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DISSERTATION

Effects of naturally occurring partial sleep loss on the physiological stress response

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Vorwort

Teilergebnisse dieser Arbeit basieren auf den gleichen Daten wie der Artikel *„Natural sleep loss is associated with lower mPFC activity during negative distracter processing*“ von Annika Dimitrov, Jonathan Nowak, Armin Ligdorf, Nicole Y. L. Oei, Mazda Adli, Henrik Walter, Ilya Veer (2021).

Der Artikel und diese Arbeit beziehen sich auf das gleiche Probandenkollektiv. Jedoch werden in dem Artikel insbesondere Daten auf bildgebenden Verfahren ausgewertet. Zudem fokussiert sich der Artikel auf eine andere Phase des Experiments in der es um die Wirkung von emotionalen Distraktoren geht.

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1 List of Abbreviations

ACC	Anterior cingulate cortex
ACTH	Adrenocorticotropic hormone
ANOVA	Univariate analysis of variance
ANS	Autonomic nervous system
ARAS	Ascending reticular activation system
CRH	Corticotropin Releasing Rormone
DEGS1	„Studie zur Gesundheit Erwachsener in Deutschland – Erste Welle“
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
fMRI	Functional magnetic resonance imaging
H	hypothesis
HF	High Frequency
HPA axis	Hypothalamic-Pituitary-Adrenal axis
HRV	heart rate variability
ICD-10	International Classification of Diseases and related health problems – 10th version
ICD-11	International Classification of Diseases and related health problems – 11th version
ICSD	International Classification of Sleep Disorders
IQR	Interquartile range
LF	Low Frequency
MIST	Montreal Imaging Stress Task
mPFC	Medial prefrontal cortex
MRI	Magnetic resonance imaging
NREM	Non-Rapid-Eye-Movement
PVT	Psychomotor vigilance test
R1 / R2	Resting State 1 / 2
REM	Rapid eye movement
RMSSD	Root mean square of successive differences
SD	Standard deviation
SDNN	Standard deviation of N-N-intervals
TSST	Trier Social Stress Test
WHO	World Health Organization

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2 Abstract

English

Our research examined the effects of partial sleep loss on the psychophysiological stress response in working male adults. Previous studies showed mixed results for the effects of in most cases artificially induced partial or total sleep restriction on markers of the autonomic stress response. In contrast, we examined the effects of naturally occurring sleep loss measured by the participants via a sleep questionnaire and a sleep diary over 7 days. The stress response was measured via subjective rating, cortisol, heart rate and heart rate variability (HRV). These markers were collected during a standardized social stress test for magnetic resonance imaging. These measures were analysed according to the different phases of the stress test.

We found a significant effect of stress induction on perceived stress, salivary cortisol, heart rate and one of the HRV markers. Yet no correlation was found between the reactivity or recovery of stress markers and sleep loss.

Our research with the limitation of using only self-reported sleep loss calls into question the applicability of previous results, which showed associations between sleep loss and the stress response to naturally occurring sleep loss.

Deutsch

Die Forschung, die Gegenstand dieser Arbeit ist, untersucht die Wirkungen von natürlich auftretendem Schlafmangel auf die psychophysiologische Stressantwort bei arbeitenden erwachsenen Männern. Die bisherige Forschung zu diesem Thema zeigte uneinheitliche Ergebnisse für die Auswirkung von teilweisen oder kompletten Schlafmangel, welcher zumeist künstlich induziert wurde.

In unserer Forschungsarbeit untersuchten wir den natürlich vorkommenden Schlafmangel, welcher durch einen Fragebogen und ein Schlaftagebuch über 7 Tage erfasst wurde.

Die Stressreaktion wurde während einer MRT-Messung in zwei Ruhephasen und während eines standardisierten sozialen Stresstests für MRTs über eine subjektive Stressskala, Speichelkortisolspiegel, Puls und die Herzfrequenzvariabilität erfasst. Diese Variablen wurden weiter unterteilt nach den verschiedenen Phasen des Experiments.

Für die Herzfrequenz, subjektiven Stress, Kortisolspiegel und einen von drei Herzratenvariabilitätsmarkern zeigten sich signifikante Veränderung über die Phasen. Die

statistische Auswertung zeigte jedoch keine Korrelation zwischen Schlafmangel und subjektiven Stress oder physiologischen Stressmarkern.

Diese Ergebnisse sind unter anderem dadurch limitiert, dass sie die selbsterfassten Schlafenszeiten der Probanden nutzten. Dennoch weisen sie auf die fragliche Übertragbarkeit der in früheren Studien beschriebenen Korrelation zwischen Schlafmangel und Stressantwort auf alltäglichen Schlafmangel zum Beispiel in der Arbeitswelt hin.

3 Introduction

3.1 Definitions & Epidemiology

This work will focus on two common health-related conditions, sleep deprivation and stress. In our study we investigated the effects of sleep deprivation on the stress response. Sleep deprivation, meaning insufficient sleep, can be caused by either short sleep duration or poor quality of sleep (Lieb et al., 2016). Occasional acute sleep deprivation can have widespread triggers such as occupational demands, poor sleep hygiene, or nightly entertainment (Hublin et al., 2001; Owens et al., 2014). Stress has become a widespread issue. The term 'stress' is broadly used in colloquial language to describe conditions of negative emotion or high demands. Von Känel (2012) argues that since it is only defined vaguely, consequently, a scientific approach requires specific terms and definitions for different aspects of stress. As will be explained in detail later on, one of these aspects is the stress reaction, which will be part of this work.

We come across sleep deprivation and chronic stress regularly in our daily lives. Sleep problems are very common, with a reported prevalence of 21.9% in the adult population in Germany according to the 'Study on health of adults in Germany', known as DEGS1 (Schlack et al., 2013). Therefore, it is important understand the effects it has. On the other hand, severe chronic stress has been reported by 11% of the German working age population (Hapke et al., 2013), while 23% report to often feel stressed according to a cross-sectional survey by a German health insurer (Techniker Krankenkasse, 2016). What makes both stress and sleep loss subjects of interest in healthcare and research is that chronic sleep deprivation and chronic stress are associated with morbidity, and that these associations sometimes overlap. For example, they have associations with an increased incidence of heart disease or affective disorders (Nagai et al., 2010; Owens et al., 2014; Techniker Krankenkasse, 2016). Due to their high prevalence, these two factors are important health issues with effects on a societal level.

Yet, the studies on both sleep deprivation and stress have used a variety of mixed approaches. One cause is that both sleep deprivation and stress do not have internationally agreed upon definitions and constructs, and hence a variety of markers exist. For instance, sleep loss in our research refers to short sleep duration that is naturally occurring, while other studies have induced sleep loss artificially. Here, sleep loss was self-reported using a sleep diary, while other studies monitored it via polysomnography or wrist actigraphy.

Our research focuses on this stress reaction and on the effects of a decreased sleep duration on it. The next chapters first give an overview of the topic of sleep deprivation, then expand on different models of stress, including the physiological stress response and the related central nervous processes. Furthermore, the connection of sleep loss and the stress response will be explained.

3.2 Sleep

3.2.1 Definition of sleep

Before discussing sleep deprivation, this chapter will introduce the different aspects of physiological sleep. Most people have an intuitive understanding of what sleep is, although the explicit definitions are challenging. For instance, in the ancient Greek Pantheon, the god of sleep *Hypnos* is a gentle god of the underworld. He is the son of *Nyx*, the divine and personified night, by which general sleep comes over every man every day as certain as nightfall. Yet, we need to transfer this to a plainer definition. Here, sleep is defined as a recurring physiological state that alternates with wakefulness (Borbély et al., 2016). In other words, sleep is the time during which we do not consciously experience our surroundings. While this is also true for a coma or unconsciousness, in contrast, the sleeping mind is more reactive and active. More on its specific functions will be explained later on. Borbély, Daan, and colleagues (2016) introduced a two-process model of this cycle of sleep and wake in the 1980s, in which Process S is a process balancing sleep and wakefulness and Process C (as in “circadian”) is an internal clock or pacemaker as a second factor (Borbély et al., 2016). Process S triggers sleep after periods of being awake and vice-versa triggers wakefulness after sufficient periods of sleep. This works in an optimal way when synchronized to the internal biological rhythm or Process C. These two processes shape the sleep-wake cycle and are also thought to influence each other. Typically, these processes adjust roughly to a period of 24 hours, in which Process C is referred to as circadian rhythm (Halberg, 1959), a well-known concept which has been adapted here. The following paragraph will further expand on this process.

3.2.2 Circadian rhythm & chronotype

The circadian rhythm is important for sleep. In general, multiple organ systems synchronize with the time of the day through circadian processes. Important cerebral structures for the circadian clock are the suprachiasmatic nucleus (SCN) and the hypothalamus (Hastings et al.,

2018). This internal clock, with the SCN as a central structure, influences activity levels, energy metabolism and sleep quality (Borbély et al., 2016; Dallmann et al., 2014). Beyond an individual preference for sleep duration, there is also an individual circadian rhythm called chronotype which impacts when we prefer to sleep (Roenneberg et al., 2003). A marker thereof is the midpoint of night-time sleep. One example where chronotype and circadian rhythm become apparent is jetlag, where your internal schedule cannot adapt quickly enough to changes of the external schedule after crossing several time zones. Another example is that in adolescence, preferred sleep duration is longer and sleep chronotype is later than in adulthood, which adds up to a preference for waking up later. The ideal sleep for the average adolescent may incompatible with school starting at 8 am, and improvements in sleepiness and mood were shown as a result of starting school later (Boergers et al., 2014). In adults these effects would not be as pronounced and there is a shift towards an earlier chronotype (Roenneberg et al., 2003). While the circadian rhythm facilitates periods of good conditions for rest and sleep on a daily basis, the chronotype describes individual differences. These differences are small for many, yet some people are definite owls or larks, meaning evening and morning types (Natale & Cicogna, 2002).

3.2.3 Function of sleep

The purpose of sleep has only been explored in parts, yet its importance is undisputed. The above-mentioned *Hypnos* is often portrayed with his sibling *Thanatos*, the god of (gentle) death, while sleep is not deadly, but to the contrary, vitally important. Sleep serves as a state of rest for the brain. Its functions include restoring alertness, concentration and emotional regulation (Krueger et al., 2008). Tononi & Cirelli (2014) address the hypothesis that sleep is necessary for the restoration of homeostasis in the brain, particularly nerve cell connections and neural plasticity. It is furthermore a phase of consolidation, where memories are appraised, sorted and linked (Diekelmann & Born, 2010). The domain of *Morpheus* (*Hypnos'* son), the dream state, has been a source of fascination and discussion for scientists. Yet, the physiological function of this process cannot be fully explained to date. In one hypothesis, Solms (2000) references Freud's "The interpretation of dreams" (1900) in the idea that dreams protect the sleep and are also are expressions of emotional desires. The functions of sleep reach beyond the brain, however. For instance, sleep interacts with energy metabolism. Sleep promotes a state of rest and in general an anabolic state (Aschoff, 1993). In this context, it has been observed that endocrine activity differs over the course of the sleep-wake cycle. During the night cortisol

levels are initially low, yet they rise and peak around awakening. During wakefulness, the secretion of insulin and glucocorticoids like cortisol are increased, while during sleep, release of the hormones melatonin (promotes sleep), leptin (promotes satiety) and somatotropin (= growth hormone) is higher (Bass & Takahashi, 2010). Therefore, sleep may also serve the temporal segregation of different or opposing metabolic processes (Krause et al., 2017). The importance of sleep becomes even clearer when considering the effects of insufficient sleep, which will be discussed further in section 3.3.

3.2.4 Factors impacting sleep

To understand sleep deprivation, it is important to consider how the endogenous rhythm and the extent of wakefulness are impacted by external factors or stimuli. These can either promote or disturb sleep and vary from person to person. The behavioural and environmental factors for sleep are often summarised as sleep hygiene (Irish et al., 2015). It is a practical concept, but has limited evidence to date (Irish et al., 2015). The concept of sleep hygiene includes social and physical activity, which significantly impact our internal schedule. Another predominant environmental factor, the so-called *zeitgeber*, is brightness, especially exposure to sunlight, which stimulates wakefulness. In addition, the perception of darkness, typically at night-time, leads to the triggering of sleep. This process mediated by the release of the neurotransmitter melatonin. Sleep hygiene also includes substance use, such as coffee and alcohol consumption or smoking, which may impact sleep quality negatively (Roehrs & Roth, 2008; Skarupke et al., 2017).

3.3 Sleep deprivation

3.3.1 Definition of sleep deprivation and symptoms

Sleep deprivation is a key topic in this work. As mentioned above, the definition of sleep deprivation in research varies significantly (Krause et al., 2017). Sleep deprivation describes a lack of sleep duration or reduced sleep quality. Here, an insufficient sleep duration, or prolonged wakefulness, will be referred to as sleep loss.

How does sleep deprivation affect your health? Clinical signs of sleep deprivation are sleepiness and fatigue, yawning and irritability. Sleep deprivation may also be a part of sleep disorders. However, it is not synonymous with the diagnosis of insomnia. In the current International Classification of Diseases (ICD-10), the criteria for insomnia include sleep disturbances “at least three times a week over a period of 1 month” and that it “is coupled with

a high degree of suffering or impairs daily activities" (WHO, 2016). Therefore, sleep deprivation has a broader definition than clinical insomnia and its prevalence will differ with the criteria of sleep loss and the selection of participants.

The key features of sleep deprivation in research differ, specifically in the following four points: First in data acquisition - population-wide studies typically use self-reported sleep deprivation or sleep loss, while studies with a laboratory setting use devices like polysomnography to measure sleep more objectively. Polysomnography measures electrical signals in the brain and muscles to determine sleep phases. Second, sleep deprivation can be induced in a laboratory setting or it can be 'naturally' occurring, for instance during long shifts at work. Third, we can differentiate between total sleep loss, indicating uninterrupted wakefulness, and partial sleep loss. The effects of partial sleep loss are typically analysed over several nights. Finally, quantitative and /or qualitative aspects of sleep impairment can be taken into account. Reduced sleep duration alone may not entirely explain the difference between a 'good' or 'bad' night of sleep. And there are external factors like substance use, temperature or light which lead to qualitative differences in sleep (Irish et al., 2015). Polysomnography, for instance, gathers both qualitative and quantitative data on sleep. While studies are relatively heterogenous in these aspects, they may nonetheless be specific and focus on their respective aspects of sleep deprivation.

3.3.2 Epidemiological aspects of sleep loss

As mentioned in Section 3.1., sleep loss is a widespread problem. Yet, it is difficult to compare epidemiological data, since there is no clear consensus on a cutoff for sleep loss. The recommended sleep duration for adults is 7-9 or 7-8 hours according to a US-American Consensus Conference (Hirshkowitz et al., 2015). People can differ significantly in the hours of sleep they need and get, even intra-individually depending on their age, yet there is a general tendency towards insufficient sleep duration (National Sleep Foundation, 2008; Riemann et al., 2017). In the United States of America, the average sleep duration is reportedly 6:40 hours, which is 45 minutes below the sleep duration on a non-workday and 38 minutes below the self-reported optimum of the participants (National Sleep Foundation, 2008). In addition, the amount of recommended sleep is higher for children and teenagers (Paruthi et al., 2016). For adults, a sleep duration of less than 7 hours is associated with several negative consequences, while longer sleep duration is considered to be appropriate under certain conditions and an association of longer sleep duration with negative health effects is discussed critically

(Consensus Conference Panel et al., 2015; Watson et al., 2015). As Cappuccio, D'Elia, Strazzullo, and Miller (2010b) reported, short sleep duration was defined as either shorter than 5, 6 or 7 hours per night depending on the study. In the same review, the studies defined normal sleep as somewhere between 7-9 hours, and long sleep often as greater than 9 or greater than 10 hours. These variations contribute to differences in epidemiological information on sleep loss. According to Ellis et al. (2012), the point prevalence of acute insomnia in the UK is 7.9 % but the annual prevalence may reach 31.2 % to 36.6 %. In a longitudinal review on adults in the United States, 9.6 % of participants reported less than 6 hours of sleep overall in time-use diaries (Knutson et al., 2010). These rates were significantly higher in people in full-time employment. Hublin (2001) showed a prevalence of 20.4 % for the middle-aged Finnish population, with a slightly higher prevalence in women. Other recent studies have shown 34.8 % and 40 % of participants sleeping less than 6 hours for weeknights (Liu, 2016; Grandner, Chakravorty, Perlis, Oliver, & Gurubhagavatula, 2014). In a meta-analysis, both short and long sleep were also correlated with increased mortality (Cappuccio et al., 2010b). Sleep loss is associated with several negative health effects, as will be explained in the following sections. In general, we see the prevalence of sleep loss often reported above 10% and therefore it did, and to date does constitute a relevant public health issue affecting large numbers of the adult population in many countries (Ford et al., 2015).

3.3.3 Aetiology of sleep deprivation

Sleep deprivation and its causes have been conceptualized in several different models. Multidimensional models such as the bio-psycho-social model are commonly used for describing the aetiology of health conditions today (Egger, 2005). This concept has been adapted for sleep deprivation in a model distinguishing societal factors, social factors and individual factors, which is illustrated in **Figure 1** (Grandner et al., 2010). Societal factors can be new technologies, such as television or social media, or greater trends such as globalisation or the constant availability of goods, services and workforces called the "24/7 society", while social factors are for instance living conditions, ethnicity or socioeconomic status.

