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How Different Parameters of Sleep Can Influence Cognitive Ageing

Bachelor thesis for the major Integrative Biology by Tijana Kyra Beintema, s4155793
Supervised and graded by Cato Drion

Foreword

As I am highly interested in cognition and sleep, this thesis aims to research the effect of changes in sleep on ageing in terms of cognition. A previous research project of mine also covered the topic sleep, specifically the effect of ambient temperature on the amount of REM sleep. I had enjoyed this topic to such an extent that I wanted to elaborate on the topic of sleep in my bachelor thesis. This thesis combines the topic with cognition as an aspect of ageing. It will review the direct influences of changes in sleep on cognition in elderly as well as the consequences of changes in sleep that affect cognition.

Abstract

Sleep is important for loads of processes such as emotions, memory, information processing and alertness. Certain parameters of sleep such as structure, quality and duration can change with ageing. Also, ageing is associated with cognitive decline. However, it is not known yet whether the age-related sleep changes in elderly affect cognitive decline. So, this thesis aimed to research whether changes in the parameters of sleep influence ageing in terms of cognition. The direct influence of sleep changes on cognitive decline in elderly will be discussed. Also, the indirect effect of sleep changes on cognitive decline in elderly will be discussed. It was found that lowered sleep efficiency, more night-time awakenings, more wake episodes, late-life onset of insomnia, less REM and less NREM sleep are all associated with cognitive decline. The same accounted for self-reported sleep problems, although opposed by one study. Also, people with self-reported sleep problems were more likely to suffer from early cognitive decline. Sleep complaints and poor sleep quality were found to predict cognitive decline. Changes in sleep have also been found to indirectly affect cognition, through inflammation and accumulation of tau and Aβ. Adenosine was found to play a role in the severity of the effect of sleep on cognition. It was also suggested that sleep could indirectly lead to cognitive decline via depression, but this was opposed by a different study. Overall, it could be concluded that changes in parameters of sleep are able to affect ageing in terms of cognition, either directly or indirectly.

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1. Introduction

1.1 Sleep and its function in cognition

Humans, other mammals and birds spend a considerable part of their lives asleep (Meerlo et al., 2015). Sleep an essential biological function and it is known to be a biomarker for general health as well as pathological conditions (Luca et al., 2015). Although the actual function of sleep remains one of the largest mysteries in the field of behavioural neuroscience, many researchers believe that sleep might be important for recovery, maintenance and plasticity of neurons. This would mean sleep is important for loads of processes such as emotions, memory, information processing and alertness. It has been shown that too little sleep can make the processes unable to work properly, affecting a person negatively in terms of physical as well as mental well-being (Meerlo et al., 2015).

Sleep is considered to be a natural state that is characterized by a reduced ability to voluntarily induce motor activity and respond to environmental stimuli, as well as by a stereotypical posture (Fuller et al., 2006). In the sleeping state, consciousness differs from other states such as comas or anaesthesia as sleep is easily reversed and also self-regulating (Fuller et al., 2006). Studying sleep often happens with the help of electrodes called electroencephalograms (EEGs), which detect the fluctuating electrical activity of the brain and represents it in a pattern of waves (Deboer, 2013). In such a recording, sleep can be roughly subdivided into two states, which are non-rapid eye movement sleep (non-REM) and rapid eye movement sleep (REM) (McNamara, 2019). Each so-called NREM-REM cycle lasts about 90 minutes, in which one REM phase and one NREM phase occurs (McNamara, 2019). The cycles start with the NREM phase, recognizable by high amplitude, slow waves, which represent increased cortical firing synchrony (Fuller et al., 2006). After a little less than the 90 minutes of one complete cycle, the EEG amplitude starts to decline and the frequency of the waves start to get higher, which signals the onset of the REM phase (McNamara, 2019). The theta waves that are often visible during REM sleep are generated by signals from cholinergic and GABAergic neurons (short for gamma-aminobutyric acid neurons) (Fuller et al., 2006). The REM waves resemble those of wakefulness. However, unlike during wakefulness, there is no muscle tone during REM. At the end of the night, the depth of sleep declines, which eventually leads to wakefulness (McNamara, 2019).

It is argued that the increase of activity in the neurons in the anterior hypothalamus acts as a so-called sleep switch (Saper et al., 2005; McNamara, 2019). GABA neurons are guided by the suprachiasmatic nucleus (SCN), which lies in the hypothalamus and guides the dark-light circadian cycle by receiving light signals. The NREM-REM sleep cycle is triggered by the dark noticed by the SCN, which signals to the anterior thalamus to activate the GABA neurons that inhibit the brain stem from maintaining wakefulness. At the end of a full sleeping bout, light is noticed by the SCN, which triggers the opposite response and initiates wakefulness (McNamara, 2019).

Also, multiple studies have researched the role of adenosine on sleep (Radulovacki, 1989). The nucleoside acts as a neuromodulator and co-transmitter in the brain, to inhibit the excitatory effect of some neurotransmitters such as glutamate (Elmenhorst et al., 2018). It is believed that adenosine inhibits neuronal responses, that it has a hypnotic effect, that it leads to sedation and hypothermia and that it has a role in sleep. Administration of adenosine has been found to have a reducing effect on wakefulness and thus enhances sleepiness, clearing up the role of adenosine in sleep (Radulovacki, 1989). Of the four receptors existing for adenosine, the A_1-subtype receptor is the most widespread in the brain (Elmenhorst et al., 2018).

As mentioned previously, sleep is an essential biological function that is believed to be important for recovery, maintenance and plasticity of neurons (Luca et al., 2015; Meerlo et al., 2015). One of the

most important functions of sleep is long-term memory formation (Klinzing et al., 2019). Episodic memory consolidation happens in the hippocampus and is highly dependent on sleep. During sleep, the neurons in the hippocampus holding the memory are repeatedly activated, which causes the whole associated memory network to be activated as well. The memory is then integrated into existing long-term memories. This process also yields more abstract, generalised and efficient memories. This type of consolidation also occurs for non-hippocampal memories in which hippocampal activity is involved in sleep-dependent consolidation as well (Klinzing et al., 2019).

