia; among these are sleep apnea and restless leg syndrome. (Winkelman, 2015)

Brain structures and sleep-wake cycle

The sleep-wake cycle is heterogenous. This means that the parts of the brain that control the sleep wake cycle are spread throughout the brain rather than just localized in a single area of the brain. While there are several structures that are important in allowing the sleep-wake cycle to function properly, each structure has its own function and they all need to work in tandem for the brain's proper functioning of the sleep-wake cycle. (Gent et al., 2018)

One of the most important structures in the brain is the thalamus; this is often referred to as the "switchboard" of the brain, as it sends and receives neural signals. The thalamus is composed of two lobes that are separated medially by the interthalamic adhesion. The thalamus receives many of its connections from cortical structures that control sleep, especially the midline nuclei of the thalamus where many of these connections meet. Since sleep-wake cycle structures connections pass through the thalamus it is believed that the thalamus has a regulatory role in the sleep-wake cycle. (Gent et al., 2018)

The hypothalamus is another structure that is implicated in the sleep-wake cycle. It is located in the center of the brain, between the thalamus and the pituitary gland. The hypothalamus is responsible for maintaining homeostasis, controlling important processes like hormone production and regulation of body temperature to maintain a steady internal environment. The anterior hypothalamus is believed to be responsible for arousal during the sleep-wake cycle, while the lateral hypothalamus is believed to be responsible for prolonging sleep during the sleep wake cycle. Damage to the hypothalamus has been found to be closely related to sleep disorders. (Gent et al., 2018)

The locus coeruleus is another region of the brain that has a role in the sleep-wake cycle. The locus coeruleus is part of the reticular activating system and plays an important role in arousal. It is the primary norepinephrine producing structure in the brain and is located in the brain stem. It plays an important role in the "fight or flight" response. The locus coeruleus is believed to promote activities like wakefulness, attention, learning and memory (Spiers & Chen, 2019).

The Suprachiasmatic nucleus is another region of the brain that plays a role in the sleepwake cycle. The suprachiasmatic nucleus is located superiorly to the optic chiasm. It regulates the circadian rhythm, which is the internal timing system of the brain controlled by a variety of inputs. It is believed that the retinohypothalamic tract causes a release of glutamate to the suprachiasmatic nucleus in the presence of environmental light. This allows for the distinction between day and night in the circadian rhythm. Additionally, serotonin is input into the suprachiasmatic nucleus from the dorsal raphe in regard to the activity state of the individual. The locus coeruleus alone inputs norepinephrine to the suprachiasmatic nucleus to transmit arousal information. The suprachiasmatic nucleus uses melatonin levels to assess dawn vs. dark. (Abbott et al., 2013)

Sleep Deprivation and Anxiety

The idea that sleep deprivation causes anxiety is not a new concept; however, the extent to which sleep deprivation causes anxiety is not clear. One study showed that sleep deprivation greatly increases anxiety. This could be of significance when taking into consideration how duration and quality of sleep could impact undergraduate or graduate students, as they are likely to have some level of anxiety simply due to the nature of what is required of them in their daily lives. Interestingly, it was shown that sleep restriction did not impact the levels of anxiety experienced**.** Sleep restriction is a strategy used for individuals suffering from insomnia in an attempt to make their sleep more restful, even though the amount of sleep they get is limited. This is accomplished by limiting the amount of time a person tries to sleep to the duration of sleep they generally get in a night. (Pires et al., 2016)

Another study added an additional variable to this concept; researchers wanted to determine if gender played a role and whether men or women were more susceptible to anxiety caused by sleep deprivation. The researchers tested healthy individuals when they were in a state of rest and when they were in a state of sleep deprivation in order to determine their levels of anxiety. While both men and women evidenced increased anxiety as a result of sleep deprivation, it was determined that women were more susceptible to sleep deprived related anxiety than men. (Goldstein-Piekarski et al., 2018) It should be taken into consideration that the fact that women have a higher prevalence of anxiety disorder than men in general and may have played a role in this outcome.