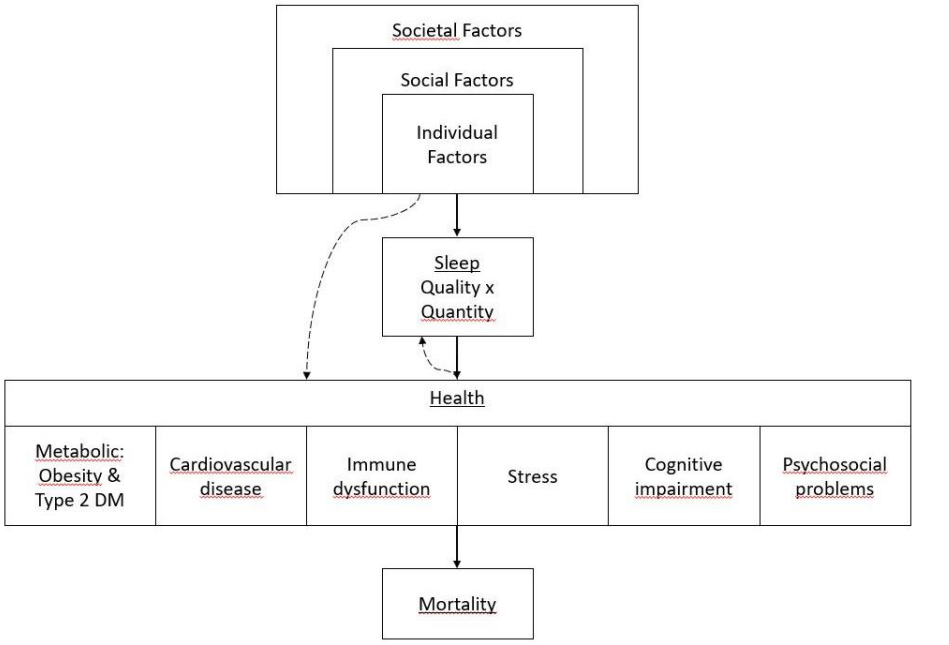

Figure 1: Model of sleep loss adapted from Grandner (2014). Factors on different levels – societal, social and individual – affect sleep and may lead to sleep deprivation. Sleep deprivation in turn affects health especially contributing to the mentioned health issues. For completeness, it is also addressed here that the abovementioned factors can influence health directly as well and that poor health may also worsen sleep (dotted lines).

One factor which has received a special focus is employment and working conditions. Rajaratnam & Arendt (2001) point out that modern working life may go against physiological sleep, with negative social and health consequences (Rajaratnam & Arendt, 2001). Multiple factors in the workplace, such as night shifts, social problems and high workloads can interfere with sleep quality or quantity (Chazelle et al., 2016). Shift work, which become common with the advent of industrialisation, interferes with the physiological internal clock. It has a negative impact on health and is statistically correlated with concomitant sleep deprivation (Kecklund & Axelsson, 2016). Shift work has been identified as a risk factor in, for instance, cardiovascular disease and major depression (Lee et al., 2017; Torquati et al., 2018).

Furthermore, genetics or behaviour patterns are examples of individual factors. Poor sleep habits are a very prevalent cause of sleep loss (Hillman & Lack, 2013). These may include restriction of sleep duration or poor sleep hygiene, for example due to media and light exposure or use of stimulants before bedtime. An underlying motivation for these factors could be nightly entertainment, both at home and when going out. Another cause of sleep deprivation, which will be subsequently discussed further, are medical problems. Sleep is particularly impaired by psychiatric diseases, sleep apnoea syndrome and chronic illnesses. On the other hand, there are

individual factors with beneficial effects on sleep like physical activity and exercise (Kredlow et al., 2015).

Aetiological factors for sleep loss can also be categorized into predisposing, precipitating and perpetuating factors, summarized under the "3 P model" (Spielman et al., 1987). Chronic stress may be a predisposing factor to sleep problems and increases the risk of chronic sleep disorders (Hapke et al., 2013). Acute sleep loss is often triggered or precipitated by acute stress. Furthermore, perpetuating factors may facilitate the shift to chronic sleep loss (Riemann et al., 2017). One perpetuating factor suggested by Van Dongen, Maislin, Mullington and Dinges (2003) could be that habituation to chronic sleep loss leads to a decrease of subjective sleepiness, which may in turn contribute to its high prevalence. Evening chronotype, for instance, can be a predisposing factor which is taken into account in this work.

3.3.4 Sleep troubles and mental health

As mentioned above, sleep impairments often cooccur with other conditions, for instance psychiatric disorders. Atypical sleep patterns are part of the diagnostic criteria of delirium, psycho-organic syndrome and different substance withdrawal syndromes (WHO, 2016). As generalized disorders of the central nervous system these conditions may interfere with the finely tuned sleep physiology. Sleep can also have a significant effect on the emotional state, which can be observed in everyday or clinical experience - for example, sleep disorders are very commonly seen in patients suffering from affective disorders (Riemann & Voderholzer, 2003). The effects on sleep range from a reduced need for sleep in mania to early arousal, hypersomnolence or symptoms of insomnia in depressive disorders (WHO, 2016). Insomnia symptoms and circadian disruption were shown to be predictive of depressive episodes (Riemann & Voderholzer, 2003; Palagini et al., 2019). Furthermore, it was also suggested that they could be predictive of suicidality, yet the effect of sleep loss on suicidal behaviour was also dependent on psychiatric symptoms (Porras-Segovia et al., 2019) In addition, light therapy in seasonal affective disorder or sleep withdrawal in depression indicate a (positive) impact of sleep-related interventions in mood disorders (Boland et al., 2017; Pflug & Tölle, 1971).

Furthermore, sleep disorders are part of the diagnostic criteria of generalised anxiety disorder, post-traumatic stress disorder, and neurasthenia or fatigue syndrome (WHO, 2016). These conditions are often comorbid with insomnia symptoms (Riemann et al., 2017). Thus, sleep deprivation is a common indicator of decreased (mental) health and should be routinely screened for in hospitalised or psychiatric patients (Becker et al., 2009; Lieb et al., 2016). This

has made it a topic of interest in psychiatric research. While there is an association between sleep and mental state, the underlying mechanisms and causality have not been thoroughly identified yet (Krause et al., 2017).

Sleep disorders are often diagnosed as comorbid conditions of mental and organic diseases. They can be classified with an independent classification, the International Classification of Sleeps Disorders or ICSD (American Academy of Sleep Medicine, 2014). It distinguishes organic and non-organic sleep disorders categorized in insomnia, sleep related breathing disorders, hypersomnolence, circadian rhythm disorders, parasomnias and sleep related movement disorders. Furthermore, the commonly used ICD-10 by the World Health Organization (WHO) uses similar categories (WHO, 2016). Chronic short sleep duration may fall under the umbrella term of insomnia in the German clinical guidelines, in contrast to non-restorative sleep with adequate sleep duration (Becker et al., 2009). As mentioned above, sleep loss may or may not be classified as a clinical sleep disorder.

3.3.5 Adverse effects of sleep loss

Sleep loss increases the risk for somatic diseases. It was shown that reduced sleep quantity can negatively affect a person's health in general and on multiple organ systems (Steptoe et al., 2006; Stranges et al., 2008). Among the consequences of sleep loss in the long term are an increased morbidity and mortality (Åkerstedt et al., 2017; Cappuccio et al., 2010b; Liu et al., 2017). The main factors for these adverse effects include individual sleep deficit and chronicity (Riemann et al., 2017). One recent meta-analysis showed an increased risk for cardiovascular and metabolic diseases as well as higher mortality rates due to short sleep duration (Itani et al., 2017). The effects of short sleep on cardiovascular health have been shown by many studies. For example, Grandner et al. (2014) showed that short sleep increased cardiovascular and metabolic risk slightly at 5-6 hours of sleep per night, and even more at less than 5 hours. This hints at a cumulation of risk (Grandner et al., 2014). Furthermore, several studies have shown that self-reported sleep problems are a risk factor for acute cardio-ischemic events (Ayas et al., 2003; Eguchi et al., 2008; S. W. Schwartz et al., 1998). In a longitudinal study of patients with obstructive sleep apnoea, shorter sleep duration correlated with a significantly increased cardiovascular risk (Kendzerska et al., 2014). Mediating factors for higher cardiovascular risk due to sleep loss could be alterations in autonomic cardiovascular regulation (Tobaldini, Cogliati, et al., 2013), an increased incidence of hypertension (Grandner et al., 2014; Meng et

al., 2013) and immunological alterations (Grandner et al., 2013; Irwin et al., 2016). Further mental factors might interfere with health behaviour (Alkadhi et al., 2013).

Additional relevant consequences of sleep deprivation are negative metabolic changes. Short sleep was associated with obesity in cross-sectional and longitudinal studies as described in a review by Morselli, Guyon, & Spiegel (2012). Furthermore, a recent study found that artificial light during sleep may have an impact on weight gain (Park et al., 2019). Several studies have shown a link between sleep loss and an increased risk of developing type 2 diabetes mellitus (Cappuccio et al., 2010a; Itani et al., 2017; Spiegel et al., 2005). A meta-analysis provided further evidence for this association and stressed that long sleep duration may have similar adverse effects (Shan et al., 2015). Hence, sleep loss is also a possible contributing factor to metabolic syndrome. **Figure 1** gives an overview of the different adverse health effects, wherein metabolic and cardiovascular disorders are the central somatic complications. The abovementioned studies and **Figure 1** reflect the complex interactions and adverse effects of sleep deprivation.

Sleep deprivation has impacts on several levels. In addition to the abovementioned physical complications, the negative psychological and economic consequences of sleep deprivation are well established. While sleepiness is the most common consequence of insufficient sleep, many people may also experience impaired performance at work or school, emotional irritability and depressive mood (Pilcher & Huffcutt, 1996; Fietze, 2016). In the work environment, sleep loss leads to a reduced performance, and thus reduced productivity, but it has also been linked to an increased rate of accidents (Fietze, 2016; Kecklund & Axelsson, 2016; Philip & Åkerstedt, 2006). Elmenhorst et al., 2009 presented a more plastic comparison, when they showed that four nights of sleep restricted to a maximum of five hours had equal effects on performance as a blood alcohol level of 6 mg per 100 ml. The reduced performance and increased risk of accidents may be explained by a decrease in vigilance, particularly the ability to stay attentive. Vigilance is vital to avoiding accidents, but was impaired over time in a standardised test, the Psychomotor Vigilance Test (PVT), after total sleep loss (Doran et al., 2001; Lim & Dinges, 2008). Furthermore, a meta-analysis by Lowe and colleagues (2017) showed that sustained attention was one of the cognitive factors most vulnerable to induced sleep loss (Lowe et al., 2017). On the other hand, not every person’s vigilance is affected equally by sleep loss, rather interindividual vulnerability levels have been observed as well as cumulative effects (Hudson et al., 2019).

Another cognitive domain affected by sleep deprivation is executive function, which means complex cognitive control processes which regulate behaviours. It was also shown to be significantly impaired by sleep loss (Lowe et al., 2017; Ratcliff & Van Dongen, 2009). In contrast, another study with partial sleep restriction by 3 hours did not replicate these findings on executive function (Schaedler et al., 2018). Only specific features of cognitive functioning are impaired by insomnia according to one meta-analysis (Fortier-Brochu et al., 2012). This included memory as well as problem-solving, which is a domain of executive function, while other domains of executive functioning remain unaffected. Analogously to the abovementioned findings on vigilance, successive or chronic sleep restriction showed a cumulative effect on cognitive function (Lowe et al., 2017; Van Dongen et al., 2003).

All in all, chronic sleep deprivation has been linked to several widespread and highly relevant mental and physical health conditions, such as depression, type 2 diabetes mellitus and metabolic syndrome or cardiovascular disease. Furthermore, it can impair cognitive functioning and may be a chief complaint of sleep disorders, specifically insomnia. Considering its association with health issues, cognitive impairment and accidents, it is an economic issue as well. According to estimations, the economic burden of sleep deprivation may reach between 1.35 and 2.92 % of the GDP (gross domestic product) for developed countries (Hafner et al., 2016). For these reasons, it is of considerable interest to research the underlying mechanisms of such associations.

3.4 The Stress Response

3.4.1 Adverse effects of stress

As mentioned above, a significant part of the population experiences chronic stress (Hapke et al., 2013). Similarly to sleep loss, it constitutes a relevant risk factor for morbidity (Hemingway & Marmot, 1999; McEwen, 2003) and mortality (Russ et al., 2012). In the cardiovascular system, stress induces an increase in blood pressure. Occupational and chronic stress increase the risk of arteriosclerosis and coronary artery disease (Lagraauw et al., 2015). It was shown that perceived stress is a risk factor for acute myocardial infarction (Rosengren et al., 2004). Furthermore, it increases the risk ratio for acute ischemic events in general (Steptoe & Kivimäki, 2013). Decreased time and frequency domain measures of HRV were associated with an increased risk of cardiovascular events in a large sample group (Tsuji et al., 1996). Regarding mental health, constant stress increases the risk for feeling “burned-out”,

nervousness, anxiety, and depressed mood. Yet, different levels of autonomic activation and recovery are important so as to achieve optimal performance (Thayer et al., 2009). A meta-analysis showed that psychological interventions could be used to counter some of the adverse effects, yet further research is still needed in this field (Richards et al., 2018). Hence, chronic stress, with its adverse effects on cardiac and mental health, is a current topic of interest.

3.4.2 Concepts of stress

In our study we examined how sleep loss may impair the stress response, specifically on a physiological level. To this end, the following paragraphs will outline common conceptualisations of stress as well as the parameters that can be used as its markers.

As mentioned at the beginning of the introduction the word ‘stress’ is used broadly. For instance, it can be attributed both internally (“I felt stressed out.”) or externally (“There is so much stress at work today.”). In medical and psychological research, stress is often described as a survival and adaption mechanism (Thayer & Lane, 2009; Ulrich-Lai & Herman, 2009). When the organism feels threatened, the stress response supports meeting these demands, for example through facilitating fight or flight responses to restore a state of safety (LeDoux, 1996). The following paragraphs will give a summary of the various definitions, concepts, and markers of stress that are relevant in this work.

To continue with another perspective, stress can be generally defined as a primarily adaptive process of the body to its environment or to its perception of the environment (Julian F. Thayer et al., 2012). As illustrated in **Figure 2**, stress can be viewed as a mediator in the subject-environment interaction (von Uexküll, 1920). As mentioned above, signals from the environment can be perceived as stressors by the subject. The subject will engage in an action that aims to reduce stress. In other words, the stress response mechanisms are continuously aiming to restore a state of balance or homeostasis (Ulrich-Lai & Herman, 2009). In this loop, an action or response will be appraised as successful if the perceived stressor is decreased or gone. If unsuccessful, the stressor persists, and the action will be appraised as unhelpful. To digress a bit, repeated experiences of unsuccessful coping may lead to a condition called “learned helplessness”, which is thought to play a role in depression (Seligman, 1978). Overall, feedback loops are also an important part of further models of stress.

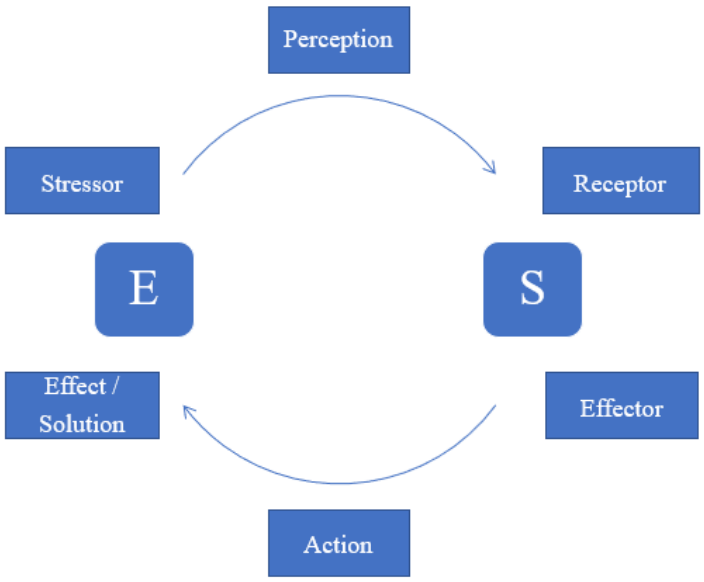

Figure 2: Adapted from "function-circle" by von Uexküll (1920); S = Subject, E=Environment.