It has been suggested by animal studies that memory consolidation might be disrupted by sleep fragmentation. Spatial learning can be impaired by inhibiting hippocampal long-term potentiation when sleep is interrupted. In fact, the total amount of sleep does not seem to matter concerning memory consolidation. However, a minimal amount of uninterrupted sleep is necessary for the process (Conte et al., 2012).

1.2 How sleep changes with increasing age

There are many aspects of sleep that can differ between individuals, such as the depth of sleep, the amount of sleep, or even the sleeping schedule. It is known that parameters like the structure, quality as well as the duration of sleep can be altered by ageing (Luca et al., 2015).

With increasing age, sleep latency significantly increases as well. However, the change is very gradual, and is only visible when comparing young adults to elderly and as little as less than ten minutes. Also, the percentage of stage 1 and 2 sleep increases, which are the first and lightest sleeping phase. The increase is less gradual than the sleep latency and also visible between young adults and middle aged, and between middle aged and elderly. On top of that, the percentage of REM sleep decreases in elderly. While this amount increases from childhood to adolescence, it decreases when ageing towards middle-aged. From then onwards, the amount of REM sleep remains unchanged. Interestingly, the changes in the amount of phase 2 sleep and amount of REM sleep are sensitive to changes in sleep such as sleep disorders and sleep apnoea (Ohayon et al., 2004).

Also, changes in sleep due to ageing differ between stages according to Feinberg, 1974. In elderly, slow-wave sleep is changed in the first cycle in terms of lowered amount of deep sleep, while it remains the same in the 2nd to 5th cycle. The total duration of REM sleep also increases in the 1st to 3rd cycle in elderly, except for elderly older than +/- 75 years, in which the amount remained constant (Feinberg, 1974).

Sleeping problems are very common in adults, especially in elderly. In the Netherlands, more than 20% of people older than 50 years – which are considered elderly from now on – have reported to suffer from sleep problems in the last two weeks (Exalto et al., 2022). Changes in sleep as well as sleeping problems have been proven to be able to affect cognition (Lo et al., 2016). The dynamics of the changes that sleep undergoes differs between normal ageing and intrinsic sleep disorders, but some common patterns are visible in both. Those common patterns of changes in sleep that most people start to suffer from when getting older, are for example wakefulness after sleep onset (WASO), increased sleep onset latency, increased non-rapid eye movement (NREM) sleep (shallow sleep) and also a reduction in the amount of slow-wave sleep (deep sleep). Meaning, the parameters of sleep such as structure, quality and duration change in people that age healthy as well as in people coping with sleep disorders. In fact, ageing causes a decrease in sleep quality, an increase in sleep duration and changes in sleep structure (Luca et al., 2015).

1.3 How cognition changes with increasing age

Ageing is a biological process that makes organisms more susceptible to physical decline, as well as cognitive decline (Bettio et al., 2017). Changes in the brain due to ageing such as reduction of neuronal arborization and the density of spines, lead to cognitive impairments in elderly (Bano et al., 2011). Memory consolidation is one of the important features of cognition. The brain region in which the process occurs is highly subjected to structural and functional plasticity when ageing. Many neurobiological changes that have been noticed in the hippocampus have been linked to cognitive decline. Examples are increased oxidative stress and neuroinflammations, changed intracellular signalling as well as reduced neurogenesis and synaptic plasticity (Bettio et al., 2017). A decrease in grey matter has also been associated with age-related cognitive decline (Juan and Adlard, 2019).

Older age and age-related disorders are often associated with cognitive dysfunctions such as increased difficulties with learning and memory (Bano et al., 2011). Cognition consists of information processing or memory formation, planning as well as reasoning (Juan and Adlard, 2019). Cognitive decline can occur in normal "healthy" ageing and in pathological conditions such as neurodegenerative diseases like Alzheimer's disease. In normal ageing people, impairments in episodic or declarative memory, spatial learning impairments and impairments in working memory as well as attention often occur as part of cognitive decline. However, the severity of the symptoms can differ greatly between individuals. Factor like intelligence, education and mental stimulation are highly involved in the determination of the severity of the symptoms, as they can help the brain adapt to the pathological damage (Bettio et al., 2017).

On top of that, not all cognitive domains are affected equally by ageing. For example, word processing declines with age, as well as processing speed, executive functioning and visual processing. However, short-term memory formation and world knowledge remains unharmed by ageing. Emotional processing, which is also a cognitive function, is also preserved in elderly (Juan and Adlard, 2019). Semantic knowledge, recognition and emotional declarative memory are not affected by age-related cognitive decline, while working memory, short-term episodic memory formation and processing speed are affected (Pace-Schott and Spencer, 2014). Overall, age-related cognitive decline negatively impacts cognition (Juan and Adlard, 2019).

1.4 Possible causal relationship between the changes in sleep and cognition

Our knowledge of sleep and its role in cognitive functioning has rapidly increased over the last few years. While the topic is of great importance for science and society, there are relatively few studies on the relationship between ageing, sleep and cognition, even for neurodegenerative disease patients. On top of that, most of the research yielding the data has been performed on young adults, which does not take into account that sleep is an age-dependent concept that can many changes in human functioning, which can affect daily cognitive functioning as well (Rauchs et al., 2013). So, only little is known about whether changes in sleep affect ageing in terms of cognitive decline.