Sleep Habits of Medical Residents

Medical residents play a very important role in hospitals and patient care; they are analogous to “foot soldiers” for their attending physicians, who are analogous to “generals” of the hospital. Residents assume the demanding dual roles of both student of medicine and provider of patient care. Hospitals rely heavily on work provided by residents to provide consistent and valuable care, for which they generally receive government subsidies, in order to maintain their budgets. Residents are expected to carry out a wide variety of duties that require them to be constantly vigilant when it comes to their patients. These duties can include initial and ongoing assessment of patients, which can involve their mental, physical, and psychological wellbeing. Residents are often required to perform detailed physical examinations on their patients and record relevant data. In addition to understanding and recording patients' personal and family medical histories, residents also monitor patient progress and, in conjunction with the attending physician and possibly other residents at varying levels of training, determine a treatment plan, which residents are often responsible for implementing. Residents order tests, perform examinations, order medicine and therapies, and perform procedures under attending physician or senior resident supervision. In addition to a myriad of duties which directly impact patient care, residents are also responsible for a wide variety of academic materials, research, and preparation for standardized exams at various levels of their training and based on their chosen specialty. With all of these responsibilities, and many others, it is reasonable to assume that some residents may be stressed and lose sleep as a result of it.

When considering the sleeping habits of medical residents, it is also important to take into consideration the high number of hours they are required to work in order to complete their assigned tasks. Stress alone is not the only reason that many are sleep deprived. During the first years of their training, residents are generally expected to subject themselves to grueling work hours. At the current time, residency programs are not permitted to schedule residents to work more than 80 hours a week due to regulations imposed on hospitals by the Accreditation Council for Graduate Medical Education (ACGME), which oversees residency programs nationwide. However, during these 80 hours they are allowed to work up to a 28-hour shift, 24 of which are technically working and an additional four of which they responsible for managing the delegation of care of their patients to their resident replacements. ACGME guidelines, only impact the number of hours residents spend working inside the hospital. Most residents devote many more hours to the academic component of residency, including keeping up with journals, doing research, and studying for standardized testing for licensure. On its face, in any residency program that requires its residents to put in an 80-hour work week, it seems fairly obvious that sleep deprivation would be an issue. It's important to realize, however, that the 80-hour guidelines have been in effect only since 2011. Prior to that, it was not uncommon for medical residents to work even more than 80 hours in a week, depending on their specialty and the specific rotation in which they were engaged at any given time. (Mercer, 2019)

A study conducted in 2005 focused upon the sleeping patterns of residents prior to the 80-hour limitation imposed by the ACGME. Utilizing a web-based survey to gather information, researchers looked at the sleep schedule and hours of work done by 2,737 first year residents. Specifically, this study assessed the level to which their cognitive and physical functions were affected in regard to their ability to drive a motor vehicle and potentially become engaged in vehicular accidents. The results of this study indicated that extended shifts in the hospital increased the likelihood of motor vehicle accidents, due to the fatigue experienced by the firstyear residents. The study also concluded that that working for extended periods of time with too little sleep poses a safety risk for those employees.

A study on depression, sleep deprivation, and the number of perceived medical errors was performed on 1,215 nondepressed first year medical residents to determine if sleep deprivation due to the nature of their work increased the chances that the residents would become depressed. In this study, the amount of sleep (more or less than 6 hours of sleep a night) was compared to the number of hours they were working (more or less than 70). After researchers gathered information from three different time points, it was shown that decreased sleep and increased work hours positively correlated with depression in first year medical residents. In addition to showing that there was a correlation between decreased sleep and depression, it was also shown that poor sleep habits prior to residency increased the likelihood of depression. Additionally, the research indicated that first year residents who were depressed, had poor sleep habits, and worked long hours also had a higher incidence of perceived medical errors. (Kalmbach et al., 2017)