There are multiple aspects to the function of stress. As mentioned above, the stress response evolved to deal with objectively demanding or threatening situations (Thayer et al., 2012). Stress prepares us for a possible physical response, which we know as “fight or flight”, thus this response can be viewed as an automated and stereotypical process. In addition, such psychophysiological responses can happen without conscious appraisal (van der Ploeg et al., 2017). Yet, there are a large variety of triggers of a stress response. For instance, Freud (1926) already distinguished between an appropriate fear response to an objective threat called ‘realangst’ and pathological fear responses without appropriate environmental stimuli, meaning, that it matters what is individually perceived as a threat. In this appraisal, an evolutionary negativity bias can be observed, meaning that it has been advantageous for survival to be more sensitive to potential dangers (Cacioppo et al., 1999; Kanouse & Hanson Jr., 1987). On the other hand, in modern society, environmental and lifestyle factors have changed significantly from when these mechanisms evolved, so that the stress response may become maladaptive in several circumstances (Chrousos, 2009). Hence, stress has both relatively positive and negative aspects. The idea of positive *eustress* and negative *distress* has been supported by many researchers (Monat & Lazarus, 1991; Selye, 1976). In *eustress,* stressors are considered challenges, while in *distress* they are viewed as threats. For this appraisal, it is important to consider the individual and social coping mechanisms of the subject (Monat & Lazarus, 1991). Coping mechanisms are individual resources for managing stress.

As a response to stressors, different mechanisms or resources can be employed to reduce stress levels, for example the seeking of social support or avoidance behaviour (van Schalkwijk et al., 2015).

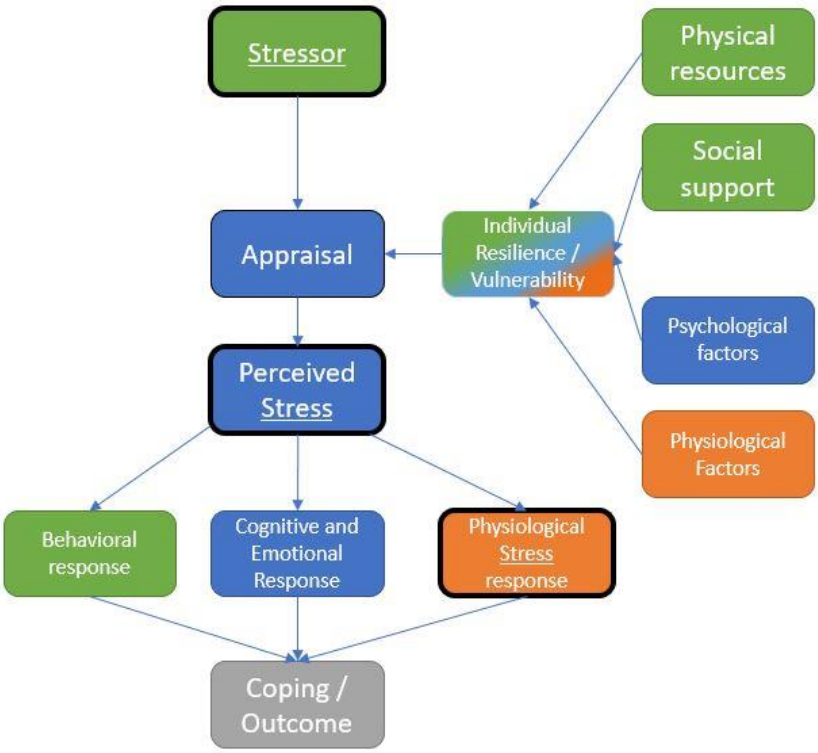

Figure 3: A bio-psycho-social transactional model of the stress response (Lazarus & Folkman, 1984). Green: social / environmental factors, Blue: psychological factors, Orange: biological / physiological factors. The stressor presents as a stimulus. In the first step it is appraised, which is already an individual process. Most factors are not steady, therefore you can appraise the same stressor differently at different times. You thus perceive a certain level of stress and your response can consist of one or more of these factors. As a result, you "cope", which leads to a feedback loop to the stressor and its appraisal.

All in all, stress can be viewed as a complex process, as displayed in **Figure 3**. In an illustrative example, a student is tasked with a presentation in class. This task can be a stressor, because the student will be evaluated both socially and academically, with possibly negative outcomes. In turn, this person subconsciously, and at times consciously, appraises the overall situation they are in on different levels, considering potential resources including: well-prepared visual aids, notes, or a nice outfit (physical), as well as support from friends (social), which helps build up confidence and lessens performance anxiety (emotional). The student may unfortunately have a sore throat, which is disadvantageous, or feel healthy and fit

(physiological). These, among other factors, can be viewed from the perspectives of either vulnerability or resilience. The evaluation has two key aspects: to determine how a stressor is perceived and what options for coping with it are to be considered. This leads to a perceived stress level. Feeling stressed or anxious may be an emotional result. A behavioural response may involve increased preparation. The physiological stress response can be seen in an increased heart rate and blood pressure. This response then leads to an outcome - for instance finishing the presentation and receiving positive feedback - which in turn is reappraised. In addition to the model in **Figure 3**, models of the stress response may include additional interconnections and feedback loops.

For this work, and in general, it is important to distinguish between chronic and acute stress. While for acute stress the stressor passes, in chronic stress the body does not return to a state of rest. Acute stress shows the healthy responsiveness of the body. In contrast, negative consequences are mainly attributed to chronic stress. Hence the potential recovery phase- analogue to the stage of exhaustion in Selye's model is commonly included in investigations of the acute stress response. The recovery phase may be defined as a natural striving for homeostasis (Juster et al., 2010; McEwen, 2003). In some publications, this dynamic striving is also called allostasis, while the accumulation of negative 'wear and tear' effects due to allostasis is subsequently termed allostatic load. The respective definitions are as follows:

- *Allostasis*, defined as a dynamic regulatory process wherein homeostatic control is maintained by an active process of adaptation during exposure to physical and behavioural stressors, and
  Allostatic load, defined as the consequence of allodynamic regulatory wear-and-tear on the body and brain promoting ill health, involving not only the consequences of stressful experiences themselves, but also the alterations in lifestyle that result from a state of chronic stress.
  (McEwen & Gianaros, 2010)

This concept is applied to describe the effects of chronic stress. It bears a similarity to the original use of the word 'stress' as a term to describe mechanical wear. Overall, the definitions of stress are heterogenous and include psychological and/or physiological perspectives. In our

research, we focus on stress as an appraisal of stressors and a consecutive acute psychophysiological stress response.

The Trier Social Stress Test

The stress response can be investigated by artificially inducing stress. The most common methods for this are the Trier Social Stress Test (TSST) and variations thereof (Kirschbaum et al., 1993; Frisch et al., 2015). During the test, physiological parameters like heart rate and cortisol levels can be recorded. In the TSST, a standardised social situation is created by introducing a panel to the participant. The perceived social evaluation by the panel functions as a stressor here. The researchers in the panel observe the participants with neutral expressions and without commenting. Meanwhile, the participants are tasked, for instance, with a presentation on their personal attributes and weaknesses or exercises in mental arithmetic. These stressors have been shown to reliably induce a physiological stress response (Dickerson & Kemeny, 2004). How this test was adapted for this study will be explained in *Methods*.

Work-related concepts

Furthermore, stress has been linked to working environments and specific models were conceived to describe this connection, e.g., the job-strain or the job-demand-control model (R. Karasek, 1998; R. A. Karasek, 1979), or the effort-reward imbalance model (Siegrist, 1996). The job-demand-control model identifies concerns about jobs with high psychological demand and low control over the personal tasks. Another concept is the effort-reward imbalance model. It is concerned with stress arising from inadequate personal, social or monetary rewards in relation to task difficulty (Siegrist, 1996). Stress may arise from the combination of high effort and low reward. Sonnentag and Fritz (2015), on the other hand, focused on psychological detachment from the work as a precondition for recovery from work stress.

All of these models are often used in reference to a work-related condition called burnout. In this phenomenon, workplace stress leads to mental health problems like a cynical attitude and feelings of inefficacy. Additionally, poor sleep may be an early predictor of burnout symptoms (Elfering et al., 2018). This condition is hypothesised to arise from an imbalance between individual preference and work environment (Maslach & Leiter, 2016). The World Health Organization (WHO) included burnout in the 11th version of the International Classification of Disease, or ICD-11 for short, as a syndrome “resulting from workplace stress,

that has not been successfully managed" (WHO, 2018). While this work does not apply these work-related concepts of stress, they underline the importance of stress for workers' health.

To summarize, stress is an anticipatory adaption to potentially adverse environmental factors. Yet, it is important that it is also a crude and automated response with respect to the evolutionary advantages that fight or flight responses had for our ancestors. On the other hand, chronic stress is maladaptive and disadvantageous. The physiological stress response should be a limited, focused response to escape or eliminate the adverse situation or stressor as quickly as possible. To fulfil this demand, the mind is constantly evaluating the environment on a spectrum of safety or potential threat. In stress, several processes have to function simultaneously and dynamically: the assessment of the stressor, the adaptive stress response and importantly recovery tendencies (Thayer et al., 2012). The underlying mechanism will be explained in more detail in the following paragraphs.

3.4.3 The Neuro-Physiological Stress Response

The fact that emotions have physiological effects on the heart was already acknowledged in the 17th century by the same scientist who described the blood circulation in the cardiovascular system (Harvey, 1628). In the first half of the 20th century, Hess (1949) had discovered that the hypothalamus is a key structure for the neural network linking body and mind. He described that the hypothalamus controls the two antagonistic branches which regulate the cardiovascular system. This lay the basis for further research into the autonomic nervous system (ANS). Furthermore, he hypothesized that this system used sleep as a means to facilitate rest and restoration (Hess, 1932). Additionally, McEwen & Gianaros (2010), among others, found that cerebral structures function as top-down regulators – meaning control centers - of the stress response. These brain structures include the prefrontal cortices, the amygdala, and the hippocampus. They are central to integrating stimuli and memories, and their respective responses.

The amygdala is part of the limbic system, which facilitates emotions and drives. One of its vital functions is the fear response. The amygdala's activation stimulates the sympathetic nervous system via the hypothalamus in reaction to any potential threat (Thayer et al., 2012). It is in turn inhibited by higher cortical structures, especially via the medial prefrontal cortex (mPFC) (Buchanan et al., 2010). The mPFC supervises the emotional and behavioural responses to sensory stimuli. Both the mPFC and the hippocampus are important for correlating

these stimuli with memories. The stimulation by the amygdala and its suppression by the prefrontal cortex and the hippocampus play a key role in integrating the multitude of information on threat levels and safety queues (Smith et al., 2017). These are important determinants in the activation of the effectors, the autonomous nervous system and the hypothalamic-pituitary-adrenal axis (HPA-axis) (Chrousos, 2009). These pathways of stress were summarized in the Model of Neuro-Visceral Integration (Thayer & Lane, 2000). It describes a top-down regulation between cortical structures, including the amygdala, the hippocampus and the pre-frontal cortex, and the autonomic nervous system is described (Thayer & Lane, 2000). This model was later appended and updated, including further studies on the connection between cerebral structures and effectors such as heart rate (Smith et al., 2017; Thayer & Lane, 2009). Several other CNS structures have also been identified to contribute and were summarized in an earlier model as the central autonomic network (Benarroch, 1993). On the level of the cerebrum, this includes the insular cortex, anterior cingulate cortex, and the amygdala, which integrate sensations and various responses. The hypothalamus is a central link for the regulation of the effectors. The hypothalamus modulates and activates the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal axis. Stress, or in this case the physiological stress response, was measured in our study via cardiac markers of the ANS such as heart rate and heart rate variability, and via endocrine markers of the HPA response such as cortisol.

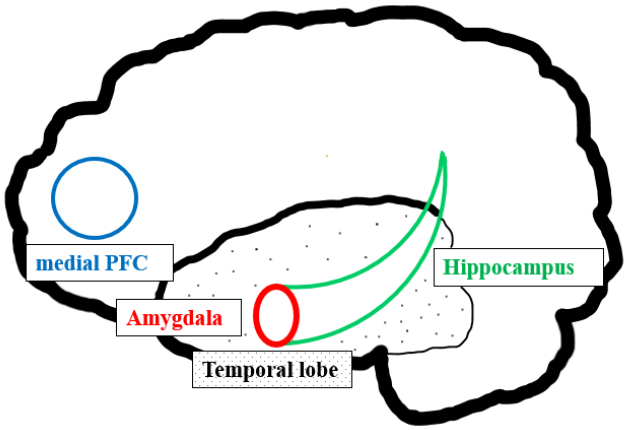

Figure 4: The key cerebral structures in the stress response are the amygdala, the hippocampus and the medial prefrontal cortex (mPFC). The amygdala is responsible for fast responses (freeze, fight, flight and fear) to environmental stimuli. The hippocampus is central for memories which include queues of safety and threat. The mPFC is important here as a regulatory structure which is primarily inhibitory.

In addition to these top-down mechanisms, the brainstem integrates bottom-up signals and regulates responses. It contains central structures in the moderation of the level of arousal. There are structures in the brainstem like the periaqueductal grey, which integrates behavioural and autonomic responses, pain modulation and sleep. Further brainstem structures, such as the parabrachial nucleus, the nucleus of the solitary tract, and the reticular formation help regulate multiple functions, for instance respiration and circulation. The reticular formation also includes the ascending reticular activation system (ARAS) which regulates attention, wakefulness and sleep-wake transition (Schwartz & Kilduff, 2015).

Notably, the abovementioned structures may be affected by sleep loss, as Chapter **3.5** describes. For instance, sleep loss results in a higher amygdala activation due a disconnection of the medial prefrontal cortex to the amygdala (Yoo, Gujar, et al., 2007).

The Autonomic Nervous System & the Hypothalamus-Pituitary-Adrenal Axis

The autonomous nervous system subconsciously controls the activity levels of vital functions. It consists of two main branches: the sympathetic and the parasympathetic nerves. On activation, the sympathetic nerve optimizes - via acetylcholine and norepinephrine - the organ activities for “fight or flight”, and also does this by reducing the parasympathetic “rest and digest” stimuli. The parasympathetic response goes through the vagus nerve and is hence referred to as vagal response. These two branches allow for a continuum of states in our everyday lives, in which our body constantly adapts.

The HPA axis controls a relatively slower adaptive response via corticotropin releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and the 'stress hormone' cortisol. The hypothalamus receives and filters several inputs, then stimulates the pituitary gland accordingly via CRH to release ACTH, which stimulates the adrenal glands to release cortisol. Cortisol then inhibits CRH and ACTH release in a negative feedback loop. As the stress hormone, it facilitates an adaption of multiple system towards 'fight or flight', such as regulating metabolic activity and inhibiting inflammatory pathways. Furthermore, cortisol and its morning peak is important in awakening, as is explained in **Chapter 3.2.3**. CRH also has further central nervous effects, like increasing attention and suppressing hunger.

All in all, the existing models focus either on stressors, psychological or physical reactions or interactions. This has led to a variety of markers being used in studies on stress to date. Commonly, studies use a combination of psychological, cardiac, metabolic, inflammatory and endocrine markers. For the present study, we have focused on autonomic markers, like heart rate and heart rate variability, as well as cortisol as an endocrine marker, which are established and widely used (Buckley & Schatzberg, 2005; Task Force on HRV, 1996).

Heart rate variability as correlate of sympatico-vagal balance

Under acute stress, the cardiac output needs to increase to achieve optimal performance. To this end, the stress response has a direct impact on the autonomic modulation of the heart. The heart receives both sympathetic and parasympathetic input. Under normal conditions, there is a tonic vagal or parasympathetic dominance on the pacemaker of the heart, the sinus node. In the heart, the quick changes have been hypothesized to reflect vagal tone (Levy, 1990; Saul, 1990). Stimulation by the vagal nerve leads to a decreased activity and heart rate as well as an increase of the variability of the heart rate (HRV), since the vagal modulation is faster and thus more variable than the sympathetic modulation (Saul, 1990; Task Force on HRV, 1996). Vice versa, sympathetic stimulation decreases heart rate variability and increases heart rate. HRV can be decreased by dysregulation due to chronic psychological or physical strain (Thayer & Lane, 2000).

According to this concept, ANS activation can be measured non-invasively through heart rate variability. You may even find commercial smartphone apps which record and calculate HRV (Perrotta et al., 2017). The beat-to-beat interval is defined as the time between one excitation of the heart and the next – marked by the R-peaks of the QRS-complex in

electrocardiographic recording. This is referred to as R-R- or N-N-interval and measured in milliseconds. Heart rate variability can thus be computed from R-R-intervals in a two-channel electrocardiograph. The different measures computed from this are subdivided into time domain, frequency domain and non-linear measures (Task Force on HRV, 1996). Time domain measures are for instance "standard deviation of N-N-intervals" (SDNN) or "root mean square of successive differences" (RMSSD). They express the variability as time, hence the term time domain. A higher SDNN or RMSSD value represents a higher variability. Both are associated with vagal tone. SDNN is widely used since it is easy to compute, yet it has its limitations, such as a high dependency on the duration of the ECG recording. RMSSD is a well-established alternative. Frequency domain values are calculated by transforming the time intervals into frequencies by using an specific algorithm, namely Fast Fourier Transformation (Cooley & Tukey, 1965). These measures are widely used in studies as a valid HRV measure (Montano et al., 2009). Key measures of heart rate variability in the frequency domain are high frequency power (HF, 0.15-0.40 Hz), low frequency power (LF, 0.04-0.15 Hz) and the LF/HF ratio (Task Force on HRV, 1996). HF-HRV is hypothesised to reflect cardiac vagal activation (Koenig et al., 2014), while LF-HRV represents sympathetic activation (or baroreceptor reflex) (Moak et al., 2009). Non-linear HRV measurements may also be used supplementarily, but are not relevant to this work (Tobaldini, Nobili, et al., 2013).

