Loss of sleep during a critical developmental period

The effects of early life sleep deprivation on the development of later life mental health disorders

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Foreword

Sleep has always been a fascinating subject to me and it has stood out to me how little there is yet known about sleep functioning during my bachelor's degree. Therefore, I decided to include sleep as the main subject of this thesis. Since brain development is another essential part of life, this combination of subjects seemed interesting to write about.

Summary

Sleep is extremely important for our daily functioning and throughout our lives, we spend approximately a third of our time in this state of reduced responsiveness. Currently, increasing numbers of people report sleep problems and at the same time, the prevalence of mental health disorders is at an all-time high. In this thesis, I tried to find a connection between sleep deprivation in early life and mental health disorders in later life. Sufficient sleep during early development plays an important role in brain development, especially in terms of brain plasticity. However, when the brain is deprived of sleep during early development, several molecular mechanisms in the hippocampal region were found to be impacted in rodents. These changes negatively affected brain plasticity. Several mental health disorders have been associated with early life sleep deprivation, and I discuss the findings from ADHD, anxiety, and depression in this thesis. However, the exact mechanisms through which this takes place and the directionality of these effects is still up for debate. Currently not many treatment options focus on the disturbed sleep pattern observed in these pathologies and therefore it is important to further assess the exact mechanisms involved in early life sleep deprivation and following brain changes, to then be able to target specific pathways involved.

Table of contents

Foreword **1**
Summary **1**
Table of contents **2**
Introduction **3**
Sleep and early brain development **4**
What is sleep? 4
Brain development and sleep 4
Healthy sleep 5
Unhealthy sleep 5
Consequences of chronically unhealthy sleep 6
Molecular mechanisms of sleep deprivation in rodents **6**
Memory and plasticity are affected by sleep deprivation 6
Long-term potentiation and sleep deprivation 7
NMDA, AMPA receptors, and cAMP signaling 7
CREB and gene transcription and translation 7
Cholinergic and GABAergic signaling 8
Adenosine and astrocytes 8
Early life sleep deprivation and behavior in rodents 9
Early life sleep deprivation and mental health disorders in humans **11**
ADHD 11
Anxiety and depression 11
Plasticity and brain development in humans 11
Treatment options **12**
Prevention 12
Intervention 12
Discussion **13**
Afterword **15**
References **16**

Introduction

Sleep is an alteration in brain functioning, which occupies almost one-third of each day and seems to be essential for daily functioning (Benington, 2000). Current theories explaining the functions of sleep are that sleep enables the repair and clearance needed to fix neuronal damage and/or sleep enables neuronal reorganization, by maintaining synaptic homeostasis (Cao et al., 2020). The brain does not have a lymphatic system, therefore it was suggested that another system would clear the brain of waste products during sleep. This is supported by an increase in the interstitial space of the brain during sleep (Bateman et al., 2006). Another supported theory is that sleep promotes brain plasticity, which is the property of the brain to reorganize and restructure, related to learning and memory, but also synaptic rescaling (Cao et al., 2020). However, the exact functions of sleep are still not clear and there is much yet to uncover.

We do know, however, that sufficient sleep is important for human functioning and health. A recent study on sleep deprivation showed that sleep deprivation prevents the clearance of the human brain of metabolites (Eide et al., 2021). This shows that even one night of insufficient sleep can harm brain function and health. Other complications have been linked to chronic sleep deficits, such as problems with mood and behavior, but also several illnesses (Jha, 2023). In the U.S., more than one-third of adults sleep less than 7 hours per night on average, indicating chronic sleep deprivation (Liu et al., 2014).

Thus, we can conclude that sleep deprivation is quite unhealthy, and common. But what if this sleep deprivation takes place during a period in life of great brain development, namely during early life (0-10 years)? During this important developmental period, brain maturation takes place through synapse formation (Jiang, 2020). These important parts of brain development take place mainly during sleep (Alrousan et al., 2022), indicating the importance of sufficient sleep for functional brain maturation. Since the brain is in an important stage of development between the ages of 0 and 10, when large-scale brain growth and reorganization takes place, it might be more sensitive to deficient sleep, leading to adverse effects in later life.

Next to this, sleep deprivation is shown to be a great risk factor for developing mental health disorders (Uccella et al., 2023). These interactions might be bidirectional, but the effects of sleep deprivation in early life on later mental health disorders have been shown (Lovato and Gradisar, 2014). However, the directionality of sleep deprivation and mental health disorders is still quite unclear and the mechanisms through which this occurs have not been discussed widely yet. Understanding more about this is crucial, since in 2019 the World Health Organization (WHO) announced that 1 in every 8 people around the world is living with a mental health disorder, where anxiety and depression are most common (World Health Organization, 2022). The onset of most mental health disorders is thought to take place during adolescence, and early intervention improves outcomes (Solmi et al., 2022).