Several arguments have been made for why the maximum number of hours worked by medical residents was correctly reduced to 80, rather than 100 or more hours in a week. Not surprisingly, disagreements about limiting the number of residency work hours continue among medical professionals continue to this day. At the time the changes were being debated among medical educators, arguments for reducing the number of hours included better patient care, fewer mistakes, better physical and emotional wellness for the residents, and the hope that working fewer hours would decrease the likelihood of physician burnout. Conversely, some medical educators believed that decreasing hours would cause residents to be poorly trained, particularly in some surgical specialties which require minimum numbers of procedures to be performed in order for residents to graduate and obtain certification. There have also been arguments regarding continuity of care, with some professionals warning that requiring residents pass off their patients to new residents at the end of shifts could result in diminished care because the new resident wouldn't have as much information or insight into patients' conditions. Research has indicated that patient care has actually improved slightly since the decrease in maximum hours. The percentage of improvement demonstrated by that research was so slight, however, that it is unclear as to whether the improvement was the result of better judgement and enhanced performance because residents were better rested, or if the hospitals featured in the study have improved in other ways since the change in work hours was instituted. (Mercer, 2019)

The thought that they are being cared for and treated by physicians who may be sleep deprived and suffering from the negative physical symptoms of sleep deprivation is very likely alarming to patients and the public in general; public outcry played a part in the ACGME's decision to require a reduction in hours for residents. Beyond day to day challenges or public perception, though, it is additionally important to consider the reality of what is happening to the brains of the physicians as a result of years of sleep deprivation experienced during their education, training, and active career. For many reasons, not the least of which is the ability of physicians to provide the best quality care for as long as they are able, the potentially negative effect of decades of sleep deprivation is not something to be ignored among medical professionals. Some studies have even suggested that sleep deprivation can lead to increased neural activity and even neural degeneration (Holth et al., 2019).

<u>Truck Driver Sleep Habits</u>

Among professions which suffer from sleep deprivation as a regular component of their work, truck drivers are an important profession to take into consideration. Truck drivers are responsible for operating very large pieces of machinery which can become lethal weapons if a driver makes an error as a result of sleep deprivation. Not only do these individuals operate large machinery on public highways, often surrounded by passenger vehicles, there were 3.5 Million truck drivers on the road in the U.S. in 2018, engaged in moving over 70% of the nation's domestic freight. Clearly, ensuring the safety of both truck drivers and those who share the road with them is an important issue. Auto accident data indicates that truck drivers are significantly more likely to die from motor vehicle accidents than the rest of the population. Collateral damage is also an issue that must be considered, as an accident involving a commercial vehicle or tractor trailer is more likely to result in the deaths of people in other vehicles who are just using the roads for travel. The cost of managing damage, medical costs, and first responders as a result of commercial vehicle or tractor trailer truck crashes is staggering; it is estimated these costs were roughly $99 Billion in 2012, according to the Federal Motor Carrier Safety Administration. In addition to protecting human lives on the roads, this truly staggering cost further highlights the importance of making sure that truck drivers are working as effectively as possible. (Chen et al., 2016)

A study conducted in 2000 suggested that sleep deprivation was a variable in 47% of the truck crashes that year that resulted in a fatality. (Heaton, 2005) Industry data indicates that the number of accidents rises with the number of continuous hours driven. Another issue facing truck drivers is that they may not personally notice the signs of sleep deprivation. They may think that they are fine and do not need to sleep; since they are so accustomed to doing their jobs they may not realize they are performing less efficiently than usual. Many truck drivers opt to do a significant portion of their driving during the night because there are few people and less traffic on the roads so that they can reach their destinations more quickly. Earlier in this paper, the function of the suprachiasmatic nucleus was discussed. It is possible that lack of exposure to light as a result of nighttime driving could also affect truck drivers' circadian rhythm and make them more inclined to fall asleep while driving.