The increasing longevity of the human species presents challenges to the current social structure as well as a financial problem as an increasing number of people is subjected to age-related cognitive disorders (Bano et al., 2011). Also, as people are getting increasingly older, the importance of knowing more about sleep and its function increases, as well as the concern for cognitive impairment and dementia (Middelkoop et al., 1994; Kaneshwaran et al., 2019). In the year 2019, about 35.6 million people suffered from dementia, globally, and this number is predicted to nearly double over 20 years. It is hypothesized that sleep disturbances might be a cause of cognitive impairments and dementia and

their biological substrates in elderly (Kaneshwaran et al., 2019). Healthy ageing becomes increasingly important as well. With healthy ageing comes appropriate sleep, in terms of duration, quality and structure (Luca et al., 2015). Having more knowledge about the relationship between ageing and sleep can help research towards aiding healthier in elderly, preferably with as few cognitive problems as possible. So, for example, if the correlation between sleep quality, duration and structure and "unhealthy" ageing is negative, it could be that increasing sleep quality could lead to slower and healthier ageing.

For those reasons, this thesis will combine and compare the results of multiple studies to see how and if age-related changes in the structure, duration and quality of sleep can influence ageing in terms of cognition. Studies on the influences of changes in sleep on cognition in elderly are compared. In the first paragraph, the direct influence of sleep changes on cognitive decline in elderly will be discussed. Also, the indirect effect of sleep changes on cognition was examined, which are other consequences of changes in sleep, which in turn affect cognition will be discussed in the second paragraph.

2. Research findings

2.1. The direct influence of sleep changes on cognitive decline in elderly

A study by Jelicic et al. (2002) found that sleep complaints can predict cognitive decline in elderly as well as middle aged people. The study aimed to research whether subjective sleep complaints predicted cognitive decline over the course of three years, with a sample size of 838 elderly (50 years or older) from the MAAS (Maastricht Ageing Study). The type of complaints being falling asleep difficultly, waking up too early and restlessness in sleep were compared to Mini Mental Status Examination scores. Subjective complaints for any of the three variables was associated with cognitive decline and it was found that waking up early was most strongly associated with cognitive decline over the course of three years (Jelicic et al., 2002).

Ji and Fu (2020) recently studied the relationship of onset age of insomnia and sex with different sleep parameters and cognition and depression in elderly with a mean age of 75 years old, suffering from insomnia. It became clear that late-life onset of insomnia was strongly associated and predictive for cognitive decline in female elderly. Also, a clear association between sleepiness during the day, depression and cognitive decline was found. For this study, 2068 participants with sleep complaints were used. Sleep was measured using surveys, which included the age of insomnia onset, three factors from the insomnia severity index (night-time, daytime and perception scores), scorings of daytime sleepiness and sleep duration. Cognition was measured with the mini-mental state exam (MMSE) and depression was measured with the centre for epidemiologic studies depression scale (CESD). Measurements showed that age, sex (being female), late onset of insomnia and the interaction of sex and onset age of insomnia were associated with poor cognition. The results differed between females and males, as in females, late onset of insomnia, night-time insomnia, daytime sleepiness and depression were indicative of future cognitive decline. For males, more daytime sleepiness and higher depression scores were the only factors that were correlated with cognitive decline (Ji and Fu, 2020).

Niu and colleagues (2016) aimed to examine whether self-reported sleep quality and MMSE scores can change over one year in 1010 cognitive intact elderly of 65-80 years old. They concluded that elderly suffering from self-reported sleeping problems had more cognitive decline over the course of one year and were more likely to suffer from early cognitive decline compared to elderly without sleeping

problems. For this study, measurements of sleep quality and cognitive functioning were used. The Pittsburgh Sleep Quality Index (PSQI) was used to measure the former, and the MMSE (the Chinese version) was used to measure the latter. Both measurements were done twice, one year apart. Also, measurements of confounders were included, such as age, sex, lifestyle and health. Results showed 0.32 more decline in MMSE-scores in elderly with poor sleep quality. They also were more likely to develop MMSE decline. Poor sleep efficiency was also negatively associated with MMSE scores and the likelihood of MMSE decline was higher. The same results were found for short sleep durations (Niu et al., 2016).

A study by Potvin and colleagues (2012) examined the association between subjective sleep quality and one-year incident cognitive impairment in cognitively healthy elderly. It was concluded that poor subjective sleep quality can be a sign of future cognitive decline. For the study, 1664 elderly aged between 65 and 96 years were used. Sleep quality at the baseline was measured with the PSQI. Cognitive functioning was measured at both baseline and one year afterwards with the MMSE. If the MSSE scores were at least 2 points lower that the baseline scores and below the 15th percentile according to normative data, it was regarded general incidental cognitive impairment (ICI). The odds ratio was used to assess whether there was an association between sleep quality at baseline and ICI. A difference in effect between males and females was found. Although not in women, PSQI scores were negatively correlated with ICI in men. In women, there was a positive correlation between sleep disturbance score and non-amnesic ICI and between long sleep duration and amnesic ICI. In men, specifically short sleep duration was associated with amnesic ICI and habitual sleep efficiency score was associated with general ICI (Potvin et al., 2012).

The association between objective as well as subjective measured sleep with cognitive decline was examined in a study by Blackwell and colleagues in 2014. They concluded that lower sleep efficiency, more night-time awakenings, more wake episodes and poor subjective sleep quality were associated with cognitive decline. The study was purely based on 2822 cognitively intact community-dwelling (meaning living independently) elderly male participants with an average age of 76 years old, over the course of around 3.4 years. Sleep-wake patterns were measured using a wrist actigraph for about 5 nights per individual. The actigraph measured among other things the total sleep time (TST), the sleep efficiency (SE) and the wake after sleep onset (WASO) and the number of long wake episodes (LWEP). The PSQI was used to subjectively measure sleep quality and the Trail B and 3MS tasks were used to assess cognitive functioning. The trail B was to measure attention, sequencing, visual scanning and executive functioning, and the 3MS task measures cognitive function in terms of orientation, concentration, language, praxis and memory. Other measurements included medical history, physical activity, smoking, self-reported health status, demographics, caffeine intake and alcohol intake, which was measured using questionnaires. There was a negative association between amount of LWEP and the scores in the Trial B task. In terms of the 3MS task, lower SE correlated with a decrease in test scores. Disturbed sleep, higher levels of WASO and LWEP and lower SE were also associated with lower scores in the Trial B task. Having more than 8 LWEP during a night also increased the chance of a decline in scores in the 3MS task with 40%. So, overall, an increase in SE, WASO and more LWEP was associated with a higher likelihood of developing clinically significant cognitive decline over the course of five years in community-dwelling elderly men. No significant effect of objective TST on cognitive decline was found (Backwell et al., 2014).