In our study RMSSD, SDNN, and HF-HRV were used, since they are commonly reported and well-established measures of autonomic activation (Task Force on HRV, 1996). As mentioned above, all these markers are associated with vagal tone. In clinical use, HRV can be used for instance for cardiological risk assessment or stress profiling. In standardised stress tests, healthy subjects are expected to show high HRV at rest, a considerable decrease under stress and quick and complete recovery after the stressor has passed. HRV also depends on factors like sex, age and health status (Huang et al., 2013). A more recent meta-analysis showed a higher vagal tone for healthy women than for men and also confirmed an effect of age on HRV (Koenig & Thayer, 2016). Thus, HRV studies must account for these differences for example by reporting these factors. How we collected and used HRV data will be explained further in **Methods**.

3.5 Sleep deprivation and stress

Stress is also linked to sleep. Acute stress leads to increased vigilance and arousal (Thayer & Lane, 2009). People who report frequent or constant feelings of stress are more likely to suffer

from sleep problems (Techniker Krankenkasse, 2016). Stress levels have been shown to negatively correlate with sleep duration and sleep quality (Almojali et al., 2017; Roberts et al., 2011). A possible physiological link is the overactivation of the HPA axis and autonomic nervous system in phases of chronic stress interfering with the sleep physiology.

A study on adolescents reported that social support has positive effects on stress levels as well as sleep quality (van Schalkwijk et al., 2015). This emphasizes that stress exposure is associated with sleep, which is important to this work and will be further discussed in the following chapter.

In this work, we have investigated the effects of sleep loss on the stress response. Arousal, relaxation, wakefulness, and sleep interact closely. In this context, waking-up and sleep induction are linked to stress-associated pathways. Expanding on this fact, it became of interest which role stress played in the adverse effects of sleep loss.

Sleep loss has been integrated in several stress models. As mentioned above, sleep loss has been described as stressor and a contributing factor to allostatic load (McEwen, 2006; McEwen & Karatsoreos, 2015). The latter refers to different studies which support the hypothesis that sleep duration and quality may be predictors of allostatic load (Carroll et al., 2014; Chen et al., 2014; Clark et al., 2014). Sufficient sleep can be linked to improved stress recovery and to increased mental resources. It is also suggested as an upstream factor in stress models, and is recommended to be added as a factor when researching the effects of stress on health (Benham, 2010). An experimental intervention that aimed to improve stress recovery led to reduced stress levels and improved sleep quality (Hahn et al., 2011). Thus, stress and sleep not only have common consequences but may also have common opportunities for intervention. However, further studies are needed on how sleep loss affects the stress response, which is the aim of the current work.

3.5.1 Sleep loss and cortisol response

The HPA-axis regulates the release of the so-called ‘stress hormone’ cortisol. Cortisol release also underlies a circadian rhythm and peaks before awakening (Buijs et al., 2003). The circadian rhythm of cortisol has a key role for morning arousal. Sleep physiology and the HPA-axis are closely connected, a disorder of one will likely affect the other (Buckley & Schatzberg, 2005). In rats, sleep loss increases HPA axis activation and affects HPA response to stress, yet the effects in these studies are not very pronounced (Meerlo et al., 2002; Sgoifo et al., 2006).

Acute sleep loss induces an increase of the overall cortisol level in humans, an effect which is hypothesised to be blunted after prolonged sleep loss (Chapotot et al., 2001; Wright et al., 2015). One study suggests that arousal may decrease from chronic sleep loss (Meerlo et al., 2008). Sleep loss was also linked to a blunted circadian pattern of cortisol release (Backhaus et al., 2004). Abell (2016) also showed a blunted pattern that was associated with recurring short sleep of less than five hours per day in a larger sample from the Whitehall II study. As a contributing mechanism, chronic short sleep has been shown to decrease the downregulation of cortisol levels (Balbo et al., 2010).

There are few studies evaluating the endocrine stress response to social stressors after acute sleep restriction. Minkel and collegues (2014) describe an increased cortisol response after the Trier Social Stress Test in a sleep deprived group compared to controls. The same study also showed a higher baseline cortisol after sleep restriction, which was replicated by two further studies (Vargas & Lopez-Duran, 2017, Schwarz et al., 2018). Subsequently, it has been suggested that the resulting overall increase of the cortisol level leads to an increase of the allostatic load and hence facilitates adverse health effects.

To date, there is no clear conclusion on how prolonged wakefulness or sleep loss change HPA axis activation. Hypotheses to date include, that sleep loss modulates HPA activation, for example, that it promotes cortisol release or inhibits recovery processes (Vargas & Lopez-Duran, 2017). In contrast to this work, the abovementioned studies have not researched the effects of naturalistic sleep loss on cortisol release, therefore this study aims to contribute to this aspect.

3.5.2 Sleep deprivation and the Autonomic Nervous System

Sleep is a key process of day-to-day restoration for the human body. Additionally, it is closely linked to the ANS. During sleep, the ANS activation varies greatly. The vagal tone is higher than during wakefulness. In quiescent or non-rapid eye movement (NREM) sleep, the parasympathetic nervous system is relatively more active, while during rapid-eye-movement (REM) sleep, the sympathetic nervous system activation is comparable to wakefulness (Solms, 2000; Somers et al., 1993). These findings were mirrored by Trinder et al. (2001), who showed corresponding shifts in sleep onset and in phases of REM sleep (Trinder et al., 2001). Notably, HRV markers did not show circadian influence, while the heart rate seemed to correspond both with a circadian rhythm and sleep stages. This shows a close link between sleep physiology and

the autonomic nervous system. The ANS responds to sleep stages, as it has a function in regulating attention and arousal. The effects of sleep deprivation and sleep loss on the ANS are explained in the following paragraphs.

Effects of acute sleep loss

Several studies have investigated the effect of total sleep loss on the ANS. Yet, the effects on cardiac autonomic markers are, in part, inconsistent. It is hypothesised that sleep and sleep loss affect the sympathetic response of the ANS, while the vagal response shows a dependency on a circadian rhythm (Burgess et al., 1997). This has also been suggested for partial sleep loss (Irwin et al., 1999).

Multiple studies measured the heart rate after participants were subjected to acute total sleep loss. Sleep restriction did not show effects on the heart rate in one study (Kato et al., 2000), while in a different study the heart rate was increased (Zhong et al., 2005). Furthermore, heart rate recovery was tested in 30 participants after a night shift and after regular sleep, and it was reduced after the night shift (Cincin et al., 2015). Moreover, the amount of sleep loss after the night shift correlated inversely with heart rate recovery after sleep loss. The authors concluded that this hints at a cumulative effect of sleep loss.

According to Yoo et al (2007), total sleep loss leads - on a neurophysiological level - to increased limbic activation and decreased medial prefrontal cortex top-down regulation, and in turn to an increased sympathetic tone (Yoo, Gujar, et al., 2007). After acute sleep restriction, it was shown that HRV was reduced, with sympathetic markers increased and parasympathetic markers decreased (Glos et al., 2014; Zhong et al., 2005). Furthermore, several studies have tested whether the stress response was altered after sleep restriction. In rats, it was shown that after 48 hours of acute sleep restriction baseline autonomic markers were increased and also the physiological stress response was changed, as, for example, parasympathetic activation was reduced (Sgoifo et al., 2006). In humans, the response to social stressors measured by blood pressure was amplified (Franzen et al., 2011). Schwarz et al. (2018) challenged subjects with the Trier Social Stress Test (TSST) in a well-rested state and a sleep-deprived state. They exhibited no increase in autonomic markers before the TSST, and also no altered stress response between the two states (Schwarz et al., 2018). Interestingly, they also showed that there were no significant differences in the results for different age groups, given that age is generally considered a confounder.

Effects of partial sleep loss

In several studies a significant effect of chronic sleep loss on autonomic markers has been shown. Chronic partial sleep restriction led to increased sympathetic activation as measured by HRV (Spiegel et al., 1999). A similar study showed that sleep loss led to changes in heart rate levels, but not in HRV measures (Muenter et al., 2000). Dettoni et al. (2012) showed a decreased vagal tone marked by decreased HF-HRV and an autonomic shift with increased sympathetic activation as marked by increased LF-HRV in participants after they were subjected to five days of partial sleep loss (Dettoni et al., 2012). Partial sleep loss also inversely correlated with HF-HRV in undergraduate men during a stress task, meaning that vagal tone was reduced (Mezick et al., 2014). In contrast, partial sleep loss for eight days shows no impairment in HRV at baseline and during subsequent sleep phases (Tobaldini et al., 2017).

All in all, there is an inconclusive body of research on the relation between sleep loss and stress and their common complications. Most studies investigating the stress response therein focus on sleep loss that was induced in a laboratory setting. In our study, we focussed on whether naturally occurring sleep loss is associated with ANS baseline activation and responsiveness in a social stress test. Most of the studies above have researched the effects of artificially induced sleep loss or acute sleep loss in situations like night shifts. Yet, the most common form of sleep loss is chronic partial sleep loss. Therefore, this work investigates the effects of this common form of sleep loss on the stress response.

3.6 Hypotheses

First, we hypothesized that our standardized stress induction protocol evokes a stress response on behavioral, physiological, and endocrine stress markers. Specifically, we expected an increase in perceived stress, heart rate and salivary cortisol and a decrease of heart rate variability (H1).

Next, we looked at the effects of naturally occurring sleep loss on the stress response, as reported on a standardized sleep questionnaire and using a sleep diary over the last seven days. We hypothesized that sleep loss interferes with stress reactivity (H2a) and recovery (H2b). As previous research indicated conflicting results regarding the effect of sleep loss on the stress response, we expected either a positive or negative association between both sleep loss variables and perceived stress, heart rate (variability), and salivary cortisol.

4 Materials and Methods

This research was performed as part of the ChronoStress project as a cooperation between the Affective Disorders Research Group and the Mind and Brain Research Group of the Charité - Department of Psychiatry and Psychotherapy, Berlin, Germany. The ChronoStress project researches the effects of sleep patterns on the stress response.

The study was approved by the Medical Ethics Committee of the Charité – University Medicine Berlin. It was carried out in accordance with the Declaration of Helsinki (World Medical Association, 2008). An informed consent form was signed by all participants before taking part in the study.

We performed a standardised social stress test using functional magnetic resonance brain imaging (fMRI) while assessing various measures of the stress response. All experimental scans took place in the evenings of Wednesdays and Thursdays between April and October 2016 during daylight saving time to account for its effect on the circadian rhythm.

In the following paragraphs, these procedures will be described in further detail.

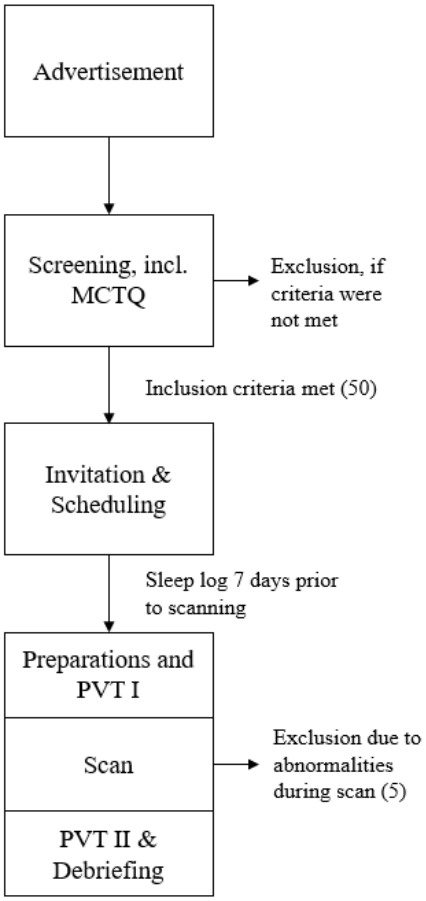

Figure 5: Study process. Overall, 50 participants met the inclusion criteria in the telephone screening. 5 of them were later excluded due to problems or abnormalities in the scan data; PVT = Psychomotor Vigilance Test; MCTQ = Munich ChronoType Questionnaire

4.1 Participants

We used mailing lists and internet-based advertisements as well as flyers to recruit participants. A monetary compensation after the experiment was granted as incentive.

Fifty participants between 20 and 48 years of age were recruited that matched the following inclusion criteria in the screening: a) a fulltime job with 30-50 hours per week over 5 workdays on weekdays, b) male sex, c) a body mass index between 18 and 29.9 kg/m², and

d) sufficient fluency in the German language to follow the instructions. Exclusion criteria were a) any psychiatric disorders as assessed by the SCID-I (First et al., 2002), b) major neurological or chronic diseases, c) shift work, d) any self-reported consumption of illegal drugs, or e) MRI scanner incompatibility, for example due to claustrophobia, metal implants or devices on or in their bodies.

All participants underwent a telephone screening in which they were given basic information about the study and asked for sociodemographic data, contact information and job information. Having met the criteria, participants were invited for an appointment, as can also be seen in **Figure 5**.

The study was approved by the Medical Ethics Committee of the Charité – Universitätsmedizin Berlin, and written consent was obtained from all participants.

4.2 Sleep assessment

In our study we used several questionnaires, including the Patient Health Questionnaire, the Beck's Depression inventory, the Brief Resilience Scale, the Positive And Negative Affect Schedule and the State Trait Anxiety Inventory. Two methods were used for sleep assessment: the Munich ChronoType Questionnaire and the sleep diary, which will both be explained in detail below.

Munich ChronoType Questionnaire

All participants were assessed for the criteria for chronotype and sleep loss as determined by the Munich ChronoType Questionnaire (MCTQ) (Roenneberg et al., 2003) during the initial interview. Only participants assessed as late-type, which are hence at risk of short sleep, were included (Roenneberg et al., 2003). The questionnaire includes sleep onset and awakening on workdays as well as free days as well as the number of workdays in a week.

In the next step, sleep duration was calculated from this data in SPSS Statistics® 24 for Windows (IBM Corp., Armonk, USA) as difference between sleep onset and awakening. Next, the midpoint of sleep was calculated as sleep onset plus half of the sleep duration. Each of these values was calculated for workdays and free days separately, since sleep loss is more likely to occur on workdays in these late chronotypes (Roenneberg et al., 2003). The midpoint of sleep on free days has been adapted to account for compensating short sleep on the weekend by subtracting half of the difference between sleep duration on average and sleep duration on free

days, if sleep duration on free days was longer. In the next step, average sleep duration was calculated both over the entire week and over workdays only. If average sleep duration over the workdays was shorter than the average sleep duration over the entire week, average weekly sleep loss was calculated by subtracting the average sleep duration over the workdays from the average sleep duration over the entire week, multiplied by the number of workdays (and vice versa if sleep duration was shorter during free days).

Sleep Diary

The sleep diary was sent to each participant via email, and they were asked to fill it out for the seven days before the scan date. Participants provided information on the time at which they woke up, the time of sleep onset, and whether they had a workday or a free day. The diary was then collected on the scan day. From this information, sleep loss during these seven days was calculated using the same method as for the MCTQ data.

4.3 Stress Induction

The experiments followed a standardised protocol to induce stress. We adapted our protocol from the ScanStress paradigm (Streit et al., 2014) using Presentation™ software (v18.1, Neurobehavioral Systems, Inc., Berkeley, USA). This paradigm was derived from the concepts of the Montreal Imaging Stress Task (MIST) and the Trier Social Stress Test (TSST) (Dedovic et al., 2005; Kirschbaum et al., 1993). In addition, on the day of the experiment participants were asked to refrain from physical activity and to not drink caffeine for a minimum of two hours before the scan, since it might bias physiological and hormonal parameters.

Before entering the scanner room, the tasks were briefly explained by one researcher. The participants were then instructed to perform at their best. For security reasons, all participants were advised to remove all metal objects and electronic devices before entering the scanner room. On the way to the scanner, the participants were briefly introduced to the ‘expert panel’, one male and one female researcher in lab coats. Meanwhile, a monitor placed in the background showed a video of generic person in a scanner, insinuating that participants are observed during the experimental procedure. The instructions were given through an intercom by one member of the expert panel. Instruction and tasks were presented to the participants on a monitor outside the scanner, which could be viewed using a mirror mounted on the head coil.

Our stress task included two conditions: A performance (or stress) condition, and a control condition. For both conditions, the stimuli were either three-dimensional figures or numbers. For the figures or mental rotation task, the participant was shown a three-dimensional figure composed of several cubes. Three more figures were shown below it. One of these matched the figure above, and participants were tasked to identify which using a handheld device. For the performance phases, the matching figures were rotated, while in the control condition they were not. For the number stimuli or mental arithmetic task, participants were tasked to subtract the number 13 continuously from a defined number, and choose the correct answer from four options below in the performance phase. If the answer was incorrect, they would have to start over. In the control conditions, they simply matched a four-digit number above with one of four numbers below. During each performance phase, there was a live video showing the two panel members, with the aim to induce social-evaluative stress. Additionally, a time limit appeared on screen which adapted with each trial to the participant's performance speed on the previous trial so as to ensure equal difficulty across participants. The participants received negative feedback to work faster or, if applicable, that an answer was incorrect. In contrast, during the control condition the video feed was crossed out and obscured, and the panel members were instructed to look away from the camera. Furthermore, there were neither time limits nor negative feedback. The order during the scan, which can be viewed in **Figure 7**, was first a resting state scan (R1), then the first task including three dimensional figures in both control and performance condition (S1 / S2), then the second task including numbers in both conditions (S3 / S4), followed by a second resting state scan (R2).