In an attempt to prevent and reduce fatigue-related accidents among truck drivers, the Federal Motor Carrier Safety Administration imposed several regulations on commercial transport companies which were passed in 2011, the same year as ACGME imposed work hour limits for residents, and went into effect in early 2012. These regulations apply to drivers transporting weights of 10,001 pounds or more and include the "hours-of-service" limits. The hours-of-service limits mandate how long drivers are permitted to operate a commercial vehicle before they are required to stop for rest. The limit is not based on a 24-hour period of time, but rather how long the driver has been driving compared to how long they have not been driving. A driver who has been off duty for 10 consecutive hours is permitted to be on duty for 14 hours, 11 hours of which may be used for driving. There are also provisions which impact the number of cumulative hours a driver is permitted to drive on a weekly basis. Provisions of the hours-ofservice regulations have continued to be refined and updated since their imposition. (FMCSA. 2015)

Commercial Airline Pilot Sleep Habits

People utilize air travel every day and most planes carry several hundred people. Most would agree that flight crews of commercial airliners need to be well rested in order to perform their jobs as safely and efficiently as possible. A fatigue-related error on one of their parts could potentially be fatal to their passengers. And even if an error does not occur, if there is any kind of problem the crew needs to be prepared to effectively handle the situation and protect the lives of their passengers. For these reasons it is important to take into consideration the amount of sleep gotten by airline crews and pilots to make sure they are functioning optimally, both physically and mentally.

A study took enrolled 237 pilots, monitored their sleep, asked them to keep log-books, and measured their response time. This was done before, during, and after scheduled flights. They found that pilots who got more sleep in the 24 hours leading up to piloting were less tired prior to the flight and reported less fatigue during the flight. The researchers used “domicile” time as the pilot’s normal time schedule; domicile time was calculated as the time of the location where the flight began. Time zones add an interesting variable to sleep schedules of pilots. The location from which a flight originates might be the middle of the day for that location, whereas a pilot's natural circadian rhythm for where they live could be the middle of the night. The researchers note that if domicile time was night or early morning when a flight was departing the pilots reported additional sleepiness and fatigue before and during the flight. Interestingly, the researchers did not report a change in the response time of the pilots due to their amount of sleep; it is thought that this may have been due to only moderate levels of fatigue among the participating pilots or that pilots have atypically fast responses. (Gander et al., 2015)

Regulations regarding how long pilots are allowed to work were set by the Federal Aviation Administration in 2011. A pilot's duration of work begins at the start of a work day and can range from 9-14 hours if the aircraft is operating with a single flight crew. If there are multiple flight crews the time is extended to 13-19 hours, as pilots are able to rest and work in shifts. Rest periods for pilots are a minimum of 10 hours and there are no provisions to reduce this. In addition to mandating a maximum and a minimum amount of time that a pilot can fly and sleep respectively, pilots are permitted to fly a maximum of 60 hours a week. In addition, pilots cannot exceed 290 hours in a 28-day period or 1,000 hours in 365 days. (FAA. 2011) These requirements may seem strict, but the importance of the role of pilots and their duty to passenger safety merits realistic limits.

It is interesting to note that work hour limitations designed to ensure that medical residents, truck drivers, and pilots are able to obtain adequate hours of sleep in order to better perform their professional duties were all adopted in 2011.

Alzheimer’s Disease

Alzheimer’s disease is the most common cause of dementia and accounts for the majority of dementia cases. While this is true, there are certain actions or risk factors that may increase the likelihood of getting Alzheimer’s disease. In this literature review, we are specifically looking at the impact of sleep deprivation as it pertains to the acquisition of Alzheimer’s disease (Qiu, H. et al., 2016). There are many symptoms associated with Alzheimer’s disease but some of the most common and notable are: problems with memory difficulty handling finances, forgetting the location of objects, reduced awareness of recent events, difficulty completing complex tasks, issues with concentration, and mood alternations (Bayles, 1991). Interestingly and perhaps ironically, many of these symptoms are the same as symptoms displayed by people who are sleep deprived (Qiu, H. et al., 2016).