A study from 1977 by Prinz aimed to research the possible correlation between sleep patterns and intellectual function. A positive correlation between the amount of REM sleep and multiple aspects of mental functioning was found. The study included 12 healthy elderly participants aged 76 to 90 years old. Using a portable Beckman EEG machine, sleeping patterns were measured at home for 3 or 4

nights. In the 18 years before this experiment, the Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Memory Scale (WMS) had already been administered 8 times. The difference in scores from the WMS and the scores from the WAIS from 6 months previous to the experiment were correlated to the amount of REM sleep as well as the amount of stage 4 sleep. Significant changes in sleeping patterns were found in elderly. Also, the amount of REM sleep and stage 4 sleep declined in elderly compared to young adults. The WAIS scores were on average lower in older groups. The same accounted for the WMS scores. Although a positive correlation between the amount of REM sleep and measurements of mental functioning was found, it could not directly be attributed to age. It was hypothesized that changes in sleep may influence neurobiological ageing and senescence, thus cognition (Prinz, 1977).

A study by Spiegel et al. from the year 1999 studied the association between sleep parameters and cognition in 30 healthy elderly participants of around 77.1 years old over the course of 14 years. They found a positive correlation between the amount of NREM at baseline and cognitive performance 14 years later. Polygraphic sleep recordings has been retrieved from the 57 baseline participants in the year 1976/1977, of which the results and their association with psychometric and medical data had already been published before. In the year 1990/1991, 30 of the participants returned for new measurements. Successful ageing was measured with two criteria, namely “health and survival” and “cognitive competence”. The latter was assessed with the Vocabulary subtest of the HAWIE, which is a German version of the WAIS, with the MMSE assessing cognitive decline and with the Évaluation rapide des functions cognitives (ERFC), which is similar to the MMSE but more extended. The polygraphic sleep parameters that were measured were the sleep stages, (REM) sleep latency, sleep disturbances like the number of shifts from REM to wake and stage 1 sleep, number of brief arousals and specific parameters of REM sleep such as constancy, efficiency and density. From the follow-up measurements, results showed that participants had higher HAWIE scores when they had low duration of REM and high REM density. MMSE scores were highest when long REM latencies and again REM density. Also, a higher number of NREM shifts was correlated with higher MMSE scores in men, and with higher ERFC scores in both sexes. There was also a positive correlation between MMSE scores and REM density and REM latency, while REM duration was negatively correlated with the scores. So, certain changes in parameters of sleep could influence cognition in the elderly participants that had aged successfully (Spiegel, 1999a).

A study by Saint Martin et al. (2012) aimed to assess the relationship between sleep quality, subjective cognitive complaints and actual neuropsychological performance by examining healthy elderly. In contrast to previously mentioned studies, it was concluded that subjective sleep quality and duration did not affect subjective cognition, nor objective cognition. 272 healthy elderlies with a mean age of 84.8 years were used. They were given questionnaires assessing cognitive functioning, anxiety, depression, sleep-related parameters and the PSQI (Pittsburgh Sleep Quality Index). Also, ambulatory polygraphy and neuropsychological tests were used. 156 elderlies were classified as poor sleepers, as their PSQI score was 5 or higher, and 116 elderly as good sleepers, with a PSQI score below 5. Lower PSQI score did not affect subjective cognitive functioning. Also, it did not affect objective cognitive functioning apart from the Trail Making Test A, in which processing speed was longer in the group with poor sleepers. So, poor quality of sleep did not negatively affect (subjective) cognition, apart from processing speed (Saint Martin et al., 2012).

2.2 Possible mechanisms that underlie the effects of sleep on cognition in elderly

From previous studies, it is known that altering the duration of sleep, by sleep deprivation, can alter gene expression of genes that are associated with inflammation and immune functioning (Kaneshwaran et al., 2019). In a study performed by Kaneshwaran et al., it was concluded that sleep fragmentation is associated with accelerated microglial ageing as well as microglial activation, which is accompanied with cognitive impairments. The study included participants from two cohort studies, called the Rush Memory and Ageing Project and the Religious Orders Study. 685 adults above 65 years old were included, of which 265 suffered from Alzheimer's disease. Cognitive functioning was measured, as well as the density of microglia in the neocortex by immunohistochemistry and RNA sequencing was used to measure the microglial marker gene expression in the neocortex. These were related to sleep fragmentation, which was assessed by actigraphy. It was found that in older adults, greater sleep fragmentation and thus change in sleep structure, was associated with more expression of genes characteristic of aged microglia and a higher density of activated microglia. The latter was associated with poorer cognition proximate to death. This was determined by considering data from previous research with available RNA sequencing of the dorsolateral prefrontal cortex and at least one cognitive assessment. It showed that poorer cognition was often associated with a higher composition of genes that are characteristic of aged microglia right before death. Also, the actigraphy of 480 deceased participants were examined in order to grasp the relationship between sleep fragmentation and cognition. More fragmented sleep was associated with worse cognitive performance proximate to death. It was also recognized that the possibility exists that poor cognition and microglial ageing are linked to sleep fragmentation (Kaneshwaran et al., 2019)

Sleep may also be associated with accumulation of tau and β-amyloid (Aβ), which are the two main pathological proteins in Alzheimer's disease. Whether sleep measures could predict Alzheimer's disease pathology in elderly was researched in a study by Winer and colleagues (2019). PET measures of tau and Aβ, EEG sleep recordings and retrospective sleep evaluations were used in elderly. It was found that sleep EEG features were highly predictive of tau and Aβ in elderly and that sleep changes in earlier life phases were associated with presence of tau and Aβ in later life (Winer et al., 2019). It is also known that Alzheimer's disease comes with great cognitive deficits (Wang and Holtzman, 2020). Tau and Aβ accumulation are believed to start before the onset of cognitive decline due to Alzheimer's disease, meaning it is able to predict cognitive decline due to Alzheimer (Winer et al., 2019). A review by Wang and Holtzman from 2020 had the same aim and found that disturbed sleep could not only lead to more production of Aβ, but also to decreased Aβ clearance. This results in even more disturbed sleep; hence a bidirectional relation exists (Wang and Holtzman, 2020).