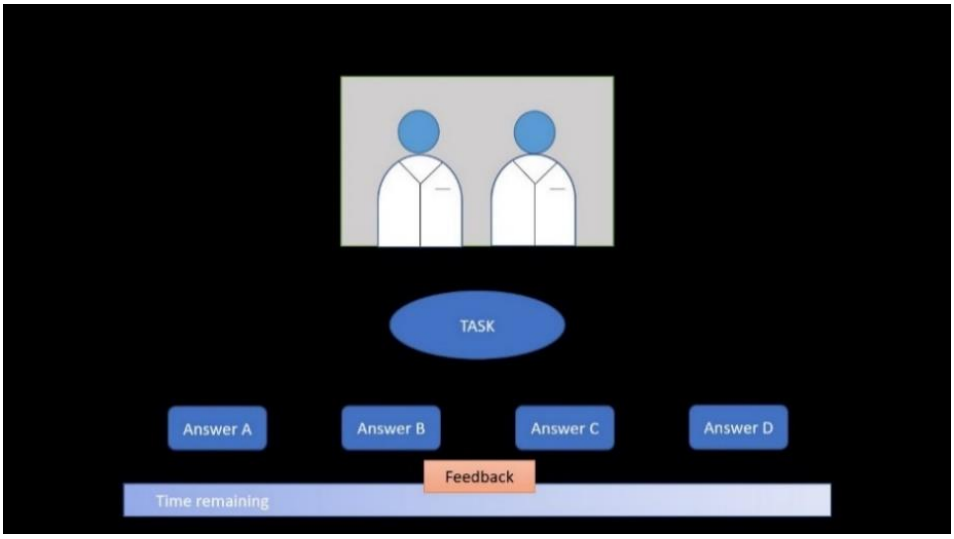

Figure 6: Illustration of the screen setup during tasks under performance condition. The task and 3 to 4 answers were displayed, as well as a countdown, occasional feedback and the camera feed from the 'expert panel'.

At the end of the experiment all participants received a debriefing on the nature and aim of the stress task, emphasizing that performance was manipulated.

4.4 Imaging

Magnetic resonance imaging uses a strong magnetic field and detectors to allow for various structural and functional scans. If contraindications and safety standards are respected and no contrast medium is applied, there are no health risks with this method (Tsai et al., 2015).

In this study, a 3 Tesla Siemens Magnetom TRIO scanner with a 32-channel head coil was used for data acquisition (Siemens Healthineers AG, Munich, Germany). At the beginning of each scanning session, a high-resolution structural image was obtained, specifically a T1-weighted anatomical scan was acquired. It was later assessed by a neuroradiologist for structural abnormalities. If abnormalities were found, the participant was notified and his data excluded, which happened in three cases.

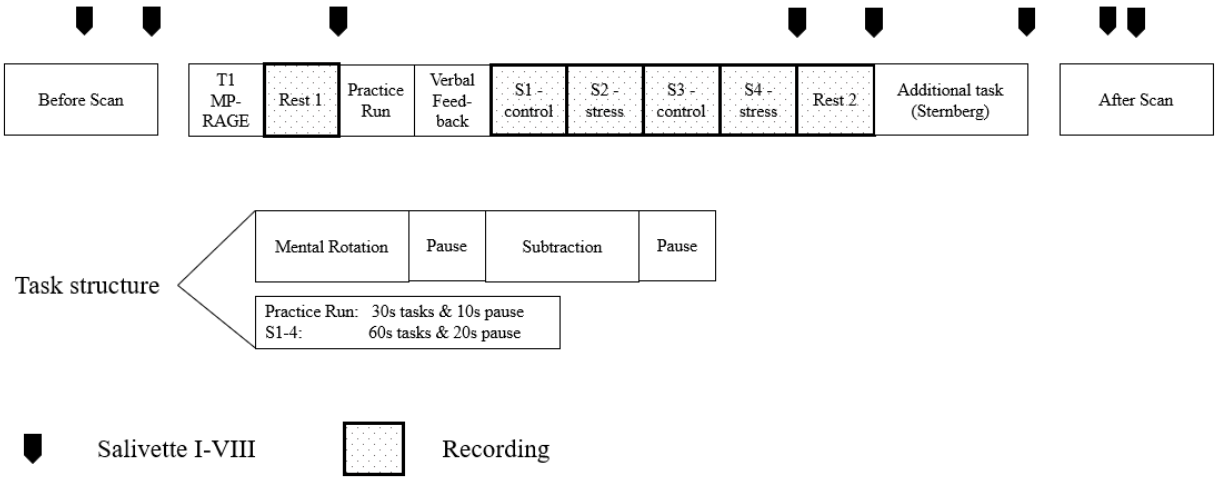

Figure 7: Scanning Procedure: in the first line this graphic shows the procedure inside the scanner. Black arrows indicate timepoints for perceived stress assessment and saliva collection. First there was a structural scan, then the first resting state scan. After a practice run, the stress induction (S1-S4) was followed by control phases and stress phases. The task structure is explained in 4.3. After these phases came a second resting phase scan. Between tasks, saliva samples were taken using Salivettes® and the PSS score was assessed.

Functional imaging was done during resting-state scans, in which participants were instructed to keep their eyes on a fixation cross on the screen and not to fall asleep, and during the stress task in between the two resting-state scans (see **Figure 7**). Another functional task and structural scan were acquired after the second resting-state scan as well. The structural and functional MRI results are not the focus of this work but are discussed in the theses of J. Nowak ‘Auswirkung von Schlafmangel und psychosozialem Stress auf die funktionelle Konnektivität

der Amygdala in der Resting-State-fMRT' ('Effects of sleep loss and psycho-social stress on functional connectivity of the amygdala in resting state functional MRI') and A. Dimitrov 'The association of sleep and stress with psychological well-being and neuronal functional connectivity'.

4.5 Heart rate

In order to record the heart rate, we used a pulse oximeter. A pulse oximeter is a clip which emits light and senses its absorption by red blood cells. Since there are pulsatile variations of blood flow with every heartbeat, it allows for recording of the heart rate. We used a finger pulse oximeter recording at 50 Hertz continuously during the stress induction task and the resting-state scans. After scanning, the data was saved and transformed with a MATLAB R2012a macro in order to calculate the intervals between beats before further processing (The MathWorks, Natick, MA, USA).

From this data, we calculated the mean heart rate and HRV for each of the phases described in **Chapter 4.3.** and **Figure 7** using Kubios 3.0 (Tarvainen et al., 2014). As biomarkers of sympathetic and vagal activation, we used different HRV markers, specifically two time-domain measures – SDNN and RMSSD - and one frequency domain measure - HF-HRV. SDNN is calculated as the standard deviation of the intervals, while RMSSD is the square root of the average squared interval, as shown in **Equation 1** below.

For some participants, data was incomplete. The data for heart rate was complete for 41 participants, while the data for HRV was complete for 42 participants.

$$\bar{I} = \frac{1}{(N-1)} \sum_{n=2}^{N} I(n)$$

$$SDNN = \sqrt{\frac{1}{(N-1)} \sum_{n=2}^{N} [I(n) - \bar{I}]^2}$$

$$RMSSD = \sqrt{\frac{1}{(N-2)} \sum_{n=3}^{N} [I(n) - I(n-1)]^2}$$

$\bar{I}$ = mean of heartbeat to heartbeat intervals
N = total number of heartbeats
$SDNN$ = Standard Deviation of N-N-intervals (N here referring to heartbeat)

Equation 1: Formulas for SDNN and RMSSD adapted from Kang et al., (2016).

4.6 Salivary cortisol sampling

Saliva sampling is a non-invasive diagnostic method to determine cortisol levels, because saliva is produced from fluids and molecules in our blood serum and has been established as a marker of blood cortisol level (Kirschbaum & Hellhammer, 1994). Saliva samples for cortisol were taken at 8 time points, twice before the participants entered the scanner room, four times between the different phases in the scanner and twice after the scans. In between the different measures, the experimenter entered to collect the salivary cortisol samples at different time points as shown in **Figure 6** using Salivettes® (Sarstedt AG, Nürmbrecht, Germany).

Right after the sessions, these would be centrifuged for 15 minutes at 2500 rounds per minute and stored in a freezer at -20°C. The samples were analysed by the Max Planck Institute for Psychiatry, Munich, Germany, using an electrochemoluminescence immunoassay (ECLIA) on a Cobas e601 module (Roche Diagnostics, Mannheim, Germany). Intra- and inter-assay variability coefficients were reported below 10% or 15%, respectively.

When collecting saliva samples, the experimenter also asked the study participant for the perceived stress level on a Likert scale from 1-10, i.e., from 1 = very low to 10 = very high (Likert, 1932). Data on perceived stress was complete for 45 participants, and for salivary cortisol for 43 participants, which we included in the analyses.

4.7 Psychomotor Vigilance Test

After this, the participants were instructed to do the Psychomotor Vigilance Test (PVT) (Loh et al., 2004). For this test, participants tapped the mouse every time a visual stimulus appeared on the screen. This standardised test is used to measure participants reaction time over several minutes and to assess how well the attention can be sustained over time. The PVT was repeated after the stress induction.

4.8 Statistical analysis

Statistical analyses were carried out with IBM SPSS 24 ® for Windows (IBM Corp., Armonk, USA). If not stated otherwise, we set a two-sided p-value < .05 as threshold for significance.

First, we reported descriptive statistics including mean, median, maximum, and minimum values, and standard deviation (SD), as well as interquartile range (IQR) of age, body mass index, work hours on the scan day and for both sleep loss variables.

In general, we tested whether the assumptions for parametric tests were met, which included a graphic representation and the Kolmogorov-Smirnov test for normal distribution. For data with non-normal distribution, we used a logarithmic transformation of the respective variable. If the data was normally distributed after log transformation, we used parametric tests. Otherwise, we used non-parametric tests, as will be discussed in more detail below.

Hypothesis 1

For H1 we used a repeated measures Analysis of Variance (ANOVA) to test for variance over time. The repeated measures ANOVA was conducted for PSS and salivary cortisol over all time points as well as for cardiac measures, specifically heart rate, HF-HRV, SDNN and RMSSD. If assumptions for sphericity were violated, we used Greenhouse-Geisser or Huynh-Field corrections, respectively. When significant changes were found, post-hoc tests were carried out. Bonferroni correction was applied to adjust for the number of tests and the adjusted thresholds for significance were reported.

Hypotheses 2a and 2b

For H2a, we tested whether sleep loss may interact with stress reactivity. We defined reactivity as difference from the pre-stress to post-stress time point - as can be seen in **Figure 8** - in perceived stress and salivary cortisol, and from resting state 1 to stress in the cardiac measures. Due to non-normal distribution of most variables and importantly for both sleep loss measures, we used non-parametric tests. Then we explored correlations of both sleep loss measures via MCTQ and sleep diary with stress reactivity in perceived stress, cortisol, heart rate and HRV measures using Spearman's *Rho*.

For H2b, we calculated stress recovery as the difference between post stress and post resting state 2 for salivary cortisol and perceived stress, and for cardiac measures as the difference between stress phase and resting state 2. Analogoulsy to H2a, we then correlated these measures to sleep loss via MCTQ and sleep diary using Spearman's *Rho*.

Note that a Bonferroni corrected α-level of $p < .00208$ was used. This is a method of correcting for the number of tests in order to reduce false-positive results (type I error).

5 Results

5.1 Descriptive statistics

We successfully recruited 50 healthy male participants in the process which can be seen in **Figure 5**. Three of them had to be excluded from analyses due to an incidental finding in the MRI scan and a further two subjects due to incomplete data. Therefore, the final sample size included 45 subjects who successfully completed the experiment. Twenty-two MRI scans took place on Wednesdays and 23 scans on Thursdays, respectively.

The mean age in the sample was 30 years (*SD* ± 4.8 years, range [20-48 years]). The mean body mass index was 23.8 kg/m² (*SD* +/- 2.3 kg/m², range [19.7-29.3 kg/m²]).

On the day of the scan, 22 participants drank caffeinated beverages, 22 stated they did not and for 1 participant this information is missing.

Sleep loss

According to the formula we used, mean weekly sleep loss was low at either 2:23 hours (SD ± 2:02 hours) with a median of 2:01 hours, or 1:54 hours (SD ± 1:48 hours) with a median of 1:28 hours, derived from the MCTQ and sleep diary respectively (see **Table 1)**.

Neither of the sleep loss measures showed a significant correlation with age or the consumption of caffeinated beverages on the day of the scan, as can be seen in **Table 2**.

Table 1: Descriptive statistics of sleep loss variables. In both cases this table refers to weekly sleep loss.

Variable (N=45)	Minimum	Maximum	Mean	SD[3]	Median	IQR[4]
Sleep Loss MCTQ [hours:minutes][1]	0:00	7:30	2:23	2:02	2:01	2:34
Sleep Loss Diary [hours:minutes][2]	0:13	9:48	1:54	1:48	1:28	1:33

Notes: [1] Sleep Loss MCTQ *[hours] - Total sleep loss according to the Munich ChronoType Questionnaire* (Roenneberg et al., 2003)*; [2]* Sleep Loss Diary *[hours] - Total sleep loss according to the sleep diary; [3] Standard Deviation; [4] Interquartile Range.*

Table 2: Correlation of age and sleep loss.

Variable (N=45)		Sleep Loss (MCTQ) [hours] *	Sleep Loss (Diary) [hours] *
Age [years]	*r*[1]	-.165	-.021
	p[2]	.140	.447

*Notes: [1]Pearson's correlation coefficient; [2] Significance (2-tailed); Significant p-values are reported at p < .05; *both variables were log-transformed; Sleep Loss (MCTQ) - Total sleep loss according to the Munich ChronoType Questionnaire* (Roenneberg et al., 2003)*; Sleep Loss (Diary) - Total sleep loss according to the sleep diary.*

5.2 Hypothesis 1: Effects of sleep loss

H1: Stress measures, meaning perceived stress, salivary cortisol, heart rate and heart rate variability measures show an effect of time in response to the stress induction over the course of the experiment.

Heart Rate

The repeated measures ANOVA for heart rate showed a significant change over time with F (1.35, 52.64) = 33.96, $p < .001$. The post-hoc (Bonferroni) test showed significant differences over all pairs at $p < .001$, except from resting state 1 to resting state 2 at $p > 0.99$.

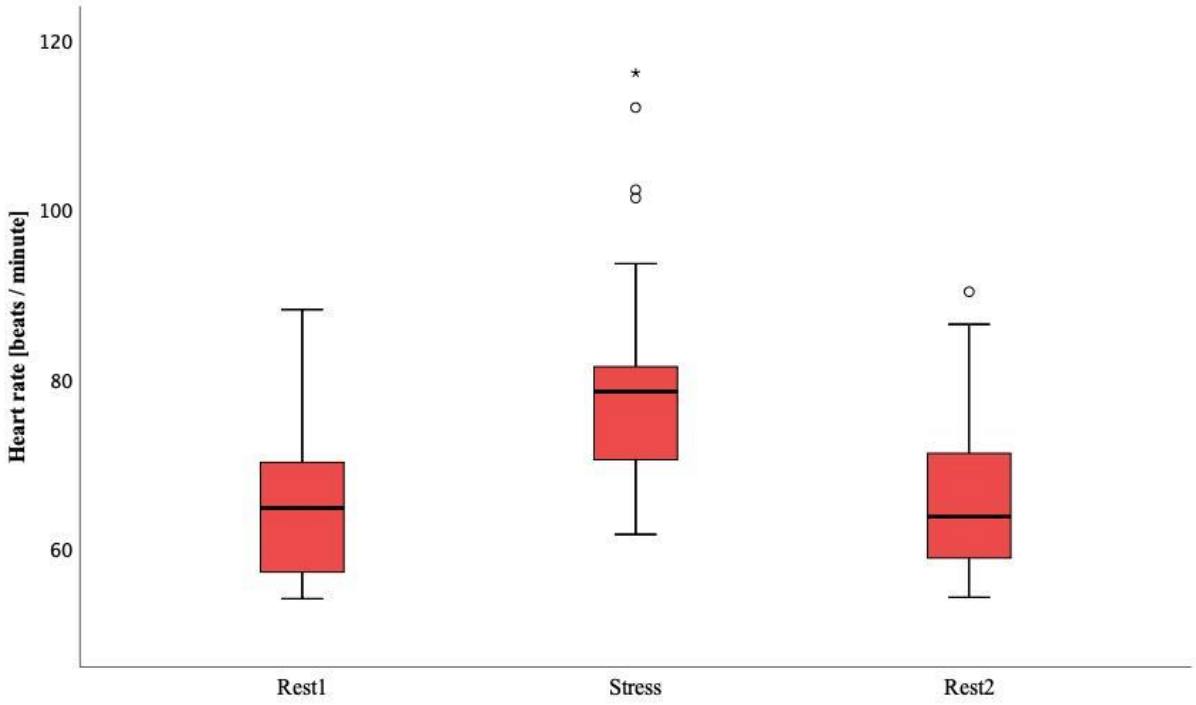

Figure 8: Boxplots of average heart rate in beats per minute for each of the three phases showed significant changes over the three phases displayed. Mean heart rate was higher during the stress induction tasks ('Stress') compared to the resting state phases ('Rest1' & 'Rest2').