Since early life sleep deprivation might be an indication of later life mental health disorders, it is important to investigate through which mechanisms this takes place and how to prevent or treat these conditions. In this thesis, I will introduce the topic of sleep and early brain development, after which I will move on to the molecular mechanisms of sleep deprivation found in rodents and the effects of early life sleep deprivation on their behavior. Next, I will examine several mental health disorders that have been

associated with early life sleep deprivation in humans, and finally, I will discuss treatment options for preventing or intervening with these disorders.

Sleep and early brain development

What is sleep?

Sleep can be defined as a reversible physiological state in which there is reduced responsiveness to stimuli from the environment (Alrousan et al., 2022). When you sleep, there is a specific pattern of electrical activity in the cortical area of the brain, which can be measured by EEG. Different stages in this sleep pattern have been defined: rapid eye movement (REM) sleep and non-REM (NREM) sleep. REM sleep (also known as paradoxical sleep) is characterized by low amplitude high-frequency EEG waves, while NREM sleep (also known as slow wave sleep (SWS)) is characterized by high amplitude low-frequency waves. This type of wave activity is named slow wave activity (SWA). During sleep, REM and NREM sleep alternate, creating sleep cycles of approximately 90 minutes (Lokhandwala and Spencer, 2022). In young children, these cycles last approximately 60 minutes (Davis et al., 2004).

Brain development and sleep

In these first years of life, dramatic developmental changes take place (Jiang, 2020). During this, sleep is one of the most important activities of the brain. This process of brain development is characterized by cortical gray matter maturation and the development of white matter. Here, the gray matter maturation is indicated by an increase in synapse formation, known as synaptogenesis (Alrousan et al., 2022). During childhood, this synaptogenesis is typically at its peak between 2 and 3 years old and is then followed by synaptic pruning, which refines and eliminates excess synapses (Figure 1). This process then continues until the adolescent stage in life, which starts around 10 years old (Sawyer et al., 2018). The development of white matter is indicated by neuronal myelination (Alrousan et al., 2022). This occurs during early life stages, including adolescence. Both this synaptogenesis and myelination appear crucial for the maintenance of normal neurobehavioral functioning (Semple et al., 2013; Milman et al., 2023).

During development, changes have been observed in sleep architecture (the alternations between REM and NREM sleep) that parallel the postnatal brain development timeline. This indicates a relationship between early brain development and sleep health. As mentioned before, an important process during early brain development is synaptogenesis. Rodent studies have shown that sleep is associated with a loss of cortical spine (Alrousan et al., 2022). Spines are important for synaptic functioning and their number and shape determine synaptic plasticity, which is thought to be important for learning and memory (Segal, 2005). Together with the finding that NREM waves were declined in the adolescent stage, this suggests that these observations are reflective of synaptic pruning during sleep. Another important process during early brain development is myelination. This myelination is important for brain connectivity maintenance and regulating functional network maturation. It is found that myelin synthesis occurs mainly during sleep in rodents (Toth and Neumann, 2013). Furthermore, brain maturation seems to be indicative of changes in behavioral and cognitive functions during development in humans (Luna and Sweeney, 2004).

Next to this, it was found that SWA amplitudes reach maximum levels during development and decrease during adolescence (Kurth et al., 2010; Campbell and Feinberg, 2009). This suggests that SWA might be involved in brain maturation processes, such as synaptic pruning and neuronal myelination (Alrousan et al., 2022).

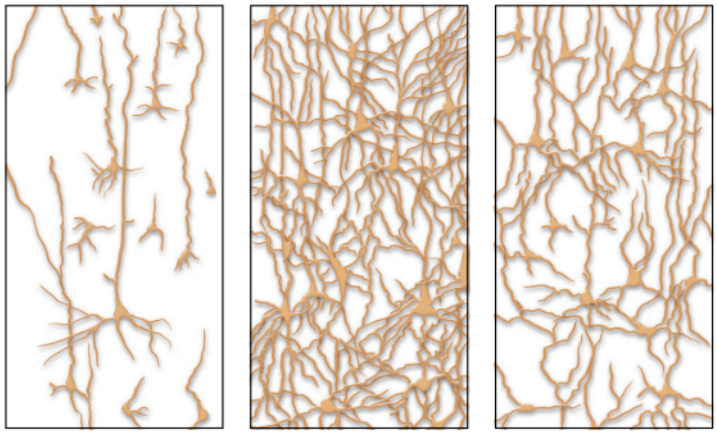

Figure 1: Synaptic pruning process in the human brain over a period of 0-14 years: Here we see the number of synapses a) right after birth, b) at the age of 6, c) at the age of 14 years, visualizing the process of synaptic pruning. Between birth and 6 years, there is mainly growth of synapses, and between 6 and 14 years more synaptic pruning has taken place and the network of synapses is cleaned. Adapted from Birkett and Carlson, 2017, p.81.