Alzheimer’s disease can be categorized into two primary types, early-onset Alzheimer’s disease, also known as familial Alzheimer’s disease or Late-onset Alzheimer’s disease, also known as sporadic Alzheimer’s disease. Each form of Alzheimer’s disease is classified by the age of patient at first presentation of symptoms. If an individual is under the age of 65 and presents with Alzheimer’s-like symptoms, they are classified as having early-onset or familial Alzheimer’s disease, which is considered to be most likely caused by a genetic factor. If an individual is over the age of 65 and presents with Alzheimer’s-like symptoms, they are classified as having late-onset or sporadic Alzheimer’s disease, which is most likely due to an accumulation of environmental factors. (Zein et al., 2019)

Alzheimer’s disease is a result of neuronal cell death which causes the brain to acquire a unique appearance, having narrow gyri and wide sulci in the frontal and temporal lobes. This appearance indicates that brain mass has been lost. In addition to narrowing and widening of gyri and sulci respectively, the ventricles of the brain enlarge greatly. The characteristic pathologies observed in Alzheimer's disease are the abnormal processing of tau protein (causing neurofibrillary tangles and neuropil threads) and amyloid beta protein (causing neuritic plaques). Accumulation of these proteins into insoluble complexes is believed to be the cause of neuronal cell death.

There are many factors that are being studied that may contribute to the neurodegeneration associated with Alzheimer's disease and other cognitive impairments. Recently, pathogens, such as Chlamydia pneumonia, have been implicated as a trigger for initiating the neuro-inflammation associated with the cascade of events leading to the pathogenesis characteristic of Alzheimer's disease (Balin et al. 1998). However, many of these factors and mechanisms have yet to be elucidated.

Tau

The tau protein is a microtubule-associated protein that is generally found in neurons, most commonly found in the distal portions of axons; it acts to stabilize the axonal microtubules. Neurodegeneration and cognitive impairment caused by the accumulation of tau protein and its propensity for forming into neurofibrillary tangles and neuropil threads have been referred to as "tauopathies." The exact mechanism of the formation of neurofibrillary tangles is not completely understood. It is believed that paired helical filaments become neurofibrillary tangles cross linked by transglutaminase. The composition of these paired helical filaments comprises several variations of the tau protein, namely tau 16, 18, 25, 34 and 36 (Appelt & Balin, 1997). The hyperphosphorylation of the tau protein causes it to change shape and, rather than supporting and maintaining the microfilaments, it detaches and aggregates with other tau proteins that have also been hyperphosphorylated. These neurofibrillary tangles are insoluble, which prevents the cell from breaking them down as they begin to accumulate. The accumulation of these tangles in conjunction with less tau protein maintaining microtubules results in poor signal transduction in neurons and ultimately neurodegeneration.

<u>Amyloid Beta</u>

In addition to tau, amyloid beta precursor protein has been implicated in neurodegeneration leading to Alzheimer's disease. Amyloid beta precursor protein is a transmembrane protein located in the neuron cell membrane. It is believed that it is a structural protein and may function in neuronal growth and repair following injury. Amyloid precursor protein is processed in one of two pathways, one of which is pro-amyloidogenic and one that is non-amyloidogenic. If amyloid beta precursor protein is initially cleaved by α-secretase (ADAM10), it leads to the non-amyloidogenic pathway. However, if the amyloid precursor protein is cleaved by β-secretase (BACE1), it leads to the pro-amyloidogenic pathway. αsecretase cleavage produces a carboxy terminal fragment of C83 whereas, β-secretase cleavage produces a carboxy terminal fragment of C99. In both pathways a second cleavage is performed by γ-secretase (PSEN). The non-amyloidogenic pathway is when the C83 is cleaved by γsecretase into an intracellular fragment and an extracellular fragment which are both soluble. In the pro-amyloidogenic pathway C99 is cleaved by γ-secretase into an intracellular fragment and an extracellular fragment. Of the extracellular fragments, those with 42 amino acids are the most neurotoxic due to the hydrophobic nature these fragments aggregate in the extracellular space becoming senile plaques. In late-onset or sporadic Alzheimer's disease it is believed that environmental factors cause ADAM10 and BACE1 to function differently by promoting the proamyloidogenic pathway. In early-onset or familial Alzheimer's disease mutations have been identified in amyloid precursor protein and in PSEN the lead to the formation of the 42 amino acid length fragments. (Zein et al., 2019)