Heart Rate Variability Measures

Since the criteria for normal distribution were violated, we used Friedman's test for differences in repeated measures. It indicated no significant differences in RMSSD over the phases, Q (5) = 6.631, p = .250, as can be seen in **Table 3** below.

Table 3: Friedman Test for Perceived Stress and HRV measures by RMSSD and SDNN

	RMSSD[3]	SDNN[4]	Perceived Stress
N[1]	41	42	41
Chi-Square (Q)	6.631	6.072	142.995
***df*[2]**	5	2	7
p	.250	**.048**	**< .001**

Notes: [1] Number of subjects included; [2]degrees of freedom; [3] heart rate variability by "root mean square of successive differences"; [4] heart rate variability by "standard deviation of successive N-N-Intervals"; Significant p-values are reported at p < .05. Perceived stress was rated by the participants on a scale from 0-10 points.

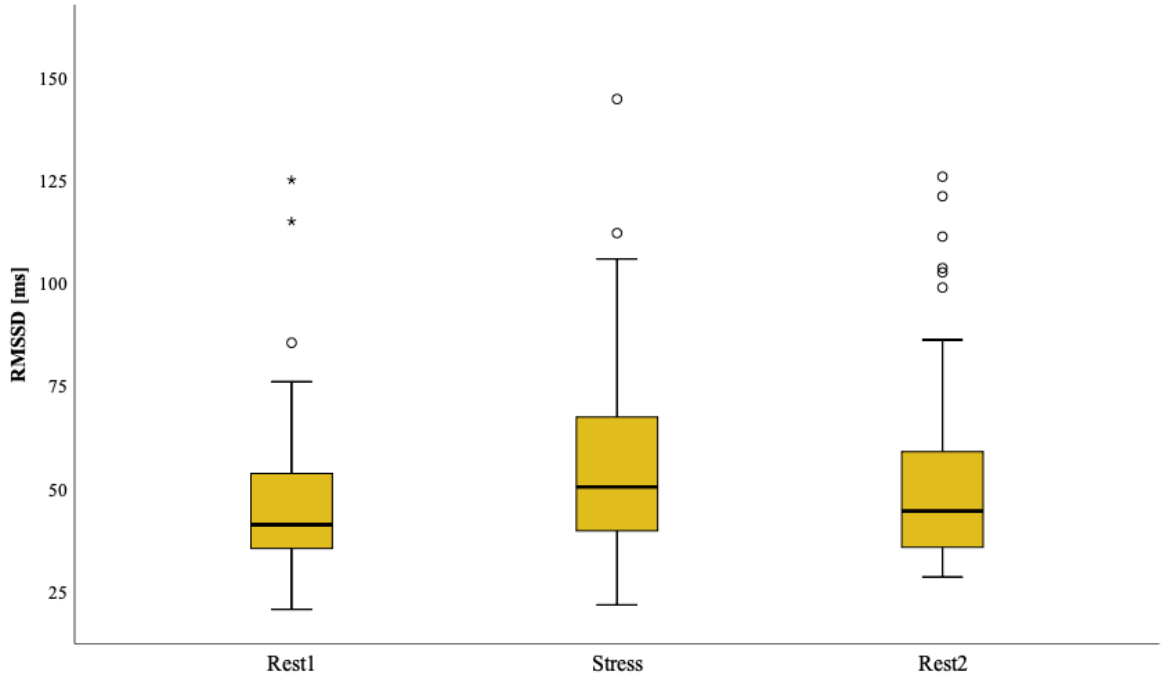

Figure 9: HRV as calculated via RMSSD displays no significant changes over the 3 phases resting state 1, stress induction and resting state 2, though the mean during the stress phase was slightly higher. Hence, this parameter was not affected by the stress induction. * marks statistical outliers.

The non-parametric Friedman's test for differences in repeated measures indicated that SDNN through the phases were different with *Friedman's Q* (7) = 6.072, which was significant at p = .049 and is displayed in **Table 4**. A higher mean over the stress phase compared to the resting state phases can be seen in **Figure 10**. However, the Wilcoxon test for dependent samples did not show a significant difference between resting state phase 1 and stress task (z = - 1.350, p = .090) or stress task and resting phase 2 (z = - .369, p = .359).

The repeated measures ANOVA for HF-HRV showed no significant change over time, F (1.71, 66.63) =.544, p = .556.

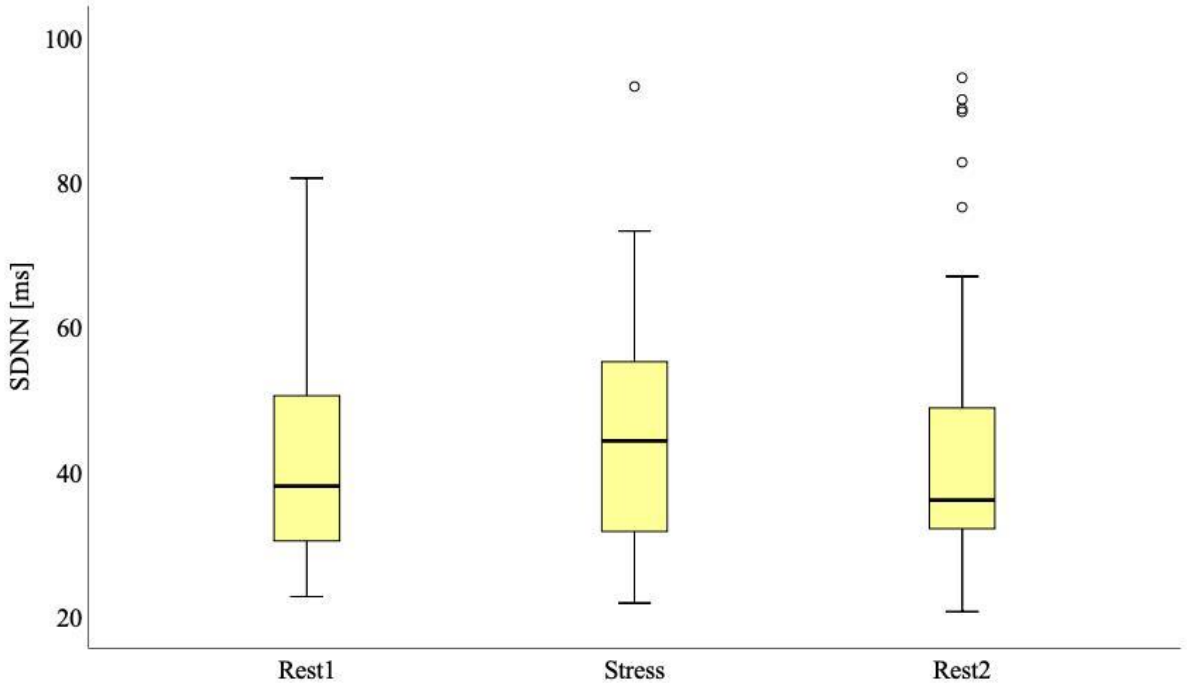

Figure 10: SDNN-HRV over both resting state phases (Rest1 and Rest2) and during the stress task displayed no significant changes in the repeated measures ANOVA. It was increased during the stress induction, but not statistically significant.

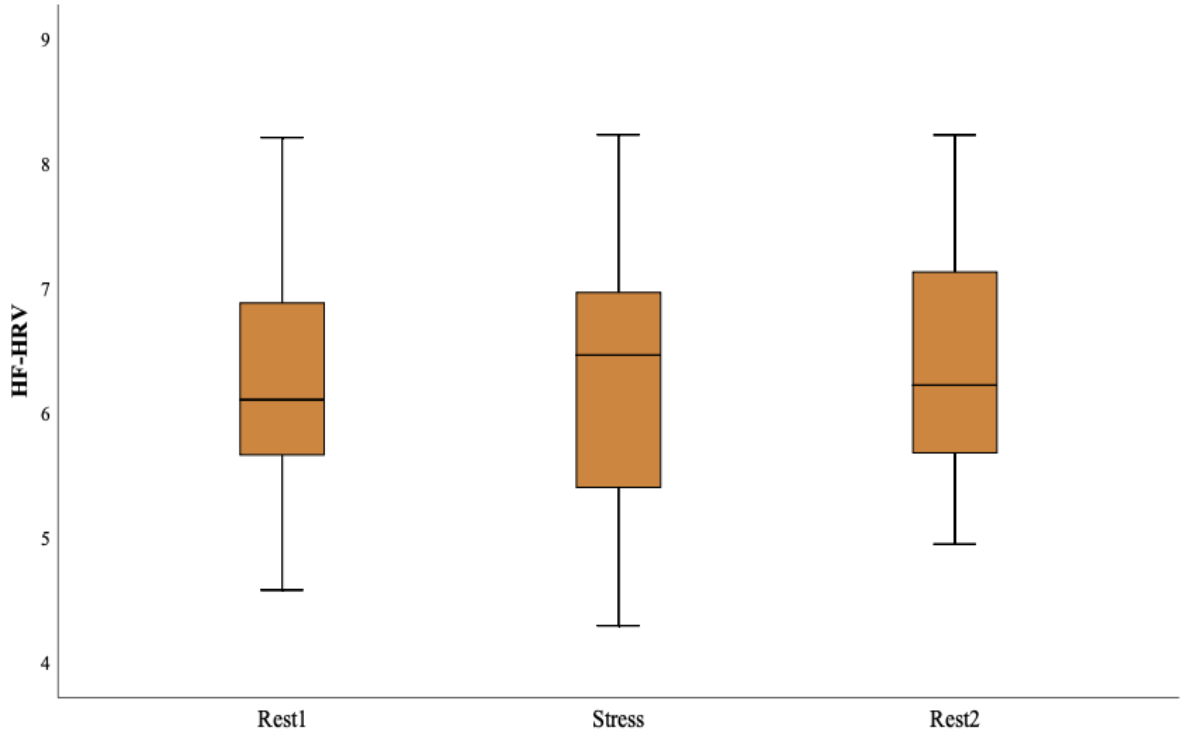

Figure 11: High-Frequency-HRV over the resting state phases (Rest1 and Rest2) and the stress task displayed no significant changes over time.

Perceived Stress

The Friedman's ANOVA for differences in repeated measures indicated that subjective stress ratings through the time points were different with *Friedman's Q* (7) = 143.00, which was significant at $p < .001$. These results are displayed in **Table 4** above and visualized in **Figure 12.**

The Wilcoxon test for dependent samples could not show a significant difference between the phases before scan and pre-stress ($z = -.450$, p (one-tailed) = .330). For all other pairs of successive phases, it showed differences which were significant using a Bonferroni corrected α of .0071 with $p = .007$ for after scan I and II and $p \leq .001$ for all other successive phases. As can be seen in **Figure 12**, the highest mean was reported after the stress induction.

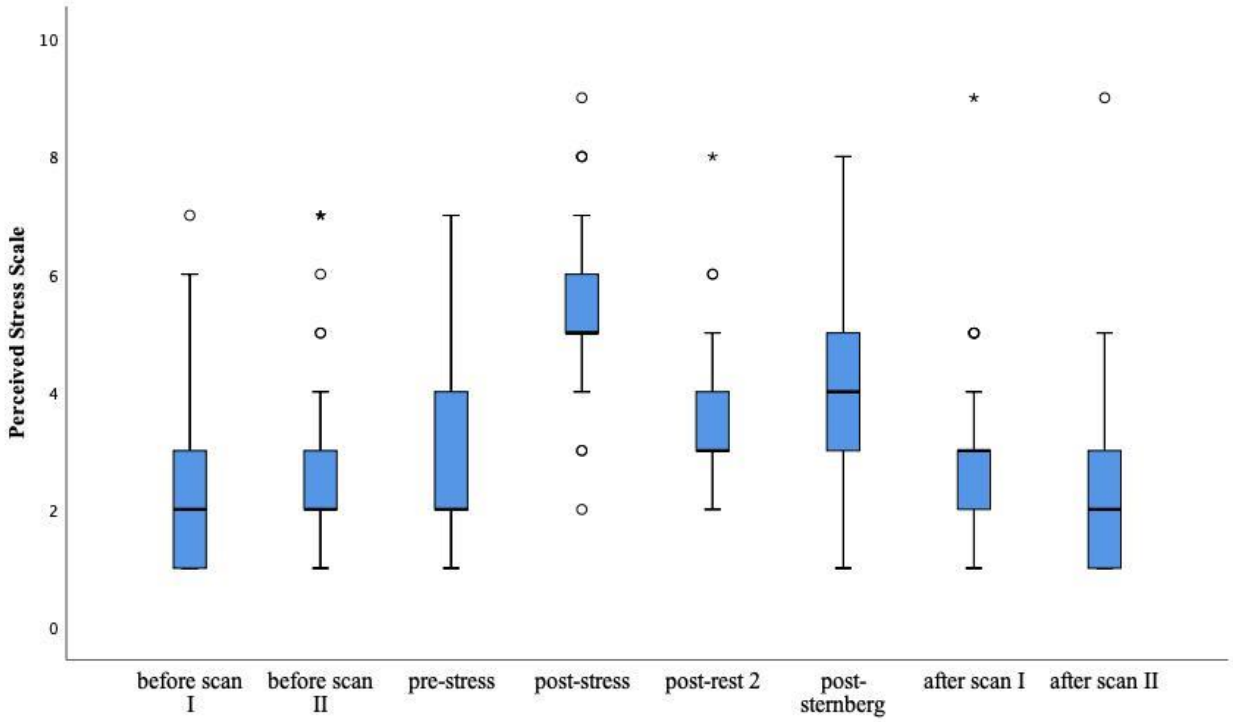

Figure 12: These Boxplots show perceived stress on a Likert scale from 0 to 10 by time point (Likert, 1932). The time points were shown in Figure 7. Stress induction took place between pre-stress and post-stress. * marks statistical outliers.

Salivary Cortisol

The repeated measures ANOVA for cortisol concentration showed significant change over time with F (2.81, 109.45) = 7.496, $p < .001$. The Bonferroni-corrected post-hoc test (corrected $p <$ .00178) showed significant differences between post-rest 2 and after scan I, indicating a recovery after leaving the scanner. Furthermore there were significant differences between after scan II and phases before scan I and II, pre-stress, post-stress and post-sternberg. Importantly, there was no increase of cortisol after the stress induction tasks, though there were significant changes in other pairs as shown in the post-hoc tests.

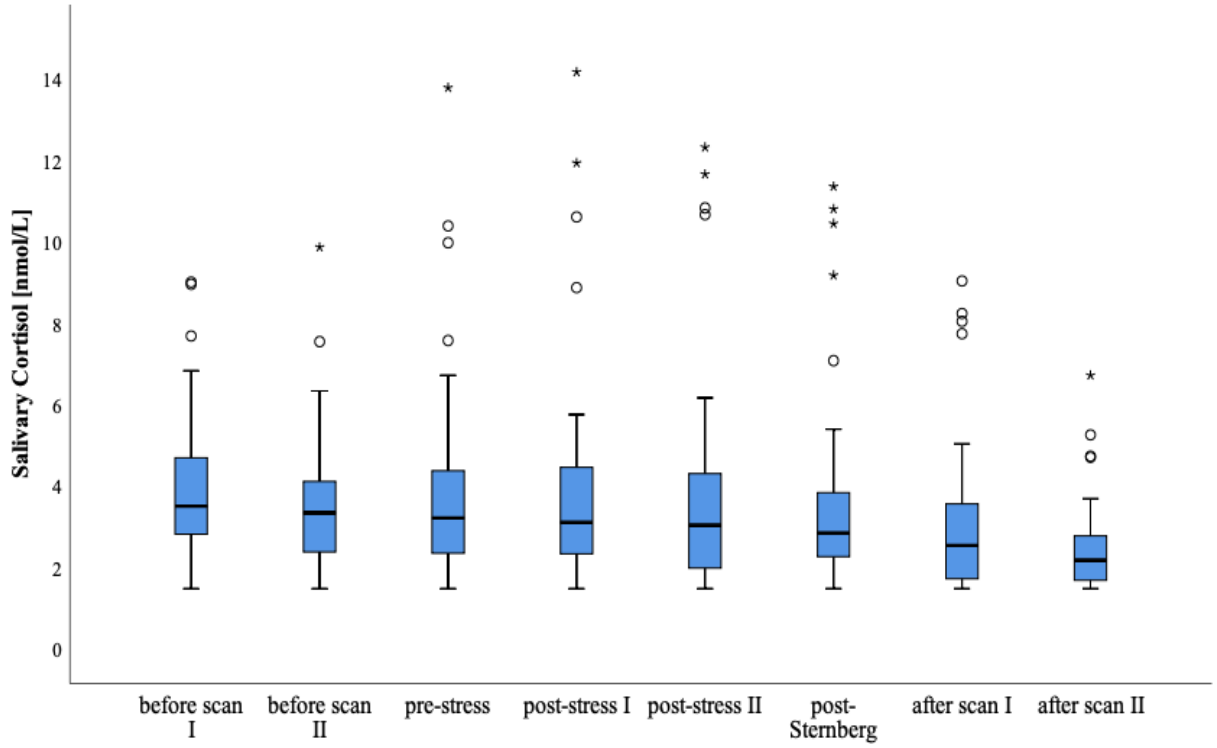

Figure 13: Salivary cortisol concentration [nmol/L] for each time point. The time points were shown in Figure 7. * marks statistical outliers.