Healthy sleep

According to the World Health Organization (WHO), children from 0 to 3 months of age should have 14 to 17 hours of good quality sleep, children of 4-11 months should have 12-16 hours of good quality sleep, at 1-2 years of age children should have 11-14 hours of good quality sleep and from 3-4 years children should have 10-13 hours of good quality sleep (World Health Organization, 2019; Hirshkowitz et al., 2015). However, what exactly can be considered ‘good quality sleep’? According to the National Sleep Foundation, sleep continuity indicates sleep quality at most ages (Ohayon et al., 2017). This sleep continuity presents as shorter sleep latency and fewer periods of awakening after sleep onset. It is widely known that good quality and quantity of sleep is important for health, but what are the main effects of healthy sleep? It has been found that adequate sleep is positively associated with healthy behaviors, for example, stress management, healthy diet, and exercise (Chen et al., 2006). In this research, it was also discovered that good sleep is associated with health status, such as a reduced chance of becoming overweight.

Unhealthy sleep

Sleeping more or less than the above-mentioned recommended hours of sleep could lead to adverse health effects (Hirshkowitz et al., 2015). Recently it has been shown that people who experience bad sleep quality are more prone to sleep fragmentation, instability, and disorganization (Conte et al., 2021). Here,

fragmentation of sleep refers to frequent, brief awakenings during the sleep period. Sleep instability refers to an unstable sleep architecture, where the alternations between NREM and REM are indecisive. Disorganization of sleep refers to the lower number of sleep cycles, total duration per cycle, and total sleep time.

Consequences of chronically unhealthy sleep

When the need for adequate sleep is not met, difficulties with health can arise. For example, following sleep deprivation individuals can become vulnerable to attention impairment as well as deficits in the working memory (a form of short-term memory) (Krause et al., 2017).

Next to this, sleep deprivation seems to lead to increased sensitivity of the brain reward system, together with increased risk-taking and impulsivity, which together can lead to higher susceptibility to addiction (Gujar et al., 2011). Finally, sleep deprivation induces inaccurate perceptions of emotions by interpreting them wrongly as negative threats more often. Shockingly, chronic sleep deprivation has been correlated with a 12% increased risk for all-cause mortality (Cappuccio et al., 2010). Chronic sleep restriction can be associated with multiple adverse health implications, including physical, behavioral, and social consequences (Landolt et al., 2014).

It seems evident that good sleep is crucial for a healthy life, and that sleep deprivation or bad quality sleep can lead to adverse health implications. But what happens when we undergo this sleep deprivation during the most important moments of brain maturation?

Molecular mechanisms of sleep deprivation in rodents

Sleep deprivation can affect multiple molecular signaling pathways in the brain (Alrousan et al., 2022). Pathways that are known to be affected by this are the hippocampal glutamate, acetylcholine, and GABA pathways. In the following sections, different findings and research methods will be described on the molecular mechanisms of sleep deprivation in rodents, subsequently, the effects of early-life sleep deprivation on rodent behavior will be discussed. Together, this might improve our understanding of the molecular mechanisms of early life sleep deprivation, and how they can lead to behavioral effects in the brain.

Memory and plasticity are affected by sleep deprivation

Behavioral rodent studies that investigated the effect of sleep deprivation on memory show that specifically the hippocampus, a brain area important for spatial learning and memory, is sensitive to sleep shortage (Havekes et al.,2012). Findings indicate that memory formation for fear conditioning is impaired when protein kinase A (PKA) and protein synthesis inhibitors are administered during a period of sleep deprivation, which suggests that sleep deprivation may act on these molecular mechanisms in the hippocampus (Graves et al., 2003). In this study, when sleep deprivation was delayed by 5 hours, memory consolidation was unaffected. This specific time window of 5 hours coincides with the learning period where transcription, translation, and cAMP-PKA signaling pathways are required (Havekes et al., 2012). The extracellular signal-regulated kinase (ERK or MAPK) pathway is known to regulate changes in

synaptic potency important for memory formation as well, and has been shown to interact with the cAMP-PKA pathway (Sindreu et al., 2007). This suggests that these pathways are involved in reduced memory consolidation following sleep deprivation (Figure 2).

Long-term potentiation and sleep deprivation

As stated in the paragraph above, sleep deprivation causes deficits in long-term memory formation. This finding suggests that sleep deprivation inhibits the synaptic potentiation in the hippocampal area of the brain, affecting brain plasticity (Havekes et al., 2012). An important form of synaptic plasticity in the hippocampus is long-term potentiation (LTP), which is a change in the strength of synaptic connections that endures for a longer period and which is impaired after sleep deprivation. In the research of Ischikawa et al., LTP effects were not observed in animals deprived of only NREM sleep (Ishikawa et al., 2006), suggesting that REM sleep plays an important role in the formation of LTP in the brain, specifically in the area of the dentate gyrus.