Sleep Deprivation Related Tauopathies

In a study, researchers found that interstitial fluid levels of tau in mice and CSF tau in humans increased when they were sleep deprived. In order to test this, researchers manually kept mice in a lab awake and then measured the levels of tau present in their interstitial fluid. When compared to the control group there was a roughly a 100% increase in tau in the ISF of the sleep deprived mice. In addition, an increase in both tau and amyloid beta was measured in the CSF of human participants after one night of sleep deprivation. The researchers stated that they believed this was due to an increase in neural activity caused by the sleep deprivation. (Holth et al., 2019)

Discussion

Sleep deprivation

There is no question that sleep deprivation causes cognitive and physical deficits. The Federal Aviation Administration, Federal Motor Carrier Safety Administration, and the Accreditation Council for Graduate Medical Education have demonstrated their understanding of this phenomenon through adoption and implementation of regulations limiting work hours in order to ensure adequate sleep. Medical residents, commercial truck drivers, and airline pilots have people’s lives in their hands on a daily basis. They need to perform as efficiently and effectively as possible in order to ensure that there are as few accidents or errors as possible.

A reduction in physical or cognitive functioning for a medical resident in particular could result in the resident exercising poor judgement or making a mistake which can result in loss of life. For a commercial truck driver, sleep deprivation could result in falling asleep at the wheel or slower than usual reflexes, either of which could cause a potentially fatal accident involving not only themselves but other individuals using the nation’s roads. Similarly, but more seriously, if lack of adequate sleep causes a pilot to make an error or to handle a mechanical problem in a less than optimal manner, hundreds of passenger’s lives could be put at risk. In all three cases, it is vital that these professionals are able to obtain an appropriate amount of rest in order to perform their duties safely.

While there was no direct link established to sleep deprivation and Alzheimer’s disease it was interesting that Holth et al in 2019, were able to demonstrate that sleep deprivation did increase ISF tau in mice and tau and amyloid beta in CSF in humans. Both Tau and amyloid beta are increased in people who suffer from Alzheimer’s disease.

In addition, it is interesting to note that several of the symptoms associated with severe sleep deprivation are also common in Alzheimer’s disease. Such symptoms include memory loss, confusion, and trouble concentrating.

Future Research

There are several different areas regarding the topic of sleep deprivation which could benefit from future research. Research regarding ideal sleeping patterns should continue to be pursued. In some cases, sleep restriction is utilized for people suffering from insomnia in an attempt to make the limited sleep that they do get more efficient. While this might not be applicable to the general public, there might be some professions in which workers do not actually suffer from insomnia but who work hours which mimic the same amount of sleep generally gotten by those who suffer from insomnia; such people might benefit from sleep restriction. In addition to improving the efficiency of sleep, studies which help us to understand what type of sleep works best to keep the brain functioning cognitively well could be beneficial. Such research would be especially useful when considering jobs that make sleeping for a solid eight to nine hours difficult. This research should include monitoring the cognitive functioning of participants who attempt different sleeping patterns with stringent schedules, as if they were working at a job with demanding hours. The goal of such research would be to find a sleeping pattern that allows individuals who do not sleep enough to get a comparable level of rest from their limited sleep as individuals who do get enough sleep.

Another avenue for research could be the idea of intermittent sleep. Commercial trucks often contain a sleeper berth which allows drivers to sleep comfortably in their truck if the opportunity presents itself. The Federal Motor Carrier Safety Administration even allows them to put their maximum of 14 hours of on-duty time on pause during their sleep. This research could analyze different periods of time in which individuals are allowed to sleep in order to see which specific amount of time or combination of shorter periods of sleep could most closely mimic a full night of sleep. Provided results show promise, changing the sleeping patterns of workers could potentially increase the efficiency and efficacy of their work.

Another avenue that could be pursued in future research might be the impact of sleep deprivation on the development of neurologic disorders later in life. Tauopathies occur because of increased levels of tau. As (Holth et al 2019) demonstrated, the stress caused by sleep deprivation increases CSF tau and amyloid beta in humans. Neurologic disorders like Late-onset or sporadic Alzheimer's disease have a constellation of environmental factors believed to contribute to their development; it would be interesting to look at the effects of sleep induced increased tau and amyloid beta in regard to neurodegeneration.