5.3 Hypotheses 2a and 2b: Correlation of sleep loss and stress markers

H2: Sleep loss measured with MCTQ and diary is associated with stress reactivity (H2a) and recovery (H2b) in perceived stress, salivary cortisol and cardiac measures.

Heart rate

When correlating sleep loss (MCTQ) with heart rate reactivity there is no significant correlation, r_s (41) = .146, p = .362 (two-tailed). Sleep loss (diary) did not correlate with heart rate reactivity at r_s (41) = -.202, p = .204 (two-tailed).

Sleep loss (MCTQ) and heart rate recovery showed no significant correlation at r_s (41) = -.168, p = .293 (two-tailed), neither did sleep loss via sleep diary correlate with heart rate recovery at r_s (41) = .222, p = .162 (two-tailed).

Table 1: Correlations between sleep loss and reactivity in cardiac stress measures.

Variable (N = 42		HR_ reactivity[5]	RMSSD_ reactivity	SDNN_ reactivity	HF_HRV_ reactivity
Sleep Loss (MCTQ) [2]*	r_s [4]	.146	.116	.192	.004
	p (2-tailed)	.362	.468	.222	.980
Sleep Loss (Diary) [3]*	r_s [4]	-.202	.298	.221	.116
	p (2-tailed)	.204	.058	.159	.470

*Notes: [1] Number of subjects included; [2] sleep loss in MCTQ; [3] sleep loss in sleep diary; [4] Spearman's Rho (correlation coefficient); [5] one more subject missing (N=41), * Significant p-values are reported at p < .00208 after Bonferroni correction.*

Table 2: Correlations between sleep loss and recovery in cardiac measures of stress. Significant correlations are marked with *.

Variable		HR_ recovery	RMSSD_ recovery	SDNN_ recovery	HF_HRV_ recovery
Sleep Loss (MCTQ) [2]	r_s [4]	.168	-.121	-.261	-.087
	p (2-tailed)	.293	.447	.090	.586
Sleep Loss (Diary) [3]	r_s [4]	.222	-.318	-.305	-.202
	p (2-tailed)	.162	.040	.046	.200

*Notes: [1] Number of subjects included; [2] sleep loss in MCTQ; [3] sleep loss in sleep diary; [4] Spearman's Rho; * Significant p-values are reported at p < .00208 after Bonferroni correction.*

Heart Rate Variability

We tested the correlation of sleep loss measures and HRV reactivity in response to and recovery after the stress induction. When correlating sleep loss (MCTQ) with RMSSD reactivity there was no significant correlation at r_s (41) = .116, p = .468 (two-tailed). Sleep loss (diary) did not correlate with RMSSD reactivity at *rs* (41) = .298, p = .058 (two-tailed).

Sleep loss (MCTQ) with RMSSD recovery showed no significant correlation at r_s (42) = -.121, p = .447 (two-tailed). Sleep loss (diary) did correlate with RMSSD recovery at r_s (42) = -.318, p = .040 (two-tailed), as can be seen in **Figure 14**. Note that after using a Bonferroni corrected α at p < .00208 the correlation is not significant.

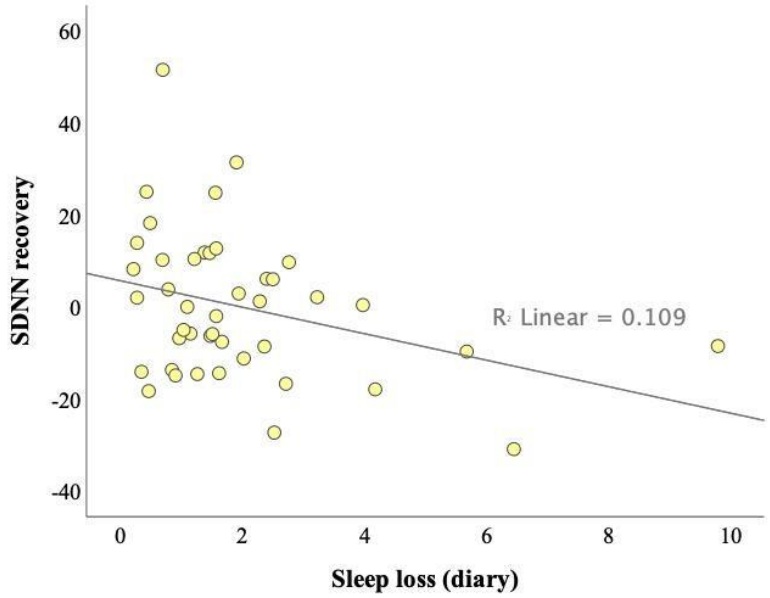

Figure 14: SDNN recovery correlates negatively with the amount of sleep loss reported in the sleep diary.

When correlating sleep loss (MCTQ) with SDNN-HRV reactivity there was no significant correlation at r_s (42) = .192, p = .222 (two-tailed). Sleep loss (diary) did not correlate with SDNN-HRV reactivity at r_s (42) = .221, p = .159 (two-tailed).

Sleep loss (MCTQ) and SDNN-HRV recovery did not correlate at r_s (43) = -.261, p = .090 (two-tailed), while sleep loss (diary) did not correlate with SDNN-HRV recovery at r_s (43) = -.305, p = .046 (two-tailed), as is displayed in the scatterplot in **Figure 15.** This correlation was not significant, since we considered the Bonferroni corrected α at $p < .00208$.

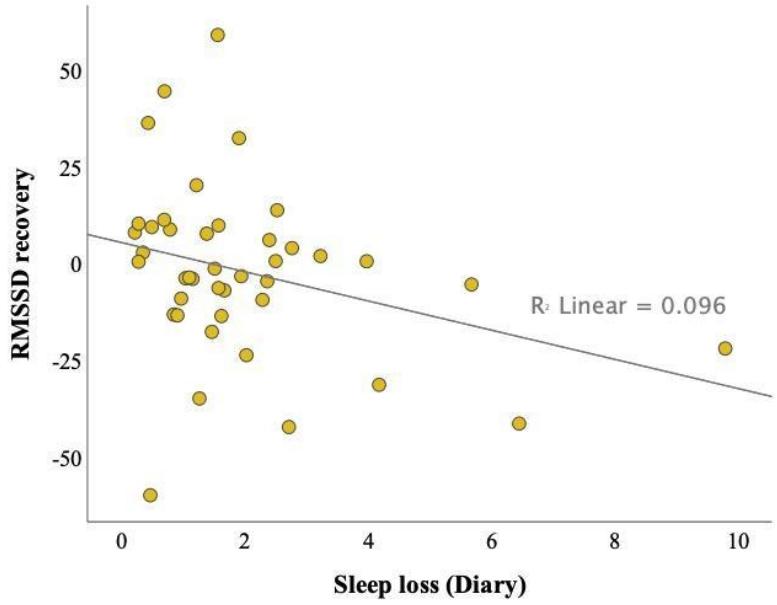

Figure 15: RMSSD recovery shows an association with sleep loss (diary).

Sleep loss (MCTQ) with High-Frequency-HRV reactivity showed no significant correlation at r_s (41) = .004, p = .980 (two-tailed). Sleep loss (diary) did not correlate with High-Frequency-HRV reactivity at r_s (41) = .116, p = .470 (two-tailed).

When correlating sleep loss (MCTQ) with High-Frequency-HRV recovery there is no significant correlation at r_s (42) = -.087, p = .586 (two-tailed). Sleep loss (diary) did not correlate with High-Frequency-HRV recovery at r_s (42) =- .202, p = .200 (two-tailed).

Perceived Stress

Sleep loss via MCTQ and Perceived Stress Scale reactivity did not correlate significantly at r_s (45) = .139, p = .362 (two-tailed). Sleep loss (diary) did not correlate with PSS reactivity at r_s (45) = -.133, p = .384 (two-tailed).

When we correlated sleep loss (MCTQ) with PSS recovery there was no significant correlation at r_s (45) = -.034, p = .824 (two-tailed). Sleep loss (diary) did not correlate with PSS recovery at r_s (45) = .085, p = .590 (two-tailed). For an overview see **Table 6**.

Salivary Cortisol

When correlating sleep loss (MCTQ) with salivary cortisol reactivity there is no significant correlation at r_s (43) = -.125, p = .424 (two-tailed). Sleep loss (diary) did not correlate with PSS reactivity at r_s (43) = -.031, p = .844 (two-tailed).

The correlation of sleep loss (MCTQ) with cortisol recovery showed no significant correlation at r_s (44) = -.014, p = .929 (two-tailed). Sleep loss (diary) did not correlate with PSS recovery at r_s (44) = .027, p = .860 (two-tailed). This is displayed in **Table 7** below.

6 Discussion

The current work focused on investigating the effects of naturally occurring partial sleep loss on the stress response. Sleep loss was measured by the MCTQ (Roenneberg et al., 2003) and a subjectively reported sleep diary over 7 days. The effects of sleep loss on stress were investigated by subjecting participants to a standardised stress test while recording subjective stress levels, salivary cortisol levels, heart rate, HRV, and for further publications structural and functional MRI data.

Higher subjective stress and heart rate were found after the stress induction. For heart rate, mean values were higher during stress condition than during the resting state phases. Salivary cortisol and SDNN also showed significant changes over time. On the other hand, RMSSD and HF-HRV did not show significant changes over time.

Next, we examined whether sleep loss affected the reactivity of the stress parameters using correlations and a Bonferroni correction. The correlations with perceived stress, salivary cortisol, or any of the cardiac markers were not significant for either of the two sleep loss markers.

When looking at correlations between sleep loss by diary and stress recovery, no significant correlations were found after applying Bonferroni correction. These null results were also found for sleep loss via MCTQ with stress recovery markers.

All in all, the expected response to the stress test was shown for perceived stress and heart rate, yet, against our hypotheses, not for cortisol and HRV measures. When testing for the effects of sleep loss, we found no significant correlations to reactivity of stress markers, but we found trends for correlations with two markers of HRV recovery.

6.1 Evaluation for stress induction (Hypothesis 1)

There were significant time effects for subjective stress via PSS and heart rate, but not for other stress markers. Here, we can observe that our stress induction protocol had both psychological and physiological effects, since it led to a rise in heart rate as well as perceived stress, as in accordance with our first hypothesis. On the other hand, there were no significant changes in HRV markers or salivary cortisol levels due to stress induction – therefore, these results in HRV and cortisol do not fit the first hypothesis.

Previous studies that also conducted the ScanStress paradigm or the Montreal Imaging Stress Task (MIST) described a significant increase of heart rate in response to psychosocial

stressors, while HRV markers were not reported (Gossett et al., 2018; Streit et al., 2014). Salivary cortisol was also used in one of the abovementioned studies, in which half of the participants showed a significant salivary cortisol response, yet the effect was not significant for the entire sample (Streit et al., 2014). Both studies had similar effect sizes. In contrast our study they included female participants.

The high variance in the reactivity of these markers that was observed in our analyses might be explained by the idea that physiological stress reactivity to psychosocial stressors can vary substantially independent of subjective perceived stress (Cacioppo et al., 1998). However, in patients with chronic psychosocial stress a decreased baseline HF-HRV and overall reduced reactivity were shown, which were attributed to the autonomic dysregulation (Lucini et al., 2005). Therefore, the blunted autonomic cardiac response shown in HRV markers may have been caused by chronic stress or increased stress levels before the test. Furthermore, a possible acute stressor in this experimental context could be the MRI scanner surroundings in our test setting. This was also discussed as a possibly confounding factor by Streit et al. (2014). Furthermore, it was shown that MRI scanner surroundings lead to an anticipatory effect on the cortisol response (Gossett et al., 2018). Therefore, participants might have already had elevated cortisol levels before testing, blunting the endocrine stress response. In our study, the decrease of the salivary cortisol levels some minutes after leaving the scanner fits this notion. Additionally, there are contradictory results for whether previous MRI experience influences the stress level before a scan (Gossett et al., 2018; Tessner et al., 2006). We did not check for previous MRI experiences; therefore, this factor is not considered in our analysis. Therefore, there are precedents and possible causes for the non-reactivity in stress markers which were not affected by stress induction, despite the subjective stress reactivity.

6.2 Evaluation of results on sleep loss (Hypotheses 2a and 2b)

In our study we expected associations of sleep loss with reactivity or recovery of stress markers. Yet, as mentioned above, self-reported sleep loss over the week before scanning was not associated with reactivity in stress markers such as PSS, heart rate, HRV, or cortisol. There were negative correlations between sleep loss derived from the sleep diary and SDNN and RMSSD recovery. Notably, these effects were not significant after using a Bonferroni correction with respect to the 24 correlation tests. In addition, neither of the correlations which were significant before using the correction showed significant effects of the stress induction in H1. Other recovery markers also showed no significant correlation. Several previous studies have shown at least in part similar results, where sleep loss and stress markers were not

significantly correlated. This suggests that this form or amount of sleep loss does not have strong effects on the stress level or response.

Heart rate

Heart rate is a common biomarker of stress. We expected a positive correlation between sleep loss and heart rate response, based on the positive results of some previous studies. For instance, one study showed an increase of heart rate after partial sleep restriction with 10 consecutive nights of 4.2 hours of sleep (Meier-Ewert et al., 2004). Blood pressure as a second marker was not affected by sleep restriction in this study.

Yet, some previous studies did not show consistent results. Dettoni et al. (2012) examined the effects of a protocol of normal sleep compared to sleep restriction to less than five hours over five nights. No changes in heart rate or blood pressure were observed (Dettoni et al., 2012). Another study showed mixed results with an association between naturally occurring shorter sleep duration and HR recovery from a stress task, but not with heart rate reactivity (Mezick et al., 2014).

We found a significant change of heart rate over time in our study. Yet, further to this, sleep loss was not associated with heart rate measures, which contrasts with Meier-Ewert et al. (2004) and Mezick et al. (2014). This might be explained by differences in the study protocols which will be discussed later. Our results mirror the conflicting results for whether sleep loss affects heart rate reactivity and recovery.

Heart Rate Variability

Our results did not verify our hypotheses H1, H2a or H2b regarding HRV measures. Compared to studies on total sleep loss, our results are similar to those of Schwarz and colleagues (2018), who found that one night of total sleep loss did not have an effect on cardiac autonomic markers, such as in this case baseline RMSSD (Schwarz et al., 2018). These effects on HRV are in contrast to the changes displayed in acute sleep loss studies with 36 or 40 hours of forced wakefulness (Glos et al., 2014; Zhong et al., 2005).

Regarding partial sleep loss, one study showed effects for sleep loss on sympathetic activity after sleep restriction to less than four hours over six nights (Spiegel et al., 1999). The sleep restriction protocol by Dettoni et al. (2012) led to a decrease in HF-HRV and an increase of LF-HRV, marking an autonomic shift with increased sympathetic and decreased vagal tone. The HF-HRV response was not affected by sleep loss in our study.

Also in contrast to Dettoni et al. (2012), two studies showed no significant changes in HRV-measures after sleep restriction over several days (Muenter et al., 2000; Tobaldini et al., 2017). Tobaldini et al. (2017) showed no impairment in the frequency domains of HRV during wakefulness or sleep after eight days of sleep restriction to 2/3 of normal duration. Furthermore, Muenter et al, (2000) were able to show similar results for sleep restriction to less than four hours over four nights.

Takase and colleagues (2004) showed that chronic sleep loss in students, measured via questionnaires, that occurred during the final exams phase led to a decrease in time and frequency domain HRV measures (Takase et al., 2004). However, this study examined the effects of sleep loss under a specific stressor, where the sleep loss and stressor co-occurred.

A study by Mezick et al. (2014) showed mixed results. Naturally occurring short sleep duration with an average of 5:47 hours over 7 days inversely correlated with HF-HRV reactivity but not recovery in undergraduate men during a cognitive stress task.

With regard to our results, a possible explanation could be that other studies have subjected participants to considerably higher quantities of sleep loss (Dettoni et al., 2012; E.-M. Elmenhorst et al., 2008; Tobaldini et al., 2017). In our study, participants experienced on average less than 30 min of daily sleep loss over 3 or 4 nights. As mentioned in the introduction, there is significant variance in the amount of sleep loss between studies. This can be explained by the lack of a consistent definition of quantitative sleep loss across studies (Cappuccio et al., 2010b). Indeed, the effects of sleep loss have been shown to be dose-dependent and under the influence of adaptive processes (Belenky et al., 2003; Philip et al., 2012). Potentially, the sleep loss in our study was not pronounced enough to have the expected effect on the stress response. Another factor here might be that the accumulation of sleep loss and allostatic load is often stopped by restorative sleep over one or two nights, which may occur on weekends (Belenky et al., 2003; E.-M. Elmenhorst et al., 2008; Philip et al., 2012). To our study this is relevant, as the workdays in the sleep diary were interrupted by two free days during the weekend. Furthermore, compensation mechanisms may cancel out the peripheral physiological effects of short sleep duration, such as changes in cardiac regulation, to a certain threshold. An fMRI study showed that in response to acute sleep loss, the activity in the arousal networks of the thalamus and brainstem increased (Yoo, Hu, et al., 2007). These mechanisms might temporarily compensate for sleep loss.