NMDA, AMPA receptors, and cAMP signaling

Based on the finding that REM sleep is important for LTP formation, it was then found that 24 hours of REM deprivation disrupted N-methyl-D-Aspartate receptor (NMDAr) function in the dentate gyrus (Chen et al., 2005), and 72 hours disrupted NMDAr function in the CA1 region of the brain (McDermott et al., 2006). The NMDA receptor is an important receptor for glutamate in the brain (Roche et al., 1996). When glycine, a substance that enhances NMDAr function, was given to REM sleep-deprived rats, this reversed the effect of REM sleep deprivation in the CA1 area (McDermott et al., 2006). Therefore, the changed NMDAr function seems to be involved in changing hippocampal plasticity after sleep deprivation (Figure 2) (Havekes et al., 2012).

Next to this, molecular mechanisms underlying not only the formation of LTP but also the maintenance of LTP are altered, since it was found that sleep deprivation after the induction of LTP still affected the maintenance of LTP (Ishikawa et al., 2006). This suggests that additional molecular mechanisms are likely affected by sleep deprivation as well (Havekes et al., 2012).

As we mentioned, another signaling cascade that was found to be involved in sleep deprivation is the cAMP-PKA pathway (Havekes et al., 2012). A downstream target of this pathway is AMPA receptor subunit GluR1, which controls AMPA receptor function (Roche et al., 1996). The AMPA receptor is a glutamate receptor in the brain, similar to the NMDA receptor (Figure 2).

CREB and gene transcription and translation

Another downstream target that has been studied is the cAMP response element binding protein (CREB), which is a transcription factor that plays an important role in plasticity and memory (Figure 2) (Havekes et al., 2012). Reductions in CREB serine 133 phosphorylation have been found in several parts of the brain after sleep deprivation (Hagewoud et al., 2010). Activated cAMP can only be inactivated by cAMP phosphodiesterases (PDEs), where activated cAMP is important for memory consolidation (Havekes et

al., 2012). Therefore, researchers used PDE inhibitors to observe an effect on plasticity and behavior in sleep-deprived animals. By doing this, normal behavior and memory were found to be restored, suggesting that elevated breakdown of cAMP may cause the effects of sleep deprivation on the cAMP pathway and this was later confirmed (Vecsey et al., 2009).

By use of gene expression studies, researchers found that across studies most genes that are affected by sleep deprivation were regulated by CREB (Havekes et al., 2012). However, the genes affected are not distributed uniformly throughout the brain, meaning that gene expression in one area of the brain might not be representative of another area of the brain. In addition to this, changes at the level of RNA do not per se mean that further function is affected, since downstream protein functioning might still be maintained. Therefore, a lot is yet to uncover about the implications of these gene transcription studies.

Cholinergic and GABAergic signaling

The cholinergic system is another brain signaling cascade known to be essential for memory formation and regulation of neuronal activity (Havekes et al., 2012). REM sleep deprivation of 96 hours has been shown to increase the breakdown of acetylcholine in the pons, thalamus, and medulla oblongata (Benedito et al., 2001), indicating a loss of acetylcholine after REM sleep deprivation. Activation of nicotinic acetylcholine receptors has been found to counteract memory deficits after REM sleep deprivation (Aleisa et al., 2011), showing that acetylcholine shortage is involved in memory formation and sleep deprivation (Figure 2). Specifically, studies have shown that REM sleep deprivation reduces the number of muscarinic acetylcholine receptors (mAChRs) in different brain areas (Salín-Pascual et al., 1998).

Synaptic inhibition is mediated by γ-aminobutyric acid receptors (GABArs) (Havekes et al., 2012). Regulation of these receptors at the synapses is important for memory formation (Tretter et al., 2009). Research suggested that reduced cholinergic activity might be caused by higher levels of GABAergic activity (Havekes et al., 2012). This indicates that GABA receptors could also be involved in brain plasticity and memory (Figure 2).

Adenosine and astrocytes

Adenosine is produced during the breakdown of ATP and plays a critical role in sleep by modulating slow wave activity (SWA) (Havekes et al., 2012). Prolonged wakefulness can lead to the accumulation of adenosine, which activates the adenosine receptor A1 and can then lead to increased neurotransmitter release (Newman, 2003). This A1 receptor is primarily coupled to Gi receptors, which inhibit cAMP (Libert et al.,1992). Together this indicates that higher adenosine levels, caused by sleep deprivation, could lower cAMP levels and result in memory impairments. However, how would this adenosine build-up lead to these impairments? Currently, astrocytes are thought to be responsible for this increasing adenosine in the brain after sleep deprivation, as they were shown to be involved in spatial memory formation (Havekes et al., 2012). Researchers have hypothesized that these increased adenosine levels activate A1 receptors, which will then inhibit adenylyl cyclase and consecutively reduce cAMP levels and the ERK pathway (Figure 2).

Thus it seems that several molecular mechanisms run alongside and affect memory formation and brain plasticity after sleep deprivation (Figure 2) (Havekes et al., 2012).