A study by Lo et al. (2014) aimed to research the effects of changes in sleep duration and quality on age-related changes in brain structures and cognitive performance. It was concluded that with healthy ageing, decline in sleep duration is associated with a higher amount of age-related brain atrophy as well as cognitive decline. However, this was not associated with increase in inflammation in short sleeping elderly. The study was performed on 66 community-dwelling Chinese elderly aged 55 years old or above from the year 2005 until the year 2013. Measurements were conducted every 2 years. From magnetic resonance brain scans, the volumes of the total cerebrum, gray matter, white matter, hippocampus, ventricles and the inferior and superior frontal gyrus. Multiple kinds of tests were used to assess cognition and sleep duration and quality was measured with the PSQI. Blood samples were used to test for hs-CRP. A significant effect of baseline sleep duration on the rate of ventricular expansion was found, which was not the case for any of the other brain regions. Baseline sleep duration was also associated with decline in cognitive performance, although not predictive of it. However, sleep quality had no significant effect on cognitive ageing. Also, there was no correlation

between inflammation and baseline sleep duration, brain structure or cognitive performance (Lo et al. 2014).

A study by Landolt and colleagues in 2012 investigated whether age-related changes in adenosine signal transmission cause lowered vulnerability to sleep deprivation in older individuals. As mentioned before, older age is an important risk factor for vulnerability for sleep deprivation. However, Landolt et al. (2012) found that the consequences of sleep loss on sleep and waking EEG and different aspects during wakefulness and performance are lowered in healthy elderly. Meaning, sleep loss has a much smaller effect on cognition in healthy elderly compared to unhealthy elderly. On top of that, it was also found for the first time in humans, that impaired sensitivity of the adenosine neuronal pathways helps to reduce neurobehavioral consequences of sleep deprivation in elderly. In short, not only the parameters of sleep are important, but also the health of the individual (Landolt et al., 2012).

Depression is a mental disorder that can affect elderly more severely than younger patients, which can lead to cognitive impairments (Crocco et al., 2010). Depression is also very common among elderly (Luppa et al., 2012). Cable and colleagues (2017) examined whether sleep disturbance is associated in the long term with patterns of depressive states in a total amount of 10,635 elderly aged 65 years and over. The study by Cable et al. used previously obtained data by studies from England and Japan. Worse sleep – in quality, structure and duration, due to the sleep disturbances – was found to be longitudinally associated with the depression irrespective of sex, age and other factors. This even accounted for the group of subjects that recovered from depression. The same accounted for the onset and repeatedly depressive state. As depression can lead to cognitive impairments in elderly (Crocco et al., 2010), worse sleep can indirectly lead to cognitive decline. However, it is very likely that sleep and cognitive ageing are bidirectionally related (Cable et al., 2017). Meaning, the chance that good sleep is more prevalent if not limited to those that do not suffer from depressions, is rather high. It is thus likely that describing the role of sleep on the recovery of depressive symptoms is complicated due to the possible bidirectional association and the co-occurring of anxiety disorders with depression. It was also hypothesized that good sleep is likely to prevent the onset as well as the recurrence of depression and its symptoms (Cable et al., 2017).

So, sleep disturbances were found to be correlated with depression. Since depression is very prevalent in elderly and depression can lead to cognitive impairments in elderly, sleep disturbances could indirectly affect cognition via depression (Luppa et al., 2012; Cable et al., 2017; Crocco et al., 2010). The same results were found in the study by Ji and Fu from 2020, as already mentioned in 2.1. They found that depression was indicative of future cognitive decline in elderly (Ji and Fu, 2020). However, in the study by Jelicic et al. (2002) that has been mentioned previously, it was also hypothesized that sleep complaints can lead to depression, which then could induce cognitive impairments. However, when comparing sleep complaints and cognition after controlling for depression, the decline in cognitive functioning disappeared. They concluded that it is highly unlikely that depression caused the sleep problems and cognitive decline (Jelicic et al., 2002).

3. Discussion

3.1. Summary

In short it has been found in multiple studies that different parameters of sleep that change when ageing can influence cognition directly or indirectly. Ageing comes with changes in sleep and those changes in sleep have been found to correlate with cognitive decline. People with self-reported sleeping problems were found to suffer more cognitive decline and were more likely to suffer from early cognitive decline compared to elderly without sleeping problems (Niu et al., 2016). On top of that, lowered sleep efficiency, more night-time awakenings, more wake episodes and poor subjective sleep quality were associated with cognitive decline (Blackwell et al., 2013). Specifically, the amount of REM sleep was found to be positively correlated with multiple aspects of mental functioning (Prinz, 1977). The same accounted for amount of NREM sleep and cognitive performance 14 years later (Spiegel et al., 1999). Sleep complaints as well as poor sleep quality have also been found to be able to predict cognitive decline (Jelicic et al., 2002; Potvin et al., 2012). Also, late-life onset of insomnia was strongly associated and predictive for cognitive decline in female elderly (Ji and Fu, 2020). So, a lot of studies have been found to conclude that changes in sleep parameters can affect cognition in elderly. However, one study also concluded that subjective sleep quality and duration did not affect cognition (Saint Martin et al., 2012). This study from 2012 included 272 individuals with a mean age of 84.8 years and should thus be trustworthy. The study on the same topic by Potvin et al. from 2012 did find that subjective sleep quality could predict future decline over one year. This study was conducted on 1664 elderly aged around 65 years and should thus also be trustworthy. The only differences between the studies are the mean age and the duration of the study. It could be that as people get older, they get used to their quality of sleep, rendering an overestimation of the actual quality, so the effect of subjective sleep quality on cognition disappears. Or, it could be that subjective sleep quality and duration is only correlated with future cognitive decline and not current.