As an environmental factor, caffeine is a common and potent central nervous system stimulant which counteracts the effects of sleep loss (Roehrs & Roth, 2008). Hence, in our study

the participants were instructed to refrain from caffeine consumption before testing. Still, this illustrates that sleep loss is a multifactorial process in which compensatory resources can be deployed. Nicotine is another legal stimulant which influences wakefulness. Furthermore, we did not control for hormonal, acid-base or electrolyte imbalances, which influence heart rate but are rare in a young and healthy sample (Jameson et al., 2018).

6.3 Strengths and limitations

6.3.1 Sample selection and study design

In this study, we used clear inclusion and exclusion criteria. Hence, a limitation of this study is that results apply only for young to middle-aged, healthy males. This makes the results more valid in this subgroup, yet less valid for other sociodemographic groups.

It is assumed that one in three people have a high resilience against chronic partial sleep loss, whereas another third has an increased vulnerability to it (Krause et al., 2017). The selection of healthy participants may have excluded individuals more susceptible to sleep loss and this in turn may have led to our null findings, since sleep loss affects some people's neurobehavioral markers less. In addition, the autonomic nervous system is susceptible to a wide range of factors other than sleep loss (Van Dongen et al., 2004). Therefore, the effect of mild to moderate sleep loss may not lead to a direct consequence.

Age

Roenneberg (2003) showed significant age effects, meaning sleep loss was more pronounced in participants of less than 21 years of age (Roenneberg et al., 2003). Furthermore, the recommended amount of sleep is also higher for paediatric cohorts compared to adult cohorts (Paruthi et al., 2016). Among adults, Schwarz (2018) did not find age effects of sleep loss on HRV (Schwarz et al., 2018). Nevertheless, the effects of sleep loss may be more pronounced in an adolescent cohort than in our study, where the youngest participant was 20 years old.

Gender

Notably, we did not include female participants in this study. This decision was based on the notion that stress reactivity measured by the rise of free cortisol levels depends on sex, contraceptive use and menstrual phase, and was found to be significantly less pronounced in women (Kirschbaum et al., 1999). With regard to sleep loss, another study showed no significant differences in sleep measures based on gender (Voderholzer et al., 2003). Our work

on naturally occurring sleep loss is at an early phase of research on fundamental concepts. But, it should be noted that studies including male participants should avoid the tendency to overgeneralize with respect to the gender bias (Holdcroft, 2007). Also, since women are more likely to develop insomnia symptoms, as was shown in a meta-analysis, the inclusion of female participants in studies in this field is relevant as clinical interventions are explored (Zhang & Wing, 2006).

6.3.2 Sleep loss

Our study differs from most previous works in the features of sleep loss, in our case naturally occurring partial sleep loss. Testing the effects thereof gives our study a good ecological validity for the most common form of sleep loss. Past research has for a large part focused on the effects of acute sleep loss. In contrast, our study adds to the body of knowledge on chronic partial sleep loss.

There is an apparent discrepancy between the two sleep loss measures in our study. Both focus on cumulated partial sleep loss. The differences could be explained by differences in reporting. The sleep diary used prospective reporting, whereas the MCTQ used retrospective reporting. Hence, the diary might be more sensitive when looking at the current state of sleep and sleep loss during the time of the experiment. The MCTQ assesses more trait-like sleep patterns, as it asks about persisting, explicitly “normal” sleep time (Roenneberg et al., 2003), hence deviations from this pattern could be underreported in the MCTQ. In effect, the prospective approach and the lack of reporting of unusual sleep times could explain why associations between sleep loss and cardiac measures was only found for the sleep diary.

Partial Sleep Loss

Natural sleep loss was measured using both a questionnaire and a prospective sleep diary. In contrast, artificially induced sleep loss in a laboratory setting may be measured with polysomnography. Also, we used partial sleep loss, while many other studies have researched the effects of total sleep loss (Krause et al., 2017). Despite cumulative effects in both acute and chronic sleep loss, there may be substantial physiological differences between the two (Van Dongen et al., 2003). Hence, comparability between different forms of sleep loss is partly limited.

Sleep loss measures in our study may have significant interindividual variability, especially since we used self-reported sleep time (Hirscher et al., 2015). Using subjective measures of sleep may have less accuracy than laboratory measurements. On the other hand, natural sleep loss mirrors the chronic sleep loss a person experiences and is less confounded by the method of sleep loss induction. Hirscher and colleagues (2015) suggested that there are significant differences between sleep in a sleep laboratory or sleep at home. Overall, sleep duration is reported differently, specifically as longer, in self-reported measures than in polysomnography or actigraphy measures (Kurina et al., 2013).

Furthermore, our study does not account for sleep quality, which is a significant factor besides sleep quantity for restorative sleep. It was shown that not short sleep alone, but rather short sleep and poor sleep quality together were associated with physiological effects as marked via an allostatic load index (Clark et al., 2014). Spiegelhalder (2011) showed that in patients with insomnia symptoms, short sleep duration was a significant factor for reduced HRV. Notably, a recent study suggests that poor sleep quality and poor habitual sleep recorded via wrist actigraphy is associated with increased stress reactivity in the TSST, supporting it as an additional factor in sleep loss research (Massar et al., 2017). Therefore, our subjective and quantitative sleep measures give a less accurate account of sleep deprivation than combined approaches.

One challenge in studies on sleep deprivation is the confounding effect of the circadian rhythm, which is a major process driving the sleep-wake cycle (Borbély et al., 2016). It promotes sleep or wakefulness depending on the circadian phase (Dijk & Czeisler, 1994). Therefore, one advantage of our study was that our participants all had a similar chronotype and testing took place at a similar time. Further information on circadian rhythm could have been gathered when testing over several time points over the day. However, this was impracticable in our study design, considering for instance work obligations.

A combination of qualitative and quantitative information on sleep is needed to model the complexity of sleep deprivation. Yet, a balance has to be found to impact sleep as little as feasible by the setting.

6.3.3 Stress

We looked at changes in the stress response to a standardised test. Constructs of the stress response are, as mentioned in the introduction, heterogenous across studies. Rosengren (2004)

remarked that stress is difficult to conceptualize in research, due to the complexity of the subject and the lack of generally accepted definitions (Rosengren et al., 2004).

Like previous approaches, we used a variety of stress markers, such as several cardiac markers, as well as endocrinological and subjective markers. We acquired additional information about the dynamics of the stress response during a standardised stress induction. Only a few other studies have used a standardised stress test in studies on sleep loss, yet even in this, the protocols differed from ours (Schwarz et al., 2018; Vargas & Lopez-Duran, 2017). Our protocol adapted established concepts for stress induction, like the TSST and the ScanStress and MIST protocols. In comparison to studies collecting just baseline measurements of stress markers, studies using stress induction protocols on average use smaller samples, since the effort is greater.

HRV is an established marker of stress which is associated with activation in CNS structures such as the mPFC and amygdala, which are associated with the stress response (Thayer et al., 2012). To record physiological data, specifically heart rate, we used a pulse oximeter, while many other studies have used an ECG (Tsuji et al., 1996; Dettoni et al., 2012; Tobaldini et al., 2017). ECG has the advantage that it records cardiac excitation directly, whereas pulse oximetry measures the heartbeat indirectly through changes in peripheral blood flow. On the other hand pulse oximetry is used in MRI scanner environments (Gossett et al., 2018; Streit et al., 2014). Both ECG and pulse oximetry are common clinical tools, yet small variances may be attributed to differences in heart rate recording.

One factor reducing comparability to other studies is the use of MRI during the stress test. This acquisition of imaging data has restricted the acquisition of further markers, since many standard devices are not MRI compatible. To reduce confounding by the scanner as a factor, participants had a practice run right before scanning and the procedure in the MRI scanner was explained to them beforehand. Previous studies on stress have used an MRI scanner as well, yet in a PubMed search, we found none which have also tested the effects of sleep loss.

It was pointed out by Lampert and colleagues (2016) that there is still a lack of knowledge on the mediating pathways between stress and morbidity (Lampert et al., 2016). Their study on the effects of subjective stress on autonomic stress markers like HRV used a multidimensional approach, with the cumulative stress/adversity interview including adverse life events and chronic stress as well as factoring in health behaviour, race, sex, and age. Our sample group was homogenous for sex and to some extent also for age. We did not acquire

information on chronic stress, adverse life events or health behaviour, therefore we could not control for these stressors but instead focused on the stress response.

A recent review suggests that autonomic response should be controlled for physical activity or fitness levels (Mücke et al., 2018). We controlled for recent physical activity by asking participants to refrain from such activity on the day of scanning. However, overall fitness levels were not controlled for. Therefore our results are potentially confounded, though the effects of physical activity levels on stress are likely to be small in regular samples (Mücke et al., 2018).

Our study showed that regular sleep loss during the working life was not associated with changes in physiological stress response markers. In contrast, previous studies have focused on artificially induced sleep restriction, while other studies have focused on shift work. In addition, this work also looks at partial sleep loss and its effect on a small selection of stress markers.

6.4 Perspectives

Sleep loss is a prevalent condition and has been associated with increased morbidity. The question remains as to which pathways lead to these negative consequences. To date, sleep loss and stress are often viewed as individual conditions, but a growing body of research focuses on the role of an altered stress response as a mediating factor for sleep loss.

Interventions for each exist, but the empirical basis for sleep interventions is scarce. Given the hypothesis that sleep loss and chronic stress are mutually aggravating conditions with negative health consequences, further insight into their interconnection might open a window for better interventions in the future. What complicates this research question is the variability of definitions and of factors with respect to markers for both. Yet, to evaluate causality and possible interventions, consistency is needed. Such consistency in the core measures of stress and sleep could be achieved by using broader approaches or more standardised protocols.

Future studies might use a design with groups sorted by a quantitative or qualitative cut-off for sleep deprivation. These groups can then be matched for age, sex, workload, and other variables. A cross-over design with two groups as in a study by Dettoni and Colleagues (2012) could balance groups because vulnerability to sleep loss differs inter-individually. This design tests each participant at two timepoints and partially accounts for learning effects.

6.4.1 Concepts of Sleep Deprivation: circadian and qualitative factors

Circadian disruption remains a serious problem in shift workers (Torquati et al., 2018). It is an important factor in sleep deprivation research (McEwen & Karatsoreos, 2015; Roenneberg et al., 2003). Both circadian disruption and sleep quality are important factors to be considered in future research on the effects of chronic sleep deprivation.

Sleep quantity can be assessed through a subjective sleep diary as we did in this study. Additionally, information on sleep quality and behaviour can be gathered via questionnaires such as the Karolinska Sleep Questionnaire (Akerstedt et al., 2002) or the Pittsburgh Sleep Quality Index (Buysse et al., 1989). Furthermore, the MCTQ, which we used in this study, provides insight into the role of the circadian clock (Roenneberg et al., 2003).

As was mentioned in the previous sections, it is difficult to interpret results across studies, due to the lack of standardised protocols and sleep measures. Sleep diaries are useful for comparing results with epidemiological studies, while objective actigraphy or polysomnography are useful for comparing results to studies with laboratory settings. Also, questionnaires, diaries and sleep actigraphy could be used complementarily to combine different aspects in sleep deprivation (Dettoni et al., 2012).

There are different methods to gather data on sleep quantity and quality. In this study, we used subjective sleep measures such as a sleep diary and the MCTQ. Another approach would be the use of home sleep testing, which is more objective, yet resource intensive (Mendonça et al., 2018). The advantage would be an objective sleep measurement in the natural environment of the subject, in comparison with the subjective sleep measures used in this study. A sleep lab and polysomnography require participants' habituation to the situation and are resource intensive as well. As an alternative, electroencephalography or EEG monitoring is a standard method for sleep detection (Campbell, 2009). A recent study proposed the option of a mobile EEG as a practicable and objective method for at-home sleep testing (Mikkelsen et al., 2019). In addition to being a more precise measure of sleep duration, it can also record information on sleep quality.

In this study, dose dependence of sleep loss was revealed as a central factor to its physiological effects. A study design with naturally occurring sleep loss like ours will be less likely to show pronounced effects of sleep loss than a laboratory setting. Moderate partial sleep loss paradigms in laboratory settings have used protocols over five nights of sleep restriction

(Dettoni et al., 2012; Tobaldini et al., 2017). Therefore, one option to evaluate accumulated sleep loss is having scans on Fridays, when subjects have passed their weekly workdays.

Considering that we did not find effects for sleep loss on stress markers, it seems sensible to focus on subgroups with above average sleep loss. Vulnerable groups for partial sleep loss may be jobs with a high workload, such as seasonal work, or very late or early working hours, for instance in gastronomy or facility management. In comparison, there have been several studies on the effects of acute sleep loss of hospital staff working night shifts (Cincin et al., 2015; Malmberg et al., 2010). For longitudinal studies, an induction of naturally occurring partial sleep loss will present difficulties, therefore a study design with sleep-specific therapeutic interventions in people with short sleep or insomnia symptoms could be considered.

One recent study sheds light on a different mediator between sleep loss and its negative consequences: Simon & Walker (2018) concluded that sleep loss, total or partial, led to an increase in social withdrawal. Social withdrawal is significantly associated with poor health and increased mortality (Cacioppo et al., 2014). Therefore, the focus of future studies might shift towards the psychological and behavioural consequences of sleep loss rather than the physiological pathways as in our study.

Future research should focus on naturally occurring partial sleep loss in the working life. While this study looked at self-reported quantitative sleep loss, further aspects of sleep deprivation can be added. Here, the association of qualitative factors and chronotype could be of interest.

Stress

There are a variety of stress constructs. Beyond the currently used markers of the stress response, assessment of early life and chronic stressors can be taken into account as well (Lampert et al., 2016). Preferably, a combination of biomarkers should be used in allostatic load indices (Edes & Crews, 2017). Despite the variability, an allostatic load index should include markers of at least the best-established neurophysiological domains, specifically endocrine, cardiovascular, metabolic, and immunological markers.

Future studies should include a greater variety of markers to increase comparability among studies, for instance skin conductance level, blood pressure, inflammatory markers, and muscle tone. For instance, beat-to-beat blood pressure reactivity was associated with acute sleep loss (Franzen et al., 2011) and yet showed no association with partial sleep restriction over seven days (Mezick et al., 2014). Inflammatory markers could be of interest as mediators of

cardiovascular risk or risk of infection. In addition to the HRV measures that were used in this work, newer HRV measures may be used complementarily to achieve a more accurate modelling of autonomic activation and thus stress (Porta et al., 2007; Tobaldini et al., 2017). Due to the complexity and variability of stress and sleep deprivation constructs, their markers should be selected mindfully and critically.

6.5 Summary and Conclusion

Good sleep matters, yet sleep loss remains a prevalent health condition (Riemann et al., 2017). As mentioned above, the effects of partial sleep loss are heterogenous across studies (Dettoni et al., 2012; Mezick et al., 2014; Tobaldini et al., 2017; Vargas & Lopez-Duran, 2017). Previous studies examined the effects of either artificially induced sleep loss (Dettoni et al., 2012; Tobaldini et al., 2017) or the effects of acute sleep loss in shift workers (Cincin et al., 2015). Our study adds a look at the effects of partial sleep loss occurring during the working life in adult male subjects, which is important due to the high prevalence of sleep deprivation in the working age population (Schlack et al., 2013). We found no significant alterations in stress markers related to naturally occurring sleep loss, yet there were possible trends for HRV recovery. Yet, this supports the idea, that slight to moderate partial sleep loss over 3 to 4 nights - as in this study - can be well compensated on the level of the psychophysiological stress response. Possible compensation mechanisms could be in the domains of individual stress resilience and sleep loss resilience. As mentioned above, people's ability to cope with sleep loss differs greatly, and one or two nights of sufficient sleep may be a potent recovery mechanism. Since other studies have indeed shown effects for sleep loss on physiological stress markers, there might be an individual stress and sleep loss resilience. While it is very advisable to promote positive sleep habits, there is more to be explored about the physiological consequences of sleep loss.

7 Literature

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8 Appendix

8.1 Eidesstattliche Erklärung

„Ich, Armin Spitta (geborener Ligdorf), versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema:
„Effects of naturally occurring sleep loss on the physiological stress response"
selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst."

Datum: 13.01.2023

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Armin Spitta, geb. Ligdorf

8.2 Anteilserklärung an erfolgten Publikationen

Armin Spitta hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: [Annika Dimitrov, Jonathan Nowak, Armin Ligdorf, Nicole Y. L. Oei, Mazda Adli, Henrik Walter, Ilya Veer],
[Natural sleep loss is associated with lower mPFC activity during negative distracter processing], [Cognitive, Affective, & Behavioral Neuroscience, [2021]

Beitrag im Einzelnen: Co-Autorenschaft, Mithilfe bei der Probandenrekrutierung über Flyer und ebay- Kleinanzeigen, Durchführung und Dokumentation des Telefonscreenings und Erhebung der Fragebögen, Erprobung der Abläufe, Betreuung der Probanden im Rahmen des Experiments u.a. in der Rolle des Versuchsleiters, Mitwirken bei der Übertragung der Daten in die verwendete Statistiksoftware.

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Unterschrift, Datum und Stempel der erstbetreuenden Hochschullehrerin

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Unterschrift des Doktoranden/der Doktorandin

8.3 Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

9 Danksagung

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