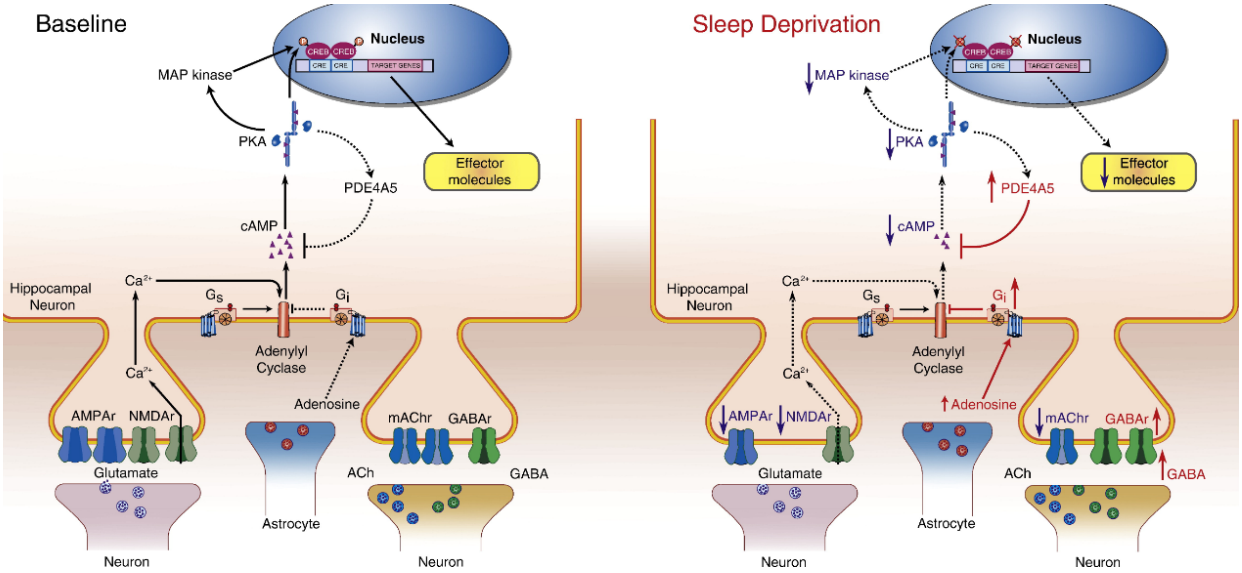

Figure 2: Overview of different hippocampal signaling pathways with a baseline situation on the left, and a sleep deprivation situation on the right: On the right side (sleep deprivation), it is shown how the effects of sleep deprivation might interact to impact brain function, compared to normal function (left side). Here, red lines indicate an increase in signaling and dashed lines and black arrows pointing down indicate a decrease in signaling. It can be seen that glutamate signaling is reduced, resulting in fewer AMPA and NMDA receptors. Similarly, cholinergic signaling is reduced, resulting in fewer mACh receptors. Next to this, adenosine levels are increased, eventually resulting in reduced cAMP, PKA, and MAPK. The cAMP pathway itself is also directly affected by sleep deprivation and impacts gene transcription through means of the CREB transcription factor, which could be leading to multiple downstream (genetic) effects. Adapted from Havekes et al., 2012.

Early life sleep deprivation and behavior in rodents

REM sleep seems to be critical for neural development, as during REM sleep synaptic downscaling and attenuation take place. In young rodents (2 weeks to 1 month old), it was found that acute sleep deprivation prevented this synaptic reorganization and therefore reduced neuronal plasticity (Milman et al., 2023). Several behavioral effects of sleep deprivation have been studied in rodents, from which we will summarize the results below.

First, developmental sleep deprivation was found to impair adult sociability in rodents (Figure 3) (Milman et al., 2023). Second, early-life sleep loss impaired adult social novelty preference and induces male dysfunctional sexual behavior in rats. Similar studies have shown that in terms of memory in later life after early life sleep deprivation, cognitive flexibility is reduced and there is a deficit in prefrontal cortex function (Jones et al., 2021). This might indicate that similar molecular mechanisms could be affected as discussed in the previous chapter. Effects that indicate anxiety-like behavior have also been observed in

several recent studies (Milman et al., 2021). However, these studies show mixed results and might not serve to make accurate statements about the effects of early life sleep deprivation on later life anxiety behavior.

At a cellular level, it was found that early life sleep deprivation in rodents caused increased dendritic spine density and therefore this might negatively impact communication between cells (Figure 3) (Milman et al., 2021). This indicates that this early life sleep deprivation might also have a similar role in the development of neurodevelopmental disorders in humans.