However, most of the studies have researched the correlation between sleep changes and cognitive decline in the elderly currently, and not causality. It could be concluded that sleep changes such as lowered sleep efficiency, poor sleep quality, lowered amount of REM and NREM sleep correlate with cognitive decline (Blackwell et al., 2013; Spiegel et al., 1999), but no conclusions were drawn in terms of causality. However, some studies did research the predictive factor of sleeping problems on cognitive decline. For example, Niu et al. concluded that people with subjective sleep problems were more likely to suffer from early cognitive decline compared to elderly without cognitive decline. Also, sleep complaints were found to predict cognitive decline (Jelicic et al., 2002). So, although a predictive factor has been found, more research should be done upon the causal relationship between age-related changes in sleep and cognition.

Changes in sleep have also been found to indirectly affect cognition, through inflammation in terms of microglial ageing and activation (Kaneshwaran et al., 2019), accumulation of tau and Aβ (Winer et al., 2019) and decreased clearance of Aβ (Wang and Holtzman, 2020) and age-related brain atrophy (Lo et al., 2014). It has also been made clear that the sensitivity of the adenosine neuronal pathways has an impact on the severity of the effect that sleep loss has on cognition (Landolt et al., 2012). In some studies, it was found that worse sleep could also indirectly lead to cognitive decline via depression (Crocco et al., 2010; Cable et al., 2017; Ji and Fu, 2020). However, a study by Jelicic et al. (2002) found that it was highly unlikely that depression caused the cognitive decline in their participants. Jelicics study was performed on 838 participants and actually assessed the effect of depression on cognitive decline, while the study by Cable et al. of more than 10,000 participants only assessed the relationship between sleep and depression. Combined with a statement from Crocco et al., it was concluded that bad sleep could lead to cognition via depression indirectly. Since the argumentation for Cable et al. can

only be drawn in combination with results from Crocco et al., the conclusions drawn by Jelicic et al. could be considered more trustworthy.

3.2. Important notions

Although this thesis has focused on the role of sleep disturbances on ageing, one other small, yet important aspect to ageing, is the change in the socio-relational network when getting older. Having fewer social interactions due to social isolation and reduction in physical activities are often a consequence of getting older and can cause a reduction of cognitive activity, with a large effect on sleep feature. Of course, not only sleep disturbances influence ageing and cognitive decline. Other influencing factors, such as socio-relational networks, should also be considered when speaking of cognitive ageing (Conte et al., 2012).

While here, it has been researched whether age-related changes in sleep parameters lead to ageing in terms of cognitive decline, sleep has also been found to affect cognition in adolescents. For example, it was found that a wide range of cognitive functions, subjective alertness and mood were impaired by only a week of partial sleep deprivation in 65 adolescents from top high schools (Lo et al., 2016). Also, sleep restriction led to more sluggish cognitive tempo symptoms, which in turn led to impaired attention in adolescents with ADHD (Becker et al., 2019). In adolescents too, subjective sleep duration was found to affect cognitive performance (Rahman et al., 2020). Taken together, these findings suggest that even when young, sleep changes might lead to a decline in cognition. So, if adolescents can already affect their cognition by changes in sleep, this might have an effect on the severity in changes in sleep as well as the changes in cognition. For example, if sleep already changes during adolescence, it might stay the same when getting older, which might lead to the same cognitive decline as one would expect with ageing. Or, sleep might be changed even more when ageing, which might lead to a worse cognitive decline when they reach older age. The most probable option would be the latter, as previous research has shown that sleep changes even in healthy ageing (Luca et al., 2015; Ohayon et al., 2004). This might mean that the severity of future cognitive decline can be predicted by looking at sleeping habits and cognitive function when adolescent. Future research might consider looking into this.

3.3. Possible ways to aid healthy cognition

It has been concluded that changes in parameters of sleep affect ageing in terms of cognition directly as well as indirectly. Often, the correlation is negative, which might seem like an inevitable consequence of ageing. However, research has been performed on possible ways to aid healthy cognition. For example, Conte and colleagues proved in 2012 that learning tasks can stimulate subsequent sleep quality in elderly, in terms of continuity, stability and organization. It has also been found that physical activity can also improve sleep quality in elderly (Seery et al., 2012). Although they observed no association between physical activity and symptomatic fatigue in the participants, they did find a positive, non-linear relationship between physical activity and the quality of sleep. It has been shown that physical activity influences both sleep quality (Seery et al., 2012) and mitochondrial dysfunction (Grassi et al., 2014). Future research might look into the possibility to prevent further age-related cognitive decline by aiding good sleep quality, duration and structure.

3.4. Conclusion

In short, it can be concluded that age-related changes in parameters of sleep such as structure, quality and duration are able to affect ageing in terms of cognition, either directly or indirectly via inflammation or accumulation of tau and Aβ. These findings are important as the relationship between changes in sleep parameters and cognition in elderly had now become clearer. It might be possible to develop early treatments to prevent age-related cognitive decline by means of improving the structure, duration or, if not also, the quality of sleep.