While we're waiting for such research to be completed, professionals who are frequently faced with inadequate opportunities to get the rest they need, along with the organizations which regulate their work and professions, would be well served to consider and implement additional measures to ensure that they obtain adequate rest. Additional research could increase their own safety and wellness as well as the safety and wellness of those they serve. This is especially important for those in the medical profession, whose training and work schedules are far too often characterized by chronic lack of sleep.

References

Abbott, S. M., Arnold, J. M., Chang, Q., Miao, H., Ota, N., Cecala, C., . . . Gillette, M. U. (2013). *Signals from the brainstem sleep/wake centers regulate behavioral timing via the circadian clock* Public Library of Science. doi:10.1371/journal.pone.0070481

Al-Atrache, Z., Lopez, D. B., Hingley, S. T., & Appelt, D. M. (2019). Astrocytes infected with chlamydia pneumoniae demonstrate altered expression and activity of secretases involved in the generation of β-amyloid found in Alzheimer disease. *BMC Neuroscience, 20*(1), 6. doi:10.1186/s12868-019-0489-5

Appelt, D. M., & Balin, B. J. (1997). *The association of tissue transglutaminase with human recombinant tau results in the formation of insoluble filamentous structures*. Brain Res. 745:21-31, 1997.

Balin, B.J., Gerard, H.C., Arking, E.J., Appelt, D.M., Branigan, P.J., Abrams, J.T., WhittumHudson, J.A.,and Hudson, A.P.: Identification and Localization of *Chlamydia pneumoniae* in the Alzheimer's Brain. Med. Micro. & Immunol. 187:23-42: 1998.

Barger, L. K., Cade, B. E., Ayas, N. T., Cronin, J. W., Rosner, B., Speizer, F. E., & Czeisler, C. A. (2005). Extended work shifts and the risk of motor vehicle crashes among interns. *N Engl J Med, 352*(2), 125-134. doi:10.1056/NEJMoa041401

Bayles, K. A. (1991). *Alzheimer's disease symptoms: Prevalence and order of appearance* doi:10.1177/073346489101000404

Chen, G. X., Fang, Y., Guo, F., & Hanowski, R. J. (2016). The influence of daily sleep patterns of commercial truck drivers on driving performance. *Accident; Analysis and Prevention, 91*, 55-63. doi:10.1016/j.aap.2016.02.027

Federal Aviation Administration. (2011). Fact sheet- pilot fatigue rule comparison . Retrieved from https://www.faa.gov/news/fact_sheets/news_story.cfm?newsKey=12445

Federal Motor Carrier Safety Administration. (2015). *Interstate truck driver's guide to hours of service*

Gander, P. H., Mulrine, H. M., van den Berg, M. J., Smith, A. A., Signal, T. L., Wu, L. J., & Belenky, G. (2015). Effects of sleep/wake history and circadian phase on proposed pilot fatigue safety performance indicators. *Journal of Sleep Research, 24*(1), 110-119. doi:10.1111/jsr.12197

Gent, T. C., Bassetti, C. L. A., & Adamantidis, A. R. (2018). *Sleep-wake control and the thalamus* Elsevier Ltd. doi:10.1016/j.conb.2018.08.002

George S., B. (2014). *Amyloid-β and tau: The trigger and bullet in Alzheimer disease pathogenesis* doi:10.1001/jamaneurol.2013.5847

Goldstein-Piekarski, A., Greer, S. M., Saletin, J. M., Harvey, A. G., Williams, L. M., & Walker, M. P. (2018). *Sex, sleep deprivation, and the anxious brain* MIT Press. doi:10.1162/jocn_a_01225

Golrou, A., Sheikhani, A., Motie Nasrabadi, A., & Saebipour, M. R. (2018). *Detecting slow wave sleep and rapid eye movement stage using cortical effective connectivity* Scientific and Technical Research Council of Turkey. doi:10.3906/elk-1804-163