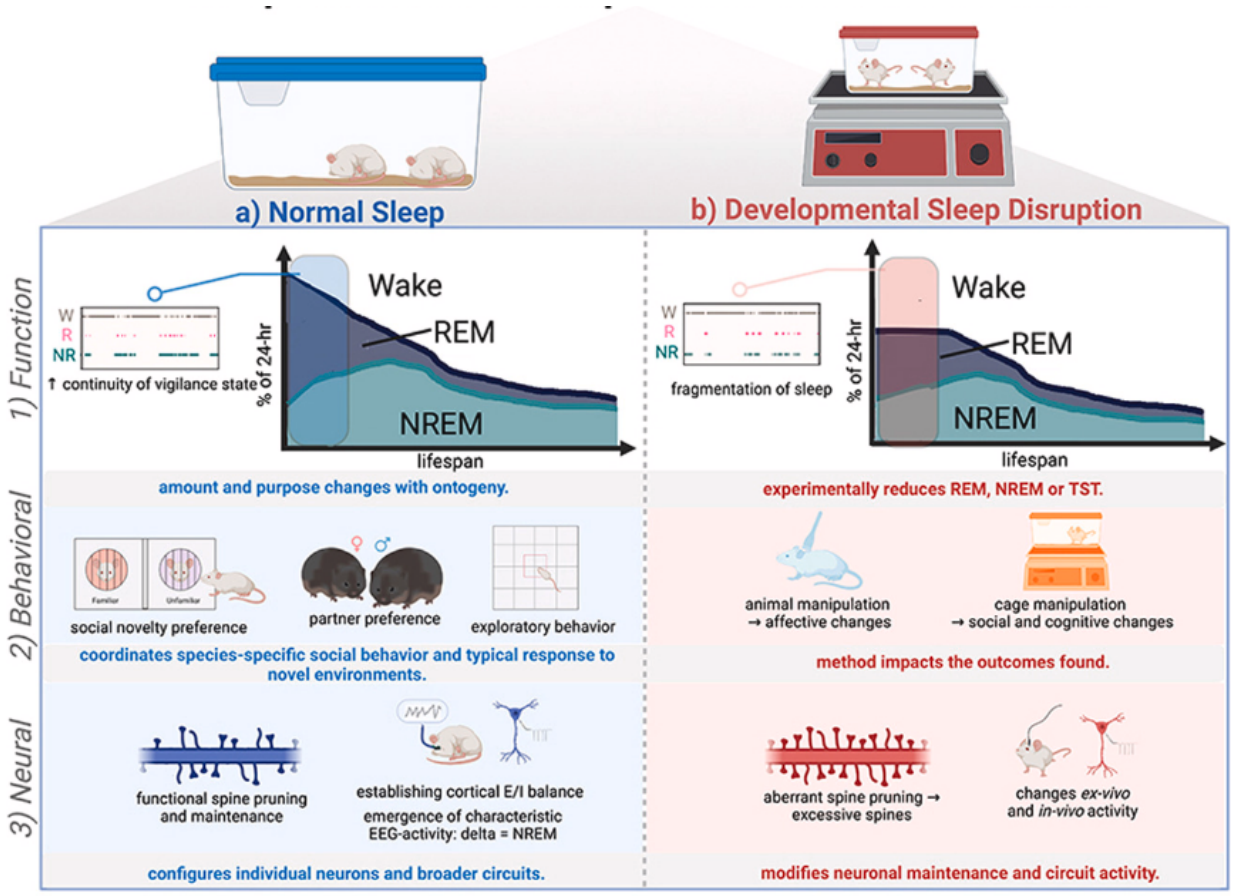

Figure 3: Sleep effects on the development of the brain and behavior with on the left a normal sleep situation, and on the right developmental sleep disruption. On the left side, we see normal sleep in rodents, where the sleep function and amount change with age. Below that we see normal behavior effects, and next we see normal neural development. On the right side, we see developmental sleep disruption effects in rodents. First, we see that the function of sleep is changed primarily by lowering REM sleep (and total sleep time) in young rodents. Below that, we see that different research methods impact the behavioral outcomes found in the developmental sleep-deprived animals, and next, we see excessive spines and neuronal activity in the brain following this developmental sleep disruption. Adapted from Milman et al., 2023.

Early life sleep deprivation and mental health disorders in humans

We have shown that early life sleep deprivation can affect brain plasticity and therefore behavior in rodents in the previous part, but how does this affect humans? There is still much unclear about the causal mechanisms of early life sleep deprivation on later life prevalence of mental health disorders, and the directionality of this relationship.

However, in humans, before 2.4 years old, the main function of sleep is neuronal reorganization, which maintains brain plasticity (Milman et al., 2023). This finding connects to the previously mentioned findings in rodent studies, where it was shown that early-life sleep deprivation greatly affects brain plasticity and development. In this chapter, we will focus on the effects of early life sleep deprivation on several neurodevelopmental disorders in humans.