References

Bano, D., Agostini, M., Melino and G. (2011). Ageing, Neuronal Connectivity and Brain Disorders: An Unsolved Ripple Effect. *Mol Neurobiol, 43,* 124–130. https://doi.org/10.1007/s12035-011-8164-6

Becker, S. P., Epstein, J. N., Tamm, L., Tilford, A. A., Tischner, C. M., Isaacson, P. A., Simon, J. O., & Beebe, D. W. (2019). Shortened Sleep Duration Causes Sleepiness, Inattention, and Oppositionality in Adolescents With Attention-Deficit/Hyperactivity Disorder: Findings From a Crossover Sleep Restriction/Extension Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *58*(4), 433–442. https://doi.org/10.1016/j.jaac.2018.09.439

Bettio, L., Rajendran, L., & Gil-Mohapel, J. (2017). The effects of aging in the hippocampus and cognitive decline. *Neuroscience and biobehavioral reviews*, *79*, 66–86. https://doi.org/10.1016/j.neubiorev.2017.04.030

Blackwell, T., Yaffe, K., Laffan, A., Ancoli-Israel, S., Redline, S., Ensrud, K.E., Song, Y. and Stone, K.L. (2014). Associations of Objectively and Subjectively Measured Sleep Quality with Subsequent Cognitive Decline in Older Community-Dwelling Men: The MrOS Sleep Study. *SLEEP, 37*(4), 655-663. http://dx.doi.org/10.5665/sleep.3562

Cable, N., Chandola, T., Aida, J., Sekine, M. and Netuveli, G. (2017). Can sleep disturbance influence changes in mental health status? Longitudinal research evidence from ageing studies in England and Japan. *Sleep Medicine*, doi: 10.1016/j.sleep.2016.11.017.

Conte, F., Carobbi, G., Errico, B.M. and Ficca, G. (2012). The effects of pre-sleep learning on sleep continuity, stability, and organization in elderly individuals. Front. Neurol., 3(109), 27-35. https://doi.org/10.3389/fneur.2012.00109

Crocco, E.A., Castro, K. and Loewenstein, D.A. (2010). How Late-Life Depression Affects Cognition: Neural Mechanisms. Current Psychiatry Reports, 12, 34-38. https://doi.org/10.1007/s11920-009-0081-2

Deboer, T. (2013). Behavioral and Electrophysiological Correlates of Sleep and Sleep Homeostasis. In: Meerlo, P., Benca, R., Abel, T. (eds) Sleep, Neuronal Plasticity and Brain Function. *Current Topics in Behavioral Neurosciences, vol 25.* Springer, Berlin, Heidelberg. https://doi.org/10.1007/7854_2013_248

Elmenhorst, E.-M., Elmenhorst, D., Benderoth, S., Kroll, T., Bauer, A. and Aeschbach, D. (2018). Cognitive impairments by alcohol and sleep deprivation indicate trait characteristics and a potential

role for adenosine A_1 receptors. *PNAS, 115*(31), 8009-8014. https://doi.org/10.1073/pnas.180377011

Exalto, L. G., Hendriksen, H. M. A., Barkhof, F., van den Bosch, K. A., Ebenau, J. L., van Leeuwenstijn-Koopman, M., Prins, N. D., Teunissen, C. E., Visser, L. N. C., Scheltens, P., & van der Flier, W. M. (2022). Subjective cognitive decline and self-reported sleep problems: the science project. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *14*(1). doi: 10.1002/dad2.12287

Feinberg, I. (1974). Changes in sleep cycle patterns with age. *Journal of Psychiatric Research*, *10*(3–4), 283-306. https://doi.org/10.1016/0022-3956(74)90011-9.

Fuller, P. M., Gooley, J. J., & Saper, C. B. (2006). Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. *Journal of biological rhythms*, *21*(6), 482–493. https://doi.org/10.1177/0748730406294627

Grassi, C., Landi, F. and Delogu, G. (2014). Lifestyles and Ageing: Targeting Key Mechanisms to Shift the Balance from Unhealthy to Healthy Ageing. *Active Ageing and Healthy Living*, IOS Press, p.106.

Jelicic, M., Bosma, H., Ponds, R.W.H.M., Van Boxtel, M.P.J., Houx, P.J. and Jolles, J. (2002). Subjective sleep problems in later life as predictors of cognitive decline. Report from the Maastricht Ageing Study (MAAS). *International Journal of Geriatric Psychiatry*, *17*(1), 73-77. https://doi.org/10.1002/gps.529

Ji, X. and Fu, Y. (2020). The role of sleep disturbances in cognitive function and depressive symptoms among community-dwelling elderly with sleep complaints. *International Journal of Geriatric Psychiatry, 36*(1), 96-105. https://doi.org/10.1002/gps.5401

Juan, S., & Adlard, P. A. (2019). Ageing and Cognition. *Sub-cellular biochemistry*, *91*, 107–122. https://doi.org/10.1007/978-981-13-3681-2_5

Kaneshwaran, T., Olah, M., Tasaki, S., Yu, L., Bradshaw, E.M., Schneider, J.A., Buchman, A.S., Bennet, D.A., de Jager, P.L. and Lim, A.S.P. (2019). Sleep fragmentation, microglial aging, and cognitive impairment in adults with and without Alzheimer's dementia. Science Advances, 5. DOI: 10.1126/sciadv.aax7331

Klinzing, J. G., Niethard, N., & Born, J. (2019). Mechanisms of systems memory consolidation during sleep. *Nature neuroscience*, *22*(10), 1598–1610. https://doi.org/10.1038/s41593-019-0467-3

Landolt H.P., Julia, R. and Martin, A. (2012). Reduced Neurobehavioral Impairment from Sleep Deprivation in Older Adults: Contribution of Adenosinergic Mechanisms. Frontiers in Neurology, 3(62). https://doi.org/10.3389/fneur.2012.00062

Lo, J.C., Loh, K.K., Zheng, H., Sim, S.K.Y., Chee, M.W.L. (2014). Sleep Duration and Age-Related Changes in Brain Structure and Cognitive Performance, *Sleep*, 39(7), 1171-1178. https://doi.org/10.5665/sleep.3832