Heaton, K. (2005). Truck driver hours of service regulations: The collision of policy and public health. *Policy, Politics & Nursing Practice, 6*(4), 277-284. doi:6/4/277

Holth, J.K., Fritschi, S.K., Wang, C., Cirrito, J.R., Mahan, T.E., Finn, M.B., Fuller, P. M. (2019). *The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans* American Association for the Advancement of Science. doi:10.1126/science.aav2546

Ju, Y.-E.S. (1,2), Sutphen, C. (1,2), Macauley, S.L. (1,2), Zangrilli, M. A. (1), Jerome, G. (1,2), Fagan, A.M. (1,2,6), . . . Mignot, E. (7). (2017). *Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels* Oxford University Press. doi:10.1093/brain/awx148

Kalmbach, D. A., Arnedt, J. T., Song, P. X., Guille, C., & Sen, S. (2017). Sleep disturbance and short sleep as risk factors for depression and perceived medical errors in first-year residents. *Sleep, 40*(3), 10.1093/sleep/zsw073. doi:10.1093/sleep/zsw073

Langille, J. J. (2019). *Human REM sleep delta waves and the blurring distinction between NREM and REM sleep*. United States: Society for Neuroscience. doi:10.1523/JNEUROSCI.0480-19.2019

Llorens, F., Zarranz, J., Fischer, A., Zerr, I., & Ferrer, I. (2017). *Fatal familial insomnia: Clinical aspects and molecular alterations*. New York: Springer US. doi:10.1007/s11910-017-0743-0

Mercer, C. (2019). *How work hours affect medical resident performance and wellness* NLM (Medline). doi:10.1503/cmaj.1095798

Morales, J., Yáñez, A., Fernández-González, L., Montesinos-Magraner, L., Marco-Ahulló, A., Solana-Tramunt, M., & Calvete, E. (2019). *Stress and autonomic response to sleep deprivation in medical residents: A comparative cross-sectional study* Public Library of

Science. Retrieved from https://search.ebscohost.com/login.aspx?direct=true&AuthType=sso&db=psyh&AN=2019-19545-001&site=eds-live&scope=site&custid=s6636215

Patrick, Y., Lee, A., Raha, O., Pillai, K., Gupta, S., Sethi, S., . . . Moss, J. (2017). Effects of sleep deprivation on cognitive and physical performance in university students. *Sleep and Biological Rhythms, 15*(3), 217-225. doi:10.1007/s41105-017-0099-5

Pires, G. N., Bezerra, A. G., Tufik, S., & Andersen, M. L. (2016). Effects of acute sleep deprivation on state anxiety levels: A systematic review and meta-analysis. *Sleep Medicine, 24*, 109-118. doi:S1389-9457(16)30136-8

Qiu, H., Liu, H., Le, W., Zhong, R., Zhang, F., & Li, S. (2016). *Chronic sleep deprivation exacerbates learning-memory disability and Alzheimer's disease-like pathologies in AβPPswe/PS1Delta;E9 mice* IOS Press. doi:10.3233/JAD-150774

Reichert, S., Pavón Arocas, O., & Rihel, J. (2019). *The neuropeptide galanin is required for homeostatic rebound sleep following increased neuronal activity* Cell Press. doi:10.1016/j.neuron.2019.08.010

Shokouhi, S., Conley, A. C., Albert, K., Gwirtsman, H.E., Newhouse, P.A., Baker, S. L., & Kang, H. (2019). *The relationship between domain-specific subjective cognitive decline and alzheimer's pathology in normal elderly adults* Elsevier Inc. doi:10.1016/j.neurobiolaging.2019.05.011

Spiers, J. G., & Chen, H. C. (2019). *Chronic sleep disruption potentiates locus ceruleus tauopathy in a mouse model of Alzheimer's disease*. United States: Society for Neuroscience. doi:10.1523/JNEUROSCI.3265-18.2019

Winkelman, J. W. (2015). CLINICAL PRACTICE. insomnia disorder. *The New England Journal of Medicine, 373*(15), 1437-1444. doi:10.1056/NEJMcp1412740