ADHD

In 2010, it was shown that sleep problems in early childhood (at 6 months and between 2 and 4 years of age) are associated with attention problems into adolescence (at 14 years of age) (O'Callaghan et al., 2010). Later, the association between early life sleep deprivation and attention-deficit/hyperactivity disorder (ADHD) was found in numerous research papers (Carpena et al. 2022; Tso et al., 2019). Dopamine is known to play a crucial role in the development of ADHD (Levy and Swanson, 2001). It was found that sleep deprivation decreases dopaminergic receptors in the brain. Taken together, this could indicate that early life sleep deprivation could lead to an (increased) ADHD phenotype (Tso et al., 2019).

Anxiety and depression

In 2008, researchers examined associations between sleep deprivation during development and later life emotional and behavioral difficulties (Gregory et al., 2008). Here, they found that sleep deprivation during early life is a risk indicator of anxiety/depression symptoms in later life. However, this data is from children aged 4-19 years old during which their early life sleep was indicated by their parents, whereas we mentioned before that synaptic plasticity is most important before the age of 2.4, and subsequent pruning is most prominent until the age of 10. Unfortunately, little research has been conducted on the connection of early life sleep deprivation and anxiety and depression in humans, and not much conclusions can be drawn from this.

Plasticity and brain development in humans

As discussed in previous chapters, changes in brain plasticity seem to be the leading cause of behavioral changes following early-life sleep deprivation. Here, SWA seems to be an important indicator of this plasticity. In children with ADHD, it was even shown that there was a different SWA pattern seen over development in the brain compared to typically developing controls of similar age (Lokhandwala and Spencer, 2022).

This early life sleep deprivation seems to contribute to several mental health disorders, where the exact directionality and causality are still unclear. In this next chapter, we will look further into treatment options for these mental health disorders.

Treatment options

In terms of treatment there are two main options to consult with early life sleep deprivation leading to neurodevelopmental disorders. The first option consists of preventing sleep deprivation during early life (prevention), whereas the second option consists of treating the mental health condition during later life (intervention).

Prevention

As early as 1999, researchers published that 20 to 30 percent of children from infancy to adolescence suffer from sleep deprivation (Stores, 1999). Over the years these numbers did not improve but worsened due to technological advances, caffeine, and more (Owens et al., 2014). Next to this, personal health was discovered to play an important role in sleep health as well. Despite this chronic developmental sleep deprivation being known to have adverse effects on health, there is still relatively little known about treatment options (Stores, 2022).

However, there are some established treatment methods. According to a study by Stores in 2022, one of the most important factors in obtaining healthy sleep is adopting healthy sleep habits and behaviors, defined as sleep hygiene, such as a fixed bedtime and awakening time (Stores, 2022; Weiss et al, 2006). One of the options to prevent sleep deprivation during early life would therefore be to inform the caregivers of the child about these healthy sleep habits. Unfortunately, not every child grows up in an environment capable of implementing these healthy sleep habits. For children in dysfunctional families or other unsafe situations, improving sleep quality might only be possible by taking children out of an unhealthy environment, which could cause different problems in later life. Another option to prevent this sleep deprivation is sleep medication. However, the use of sleep medication is still widely discussed, especially in children's healthcare, and preferably only administered in combination with behavioral treatment and healthy sleep habits (Owens et al., 2005). Research has shown that melatonin treatment together with better sleep hygiene is an effective treatment to treat sleep problems in children from 6 to 14 years old (Weiss et al., 2006). However, optimal medication has not yet been identified (Hvolby, 2015).

Intervention

Since we have identified early life sleep deprivation as preceding multiple neurodevelopmental disorders, conducting intervention would mostly consist of using the current treatments available for the different disorders. Therefore, here we will mostly focus on the effects of sleep on these disorders in later life and how to improve this.

In adult individuals with ADHD, there seems to be increased sleep onset latency, more awakenings during the night, and higher daytime sleepiness (Díaz-Román et al., 2018). However, there seems to be no significant difference in total sleep duration between ADHD adults and healthy individuals.

Unfortunately, stimulant medications used for ADHD are also associated with a negative impact on sleep (Stein et al., 2012). Since ADHD and sleep problems are found to be highly connected, it would be wise to treat patients for primary sleep disorders first, before starting treatment for ADHD (Stein et al., 2012).

In older adult individuals with anxiety disorder sleep is associated with shorter sleep duration, daytime sleepiness, and sleep disturbances (Potvin et al., 2014). In the same study, depression was associated only with the use of sleep medication, and other sleep characteristics did not seem to be significantly altered. Insomnia in mild to moderate anxiety disorder is generally successfully reduced by psychological treatment and treatment with anxiolytic benzodiazepines (Monti and Monti, 2000). For depression, several methods are known to worsen the sleep quality in patients, such as most antidepressants (Fang et al., 2019). Other treatment strategies have improving effects on sleep, such as cognitive behavioral therapy, sleep deprivation therapy, and deep brain stimulation. However, their cure rate for depression is quite low and therefore these might not be an adequate treatment option.