Lo, J.C., Ong, J.L., Leong, R.L., Gooley, J.J., & Chee, M.W. (2016). Cognitive Performance, Sleepiness, and Mood in Partially Sleep Deprived Adolescents: The Need for Sleep Study. *Sleep*, *39*(3), 687–698. https://doi.org/10.5665/sleep.5552

Luca, G., Rubio, J.H., Andries, D., Tobback, N., Vollenweider, P., Waeber, G., Vidal, P.M., Preisig, R. & Tafti, M. (2015). Age and gender variations of sleep in subjects without sleep disorders. *Annals of Medicine, 47* (6), p482-491. https://doi.org/10.3109/07853890.2015.1074271

Luppa, M., Sikorski, C., Luck, T., Ehreke, T., Konnopka, A., Wiese, B., Weyerer, S., König, H.-H. and Riedel-Heller, S.G. (2012). Age- and gender-specific prevalence of depression in latest-life – Systematic review and meta-analysis. *Journal of Affective Disorders, 136*(3). https://doi.org/10.1016/j.jad.2010.11.033.

Pages 212-221,McNamara, P. (2019). From Biological Rhythms to the Sleep Cycle. In The Neuroscience of Sleep and Dreams (Cambridge Fundamentals of Neuroscience in Psychology, pp. 28-39). Cambridge: Cambridge University Press. doi:10.1017/9781316817094.004

Meerlo, P., Benca, R. M., & Abel, T. (2015). *Sleep, neuronal plasticity and brain function* (Ser. Current topics in behavioral neurosciences, volume 25). Springer. https://doi.org/10.1007/978-3-662-46878-4

Middelkoop, H. A. M., Kerkhof, G. A., Doel, D. A. S.-V. D., Ligthart, G. J. et Kamphuisen, H. A. C.. (1994). Sleep and Ageing: The Effect of Institutionalization on Subjective and Objective Characteristics of Sleep. *Age and ageing*, *23*(5), 411-417. doi:10.1093/ageing/23.5.411

Niu, J., Han, H., Wang, Y., Wang, L., Gao, X. And Liao, S. (2016). Sleep quality and cognitive decline in a community of older adults in Daqing City, China. *Sleep Medicine, 17*, 69-74. https://doi.org/10.1016/j.sleep.2015.07.033.

Ohayon, M. M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep*, *27*(7), 1255–1273. https://doi.org/10.1093/sleep/27.7.1255

Pace-Schott, E.F., Spencer, R.M.C. (2014). Sleep-Dependent Memory Consolidation in Healthy Aging and Mild Cognitive Impairment. In: Meerlo, P., Benca, R., Abel, T. (eds) Sleep, Neuronal Plasticity and Brain Function. Current Topics in Behavioral Neurosciences, vol 25. Springer, Berlin, Heidelberg. https://doi.org/10.1007/7854_2014_300

Potvin, O., Lorrain, D., Forget, H., Dubé, M., Grenier, S., Préville, M. and Hudon, C. (2012). Sleep Quality and 1-Year Incident Cognitive Impairment in Community-Dwelling Older Adults, *Sleep*, 35(4), 491–499, https://doi.org/10.5665/sleep.1732

Prinz, P.N. (1977). Sleep Patterns in the Healthy Aged: Relationship With Intellectual Function. *Journal of Gerontology*, *32*(2), 179–186, https://doi.org/10.1093/geronj/32.2.179

Radulovacki, M. (1989). Adenosine and sleep. *International Journal of Psychophysiology*, *7*(2), 366–367. https://doi.org/10.1016/0167-8760(89)90298-5

Rahman, S. A., Rood, D., Trent, N., Solet, J., Langer, E. J., & Lockley, S. W. (2020). Manipulating sleep duration perception changes cognitive performance - an exploratory analysis. *Journal of Psychosomatic Research*, *132*. https://doi.org/10.1016/j.jpsychores.2020.109992

Rauchs, G., Carrier, J. and Peigneux, P. (2013). Sleep and cognition in the elderly. *Frontiers in Neurology, 4*(71), 4. DOI 10.3389/978-2-88919-295-3

Saint Martin, M.S., Sforza, E., Barthélémy, J.C., Thomas-Anterion, C. and Roche, F. (2012). Does subjective sleep affect cognitive function in healthy elderly subjects? The Proof cohort. *Sleep Medicine, 13*(9), 1146-1152. https://doi.org/10.1016/j.sleep.2012.06.021.

Seery, E. M. , Christie, A. & Kent-Braun, J. A. (2011). Physical Activity, Sleep Quality and Symptomatic Fatigue in Older Adults. *Medicine & Science in Sports & Exercise, 43* (5), 819. doi: 10.1249/01.MSS.0000402281.67366.04.

Spiegel, K., Leproult, R. and Van Cauter, E. (1999b). Impact of sleep debt on metabolic and endocrine function. The Lancet, 354(9188), 1435-1439. https://doi.org/10.1016/S0140-6736(99)01376-8.

Spiegel, R., Herzog, A. and Köberle, S. (1999a). Polygraphic sleep criteria as predictors of successful aging: an exploratory longitudinal study. *Biological Psychiatry, 45*(4), 435-442. https://doi.org/10.1016/S0006-3223(98)00042-0.

Wang, C. and Holtzman, D.M. (2020). Bidirectional relationship between sleep and Alzheimer's disease: role of amyloid, tau, and other factors. *Neuropsychopharmacology, 45*(1), 104-120. doi: 10.1038/s41386-019-0478-5

Winer, J.R., Mander, B.A., Helfrich, R.F., Maass, A., Harrison, T.M., Baker, S.L., Knight, R.T., Jagust, W.J. and Walker, M.P. (2019). Sleep as a Potential Biomarker of Tau and β-Amyloid Burden in the Human Brain. *J Neurosci, 39*(32), 6315-6324. doi: 10.1523/JNEUROSCI.0503-19.2019

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