Next to this, we have identified several molecular pathways that might be involved in the negative behavioral outcomes of sleep deprivation in early life in the previous chapters. One option might be to target these pathways directly, to prevent or to intervene with these disorders. For example, we mentioned several effects that could be rescued by injecting specific drugs, and reversing some negative effects of sleep deprivation, such as using PDE inhibitors or glycine. However, since much is still unclear about the exact processes, this will probably not be widely employed as treatment any time soon. For now, preventing sleep deprivation during early life and improving sleep quality in later life seems to be of significant importance in treating these neurodevelopmental disorders.

Discussion

An enormous amount of time in our lives is spent sleeping, but we still do not know the exact functions of sleep. Increasing numbers of people report sleep deprivation and at the same time, the prevalence of mental health disorders is at an all-time high. In this thesis, we tried to find a connection between early life sleep deprivation (0-10 years) and later-life (10+ years) mental health disorders. We have introduced an important relationship between brain plasticity and sleep during early life, showing that healthy sleep in this period of life contributes to a healthy developed brain into adulthood. Several molecular mechanisms have been identified in the process of sleep deprivation in rodents. Here, it seems that REM sleep deprivation is most detrimental to brain function, seemingly leading to attenuation of several molecular pathways in the hippocampus CA1 region and dentate gyrus, and eventually leading to behavioral changes in rodents. Next to this, early life sleep deprivation in rodents negatively affects brain plasticity similar to what is seen in neurodevelopmental disorders, suggesting these molecular mechanisms might play a role in human early life sleep deprivation as well.

However, multiple techniques have been used to deprive rodents of sleep in the different studies mentioned. Each of these methods has its advantages and disadvantages, but the results of these studies should be taken into consideration together with their method of inciting sleep deprivation, the duration of sleep deprivation, and relevant cofactors such as stress (Havekes et al., 2012; Alrousan et al., 2022; Milman et al., 2023).

Unfortunately, the connection between early life sleep deprivation and mental health disorders in humans has not been thoroughly researched. In this thesis, we have described several neurodevelopmental disorders that might be associated with early life sleep deprivation, namely ADHD, anxiety, and depression. Brain plasticity seems to have a connection to the progression of ADHD, and since brain plasticity was found to be reduced after early life sleep deprivation in rodents, there might be a connection between these factors in humans. For anxiety and depression, a specific correlation could not be made since the sleep deprivation was tested at a later age, however, it did indicate a correlation that might also show when testing earlier life sleep deprivation.

It has been known for quite some time that sleep is regulated by the hypothalamus and that several molecular mechanisms are involved. For example, the cholinergic, serotonergic, and GABAergic systems are known to be involved in sleep regulation (Lam and Lam, 2021). Here, reduction of the serotonergic system is also known to be related to depression (Mann, 1999), and dysfunction of the GABAergic system is related to anxiety (Staner, 2022).

However, it is important to keep in mind that early life sleep deprivation and neurodevelopmental disorders are not yet well understood, and several other factors might also play a role in this. Sleep behaviors and rituals are different between cultures, and social circumstances can differ (Jenni and O'Connor, 2005). Next to this, parents have a critical role, as they determine sleeping behaviors, but parental stress and relationships also contribute to children's health (Tikotzky, 2017). Some of these factors could be important cofactors in the overall health of children, showing that multiple factors can contribute to the observed pathologies.

Next to the disorders mentioned, there might even be many more associations to be made between developmental sleep deprivation and neurodevelopmental disorders (Verhoeff et al., 2018; Veatch et al., 2021). However, at this point, the directionality of this is still quite unclear. Currently, several genetic mouse models exist that support the idea that there is a bidirectional relationship between sleep and neurodevelopmental disorders (Milman et al., 2023), suggesting that early life sleep deprivation is not the main cause of neurodevelopmental disorders, but rather contributes to exacerbate symptoms and cause further impairment of neuronal function. For anxiety and depression, researchers have already hypothesized a similar mechanism taking place (Lam and Lam, 2021).

This highlights the importance of treating sleep deprivation either in early life or in later life even more since treating sleep deprivation might resolve part of the symptoms experienced with these types of neurodevelopmental disorders. There is still relatively little uncovered about the exact role of sleep in these disorders, which could be an opportunity for further research into treatment options.

In conclusion, early life sleep deprivation could be one of the factors causing later life neurodevelopmental disorders, especially in ADHD, anxiety, and depression. The mechanisms through which this happens are yet to be uncovered, but similarities between rodent studies and human studies give us a hypothesis of what might take place in the human brain following early life sleep deprivation. However, to improve treatment options for sleep problems in early life as well as in later life, further research needs to be conducted to determine the exact mechanisms involved in sleep deprivation and following brain changes, to be able to target specific pathways involved.

Afterword

Writing this thesis has been hard with the amazing weather outside this month, but I’m happy to say it was more fun to do than I expected. I would like to thank Lysanne Jorna for supervising me during this thesis and giving me advice where needed and hope to pursue this type of research in my master's.

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